JOC The Journal of Organic Chemistry

pubs.acs.org/joc Article

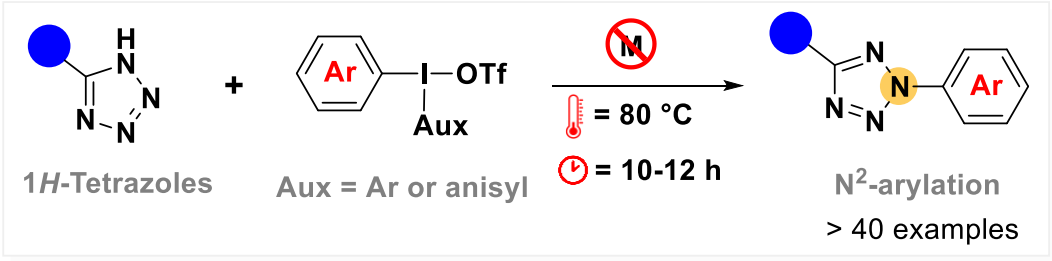
Metal-Free Regioselective N^2-Arylation of 1*H*-Tetrazoles with Diaryliodonium Salts

Raktim Abha Saikia, Anurag Dutta, Bipul Sarma, and Ashim Jyoti Thakur*

Chapter 2

Metal-Free Regioselective *N*^{2}-Arylation of 1*H*-Tetrazoles

Abstract: The chapter describes a general and simple metal-free regioselective *N*^{2}-arylation strategy for 5-substituted-1*H*-tetrazoles with diaryliodonium salts to access 2-aryl-5-substituted-tetrazoles. Diaryliodonium salts with a wide range of both electron-rich and previously challenged electron-deficient aryl groups are applicable in this method. Diversely functionalized tetrazoles are tolerable also. A one-pot system is devised to synthesize 2,5-diaryl-tetrazoles directly from nitriles. The synthetic utility of this method is furthered extended to late-stage arylation of two biologically active tetrazoles.



- operationally simple
- one-pot step-wise synthesis
- highly functionalized substrate tolerance
- two examples of pharma-relevant tetrazole

Saikia, R. A., Dutta, A., Sarma, B. and Thakur, A. J. Metal-Free Regioselective *N*^{2}-Arylation of 1*H*-Tetrazoles with Diaryliodonium Salts. *The Journal of Organic Chemistry*, 87(15):9782-9796, 2022

2.1 Introduction

2.1.1 Tetrazoles and its applications

Tetrazoles **1** (Tzs) and their *N*-substituted compounds are highly privileged nitrogen-rich five-membered heterocycles owing to their occurrence in several important bio-active compounds (Figure 2.1) [1–3]. In addition to this, the Tz moiety is found in compounds having applications in material science (photography and military) [4–6], and in agriculture as herbicides [7–8]. Owing to the presence of large number of nitrogen atoms in Tz moiety, it is useful as an environmental-friendly gas generator [9]. Since, 5-substituted 1*H*-tetrazoles (1*H*-Tzs) can be formulated as bio-isostere of carboxylic acids, drugs possessing 1*H*-Tz are widely useful as anti-bacterial, anti-hypertensive etc. (Figure 2.1C) [10–14]. For example, Valsartan **5**, a drug containing 1*H*-Tz is a multibillion-dollar angiotensin-II receptor antagonist, used for the treatment of high blood pressure and heart failure [15–16].

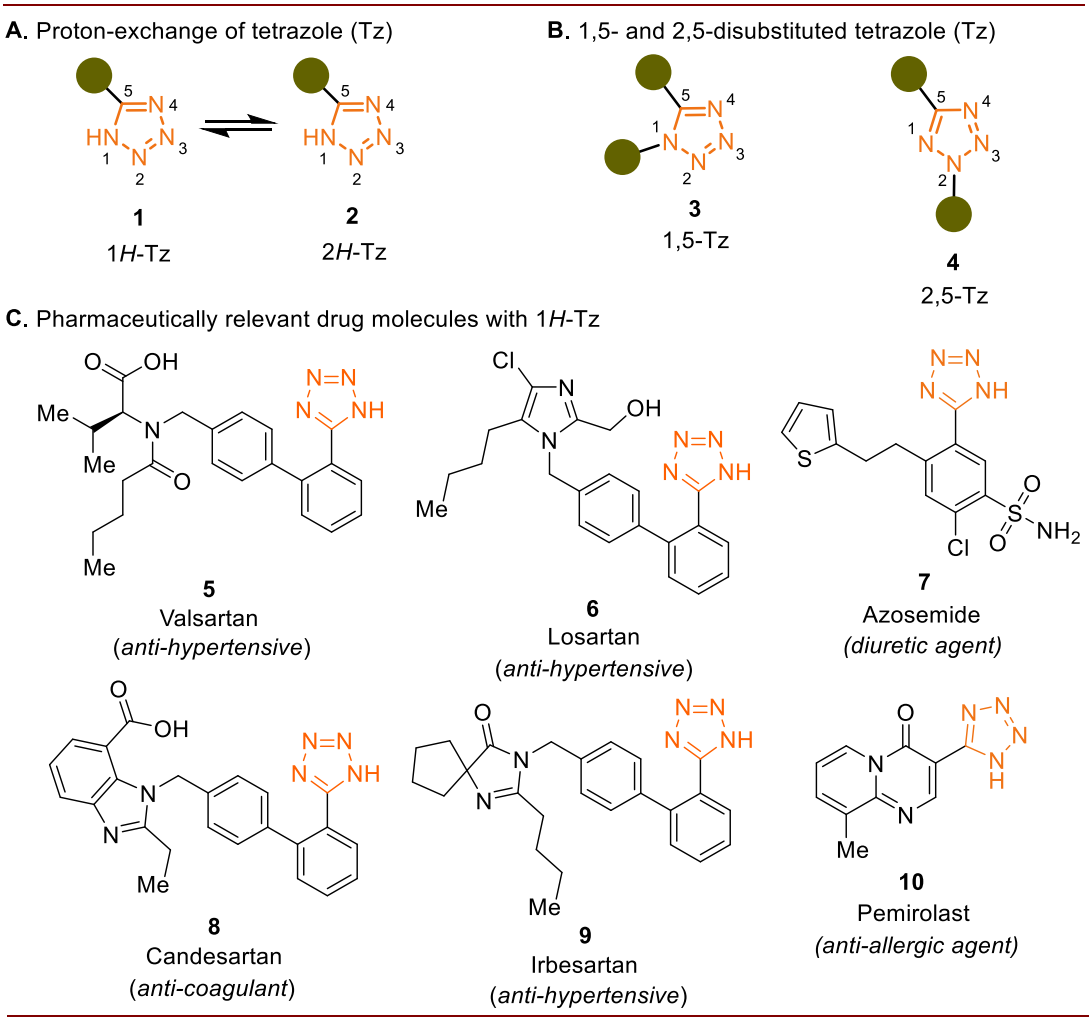


Figure 2.1. Structural description of tetrazoles and examples of bio-active 1*H*-Tzs

Likewise, both 1,5-disubstituted tetrazoles **3** (1,5-Tzs) [17−19] and 2,5-disubstituted tetrazoles **4** (2,5-Tzs) [20] have been found in a few biologically active compounds and they reveal bio-isosteric nature with an amide bond (Figure 2.2A). 2,5-Tzs display interesting biological activity as pharmacophores. For instance, HM30181 (**13**) derivatives are remarkable inhibitors of breast cancer resistant proteins (BCRP/ABCG2) [21]. Compounds with 2,5-Tz moiety can also act as a cellular imaging agent in chemotherapy due to its multidrug resistance protein-1 (MDR1) inhibitors [22]. Due to their photosensitivity, 2,5-Tzs are potential "photoclick" reagents (**15** and **16**) and their access for the bio-orthogonal synthesis of fluorescent active pyrazolines could be utilized as reporters in biological systems [23−24].

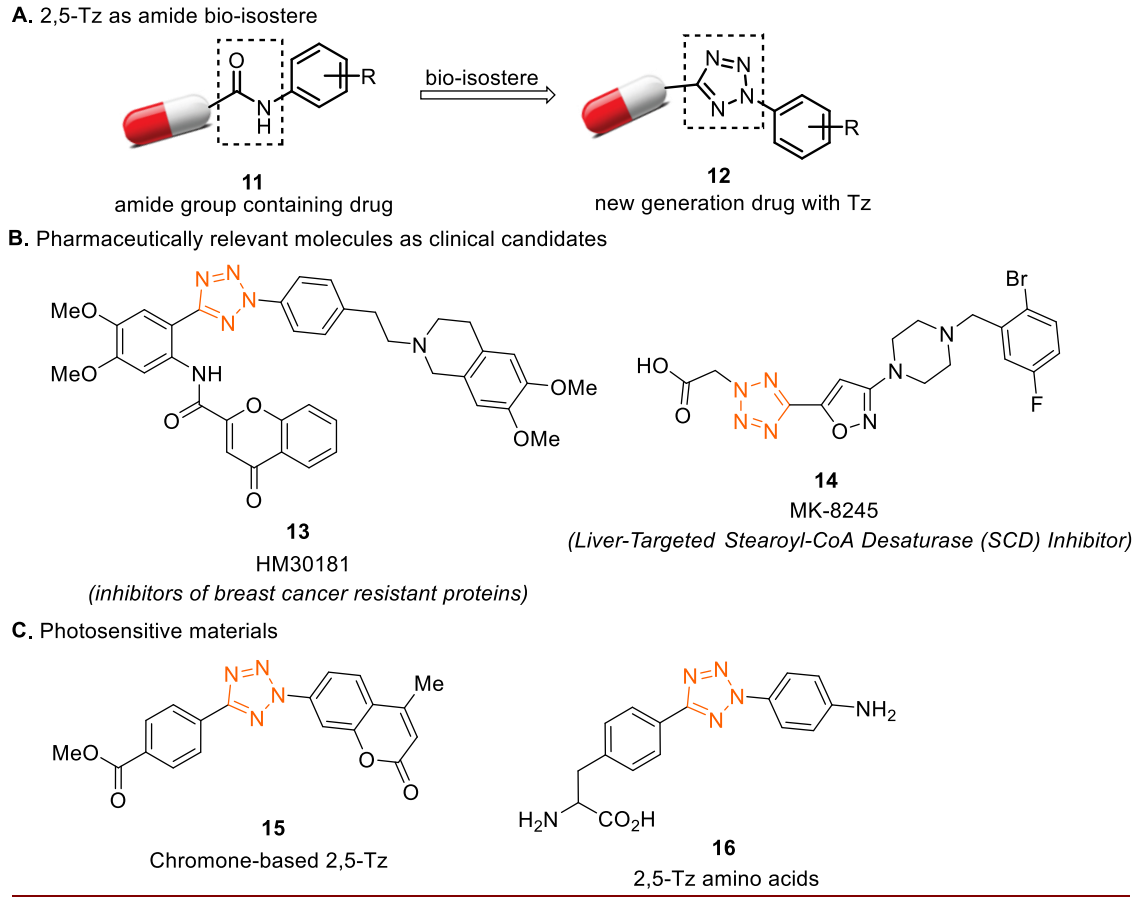
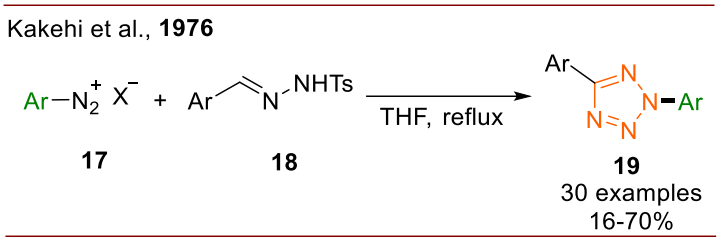


Figure 2.2 Applications of 2,5-Tzs in medicinal chemistry and material sciences

2.1.2 Previous methodologies to access 2,5-Tz scaffolds

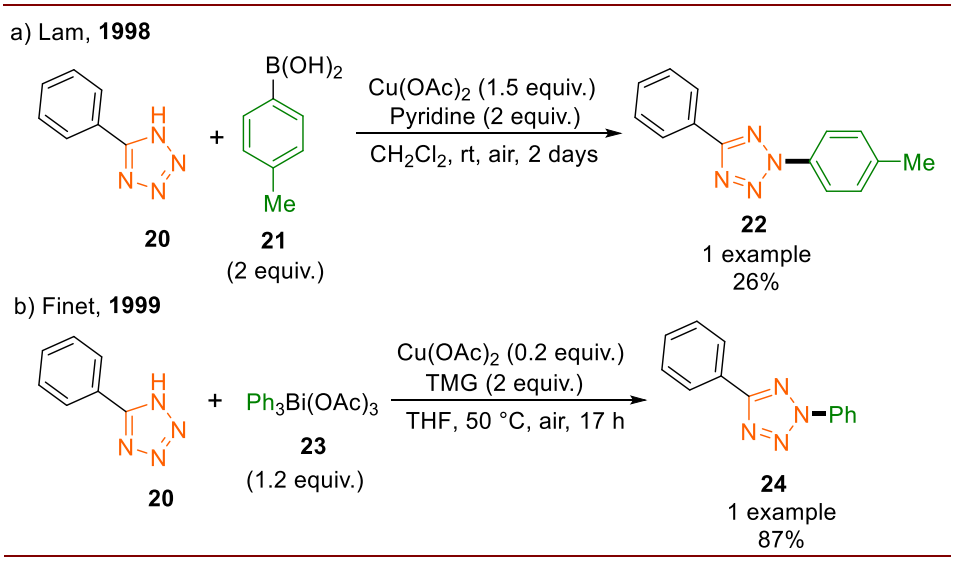
The traditional and practical approach to access 2-aryl-5-substituted Tzs was *via* Kakehi's methodology, where potentially explosive aryl diazonium salts **17** and phenyltosylhydrazones **18** were used (Scheme 2.1) [25]. Similarly, Liu and co-

workers published another cycloaddition methodology to obtain 2,5-diaryl-Tz utilizing aryldiazonium salts and amidines [26].



Scheme 2.1 Traditional 1,3-dipolar cycloaddition method

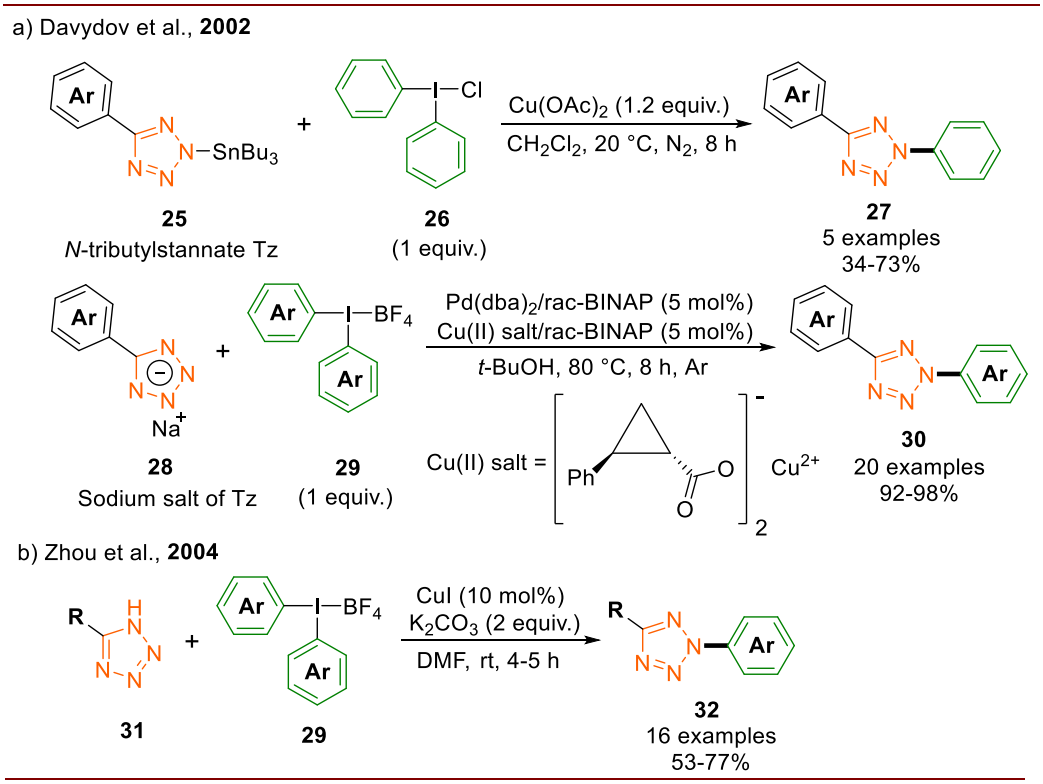
An alternative route to avail 2,5-Tzs is N^2-arylation of tetrazolic N-H under transition-metal catalysed [27–28] or metal-free conditions [29]. In 1998, Lam and co-workers mentioned one example of *N*-arylation between 5-phenyltetrazole and *p*-tolylboronic acid, but a stoichiometric amount of $Cu(OAc)_2$ was used (Scheme 2.2a) [30]. Later, another methodology for N^2-arylation was achieved with $Ph_3Bi(OAc)_2$, under copper catalysis by Finet group, however the method mentioned only one example of N^2-phenylated Tz in their study (Scheme 2.2b) [31].



Scheme 2.2 Earlier methodologies for direct N^2-arylation

Apart from the arylboronic acids and triarylbismuth as arylating precursors, the symmetrical diaryliodonium salts proved to be a useful arylating partners with Tzs. In 2002, Davydov and co-workers published two reports consecutively for the N^2-arylation of pre-functionalized tetrazolic nucleophiles under transition-metal catalysed protocols (Scheme 2.3a) [32–33]. Due to the utilization of pre-

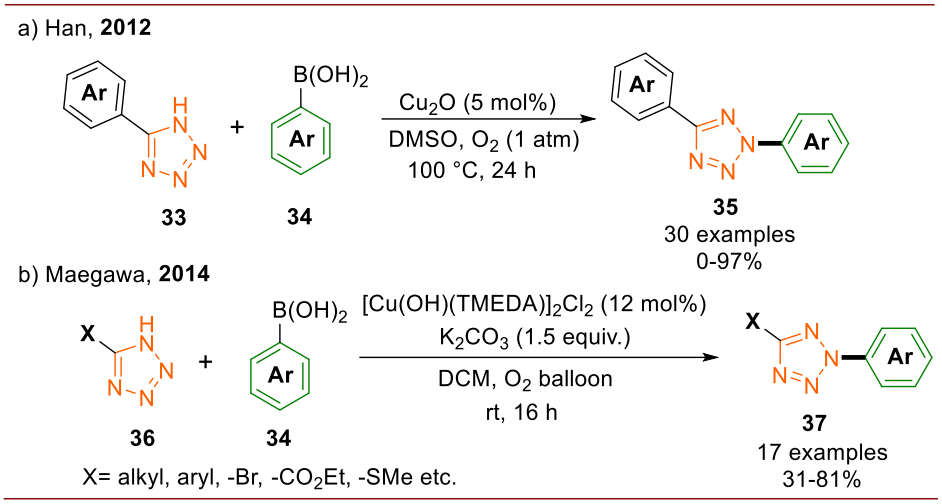
functionalized Tzs and symmetrical iodonium salts only, the methods mentioned the limited scopes of both the starting reagents. Moreover, the catalytic conditions used were much more complicated. Shortly after, Zhou's and co-workers re-investigated the diaryliodonium salts based arylation methods and came up with a convenient copper-catalyzed approach by demonstrating substantial examples of tetrazoles and symmetrical diaryliodonium salts (Scheme 2.3b) [34].



Scheme 2.3 Transition-metal based arylation with diaryliodonium salts

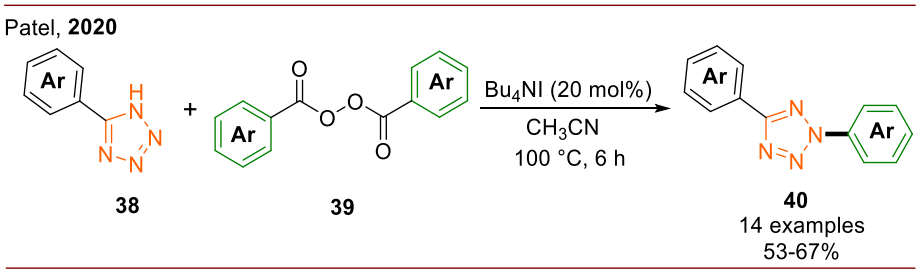
Interestingly, Han and co-workers accomplished an *N*-arylation method based on arylboronic acids under copper-catalytic version in 2012, where Cu_2O was used as catalyst and the required reaction temperature was higher (Scheme 2.4a) [35]. The method showed broad compatibility towards various types of arylboronic acids and afforded the *N*-arylated Tzs in moderate to good yields. The reaction condition showed regioselectivity issues with 5-methyl-1*H*-Tz, but the method demonstrated excellent functional group tolerance with 5-aryl-Tzs. Later, Maegawa et al. improvised Han's protocol with another copper catalyst, $[Cu(OH)(TMEDA)]_2Cl_2$ and accomplished the reaction at room temperature (Scheme 2.4b) [36]. These protocols were highly regioselective and various functionalized Tzs were exemplified; however, aryl groups possessing strong EWGs were not discussed. The

regioselectivity could be rationalized from the steric factor between the coordinated aryl moiety and C^5-aryl group of Tz. It was anticipated that the coordination of tetrazolic N-H with Cu(II)-TMEDA centre *via* the N^2-position provided a more favourable transition state than when Tz was coordinated with N^1-position.



Scheme 2.4 Copper-catalyzed methods with arylboronic acids

In a metal-free arylation approach, Patel and co-workers reported an efficient and robust protocol for regioselective *N*^{2}-alkylation or arylation where they rationalized *N*^{2}-selectivity *via* nitrogen-centred radical (NCR) (Scheme 2.5) [29]. In their work, they used aryl diacyl peroxides or aryl peroxyanhydrides as the arylating source and the mechanism was suitably evidenced with both experimental optimization and DFT calculation. Moreover, in the light of NCR mechanism of *N*^{2}-functionalization of Tzs, Patel group further reported remote functionalization of non-reactive C_{sp^3}–H alkyl groups possessing a traceless directing group with Tzs [37] and Ruan et al. developed benzylic C–H amination of Tzs *via* electro-oxidation including late-stage modification of pharmaceutically relevant drugs [38].



Scheme 2.5 Patel's metal-free method with aryl diacyl peroxides

Considering the significance of this privileged moiety, 2-aryl-5-substituted tetrazoles; developing a metal-free technique to access these moieties would be beneficial from the perspective of sustainability. Owing to the reasonably acidic N–H on Tzs and its isometric conversion from 1*H*-Tz to 2*H*-Tz [1], it was hypothesized that one aryl group from diaryliodonium salts could be transferred to the N^2-position of Tzs under a metal-free approach. As our interests laid on arylation with diaryliodonium salts, a metal-free arylation approach to explore for regioselective N^2-arylation of 5-substituted-1*H*-tetrazoles with diaryliodonium salts is described in this chapter. As the previous methods limited the scope of aryl group to electron-rich functionalized ones only, this protocol was intended to investigate and expand the aryl substrate scope for both electron-rich and electron-deficient aryl groups [36].

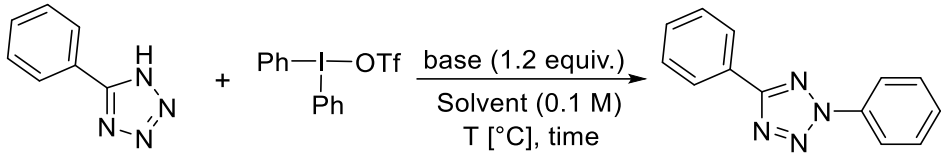
2.2 Optimization

2.2.1 Optimization of the reaction conditions

The preliminary investigations of our designed metal-free arylation started with the selection of 5-phenyl-1*H*-tetrazole (**41a**) as the model Tz substrate and diphenyliodonium triflate (**42a-OTf**) as the model diaryliodonium salt (Table 2.1). Initially, the model substrates were reacted in absence of any base, but no arylation product was observed. Elevating the temperature without adding any base could not provide any positive result (entries 1-4). When **41a** (0.2 mmol) and **42a-OTf** (1 equiv.) were treated with a base, potassium carbonate (K_2CO_3) (1.2 equiv.), in toluene, at room temperature for 24 h, cleavage of some **42a-OTf** was observed and no arylation of Tz was achieved (entry 5). Keeping all the factors the same, the temperature of the reaction was elevated to 60 °C and to our delight, N^2-arylated product **43a** was obtained in 52% isolated yield (entry 7). Surprisingly, we observed excellent regioselectivity of the reaction and the sole arylation product was N^2-arylated product with no trace of N^1-arylation of **41a**. As temperature played a vital role, the yield of **43a** reached to 72% in an optimal temperature of 80 °C (entry 8), and thereby, no significant change in yield was noticed above 80 °C and beyond 12 hrs (entries 9-10). Inorganic and organic bases were screened in the next stage and the optimizations confirmed that very week bases such as $NaHCO_3$ and Na_2CO_3 were sufficient for the formation of **43a** in remarkable yield. Between these two, $NaHCO_3$ was found to be the most efficient one (entries 10-18). Among the organic bases,

Et_3N, DABCO, DBU and pyridine were screened. A series of solvent was screened, and it was seen that toluene assisted better conversion. When polar solvents such as acetonitrile and DMF were tested, decline in the yield was noticed (entries 19-25).

Table 2.1 Optimization with diphenyliodonium triflate[a]



41a **42a-OTf** **43a**

Entry	41a (equiv.)	42a (equiv.)	solvent	base (equiv.)	T (°C)	*t* (h)	yield[b] (%)
1	1	1	Toluene	-	rt	24	ND
2	1	1	Toluene	-	45	24	ND
3	1	1	Toluene	-	60	24	ND
4	1	1	Toluene	-	100	24	ND
5	1	1	Toluene	K_2CO_3 (1.2)	rt	24	ND
6	1	1	DCE	K_2CO_3 (1.2)	rt	24	ND
7	1	1	Toluene	K_2CO_3 (1.2)	60	24	52
8	**1**	**1**	**Toluene**	**K_2CO_3 (1.2)**	**80**	**12**	**72**
9	1	1	Toluene	K_2CO_3 (1.2)	80	24	74
9	1	1	Toluene	K_2CO_3 (1.2)	100	24	70
10	**1**	**1**	**Toluene**	**$NaHCO_3$ (1.2)**	**80**	**12**	**86**
11	1	1	Toluene	Na_2CO_3 (1.2)	80	12	78
12	1	1	Toluene	Et_3N (1.2)	80	10	52
13	1	1	Toluene	NaO^{t}Bu (1.2)	80	12	43
14	1	1	Toluene	DABCO (1.2)	80	12	44
15	1	1	Toluene	DBU (1.2)	80	10	72
16	1	1	Toluene	NaOH (1.2)	80	12	trace
17	1	1	Toluene	Pyridine (1.2)	80	12	trace
18	1	1	Toluene	K_3PO_4 (1.2)	80	12	53
19	1	1	1,4-dioxane	$NaHCO_3$ (1.2)	80	12	54
20	1	1	DMF	$NaHCO_3$ (1.2)	80	12	35
21	1	1	DMSO	$NaHCO_3$ (1.2)	80	12	trace
22	1	1	CH_3CN	$NaHCO_3$ (1.2)	80	12	44
23	1	1	DCM	$NaHCO_3$ (1.2)	80	12	trace
24	1	1	DCE	$NaHCO_3$ (1.2)	80	5	trace
25	1	1	MeOH	$NaHCO_3$ (1.2)	80	24	ND
26	1.5	1	Toluene	$NaHCO_3$ (1.2)	80	12	84

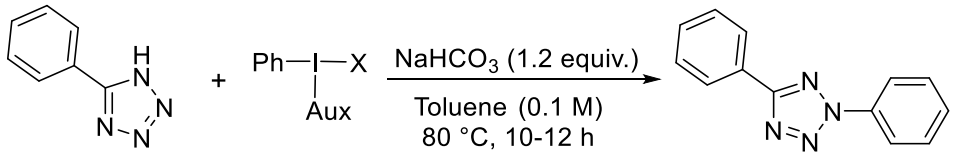
27	1.1	1.5	Toluene	$NaHCO_3$ (1.2)	80	12	86
28	1.1	1.1	Toluene	$NaHCO_3$ (1.5)	80	12	82
29	1	1	Toluene	$NaHCO_3$ (0.5)	80	12	58

[a]Reaction conditions: **41a** (0.2 mmol), **42a-OTf** salt (0.2 mmol), base (1.2 equiv.) and dry solvent (0.1 M) were added to a Schlenk tube. [b]Isolated yields. ND i.e., not detected.

2.2.2 Influence of counter-anions and selection of auxiliary

The influence of counter-anions of the diaryliodonium salts was reflected on the yield of **43a**. Only –OTf and $-BF_4$ could be used and other counter-anions –OTs and $-OCOCF_3$ (TFA) afforded lesser yield in the process (Table 2.2, entries 1-5). In arylation of diaryliodonium salt, employing unsymmetrical iodonium salts was more economical than symmetrical iodonium salts, as the former could deliver a diverse choice of functionalized aryl moieties. In our case, anisyl-containing iodonium salt (**42a-An**) resulted in the chemoselective transfer of the phenyl ring to the Tz and afforded comparable yields as **42a-OTf**, showing minor conversion to 4-methoxyphenylation of **41a**. The other auxiliaries such as mesityl (Mes) and 1,3,5-trimethoxyphenyl (TMP) were screened too, but trace amounts of product formation was observed (entries 6-10).

Table 2.2 Counter-anion and auxiliary study[a]



41a **42a-Aux** **43a**

Entry	41a (equiv.)	42a (equiv.)	aux	X	base (equiv.)	T (°C)	t (h)	yield[b] (%)
1	1	**42a-OTf** (1.0)	Ph	OTf	$NaHCO_3$ (1.2)	80	12	86
2	1	**42a-OTs** (1.0)	Ph	OTs	$NaHCO_3$ (1.2)	80	12	trace
3	1	**42a-TFA**	Ph	TFA	$NaHCO_3$ (1.2)	80	12	40
4	1	**42a-Br** (1.0)	Ph	Br	$NaHCO_3$ (1.2)	80	12	66
5	1	**42a-BF_4** (1.0)	Ph	BF_4	$NaHCO_3$ (1.2)	80	12	81

6	1	**42a-TMP** (1.0)	TMP	TFA	$NaHCO_3$ (1.2)	80	24	trace
7	1	**42a-Mes** (1.0)	Mes	OTf	$NaHCO_3$ (1.2)	80	24	trace
8	**1**	**42a-An (1.0)**	**Anisyl**	**OTf**	**$NaHCO_3$ (1.2)**	**80**	**12**	**82**
9	1	**42a-TMP** (1.0)	TMP	OTs	$NaHCO_3$ (1.2)	80	24	ND
10	1	**42a-TMP** (1.0)	TMP	OTf	$NaHCO_3$ (1.2)	80	24	Trace

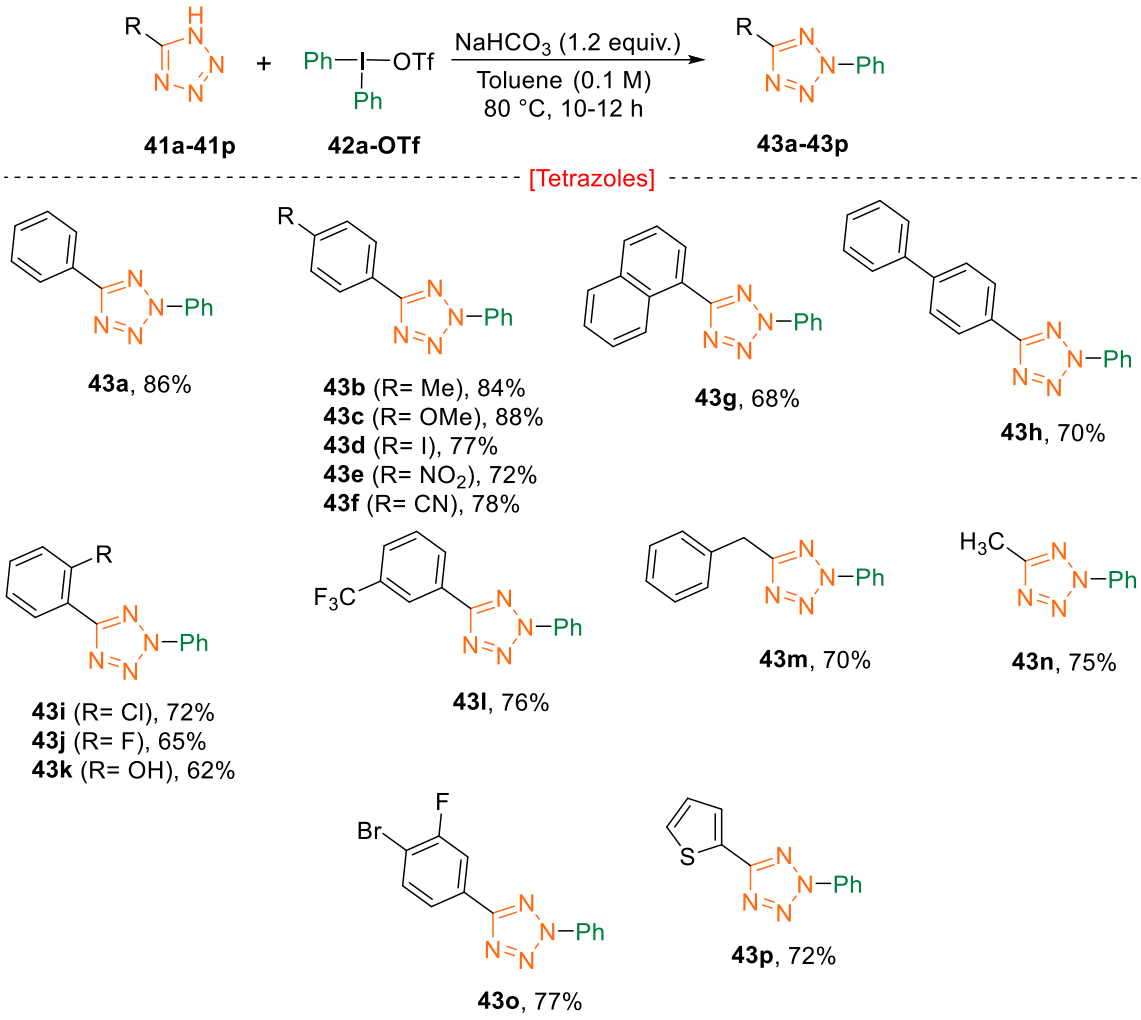
[a]Reaction conditions: **41a** (0.2 mmol), **42a-Aux** salt (0.2 mmol), $NaHCO_3$ (1.2 equiv.) and solvent (0.1 M) were added to a Schlenk tube. [b]Isolated yields.

2.3 Substrate scope

2.3.1 Scope of tetrazoles

With the optimized conditions in hand, we first explored the practicality of the reaction with electronically variable Tzs (**41a-41p**) through phenylation using diphenyliodonium triflate **42a-OTf** (Table 2.3). C^5-aryl-1*H*-tetrazole possessing electron-donating (4–Me and 4–OMe) and electron-withdrawing groups (4–I, 4–NO_2 and 4–CN) at C4-position of the phenyl ring participated smoothly in this regioselective arylation and resulted in the products (**43b-43f**) in moderate to good yields. Other arene groups such as naphthyl, **43g** and biphenyl, **43h** were suitable for the protocol affording 68% and 70% yields respectively. Interestingly, phenyl rings with *ortho*-substituents (Cl, F and OH) also furnished the desired products **43i**, **43j** and **43k** respectively. Pleasingly, the example **43k** revealed the chemoselective nature of the methodology as the presence of -OH did not alter the selectivity of the reaction through *O*-arylation. 5-Alkyl-1*H*-tetrazole groups, such as 5-benzyl and 5-methyl groups successfully accomplished this regioselective N^2-arylation and afforded the products **43m** and **43n** in 70% and 75% yields respectively. Other substituted-phenyl rings, *m*-CF_3-phenyl product **43l** and 4-bromo-3-fluorophenyl product **43o** displayed the robustness of the method, tolerating the effect of variable substituents on the phenyl ring. The product **43p** with thiophene ring obtained in 72% yield demonstrated that the protocol could be applied to 5-(heteroarene)-1*H*-tetrazole.

Table 2.3 Scope of the 5-substituted-1*H*-Tetrazoles[a,b]

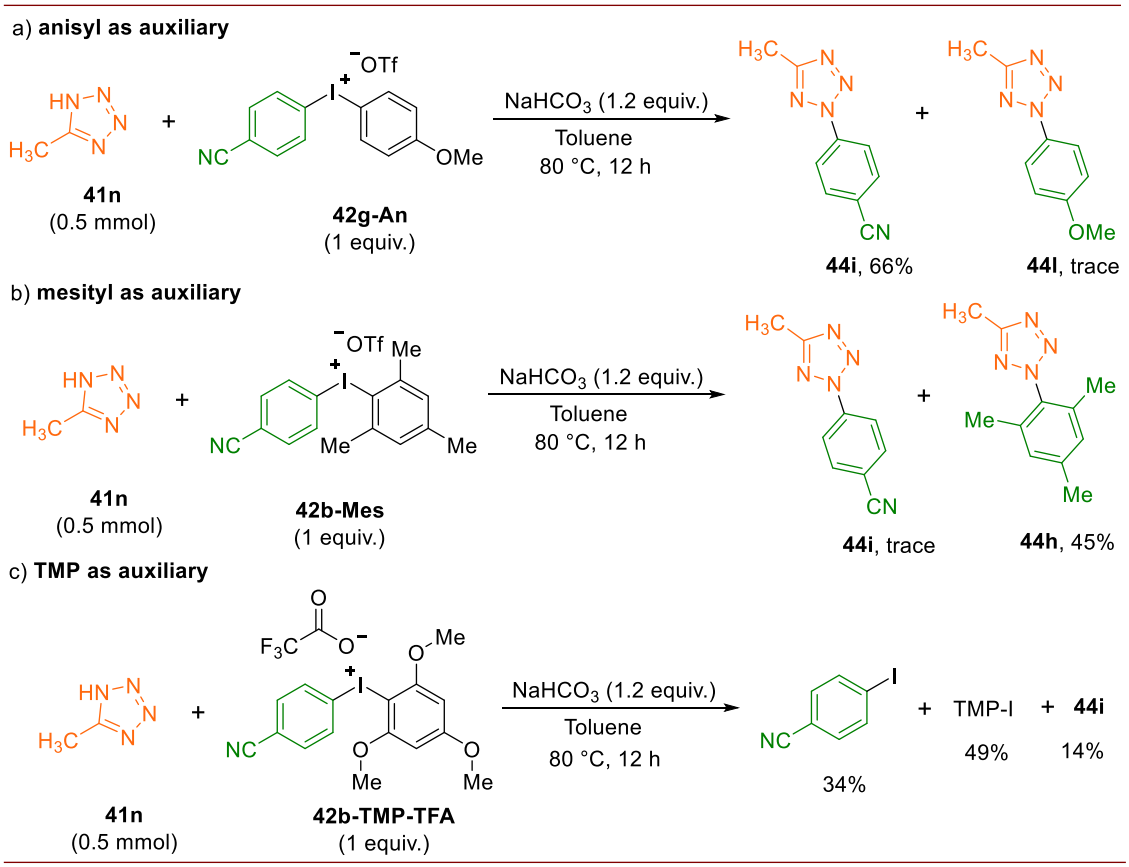


[a]Reaction conditions: **41a-41p** (0.25 mmol), **42a-OTf** salt (0.25 mmol), $NaHCO_3$ (1.2 equiv.) and dry toluene (0.1 M) were added to a Schlenk tube. [b]Isolated yields.

2.3.2 Scope of diaryliodonium salts

To explore the scope and diversity in aryl part of diaryliodonium salts, the identification of suitable auxiliary or non-transferable dummy groups (anisyl, Mes, and TMP) of an unsymmetrical iodonium salt having an electron-withdrawing aryl group was accomplished with the model reaction, i.e., 4-cyanophenylation of **41n** (Scheme 2.6). In general, anisyl and TMP are commonly observed auxiliaries in metal-free conditions [39], and Mes is a good choice when metal-catalysed methods are employed [40–41]. Under transition metal-free condition, electron-neutral or EW aryl groups are preferably transferred to the nucleophile from aryl(auxiliary)iodonium salts [42]. Accordingly, different (4-cyanophenyl)(auxiliary)iodonium salts (**42g-An**, **42b-Mes** and **42b-TMP**) were

reacted with **41n** under optimized conditions. These controlled studies revealed that in case of anisyl-iodonium salt (**42g-An-OTf**), the transfer of 4-cyanophenyl group was more preferrable affording the product **44i** in 66% yield and trace amount of the other arylated product. On the other hand, the mesityl-iodonium salt (**42b-Mes-OTf**) showed negligible formation of desired product and the mesitylated product **44h** was the dominant one. This observation was similar to the so-called "*ortho-effect*" in metal-free arylation chemistry of iodonium salts [42]. Though TMP acts as an excellent auxiliary in many metal-free arylation cases; however, TMP-iodonium salt (**42b-TMP-TFA**) exhibited low chemoselectivity in this study. Thus, anisyl-iodonium salt would be the suitable unsymmetrical salt to introduce EW aryl and other aryl groups into the Tz moiety for further study.

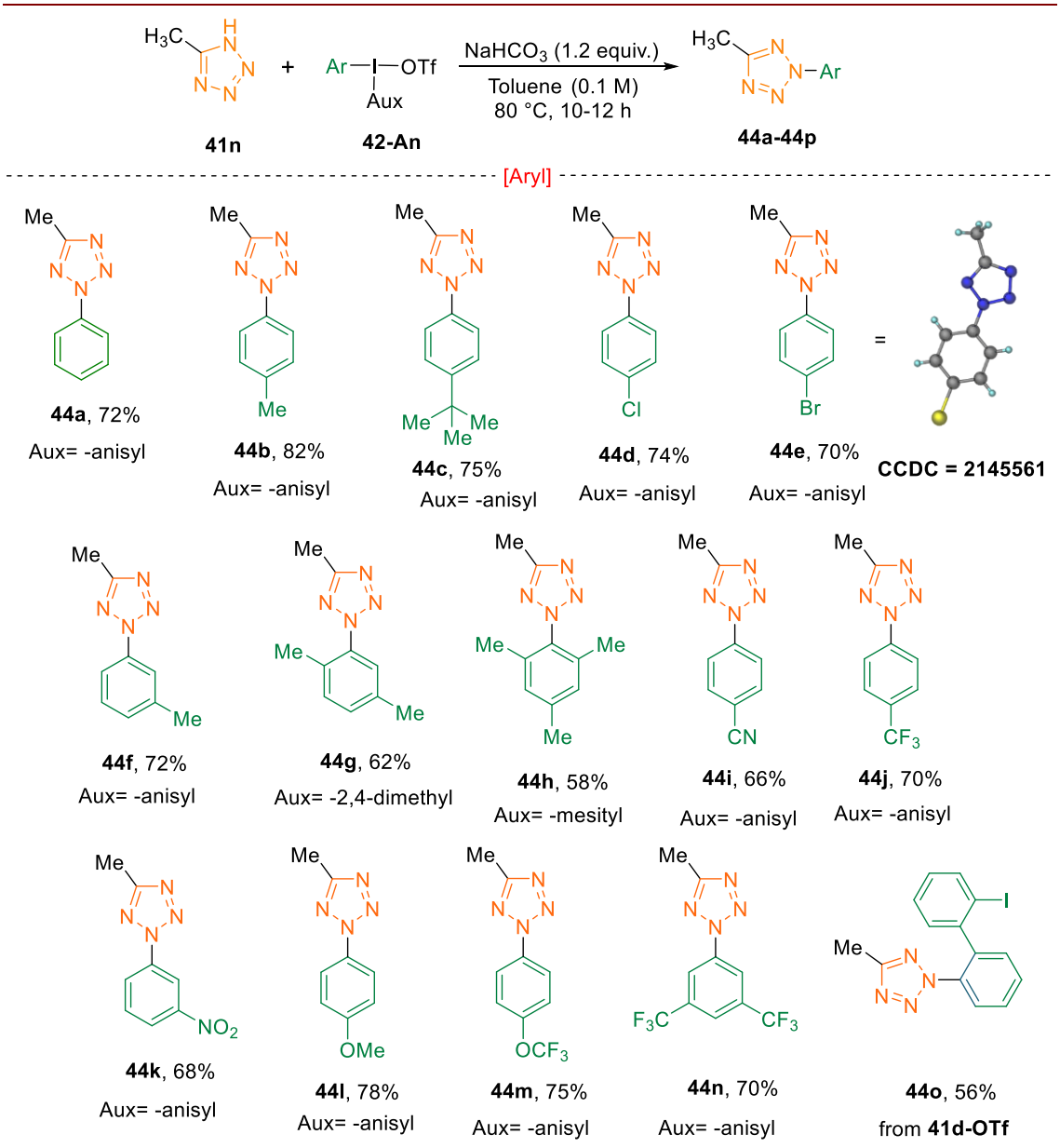


Scheme 2.6 Selection of auxiliary for EWGs by 4-cyanophenylation. Reaction conditions: **41n** (0.25 mmol), **42-Aux** salt (0.25 mmol), $NaHCO_3$ (1.2 equiv.) and dry toluene (0.1 M) were added to a Schlenk tube. All yields are isolated yields.

Confirming the suitable auxiliary, we were interested in exploring the scope of diaryliodonium salts (**42**) possessing various functional groups on the aryl ring with 5-methyltetrazole, **41n** (Table 2.4). Aryl(anisyl)iodonium salts with 4-Me, 4-^{t}Bu and

3-Me substituents on the phenyl ring showed excellent chemoselective transfer of the aryl group to N^2-position of the Tz and afforded the desired products **44b**, **44c** and **44f**, respectively in moderate yields. Electron-withdrawing halide groups such as 4-Cl and 4-Br were smoothly inducted into the Tz and provided the products **44d**

Table 2.4 Scope of diaryliodonium salts[a,b]



[a]Reaction conditions: **41n** (0.25 mmol), **42** salt (0.25 mmol), $NaHCO_3$ (1.2 equiv.) and dry toluene (0.1 M) were added to a Schlenk tube. [b]Isolated yields.

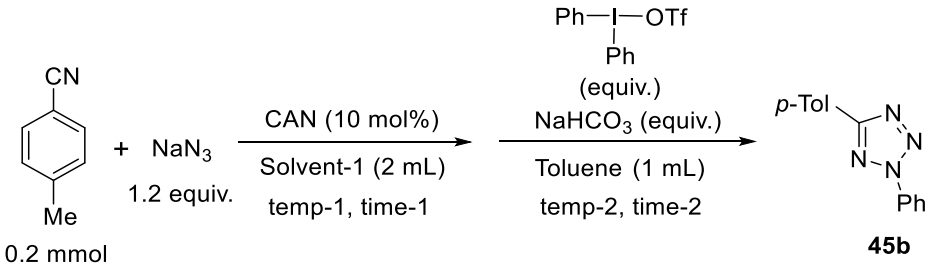
and **44e**, respectively. Further, the structure of **44e** was clarified by single-crystal X-ray structural elucidation. Interestingly, *ortho*-substituted 2,5-dimethyl and highly congested mesityl group from its respective symmetrical iodonium salts **42l-OTf** and

42m-OTf also furnished the products **44g** and **44h**, respectively. Electron-withdrawing substituents 4-CN, 4-CF_3, 3-NO_2 and 3,5-bis(trifluoromethyl) on the phenyl ring were implemented efficiently from its aryl(anisyl)iodonium salt source and the products **44i**, **44j**, **44k** and **44n** were obtained in moderate yields. Electron-donating groups such as 4-OMe and 4-OCF_3 were also incorporated. Symmetrical iodonium salt, bis(4-methoxyphenyl)iodonium triflate delivered the 4-OMe-phenyl product **44l** in yield 78% and 4-OCF_3-phenyl product **44m** was accessed easily from iodonium salt **42j-An**. This further demonstrated the substrate tolerance of this protocol. To our delight, cyclic iodonium salt, **42d-OTf** was also tolerated, and it produced an interesting biphenyl molecule **44o**, possessing bio-active Tz ring in 56% yield.

2.4 One-pot methodology

Next, we envisioned to extend the work by devising a one-pot process for the synthesis of 2,5-diaryl-tetrazole through the formation of *in-situ* Tz from 4-methylbenzonitrile [43-45], followed by adding functionalized diaryliodonium salts. The reported Tz synthetic procedure required DMF and 100 °C. However, the optimization of the solvents, and temperature was re-checked as our optimized condition for the arylation step involved toluene as solvent and the temperature was

Table 2.5 Optimization for one-pot system to obtain 2,5-diaryl tetrazoles by *in-situ* synthesis of 1*H*-tetrazoles[a]

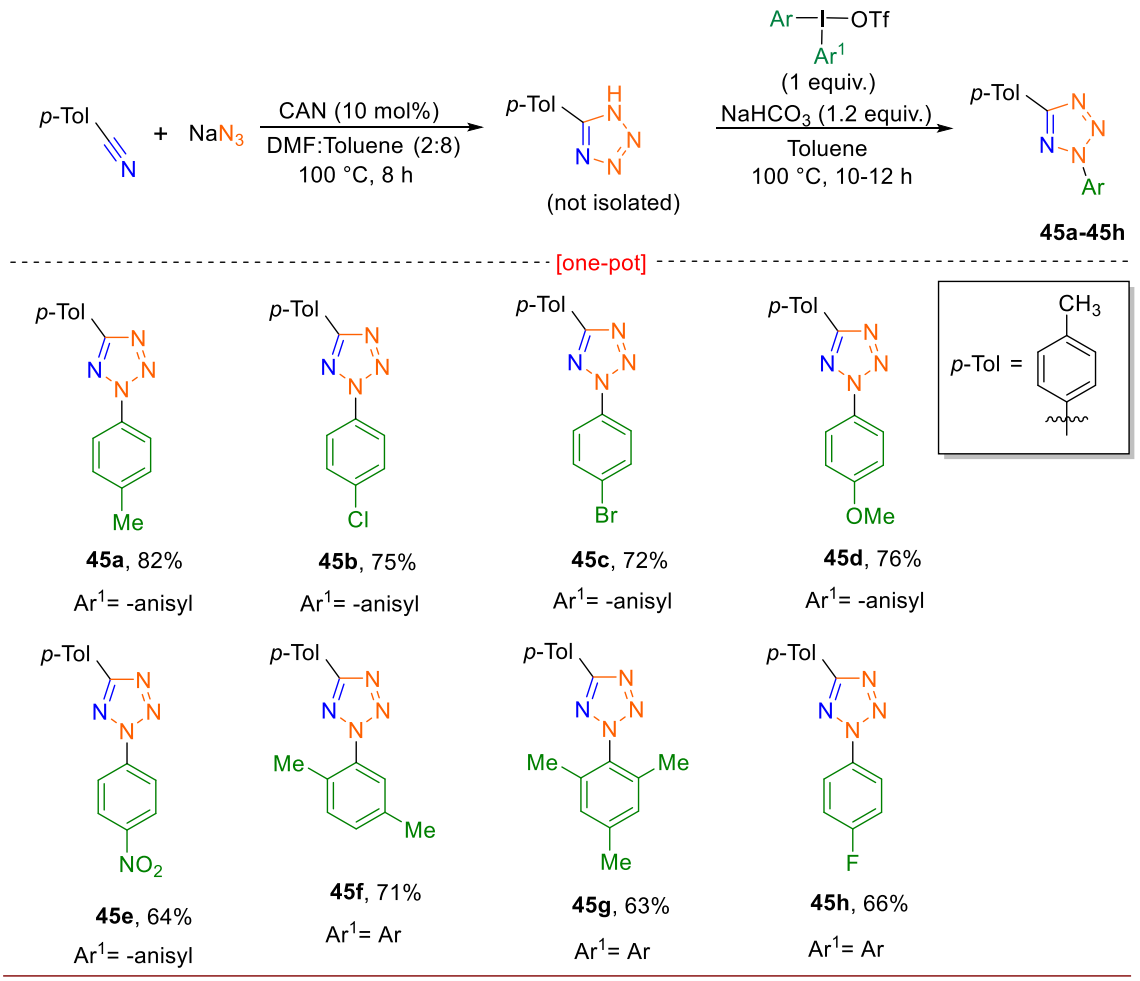


Entry	solvent-1	T-1 (°C)	t-1 (h)	T-2 (°C)	t-2 (h)	2a-OTf (equiv.)	$NaHCO_3$ (equiv.)	yield[b] (%)
1	DMF	110	6	110	12	1	1.2	45
2	DMF:Toluene (5:5)	100	8	100	12	1	1.2	52
3	**DMF:Toluene (2:8)**	**100**	**8**	**100**	**12**	**1**	**1.2**	**81**
4	DMF:Toluene (2:8)	80	12	80	12	1	1.2	68
5	DMF:Toluene (2:8)	100	8	100	12	1.5	1.2	78

6	DMF:Toluene (2:8)	100	8	100	12	1	1.5	79
7	DMF:Toluene (1:9)	100	24	100	12	1	1.1	72

[a]Reaction conditions: 4-methylbezonitrile (0.2 mmol), sodium azide (0.3 mmol, 1.2 equiv.), **42a-OTf** salt (1 equiv.), CAN (10 mol%), solvent-1 (2 mL) $NaHCO_3$ (1.1 equiv.) and solvent (0.1 M) were added to a Schlenck tube. [b]Isolated yields.

Table 2.6 Multicomponent one-pot approach towards 2,5-diaryl-Tz[a,b]



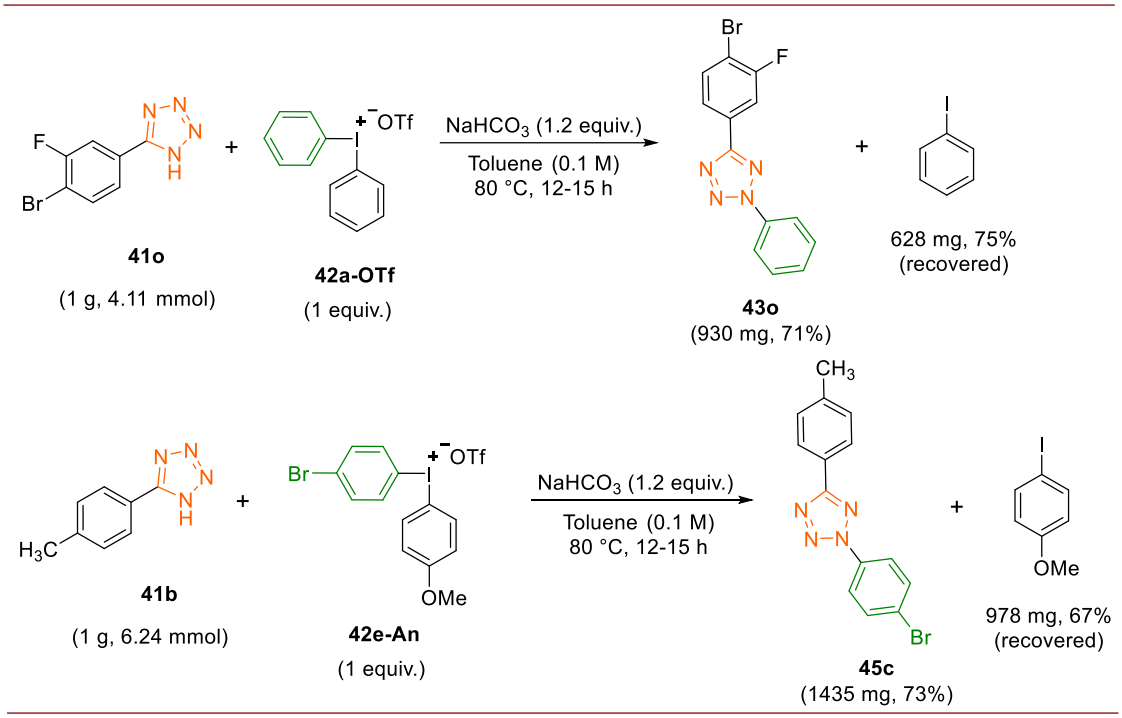
[a]Reaction conditions: 4-methylbenzonitrile (0.25 mmol), sodium azide (0.3 mmol, 1.2 equiv.) and ceric ammonium nitrate (0.025 mmol, 10 mol%) were added in solvent system**,** followed by **26** salt (0.25 mmol), $NaHCO_3$ (1.2 equiv.) and dry toluene (0.1 M) were added to a Schlenk tube. [b]Isolated yields.

80 °C (Table 2.5). The optimized strategy proceeded smoothly with iodonium salts containing electron-donating moieties such as 4-Me-, 4-OMe- and 2,5-dimethyl- and afforded the products **45a**, **45d** and **45f** in moderate yields (Table 2.6). Phenyl ring with halide groups successfully reacted under these conditions and provided its corresponding 2,5-diaryl-Tetrazole products **45b**, **45c** and **45h**. EW aromatic, (product **45e**) was easily obtained in 64% yield. In addition, sterically hindered Mes

group was also employed from its symmetrical iodonium salt, and it delivered the product **45g** in 63% yield.

2.5 Scalability of the reaction

The practicality of this metal-free arylation route was extended effectively by demonstrating the scalability of the optimized reaction and thereby, showcasing the gram scale formation of the *N*²-arylated products **43o** and **45c**, respectively (Scheme 2.7).

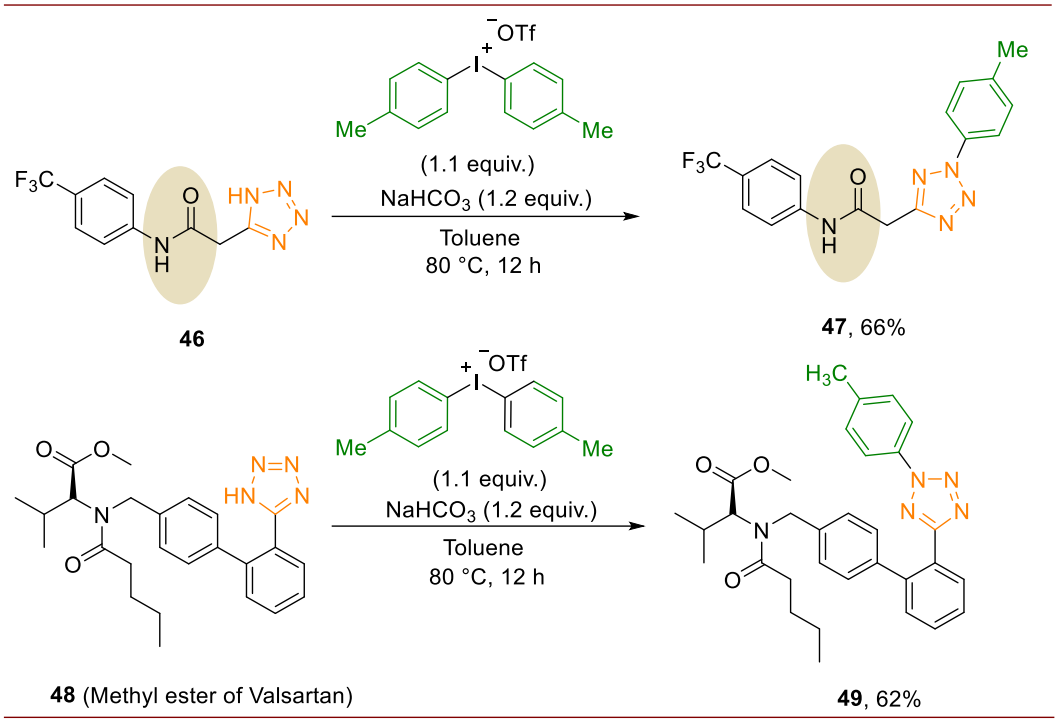


Scheme 2.7 Scalability for the *N*²-arylation of tetrazoles **43o** and **45c**

2.6 Applicability towards biologically active 1*H*-Tz scaffolds

To illustrate the applicability of this metal-free arylation protocol from a pharmaceutical perspective, we checked the flexibility of our scheme with one drug-like Tz, compound **46** (having similar (1*H*-tetrazol-5-yl)]amido linkage exhibiting G protein-coupled receptor 35 agonist) and another anti-hypertensive drug, Valsartan (Scheme 2.8). To our satisfaction, the reaction proceeded in a similar fashion as the previously explored Tzs did. Although there is an amidic N-H present in the compound **46** yet it afforded the *N*²-arylated product **47** in 66% isolated yield. In case of compound **48**, that possessed acidic C-H positions; the arylation reaction successfully afforded the product **49** in 62% isolated yield. These examples show that

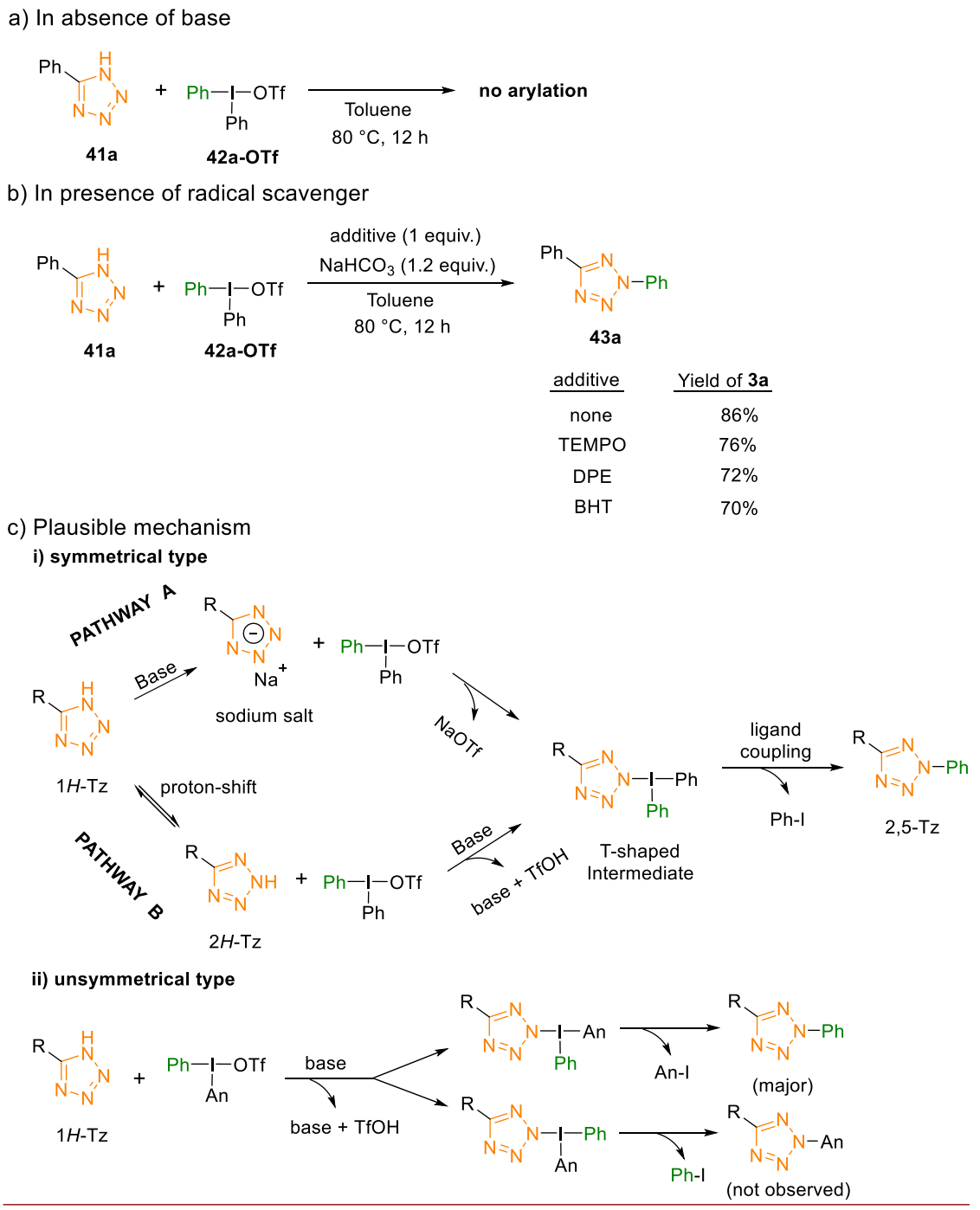
a late-stage modification of tetrazolic pharmaceuticals is possible with our N^2-arylation under metal-free conditions.



Scheme 2.8 N^2-arylation of pharmaceutically relevant 1*H*-Tz. Reaction conditions: **46** or **48** (0.25 mmol), **42b-OTf** salt (0.25 mmol), $NaHCO_3$ (1.2 equiv.) and dry toluene (0.1 M) were added to a Schlenk tube. Isolated yields.

2.7 Plausible mechanism of the reaction

Though, the mechanistic pathway for most of the transition-metal-free arylation reaction with diaryliodonium salts proceeds *via* a T-shaped intermediate (Scheme 2.9) [46]; the possibility of radical path cannot be ignored. So, we checked the arylation reaction between **41a** and **42a-OTf** under optimized reaction conditions by adding the radical scavenger reagents, such as TEMPO, DPE and BHT. As the formation of **43a** was observed in each case and the yields of the reactions were also optimal, this indicated that mechanism most likely involved ionic pathways. With the application of either symmetrical or unsymmetrical iodonium salts, the formation of the T-shaped intermediate with iodonium salt at N^2-position is the crucial step. In case of symmetrical type, the intermediate provides the N^2-arylated product along the expulsion of aryl halide. However, in case of unsymmetrical type, the electron-neutral or electron-deficient aryl part bonds to the N^2-position with the elimination of 4-iodo-anisole.



Scheme 2.9 Control experiments and plausible reaction mechanism of N^2-arylation

2.8 Summary of the chapter

In summary, we have developed an efficient, operationally simple, and scalable metal-free protocol for N^2-arylation of 1*H*-tetrazoles using diaryliodonium salts as arylating source. This offered easy access towards biologically privileged moieties i.e., 2-aryl-5-substituted tetrazoles. The developed methodology had been found to be highly regioselective towards the N^2-position of the tetrazole ring. Iodonium salts

with both symmetrical and unsymmetrical types could be used in this protocol. Auxiliary studies for unsymmetrical iodonium salts revealed anisyl as the most suitable among others. Iodonium salts and diverse 5-substituted-1*H*-tetrazoles having both electron-rich and electron-deficient aryl groups worked well under this metal-free arylation protocol. Furthermore, the desired product could be synthesized directly from aryl nitrile without isolation of 1*H*-Tetrazoles, in a one-pot method. Two biologically active Tzs were arylated smoothly to highlight the broad applicability of the methodology.

2.9 Experimental Section

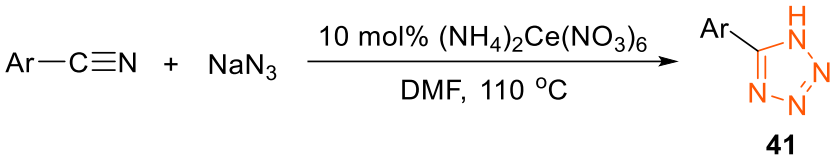
Unless otherwise stated, all reactions were carried out under ambient atmosphere and reaction progress was monitored by thin-layer chromatography (TLC) and visualized under UV irradiation. All reactions were performed using oven-dried glassware such as round-bottom flasks, pressure tubes and Schlenck tubes. Concentration under reduced pressure was performed by rotary evaporation at 40-45 °Cat an appropriate pressure. Purified Compounds were further dried under high vacuum. Dichloromethane (DCM), dichloroethane (DCE) and acetonitrile (ACN) were dried by refluxing over CaH_2 under nitrogen conditions and stored over 4Å molecular sieves. Toluene and 1,4-dioxane were dried utilising conventional drying procedures using sodium/benzophenone as indicators and stored over 4Å molecular sieves. TLC analysis was performed on pre-coated Merck silica gel 60 F_{254} plates using UV (254 nm) light and/or with $KMnO_4$-stain. Column chromatography was performed on 100-200 mesh silica gel using the gradient system, freshly distilled ethyl acetate-hexane mixture. All NMR data were recorded in a 400 MHz instrument at 298 K using $CDCl_3$ and DMSO-d_6 as solvents. Chemical shifts are given in ppm relative to the residual solvent peak (^{1}H NMR: $CDCl_3$ δ 7.26 and sometimes δ 1.56 ($CDCl_3$-water) and in DMSO-d_6 δ 2.50 and δ 3.3 (DMSO-water); ^{13}C NMR: $CDCl_3$ δ 77.16, DMSO-d_6 δ 39.52 with multiplicity (bs= broad singlet, s= singlet, d= doublet, t= triplet, q= quartet, quin= quintet, sex= sextet, sep= septet, m= multiplet, app=apparent etc.), coupling constants (in Hz) and integration. The raw NMR data were processed by MestReNova software. All chemicals were purchased from commercial suppliers and used as received unless otherwise is stated. NaOH, Cs_2CO_3, K_3PO_4 and ^{t}BuOK were stored in a desiccator. *m*CPBA (Aldrich, 77% active oxidant) was dried at room temperature

over high vacuum for 1 hour and titrated by iodometric titration [47] prior to use in the synthesis of diaryliodonium salts. Single crystal X-ray diffraction data were recorded using a Bruker APEX-II CCD Diffractometer using MoKα radiation (λ= 0.71073 Å).

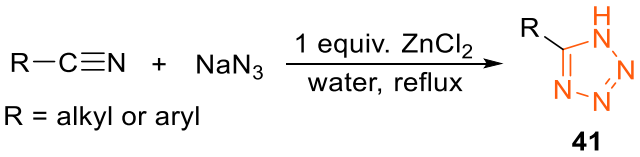
2.9.1 Synthesis of tetrazoles

Tetrazoles **41a-41l**, **41o** and **41p** were prepared by method I [43]. On the other hand, compounds **41m** and **41n** were synthesized by method II [44]. All the compounds were received as solid after hexane wash. Analytical data agreed with previous literature for all the compounds and confirmed by ^{1}H NMR spectroscopy.

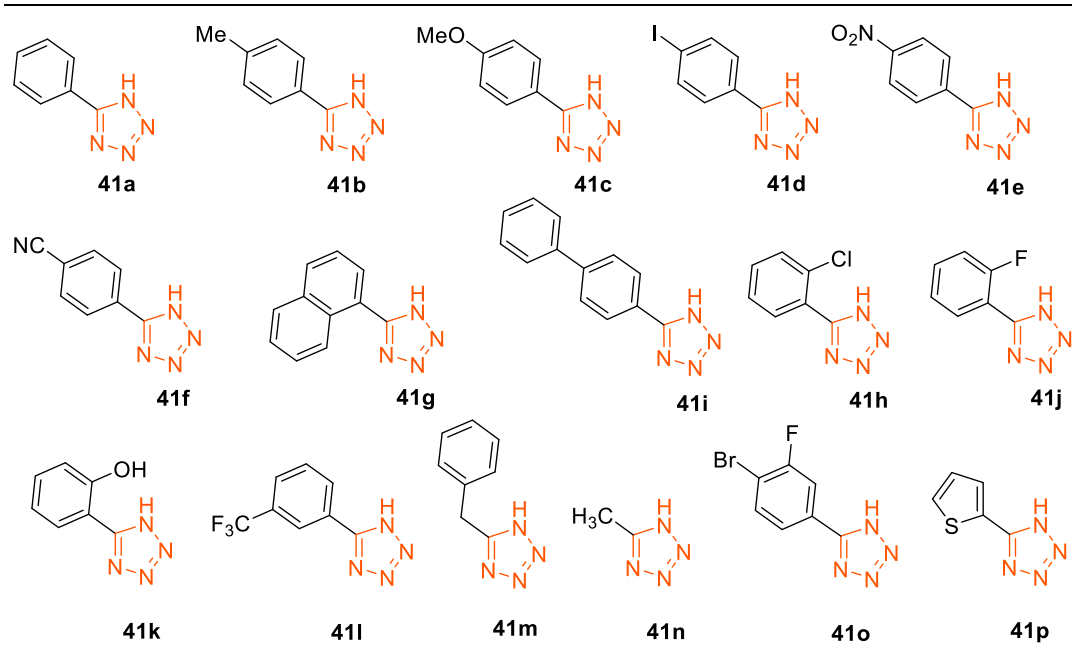
Method I:



Method II:



Synthesized tetrazoles in this work:



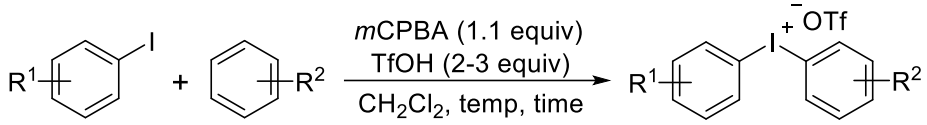
Synthesis of bio-active tetrazolic compound **46** is mentioned in the page 39-40 with the analytical data. Compound **48** (Methyl ester of Valsartan) was purchased commercially.

2.9.2 Synthesis of diaryliodonium salts

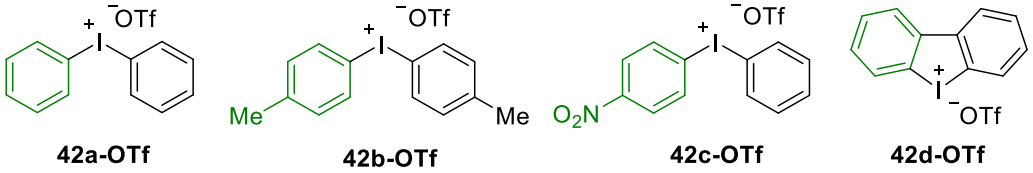
Many diaryliodonium salts are now-a-days commercially available, however; most of the salts used in this work were synthesized according to known literature without altering anything in the procedures. All the diaryliodonium salts are previously well-explored and the analytical data (especially ^{1}H NMR spectroscopy) of the synthesized diaryliodonium salts in this work were matched with literature.

Table 2.7 Synthesized diaryliodonium salts in this chapter

Method I [71, chapter 1]



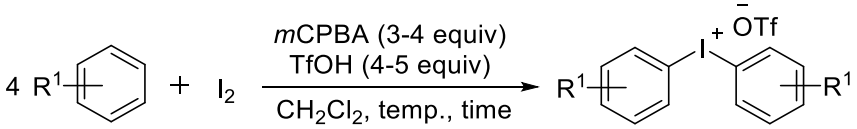
Synthesized diaryliodonium salts:



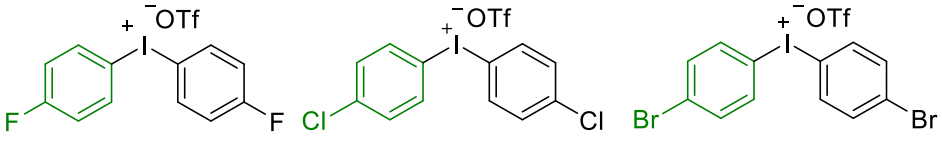
42a-OTf **42b-OTf** **42c-OTf** **42d-OTf**

42e-OTf **42f-OTf** **42g-OTf**

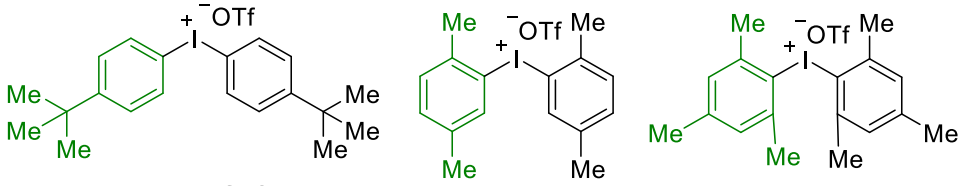
Method II [72, chapter 1]



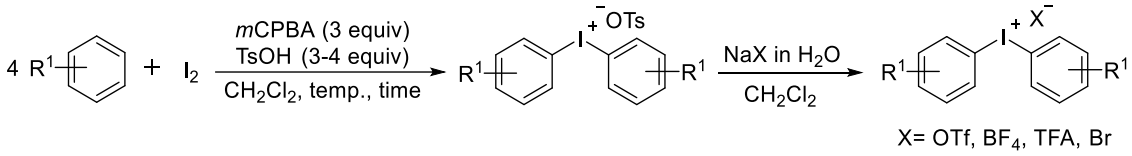
Synthesized diaryliodonium salts:



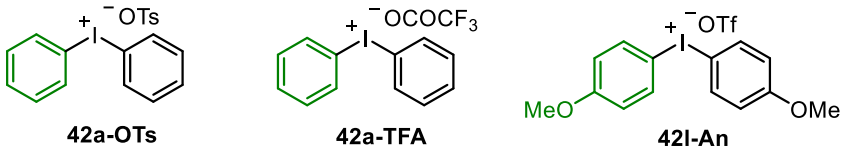
42h-OTf **42i-OTf** **42j-OTf**



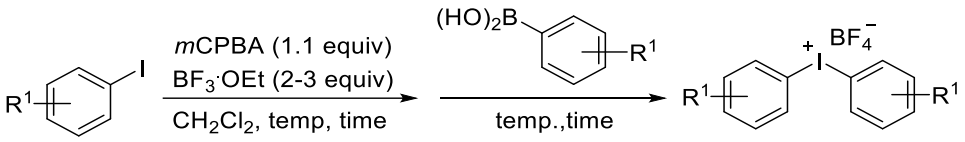
Method III [73, chapter 1]



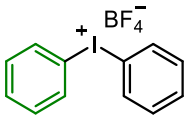
Synthesized diaryliodonium salts:



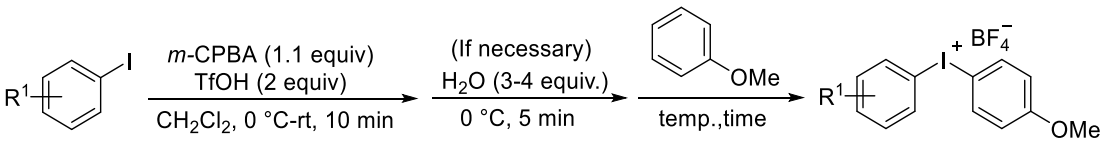
Method IV [74, chapter 1]



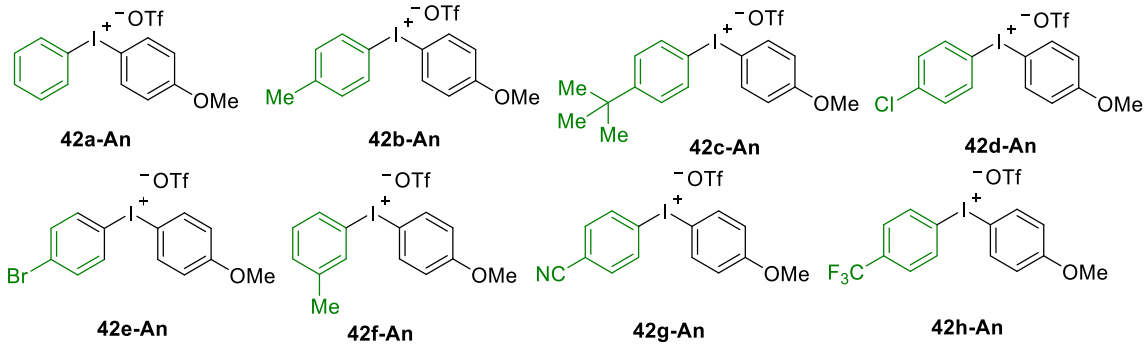
Synthesized diaryliodonium salts:

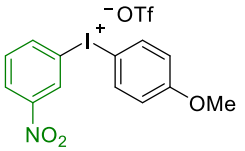


Method V [45, chapter 1]

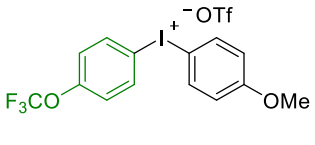


Synthesized diaryliodonium salts:

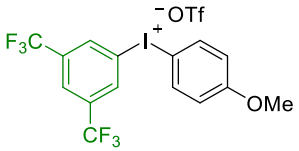




42i-An



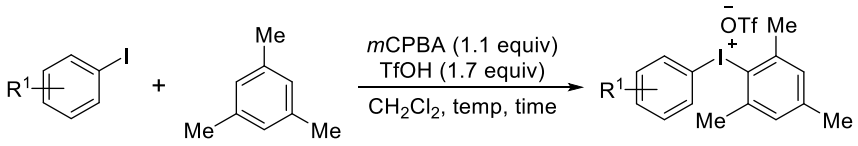
42j-An



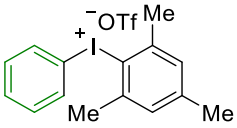
42k-An

Gaunt's modified protocol:

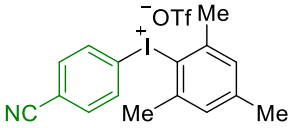
Method VI [65, chapter 1]



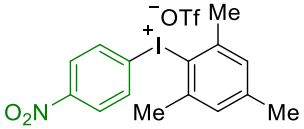
Synthesized diaryliodonium salts:



42a-Mes



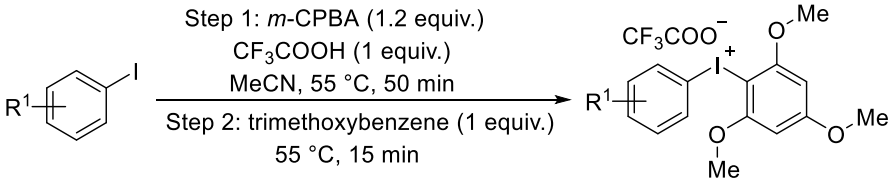
42b-Mes



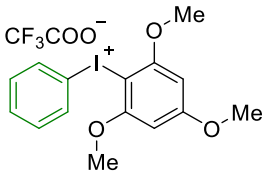
42c-Mes

Stuart's protocol:

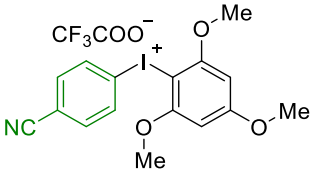
Method VII [79, chapter 1]



Synthesized diaryliodonium salts:

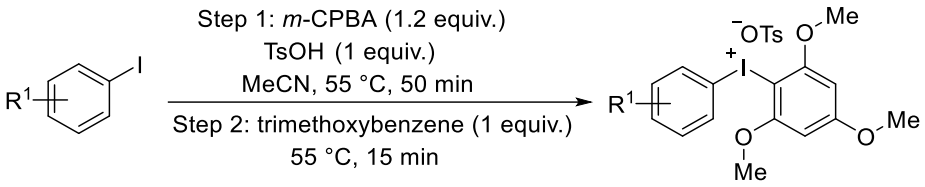


42a-TMP-TFA

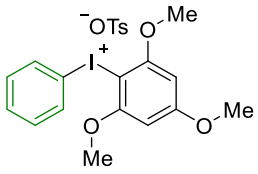


42b-TMP-TFA

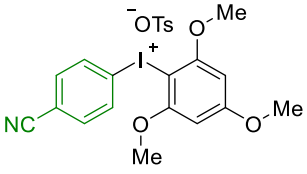
Method VIII [77, chapter 1]



Synthesized diaryliodonium salts:



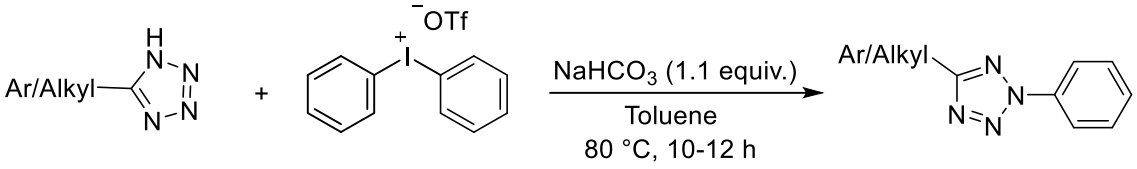
42a-TMP-OTs



42b-TMP-OTs

2.10 Experimental procedures and characterization data for the products

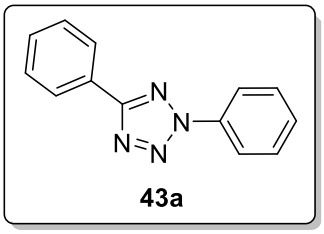
2.10.1 General procedure A (GP-A): *N*²-aryaltion of 5-substituted-1*H*-Tetrazoles with diphenyliodonium triflate



41a-41p **42a-OTf** **43a-43p**

To an oven-dried Schlenck-tube, 5-substituted-1*H*-tetrazole **41a-41p** (0.25 mmol), diphenyliodonium triflate **42a-OTf** (0.25 mmol, 1 equiv.), and $NaHCO_3$ (0.275 mmol, 1.2 equiv.) were added. After adding toluene (2.5 mL, 0.1 M), the tube was sealed and placed on a pre-heated oil bath at 80 °C. The reaction mixture was stirred till indicated time. After removing from heat, the reaction was cooled to room temperature and work-up was performed with EtOAc and water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Then, the crude product was purified using column-chromatography to obtain the desired product.

2,5-diphenyl-2H-tetrazole **(43a)** [35,36]

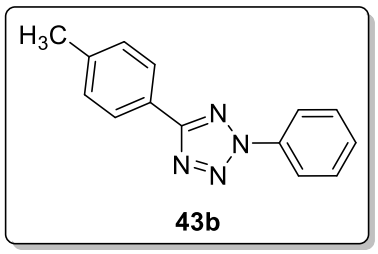


43a

In accordance with **GP-A**, 5-phenyl-1*H*-tetrazole **41a** (36.5 mg, 0.25 mmol), diphenyliodonium triflate **42a-OTf** (107.5 mg, 0.25 mmol) and $NaHCO_3$ (25.2 mg, 0.3 mmol) were used, and the following conditions gave the title compound **43a** as white solid (47 mg, 0.215 mmol, 86%). Reaction duration: 10 h. Purification method: column chromatography (2-5% ethyl acetate in hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (d, J = 8 Hz, 2H), 8.20 (d, J = 8 Hz, 2H), 7.58 (t, J = 8 Hz, 3H), 7.50-7.53 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.3,

137.01, 130.6, 129.7, 129.0, 127.1, 119.9. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{11}N_4$ 223.0983; found 223.0980.

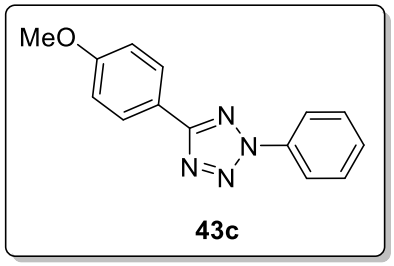
2-phenyl-5-(p-tolyl)-2H-tetrazole **(43b)** [33,36]



43b

In accordance with **GP-A**, 5-(*p*-tolyl)-1*H*-tetrazole **41b** (40 mg, 0.25 mmol), diphenyliodonium triflate **42a-OTf** (107.5 mg, 0.25 mmol) and $NaHCO_3$ (25.2 mg, 0.3 mmol) were used, and the following conditions gave the title compound **43b** as white solid (49.6 mg, 0.21 mmol, 84%). Reaction duration: 10 h. Purification method: column chromatography (2-5% ethyl acetate in hexane). ^1H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, J = 8 Hz, 2H), 8.13 (d, J = 8 Hz, 2H), 7.57 (t, J = 8 Hz, 2H), 7.49 (t, J = 8 Hz, 1H), 7.33 (d, J = 8 Hz, 2H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.3, 140.8, 137.0, 129.7, 127.0, 124.4, 119.9, 21.6. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{13}N_4$ 237.1140; found 237.1143.

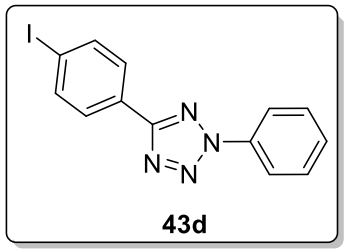
5-(4-methoxyphenyl)-2-phenyl-2H-tetrazole **(43c)**



43c

In accordance with **GP-A**, 5-(4-methoxyphenyl)-1*H*-tetrazole **41c** (44 mg, 0.25 mmol), diphenyliodonium triflate **42a-OTf** (107.5 mg, 0.25 mmol) and $NaHCO_3$ (25.2 mg, 0.3 mmol) were used, and the following conditions gave the title compound **43c** as white solid (77 mg, 0.220 mmol, 88%). Reaction duration: 10 h. Purification method: column chromatography (5% ethyl acetate in hexane). ^1H NMR (400 MHz, $CDCl_3$): δ 8.19 (d, J = 8 Hz, 4H), 7.57 (t, J = 8 Hz, 2H), 7.49 (t, J = 8 Hz, 1H), 7.04 (d, J = 8 Hz, 2H), 3.89 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 161.5, 137.0, 129.7, 128.6, 119.8, 114.4, 55.4. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{13}N_4O$ 253.1089; found 253.1101.

5-(4-iodophenyl)-2-phenyl-2H-tetrazole **(43d)**

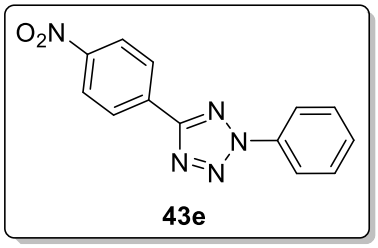


43d

In accordance with **GP-A**, 5-(4-iodophenyl)-1*H*-tetrazole **41d** (68 mg, 0.25 mmol), diphenyliodonium triflate **42a-OTf** (107.5 mg, 0.25 mmol) and $NaHCO_3$ (25.2 mg, 0.3 mmol) were used, and the following conditions gave the title compound **43d** as brown solid (67 mg, 0.19 mmol, 77%). Reaction duration: 10 h. Purification method: column chromatography (5% ethyl acetate in hexane). ^1H NMR (400 MHz, $CDCl_3$): δ 8.18 (d, J = 8 Hz, 2H), 7.98 (t, J

= 8 Hz, 2H), 7.88 (d, *J* = 8 Hz, 2H), 7.58 (d, *J* = 8 Hz, 2H), 7.51 (d, *J* = 8 Hz, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): *δ* 164.6, 138.2, 136.9, 129.8, 128.6, 126.7, 119.9, 97.1. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{10}N_4I$ 348.9950; found 348.9967.

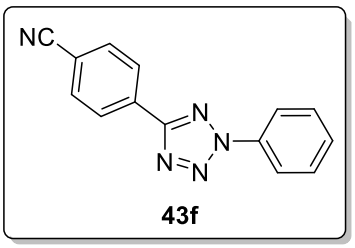
***5-(4-nitrophenyl)-2-phenyl-2H-tetrazole* (43e)** [29]



43e

In accordance with **GP-A**, 5-(4-nitrophenyl)-2-phenyl-1*H*-tetrazole **41e** (47.7 mg, 0.25 mmol), diphenyliodonium triflate **42a-OTf** (107.5 mg, 0.25 mmol) and $NaHCO_3$ (25.2 mg, 0.3 mmol) were used, and the following conditions gave the title compound **43e** as light-yellow solid (48 mg, 0.18 mmol, 72%). Reaction duration: 12 h. Purification method: column chromatography (5% ethyl acetate in hexane). ^1H NMR (400 MHz, $CDCl_3$): *δ* 8.43 (d, *J*= 8 Hz, 2H), 8.39 (d, *J* = 8 Hz, 2H), 8.21 (d, *J* = 8 Hz, 2H), 7.61 (d, *J* = 8 Hz, 2H), 7.55 (d, *J* = 8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 163.4, 149.1, 136.7, 133.1, 130.3, 127.9, 124.3, 120.1. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{10}N_5O_2$ 268.0834; found 268.0834.

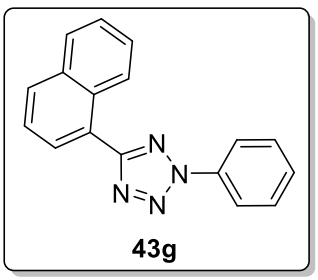
***4-(2-phenyl-2H-tetrazol-5-yl)benzonitrile* (43f)**



43f

In accordance with **GP-A**, 4-(1*H*-tetrazol-5-yl)benzonitrile **41f** (42.7 MG, 0.25 mmol), diphenyliodonium triflate **42a-OTf** (107.5 mg, 0.25 mmol, 1 equiv.) and $NaHCO_3$ (25.2 mg, 0.3 mmol) were used, and the following conditions gave the title compound **43f** as yellow solid (48.2 mg, 0.195 mmol, 78%). Reaction duration: 12 h. Purification method: column chromatography (5% ethyl acetate in hexane). ^1H NMR (400 MHz, $CDCl_3$): *δ* 8.39 (d, *J* = 8 Hz, 2H), 8.21 (d, *J* = 8 Hz, 2H), 7.84 (d, *J* = 8 Hz, 2H), 7.61 (t, *J* = 8 Hz, 2H), 7.55 (t, *J* = 8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 163.7, 136.7, 132.9, 131.4, 129.9, 127.6, 120.1, 118.4, 114. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{10}N_5$ 248.0936; found 248.0927.

***5-(naphthalen-1-yl)-2-phenyl-2H-tetrazol* (43g)**

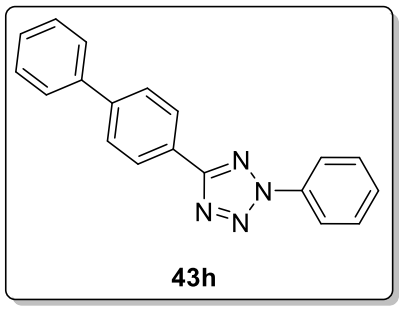


43g

In accordance with **GP-A**, 5-(naphthalen-1-yl)-1*H*-tetrazole **41g** (49 mg, 0.25 mmol), diphenyliodonium triflate **42a-OTf** (107.5 mg, 0.25 mmol) and $NaHCO_3$ (25.2 mg, 0.3 mmol) were used, and the following conditions gave the title compound **43g** as white solid (46.2 mg, 0.17

mmol, 68%). Reaction duration: 12 h. Purification method: column chromatography (5% ethyl acetate in hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.02 (d, J = 8 Hz, 1H), 8.39 (d, J = 8 Hz, 1H), 8.28 (d, J = 8 Hz, 1H), 8.01 (d, J = 8 Hz, 1H), 7.95 (d, J = 8 Hz, 1H), 7.58-7.63 (m, 5H), 7.53 (d, J = 8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.1, 136.8, 132.1, 131.7, 131.4, 130.2, 129.9, 129.8, 129.6, 128.1, 127.2, 124.0, 122.5, 119.8. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{17}H_{13}N_4$ 273.1140; found 273.1153.

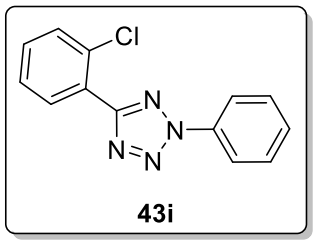
5-([1,1'-biphenyl]-4-yl)-2-phenyl-2H-tetrazole **(43h)**



43h

In accordance with **GP-A**, 5-([1,1'-biphenyl]-4-yl)-1*H*-tetrazole **41h** (55.5 mg, 0.25 mmol), diphenyliodonium triflate **42a-OTf** (107.5 mg, 0.25 mmol) and $NaHCO_3$ (25.2 mg, 0.3 mmol) were used, and the following conditions gave the title compound **43h** as white solid (52.2 mg, 0.175 mmol, 70%). Reaction duration: 12 h. Purification method: column chromatography (5% ethyl acetate in hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (d, J = 8 Hz, 2H), 8.22 (d, J = 8 Hz, 2H), 7.76 (d, J = 8 Hz, 2H), 7.66 (d, J = 8 Hz, 2H), 7.59 (t, J = 8 Hz, 2H), 7.47-7.53 (m, 3H), 7.40 (t, J = 8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.6, 160.7, 158.2, 136.7, 134.3, 130.0, 129.8, 128.4, 128.3, 123.7, 119.9, 115.1, 114.9, 111.7, 111.5. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{19}H_{15}N_4$ 299.1296; found 299.1305.

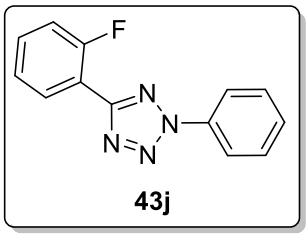
5-(2-chlorophenyl)-2-phenyl-2H-tetrazole **(43i)** [29]



43i

In accordance with **GP-A**, 5-(2-chlorophenyl)-1*H*-tetrazole **41i** (45.2 mg, 0.25 mmol), diphenyliodonium triflate **42a-OTf** (107.5 mg, 0.25 mmol) and $NaHCO_3$ (25.2 mg, 0.3 mmol) were used, and the following conditions gave the title compound **43i** as white solid (46.2 mg, 0.18 mmol, 72%). Reaction duration: 12 h. Purification method: column chromatography (5% ethyl acetate in hexane). mp 112-114 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (d, J = 8 Hz, 2H), 8.05-8.07 (m, 1H), 7.56-7.60 (m, 2H), 7.50 (d, J = 8 Hz, 2H), 7.42-7.45 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.5, 136.9, 133.3, 131.3, 131.0, 129.8, 127.0, 126.3. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{10}N_4Cl$ 257.0588; found 257.0590.

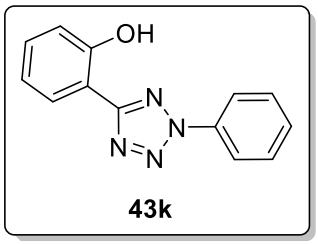
5-(2-fluorophenyl)-2-phenyl-2H-tetrazole (43j)



43j

In accordance with **GP-A**, 5-(2-fluorophenyl)-1*H*-tetrazole **41j** (41 mg, 0.25 mmol), diphenyliodonium triflate **42a-OTf** (107.5 mg, 0.25 mmol) and $NaHCO_3$ (25.2 mg, 0.3 mmol) were used, and the following conditions gave the title compound **43j** as yellowish solid (39 mg, 0.162 mmol, 65%). Reaction duration: 12 h. Purification method: column chromatography (5% ethyl acetate in hexane). ^1H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, J = 8 Hz, 2H), 7.59 (t, J = 8 Hz, 2H), 7.51 (t, J = 8 Hz, 2H), 7.26-7.34 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.6, 159.0, 136.9, 132.3, 130.2, 129.8, 124.5, 120.0, 117.0, 116.7, 115.5, 115.4. ^{19}F NMR (376 MHz, $CDCl_3$): δ -110.93. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{10}N_4F$ 241.0889; found 241.0888.

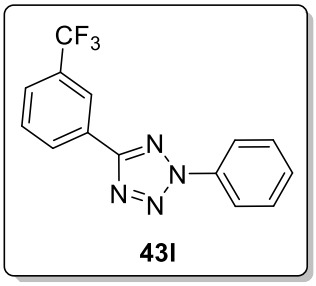
2-(2-phenyl-2H-tetrazol-5-yl)phenol (43k)



43k

In accordance with **GP-A**, 2-(1*H*-tetrazol-5-yl)phenol **41k** (40.5 mg, 0.25 mmol), diphenyliodonium triflate **42a-OTf** (107.5 mg, 0.25 mmol) and $NaHCO_3$ (25.2 mg, 0.3 mmol) were used, and the following conditions gave the title compound **43k** as white solid (36.9 mg, 0.155 mmol, 62%). Reaction duration: 12 h. Purification method: column chromatography (10% ethyl acetate in hexane). ^1H NMR (400 MHz, $CDCl_3$): δ 9.72 (s, 1H), 8.16-8.21 (m, 3H), 7.60 (t, J= 8 Hz, 2H), 7.54 (t, J= 8 Hz, 1H), 7.41 (t, J= 8 Hz, 1H), 7.13 (d, J= 8 Hz, 1H), 7.04 (t, J= 8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3, 156.7, 136.6, 132.6, 130.3, 129.9, 127.7, 120.1, 117.8, 111.0. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{11}N_4O$ 239.0933; found 239.0930.

2-phenyl-5-(3-(trifluoromethyl)phenyl)-2H-tetrazole (43l)

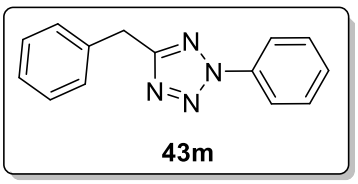


43l

In accordance with **GP-A**, 5-(3-(trifluoromethyl)phenyl)-1*H*-tetrazole **41l** (53.5 mg, 0.25 mmol), diphenyliodonium triflate **42a-OTf** (107.5 mg, 0.25 mmol) and $NaHCO_3$ (25.2 mg, 0.3 mmol) were used, and the following conditions gave the title compound **43l** as white solid (55.1 mg, 0.19 mmol, 76%). Reaction duration: 12 h. Purification method: column chromatography (10% ethyl acetate in hexane). ^1H NMR (400 MHz, $CDCl_3$): δ 8.54 (s, 1H), 8.46 (d, J = 8 Hz, 1H), 8.22 (d, J = 8 Hz, 2H), 7.77 (d, J = 8 Hz, 1H), 7.67 (t,

J = 8 Hz, 1H), 7.60 (t, *J* = 8 Hz, 2H), 7.53 (t, *J* = 8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 164.0, 136.8, 131.6 (q, $J_{C\text{-}F}$= 33 Hz), 130.2, 129.9, 129.8, 129.6, 128.0, 127.2, 125.2, 124.0, 122.5, 119.8 120.1, 117.8, 111.0. ^{19}F NMR (376 MHz, $CDCl_3$): *δ* -62.9. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{10}N_4F_3$ 291.0857; found 291.0849.

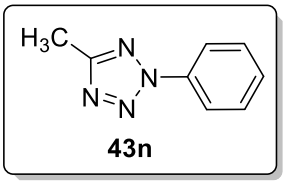
5-benzyl-2-phenyl-2H-tetrazole (43m) [36]



43m

In accordance with **GP-A**, 5-benzyl-1*H*-tetrazole **41l** (42 mg, 0.25 mmol), diphenyliodonium triflate **42a-OTf** (107.5 mg, 0.25 mmol) and $NaHCO_3$ (25.2 mg, 0.3 mmol) were used, and the following conditions gave the title compound **43m** as yellowish liquid (41 mg, 0.175 mmol, 70%). Reaction duration: 12 h. Purification method: column chromatography (5-10% ethyl acetate in hexane). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.09 (d, *J* = 8 Hz, 2H), 7.53 (t, *J* = 8 Hz, 2H), 7.46 (t, *J* = 8 Hz, 1H), 7.38 (d, *J* = 8 Hz, 2H), 7.33 (t, *J* = 8 Hz, 2H), 7.26 (t, *J* = 8 Hz, 1H), 4.33 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 165.8, 136.9, 136.5, 129.6, 128.8, 128.7, 126.9, 119.8, 31.9. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{13}N_4$ 237.1140; found 237.1155.

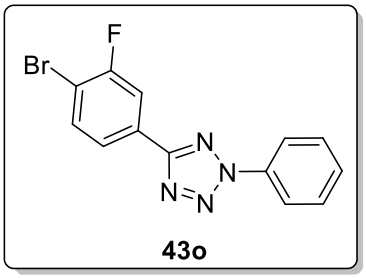
5-benzyl-2-phenyl-2H-tetrazole (43n) [36]



43n

In accordance with GP-A, 5-methyl-1*H*-tetrazole **41n** (22 mg, 0.25 mmol), diphenyliodonium triflate **42a-OTf** (107.5 mg, 0.25 mmol) and $NaHCO_3$ (25.2 mg, 0.3 mmol) were used, and the following conditions gave the title compound **43n** as colourless liquid (30 mg, 0.187 mmol, 75%). Reaction duration: 12 h. Purification method: column chromatography (5-10% ethyl acetate in hexane). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.03 (d, *J* = 8 Hz, 2H), 7.46 (t, *J* = 8 Hz, 2H), 7.40 (t, *J* = 8 Hz, 1H), 2.57 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): *δ* 163.3, 136.9, 129.7, 119.8, 11.1. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_8H_9N_4$ 161.0822; found 161.0827.

5-(4-bromo-3-fluorophenyl)-2-phenyl-2H-tetrazole (43o)

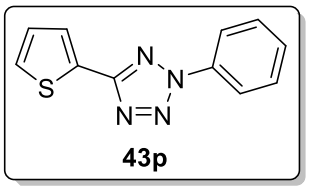


43o

In accordance with **GP-A**, 5-(4-bromo-3-fluorophenyl)-1*H*-tetrazole **41o** (60.25 mg, 0.25 mmol), diphenyliodonium triflate **42a-OTf** (107.5 mg, 0.25 mmol) and $NaHCO_3$ (25.2 mg, 0.3 mmol) were used, and the following conditions gave the title compound **43o** as white solid (61.4 mg, 0.192 mmol, 77%). Reaction duration: 12 h. Purification method: column chromatography (5% ethyl acetate in

hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (d, J = 8 Hz, 2H), 8.01 (d, J = 8 Hz, 1H), 7.95 (d, J = 8 Hz, 1H), 7.72 (t, J = 8 Hz, 1H), 7.60 (t, J = 8 Hz, 2H), 7.53 (t, J = 8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.6, 159.4 (d, $J_{C\text{-}F}$= 246 Hz), 136.7, 134.3, 130.0, 129.8, 128.4, 128.3, 123.7, 119.9, 115.1, 114.9, 111.7, 111.5. ^{19}F NMR (376 MHz, $CDCl_3$): δ -112.93. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{13}H_9N_4FBr$ 318.9989; found 318.9992.

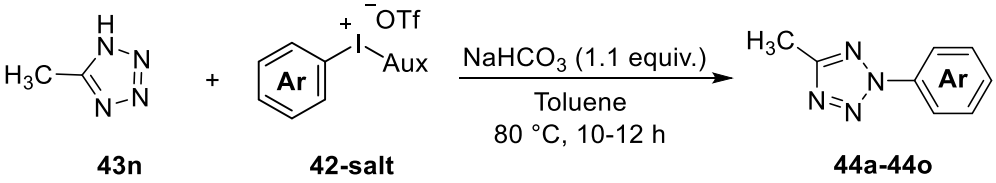
2-phenyl-5-(thiophen-2-yl)-2H-tetrazole (43p) [29]



43p

In accordance with **GP-A**, 5-(thiophen-2-yl)-1*H*-tetrazole **41p** (38 mg, 0.25 mmol), diphenyliodonium triflate **42a-OTf** (107.5 mg, 0.25 mmol) and $NaHCO_3$ (25.2 mg, 0.3 mmol) were used, and the following conditions gave the title compound **43p** as yellow solid (41 mg, 0.18 mmol, 72%). Reaction duration: 12 h. Purification method: column chromatography (5% ethyl acetate in hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (d, J = 8 Hz, 2H), 7.91-7.92 (m, 1H), 7.57 (t, J = 8 Hz, 2H), 7.49-7.52 (m, 2H), 7.19 (t, J = 8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.4, 136.8, 129.7, 128.9, 128.4, 128.1, 128.0, 119.9. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{11}H_9N_4S$ 229.0542; found 229.0548.

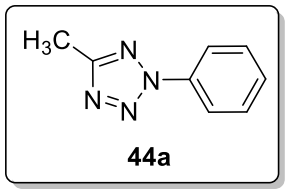
2.10.2 General procedure B (GP-B): *N*^{2}-aryaltion of 5-methyl-1*H*-Tetrazoles with diaryliodonium triflate



43n **42-salt** **44a-44o**

To an oven-dried Schlenck-tube, 5-methyl-1*H*-tetrazole **41n** (0.25 mmol), symmetrical diaryliodonium salt **42-OTf** or aryl(anisyl)iodonium triflate **42-An** (0.25 mmol, 1 equiv.), and $NaHCO_3$ (0.275 mmol, 1.1 equiv.) were added. After adding toluene (2.5 mL, 0.1 M), the tube was sealed and placed on a pre-heated oil bath at 100 ℃. The reaction mixture was stirred till indicated time period. After removing from heat, the reaction was cooled to room temperature and work-up was performed with EtOAc and water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Then, the crude product was purified using column-chromatography to obtain the desired product.

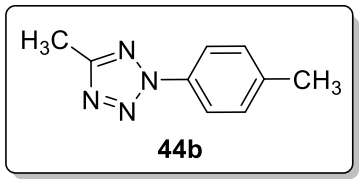
5-methyl-2-phenyl-2H-tetrazole (44a) [36]



44a

In accordance with **GP-B**, 5-methyl-1*H*-tetrazole **41n** (22 mg, 0.25 mmol), (4-methoxyphenyl)(phenyl)iodonium triflate **42a-An** (115 mg, 0.25 mmol) and $NaHCO_3$ (25.2 mg, 0.3 mmol) were used, and the following conditions gave the title compound **44a** as colourless liquid (28.8 mg, 0.18 mmol, 72%). Reaction duration: 12 h. Purification method: column chromatography (5-10% ethyl acetate in hexane). ^1H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, J = 8 Hz, 2H), 7.46 (t, J = 8 Hz, 2H), 7.40 (t, J = 8 Hz, 1H), 2.57 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.3, 136.9, 129.7, 119.8, 11.1. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_8H_9N_4$ 161.0822; found 161.0827.

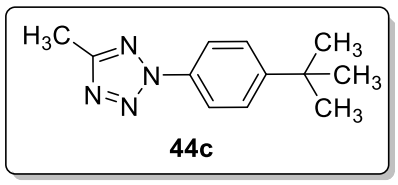
5-methyl-2-(p-tolyl)-2H-tetrazole (44b) [36]



44b

In accordance with **GP-B**, 5-methyl-1*H*-tetrazole **41n** (22 mg, 0.25 mmol), (4-methoxyphenyl)(*p*-tolyl)iodonium triflate **42b-An** (118.5 mg, 0.25 mmol) and $NaHCO_3$ (25.2 mg, 0.3 mmol) were used, and the following conditions gave the title compound **44b** as white solid (35.7 mg, 0.205 mmol, 82%). Reaction duration: 12 h. Purification method: column chromatography (5-10% ethyl acetate in hexane). ^1H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, J = 8 Hz, 2H), 7.32 (d, J = 8 Hz, 2H), 2.62 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.0, 139.7, 134.6, 130.1, 119.5, 21.2, 11.0. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_9H_{11}N_4$ 175.0978; found 175.0976.

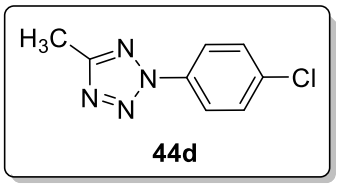
2-(4-(tert-butyl)phenyl)-5-methyl-2H-tetrazole (44c)



44c

In accordance with **GP-B**, 5-methyl-1*H*-tetrazole **41n** (22 mg, 0.25 mmol), (4-(tert-butyl)phenyl)(4-methoxyphenyl)iodonium triflate **42c-An** (129 mg, 0.25 mmol) and $NaHCO_3$ (25.2 mg, 0.3 mmol) were used, and the following conditions gave the title compound **44c** as colourless liquid (40.5 mg, 0.187 mmol, 75%). Reaction duration: 12 h. Purification method: column chromatography (5-10% ethyl acetate in hexane). ^1H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, J = 8 Hz, 2H), 7.55 (d, J = 8 Hz, 2H), 2.63 (s, 3H), 1.38 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.1, 152.9, 134.5, 126.6, 119.4, 34.9, 31.3, 11.1. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{17}N_4$ 217.1446; found 217.1443.

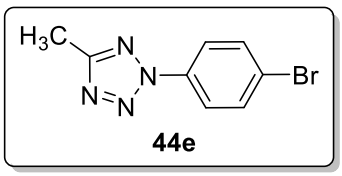
2-(4-chlorophenyl)-5-methyl-2H-tetrazole (44d) [36]



44d

In accordance with **GP-B**, 5-methyl-1*H*-tetrazole **41n** (22 mg, 0.25 mmol), (4-chlorophenyl)(4-methoxyphenyl)iodonium triflate **42d-An** (123.6 mg, 0.25 mmol) and $NaHCO_3$ (25.2 mg, 0.3 mmol) were used, and the following conditions gave the title compound **44d** as white solid (36 mg, 0.185 mmol, 74%). Reaction duration: 12 h. Purification method: column chromatography (5-10% ethyl acetate in hexane). ^1H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, J= 8 Hz, 2H), 7.52 (d, J= 8 Hz, 2H), 2.64 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.5, 135.3, 129.9, 120.9, 11.0. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_8H_8N_4Cl$ 195.0432; found 195.0434.

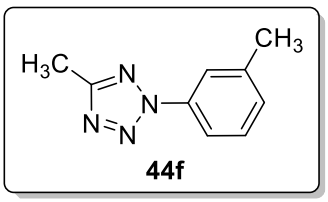
2-(4-bromophenyl)-5-methyl-2H-tetrazole (44e) [36]



44e

In accordance with **GP-B**, 5-methyl-1*H*-tetrazole **41n** (22 mg, 0.25 mmol), (4-bromophenyl)(4-methoxyphenyl)iodonium triflate **42e-An** (135 mg, 0.25 mmol) and $NaHCO_3$ (25.2 mg, 0.3 mmol) were used, and the following conditions gave the title compound **44e** as white solid (41.8 mg, 0.175 mmol, 70%). Reaction duration: 12 h. Purification method: column chromatography (5-10% ethyl acetate in hexane). ^1H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, J = 8 Hz, 2H), 7.68 (d, J = 8 Hz, 2H), 2.64 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.5, 135.8, 132.9, 123.9, 121.2, 11.0. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_8H_8N_4Br$ 238.9927; found 238.9930.

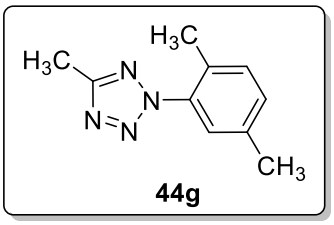
5-methyl-2-(m-tolyl)-2H-tetrazole (44f)



44f

In accordance with **GP-B**, 5-methyl-1*H*-tetrazole **41n** (22 mg, 0.25 mmol), (4-methoxyphenyl)(*m*-tolyl) iodonium triflate **42f-An** (118.5 mg, 0.25 mmol) and $NaHCO_3$ (25.2 mg, 0.3 mmol) were used, and the following conditions gave the title compound **44f** as colourless liquid (31.3 mg, 0.18 mmol, 72%). Reaction duration: 12 h. Purification method: column chromatography (5-10% ethyl acetate in hexane). ^1H NMR (400 MHz, $CDCl_3$): δ 7.92 (s, 1H), 7.88 (d, J = 8 Hz, 2H), 7.42 (t, J = 8 Hz, 1H), 7.28 (d, J = 8 Hz, 1H), 2.63 (s, 3H), 2.46 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.8, 136.8, 130.3, 129.5, 120.3, 116.9, 21.4, 11.0. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_9H_{11}N_4$ 175.0978; found 175.0981.

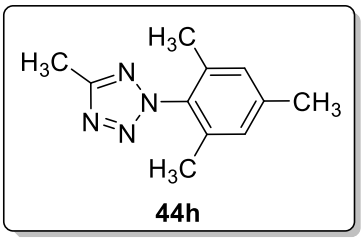
2-(2,5-dimethylphenyl)-5-methyl-2H-tetrazole (44g)



44g

In accordance with **GP-B**, 5-methyl-1*H*-tetrazole **41n** (22 mg, 0.25 mmol), *bis*-(2,5-dimethylphenyl)iodonium triflate **42i-OTf** (122 mg, 0.25 mmol) and $NaHCO_3$ (25.2 mg, 0.3 mmol) were used, and the following conditions gave the title compound **44g** as yellowish liquid (29 mg, 0.155 mmol, 62%). Reaction duration: 12 h. Purification method: column chromatography (5-10% ethyl acetate in hexane). ^1H NMR (400 MHz, $CDCl_3$): δ 7.37 (s, 1H), 7.26 (d, J = 8 Hz, 1H), 7.23 (d, J = 8 Hz, 1H), 2.63 (s, 3H), 2.39 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.7, 136.9, 136.2, 131.7, 130.9, 129.7, 125.6, 20.8, 18.2, 10.9. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{10}H_{13}N_4$ 189.1134; found 189.1133.

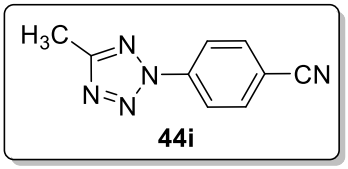
***2-mesityl-5-methyl-2H-tetrazole* (44h)**



44h

In accordance with **GP-B**, 5-methyl-1*H*-tetrazole **41n** (22 mg, 0.25 mmol), *bis*(mesityl)iodonium triflate **42j-OTf** (128 mg, 0.25 mmol) and $NaHCO_3$ (25.2 mg, 0.3 mmol) were used, and the following conditions gave the title compound **44h** as colourless liquid (29.3 mg, 0.145 mmol, 58%). Reaction duration: 12 h. Purification method: column chromatography (5-10% ethyl acetate in hexane). ^1H NMR (400 MHz, $CDCl_3$): δ 6.99 (s, 2H), 2.66 (s, 3H), 2.36 (s, 3H), 1.95 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 162.9, 140.7, 135.1, 133.9, 129.1, 21.2, 17.2, 11.0. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{11}H_{15}N_4$ 203.1290; found 203.1283.

***4-(5-methyl-2H-tetrazol-2-yl)benzonitrile* (44i)**

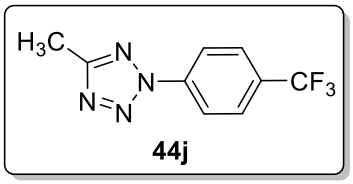


44i

In accordance with **GP-B**, 5-methyl-1*H*-tetrazole **41n** (22 mg, 0.25 mmol), (4-cyanophenyl)(4-methoxyphenyl)iodonium triflate **42g-An** (121 mg, 0.25 mmol) and $NaHCO_3$ (25.2 mg, 0.3 mmol) were used, and the following conditions gave the title compound **44i** as white solid (30.5 mg, 0.165 mmol, 66%). Reaction duration: 12 h. Purification method: column chromatography (5-10% ethyl acetate in hexane). ^1H NMR (400 MHz, $CDCl_3$): δ 8.27 (d, J = 8 Hz, 2H), 7.87 (d, J = 8 Hz, 2H), 2.66 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.1, 139.3, 133.8,

120.1, 117.7, 113.2, 11.0. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_9H_8N_5$ 186.0774; found 186.0767.

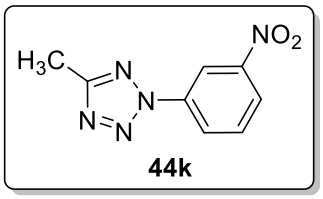
5-methyl-2-(4-(trifluoromethyl)phenyl)-2H-tetrazole **(44j)**



44j

In accordance with **GP-B**, 5-methyl-1*H*-tetrazole **41n** (22 mg, 0.25 mmol), (4-methoxyphenyl)(4-(trifluoromethyl)phenyl)iodonium triflate **42h-An** (132 mg, 0.25 mmol) and $NaHCO_3$ (25.2 mg, 0.3 mmol) were used, and the following conditions gave the title compound **44j** as yellow solid (39.9 mg, 0.175 mmol, 70%). Reaction duration: 12 h. Purification method: column chromatography (5-10% ethyl acetate in hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (d, J = 8 Hz, 2H), 7.80 (d, J = 8 Hz, 2H), 2.64 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.8, 139.1, 131.5 (q, $J_{C\text{-}F}$ = 30 Hz, 1-CF_3), 127.0, 124.9, 122.2, 119.9, 11.0. ^{19}F NMR (376 MHz, $CDCl_3$): δ -62.8 ppm. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_9H_8N_4F_3$ 229.0701; found 229.0695.

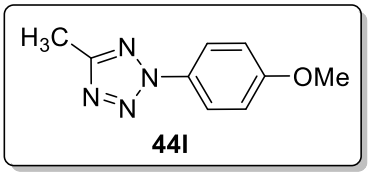
5-methyl-2-(3-nitrophenyl)-2H-tetrazole **(44k)**



44k

In accordance with **GP-B**, 5-methyl-1*H*-tetrazole **41n** (22 mg, 0.25 mmol), (4-methoxyphenyl)(3-nitrophenyl)iodonium triflate **42i-An** (126.3 mg, 0.25 mmol) and $NaHCO_3$ (25.2 mg, 0.3 mmol) were used, and the following conditions gave the title compound **44k** as yellow solid (34.8 mg, 0.17 mmol, 68%). Reaction duration: 12 h. Purification method: column chromatography (5-10% ethyl acetate in hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.99-9.00 (m, 1H), 8.49 (d, J = 8 Hz, 1H), 8.35 (d, J = 8 Hz, 1H), 7.78 (t, J = 8 Hz, 1H), 2.64 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.1, 149.0, 137.4, 130.9, 125.1, 123.9, 115.1, 11.1. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_8H_8N_5O_2$ 206.0678; found 206.0687.

2-(4-methoxyphenyl)-5-methyl-2H-tetrazole **(44l)** [36]

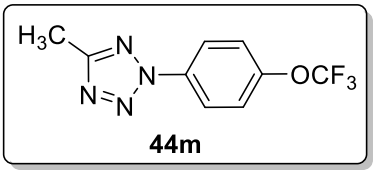


44l

In accordance with **GP-B**, 5-methyl-1*H*-tetrazole **41n** (22 mg, 0.25 mmol), bis(4-methoxyphenyl)iodonium triflate **42l-An** (122.5 mg, 0.25 mmol) and $NaHCO_3$ (25.2 mg, 0.3 mmol) were used, and the following conditions gave the title compound **44l** as white solid (37 mg, 0.195 mmol, 78%). Reaction duration: 12 h. Purification method: column chromatography (5-10% ethyl acetate in hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, J = 8 Hz, 2H), 6.95 (d, J = 8

Hz, 2H), 3.80 (s, 3H), 2.55 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.0, 160.4, 130.5, 114.6, 55.6, 11.0. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_9H_{11}N_4O$ 191.0933; found 191.0927.

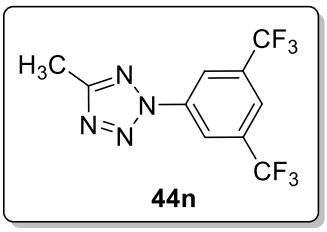
***5-methyl-2-(4-(trifluoromethoxy)phenyl)-2H-tetrazole* (44m)**



44m

In accordance with **GP-B**, 5-methyl-1*H*-tetrazole **41n** (22 mg, 0.25 mmol), (4-methoxyphenyl)(4-(trifluoromethoxy)phenyl)iodonium triflate **42j-An** (136 mg, 0.25 mmol) and $NaHCO_3$ (25.2 mg, 0.3 mmol) were used, and the following conditions gave the title compound **44m** as white solid (45.7 mg, 0.187 mmol, 75%). Reaction duration: 12 h. Purification method: column chromatography (5-10% ethyl acetate in hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, J = 8 Hz, 2H), 7.40 (d, J = 8 Hz, 2H), 2.64 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.6, 149.6, 135.1, 122.2, 121.7, 121.2, 119.1, 11.1. ^{19}F NMR (376 MHz, $CDCl_3$): δ -58.8. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_9H_8N_4OF_3$ 245.0650; found 245.0643.

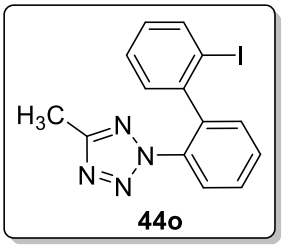
***2-(3,5-bis(trifluoromethyl)phenyl)-5-methyl-2H-tetrazole* (44n)**



44n

In accordance with **GP-B**, 5-methyl-1*H*-tetrazole **41n** (22 mg, 0.25 mmol), (3,5-*bis*(trifluoromethyl)phenyl)(4-methoxyphenyl)iodonium triflate **42k-An** (149 mg, 0.25 mmol) and $NaHCO_3$ (25.2 mg, 0.3 mmol) were used, and the following conditions gave the title compound **44n** as white solid (51.8 mg, 0.175 mmol, 70%). Reaction duration: 12 h. Purification method: column chromatography (5-10% ethyl acetate in hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55 (s, 2H), 7.92 (s, 1H), 2.60 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3, 137.6, 133.6 (q, $J_{C\text{-}F}$=35 Hz, 2-CF_3) 123.9, 122.8, 121.2, 119.8, 11.0. ^{19}F NMR (376 MHz, $CDCl_3$): δ -63.6. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{10}H_7N_4F_6$ 297.0575; found 297.0576.

***2-(2'-iodo-[1,1'-biphenyl]-2-yl)-5-methyl-2H-tetrazole* (44o)**

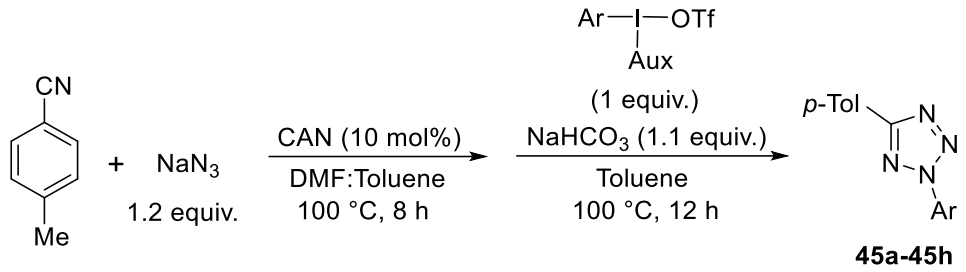


44o

In accordance with **GP-B**, 5-methyl-1*H*-tetrazole **41n** (22 mg, 0.25 mmol), 5*H*-dibenzo[*b,d*]iodonium triflate **42d-OTf** (107 mg, 0.25 mmol) and $NaHCO_3$ (25.2 mg, 0.3 mmol) were used, and the following conditions gave the title compound **44o** as colourless liquid (50.7 mg, 0.14 mmol, 56%). Reaction duration: 12 h. Purification method: column chromatography (5-10% ethyl acetate

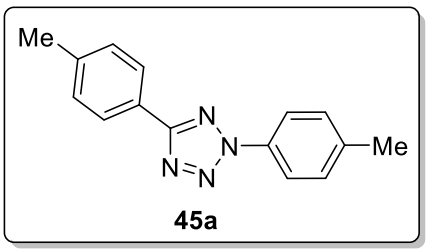
in hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77-7.82 (m, 2H), 7.59-7.61 (m, 2H), 7.40-7.43 (m, 1H), 7.28-7.30 (m, 1H), 7.16-7.19 (m, 1H), 6.97-7.02 (m, 1H), 2.46 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.6, 142.9, 139.0, 138.8, 135.3, 132.0, 130.2, 129.9, 129.3, 129.2, 127.9, 124.8, 99.0, 10.8. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{12}N_4I$ 363.0106; found 363.0106.

2.10.3 General procedure C (GP-C): One-pot *N*^{2}-aryaltion of 5-(*p*-Tolyl)-1*H*-Tetrazole directly from 4-methylbenzonitrile



To an oven-dried Schlenck-tube, 4-methylbenzonitrile (29.2 mg, 0.25 mmol), sodium azide (19.5 mg, 0.3 mmol, 1.2 equiv.) and ceric ammonium nitrate (14 mg, 0.025 mmol, 10 mol%) were added in solvent system DMF:Toluene (2:8) (total volume = 2.5 mL). The reaction pot was sealed and placed on a pre-heated oil bath at 100 ^{o}C. After the consumption of nitrile (checked by TLC, 12 h), the reaction vessel was lifted over the oil bath and diphenyliodonium triflate **2a-OTf** (0.25 mmol, 1 equiv.), and $NaHCO_3$ (0. mmol, 1.1 equiv.) were added. Additional toluene (2 mL) was added to the tube and placed on the pre-heated oil bath at 100 ^{o}C. The reaction mixture was stirred till indicated time period (12 h). The reaction was worked-up with EtOAc and water and the organic portion was dried over Na_2SO_4. The mixture was concentrated under reduced pressure and the crude product was purified as described.

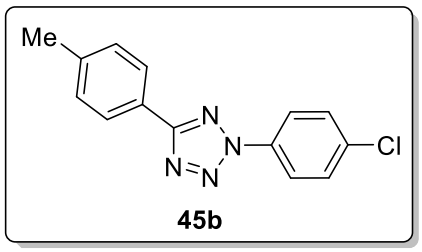
2,5-di-p-tolyl-2H-tetrazole **(45a)** [32]



In accordance with **GP-C**, 4-methylbenzonitrile (29.2 mg, 0.25 mmol), sodium azide (19.5 mg, 0.3 mmol), CAN (14 mg, 10 mol%), (4-methoxyphenyl)(*p*-tolyl)iodonium triflate **45b-An** (118.5 mg, 0.25 mmol) and $NaHCO_3$ (25.2 mg, 0.3 mmol) were used, and the following conditions gave the title compound **45a** as pink solid (51.3 mg, 0.205 mmol, 82%). Reaction duration: 24 h. Purification method: column chromatography (5% ethyl acetate in hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ

8.13 (d, *J* = 8 Hz, 2H), 8.05 (d, *J* = 8 Hz, 2H), 7.31-7.36 (m, 4H), 2.44 (s, 3H), 2.43 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 165.2, 140.7, 139.8, 134.8, 130.2, 129.6, 127.0, 124.5, 119.8, 21.6, 21.2. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{15}N_4$ 251.1296; found 251.1302.

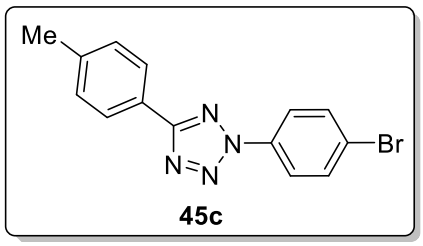
2-(4-chlorophenyl)-5-(p-tolyl)-2H-tetrazole **(45b)** [32]



45b

In accordance with **GP-C**, 4-methylbenzonitrile (29.2 mg, 0.25 mmol), sodium azide (19.5 mg, 0.3 mmol), CAN (14 mg, 10 mol%), (4-chlorophenyl)(4-methoxyphenyl)iodonium triflate **42d-An** (123.6 mg, 0.25 mmol) and $NaHCO_3$ (25.2 mg, 0.3 mmol) were used, and the following conditions gave the title compound **45b** as light pink solid (50.7 mg, 0.187 mmol, 75%). Reaction duration: 24 h. Purification method: column chromatography (5% ethyl acetate in hexane). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.11-8.16 (m, 4H), 7.54 (d, *J*= 8 Hz, 2H), 7.33 (d, *J*= 8 Hz, 2H), 2.43 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 165.5, 141.0, 135.4, 129.9, 127.0, 124.1, 121.0, 21.6. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{12}N_4Cl$ 271.0750; found 271.0733.

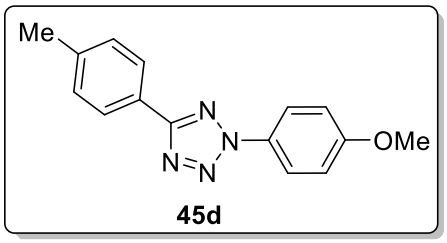
2-(4-bromophenyl)-5-(p-tolyl)-2H-tetrazole **(45c)**



45c

In accordance with GP-C, 4-methylbenzonitrile (29.2 mg, 0.25 mmol), sodium azide (19.5 mg, 0.3 mmol), CAN (14 mg, 10 mol%), (4-bromophenyl)(4-methoxyphenyl)iodonium triflate **42e-An** (134 mg, 0.25 mmol) and $NaHCO_3$ (25.2 mg, 0.3 mmol) were used, and the following conditions gave the title compound **45c** as light brown solid (56.7 mg, 0.18 mmol, 72%). Reaction duration: 24 h. Purification method: column chromatography (5% ethyl acetate in hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07-8.13 (m, 4H), 7.70 (d, *J* = 8 Hz, 2H), 7.33 (d, *J* = 8 Hz, 2H), 2.43 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.5, 141.0, 135.9, 132.9 129.8, 127.0, 124.1, 123.4, 121.3, 21.6. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{12}N_4Br$ 315.0245; found 315.0248.

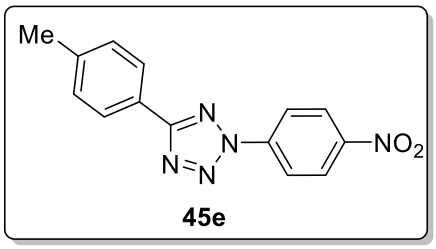
2-(4-methoxyphenyl)-5-(p-tolyl)-2H-tetrazole **(45d)**



45d

In accordance with **GP-C**, 4-methylbenzonitrile (29.2 mg, 0.25 mmol), sodium azide (19.5 mg, 0.3 mmol), CAN (14 mg, 10 mol%), bis(4-methoxyphenyl)iodonium triflate **42l-An** (122.5 mg, 0.25 mmol) and $NaHCO_3$ (25.2 mg, 0.3 mmol) were used, and the following conditions gave the title compound **45d** as light yellowish solid (50.5 mg, 0.19 mmol, 76%). Reaction duration: 24 h. Purification method: column chromatography (5% ethyl acetate in hexane). ^1H NMR (400 MHz, $CDCl_3$): δ 8.11 (d, J = 8 Hz, 2H), 8.07 (d, J = 8 Hz, 2H), 7.30 (d, J = 8 Hz, 2H), 7.03 (d, J = 8 Hz, 2H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 160.5, 140.6, 130.6, 129.6, 127.0, 124.6, 121.4, 114.6, 55.5, 21.6. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{15}N_4O$ 267.1246; found 267.1249.

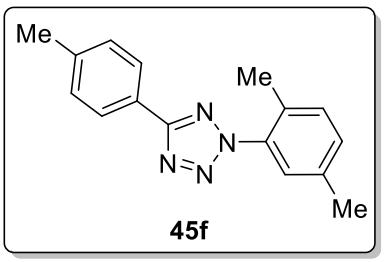
2-(4-nitrophenyl)-5-(p-tolyl)-2H-tetrazole **(45e)**



45e

In accordance with **GP-C**, 4-methylbenzonitrile (29.2 mg, 0.25 mmol), sodium azide (19.5 mg, 0.3 mmol), CAN (14 mg, 10 mol%), (4-methoxyphenyl)(4-nitrophenyl)iodonium triflate **42c-OTf** (126.3 mg, 0.25 mmol) and $NaHCO_3$ (25.2 mg, 0.3 mmol) were used, and the following conditions gave the title compound **45e** as pink solid (45 mg, 0.16 mmol, 64%). Reaction duration: 24 h. Purification method: column chromatography (5% ethyl acetate in hexane). ^1H NMR (400 MHz, $CDCl_3$): δ 8.41 (d, J = 8 Hz, 2H), 8.38 (d, J = 8 Hz, 2H), 8.12 (d, J = 8 Hz, 2H), 7.33 (d, J = 8 Hz, 2H), 2.43 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.1, 147.8, 141.5, 140.7, 129.9, 127.2, 125.5, 123.6, 120.2, 21.6. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{12}N_5O_2$ 282.0991; found 282.0963.

2-(2,5-dimethylphenyl)-5-(p-tolyl)-2H-tetrazole **(45f)**

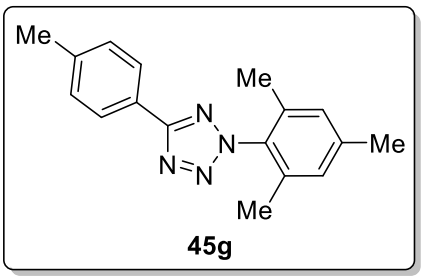


45f

In accordance with **GP-C**, 4-methylbenzonitrile (29.2 mg, 0.25 mmol), sodium azide (19.5 mg, 0.3 mmol), CAN (14 mg, 10 mol%), bis(2,5-dimethylphenyl)iodonium triflate **42i-OTf** (0.25 mmol) and $NaHCO_3$ (25.2 mg, 0.3 mmol) were used, and the following conditions gave the title compound **45f** as yellow solid (46.9 mg,

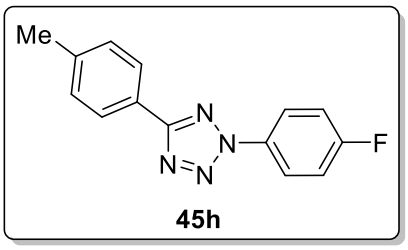
0.177 mmol, 71%). Reaction duration: 24 h. Purification method: column chromatography (5% ethyl acetate in hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, J = 8 Hz, 2H), 7.47 (s, 1H), 7.32 (d, J = 8 Hz, 2H), 7.26 (d, J = 8 Hz, 2H), 2.43 (s, 3H), 2.41 (s, 3H), 2.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165, 140.7, 137, 136.3, 131.7, 131.1, 127, 125.6, 124.5, 21.6, 20.8, 18.3. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{16}H_{17}N_4$ 265.1463; found 265.1461.

***2-mesityl-5-(p-tolyl)-2H-tetrazole* (45g)**



In accordance with **GP-C**, 4-methylbenzonitrile (29.2 mg, 0.25 mmol), sodium azide (19.5 mg, 0.3 mmol), CAN (14 mg, 10 mol%), dimesityliodonium triflate **42j-OTf** (128 mg, 0.25 mmol) and $NaHCO_3$ (25.2 mg, 0.3 mmol) were used, and the following conditions gave the title compound **45g** as white solid (42.4 mg, 0.152 mmol, 63%). Reaction duration: 24 h. Purification method: column chromatography (5% ethyl acetate in hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, J = 8 Hz, 2H), 7.31 (d, J = 8 Hz, 2H), 7.01 (s, 2H), 2.41 (s, 3H), 2.36 (s, 3H), 2.00 (s, 6H) . ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.2, 140.9, 140.7, 135.2, 134, 129.8, 129.6, 129.3, 129.1, 126.9, 124.6, 21.6, 21.3, 17.3. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{17}H_{19}N_4$ 279.1591; found 279.1602.

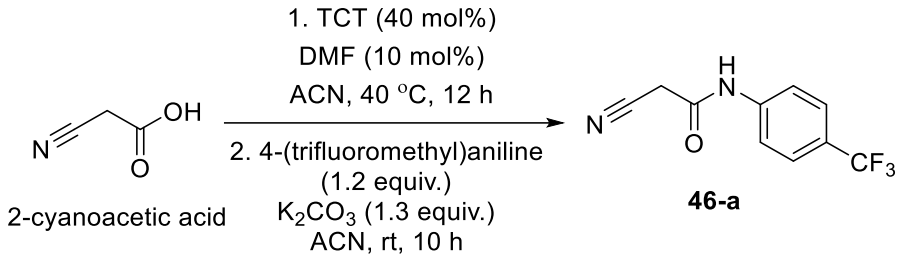
***2-(4-fluorophenyl)-5-(p-tolyl)-2H-tetrazole* (45h)**



In accordance with **GP-C**, 4-methylbenzonitrile (29.2 mg, 0.25 mmol), sodium azide (19.5 mg, 0.3 mmol), CAN (14 mg, 10 mol%), bis(4-fluorophenyl)iodonium triflate **42e-OTf** (116.5 mg, 0.25 mmol) and $NaHCO_3$ (25.2 mg, 0.3 mmol) were used, and the following conditions gave the title compound **45h** as white solid (41.9 mg, 0.165 mmol, 66%). Reaction duration: 24 h. Purification method: column chromatography (5% ethyl acetate in hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05-8.08 (m, 2H), 8.01 (d, J = 8 Hz, 2H), 7.22 (d, J = 8 Hz, 2H), 7.14 (t, J = 8 Hz, 2H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.4, 163 (d, $J_{C\text{-}F}$ = 249 Hz), 140.9, 133.2, 129.8, 127.0, 124.2, 121.9, 116.6 (d, $J_{C\text{-}F}$= 30 Hz), 21.6. ^{19}F NMR (376 MHz, $CDCl_3$): -112.9. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{14}H_{12}N_4F$ 255.1032; found 255.1040.

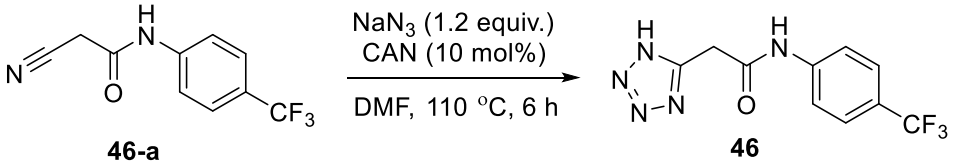
2.10.4 Synthesis of tetrazole 46

Step 1:



In adaptation of the literature [48], 2-cyanoacetic acid (255 mg, 3.00 mmol) was added to react with 2,4,6-trichloro-1,3,5-triazine (TCT) (221 mg, 1.2 mmol, 40 mol%) in the presence of DMF (300 μmol, 10 mol%) in MeCN (2 mL) for 12 h at rt. Next, MeCN (1 mL), amine (580 mg, 3.6 mmol, 1.2 equiv.) and K_2CO_3 (538 mg, 3.9 mmol, 1.3 equiv.) were added successively and the reaction mixture was stirred for 10 h at room temperature. After the reaction, the desired product was isolated by column chromatography and obtained as yellowish solid **46-a** (492 mg, 2.15 mmol, 72%). mp 156-158 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.6 (s, 1H), 7.72 (d, J = 8 Hz, 2H), 7.65 (d, J = 8 Hz, 2H), 3.92 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.4, 142.4, 126.7, 124.2, 123.9, 123.4, 119.7, 116.1, 27.5.

Step 2:



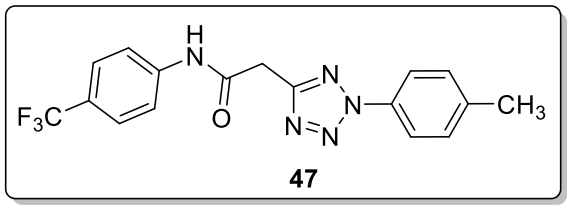
The procedure was adapted according to literature [43], **46-a** (456 mg, 2 mmol), sodium azide (156 mg, 2.4 mmol) and ceric ammonium nitrate (109 mg, 0.2 mmol) were taken in a round bottom flask and DMF (2 mL) was added on it. The reaction mixture then placed in a pre-heated oil bath at 110 °C. After the consumption of nitrile (checked by TLC), the reaction mixture was diluted with ethyl acetate (50 mL) and then acidified with 4N HCl (30 mL, 2 times). The organic layer was collected using a separatory funnel dried over Na_2SO_4. The solvent evaporated under reduced pressure and product was purified with hexane wash and obtained as yellowish solid **46** (328 mg, 56%). mp 192-194 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.76 (s, 1H), 7.64-

7.73 (m, 4H), 4.17 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.3, 162.3, 142.7, 126.7, 124.3, 124.0, 123.4, 119.6, 32.2.

2.10.5 General procedure D (GP-D): *N*^{2}-arylation of 47 and 49

To an oven-dried Schlenck-tube, 5-substituted-1*H*-tetrazole **46** or **48** (0.2 mmol), diaryliodonium triflate **42b-OTf** (0.2 mmol, 1 equiv.), and $NaHCO_3$ (0.22 mmol, 1.1 equiv.) were added. After adding toluene (2 mL, 0.1 M), the tube was sealed and placed on a pre-heated oil bath at 80 °C. The reaction mixture was stirred till indicated time period. After removing from heat, the reaction was cooled to room temperature and performed work-up with EtOAc and water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Then, the crude product was purified using column-chromatography to obtain the desired product **47** and **49** respectively.

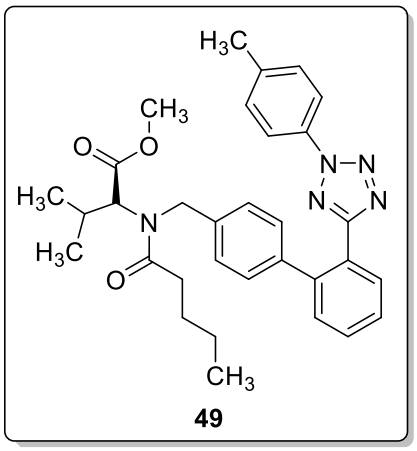
***2-(2-(p-tolyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)acetamide* (47)**



47

The compound was prepared according to **GP-D** using **46** (67.8 mg, 0.25 mmol), (di-*p*-tolyl)iodonium triflate **42b-OTf** (115 mg, 0.25 mmol, 1 equiv.) and $NaHCO_3$ (25.2 mg, 0.3 mmol). After 12 h, purification by column chromatography (2-5% ethyl acetate in hexane) gave **47** as white solid (59 mg, 0.163 mmol, 66%). mp 176-178 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, J = 8 Hz, 2H), 8.13 (d, J = 8 Hz, 2H), 7.54 (t, J = 8 Hz, 2H), 7.46 (d, J = 8 Hz, 1H), 7.31 (d, J = 8 Hz, 2H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.3, 140.8, 137.0, 129.7, 127.0, 124.4, 119.9, 21.6. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{17}H_{15}N_5OF_3$ 362.1228; found 362.1224.

***Methyl N-pentanoyl-N-((2'-(2-(p-tolyl)-2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-D-valinate* (49)**



49

The compound was prepared according to **GP-D** using **48** (113 mg, 0.25 mmol), (di-*p*-tolyl)iodonium triflate **42b-OTf** (115 mg, 0.25 mmol) and $NaHCO_3$ (25.2 mg, 0.3 mmol). After 12 h, purification by column chromatography (2-5% ethyl acetate in hexane) gave **49** as colourless liquid (81 mg, 0.15 mmol, 62%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (t, J = 8 Hz, 1H), 7.81 (d, J = 8 Hz, 2H), 7.48-7.55 (m, 2H), 7.40-7.44 (m, 1H), 7.27 (d, J= 8 Hz, 2H), 7.21 (d, J = 8 Hz, 1H), 7.07-7.13 (m, 3H), 4.91 (d, J = 8 Hz, 1H), 4.60 (s, 1H), 3.34 (s, 3H), 2.39 (s, 3H), 2.24-2.32 (m, 2H), 2.18 (s, 1H), 1.53-1.72 (m, 2H), 1.20-1.25 (m, 2H), 0.94-0.96 (m, 3H), 0.79-0.86 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.6, 171.1, 165.2, 142.1, 141.6, 140.0, 139.8, 139.4, 137.0, 136.1, 134.6, 131.0, 130.5, 130.2, 130.1, 129.6, 129.1, 127.7, 127.1, 126.0, 125.5, 119.7, 119.5, 65.9, 61.8, 51.6, 48.1, 45.4, 33.3, 31.6, 27.8, 27.5, 22.5, 21.1, 19.9, 18.7, 13.9. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{32}H_{38}N_5O_3$ 540.2917; found 540.2963.

2.10.6 Larger-scale Synthesis Procedure:

i) *5-(4-bromo-3-fluorophenyl)-2-phenyl-2H-tetrazole (43o)*

5-(4-bromo-3-fluorophenyl)-1*H*-tetrazole (**41o**) (1 g, 4.11 mmol), diphenyliodonium triflate (**42a-OTf**) (1.768 g, 4.11 mmol), and $NaHCO_3$ (415 mg, 4.93 mmol) were added in a 100 mL round bottom flask. After addition of the dry toluene (40 mL, 0.1 M), the reaction vessel was placed on a pre-heated oil bath at 80 °C. The reaction mixture was stirred for 12-15 h. After removing from heat, the reaction was cooled to room temperature and performed work-up with EtOAc and water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The mixture was purified by column chromatography (AcOEt/Hexane: 5/95) to afford **43o** (930 mg, 2.9 mmol, 71%) as white solid.

ii) *2-(4-bromophenyl)-5-(p-tolyl)-2H-tetrazole (45c)*

5-(*p*-tolyl)-1*H*-tetrazole (**41b**) (1 g, 6.24 mmol), di(*p*-tolyl)iodonium triflate (**42e-An)** (3.364 g, 2 mmol), and $NaHCO_3$ (630 mg, 7.48 mmol) were added in a 100 mL

round bottom flask. After adding toluene (50 mL, 0.1 M), the reaction vessel was placed and placed on a pre-heated oil bath at 80 ℃. The reaction mixture was stirred 12-15 h. After removing from heat, the reaction was cooled to room temperature and performed the work-up with EtOAc and water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The mixture was purified by column chromatography (AcOEt/Hexane: 5/95) to afford **45c** (1435 mg, 4.55 mmol, 73%) as light brown solid.

2.11 Representative ^{1}H and ^{13}C NMR spectra

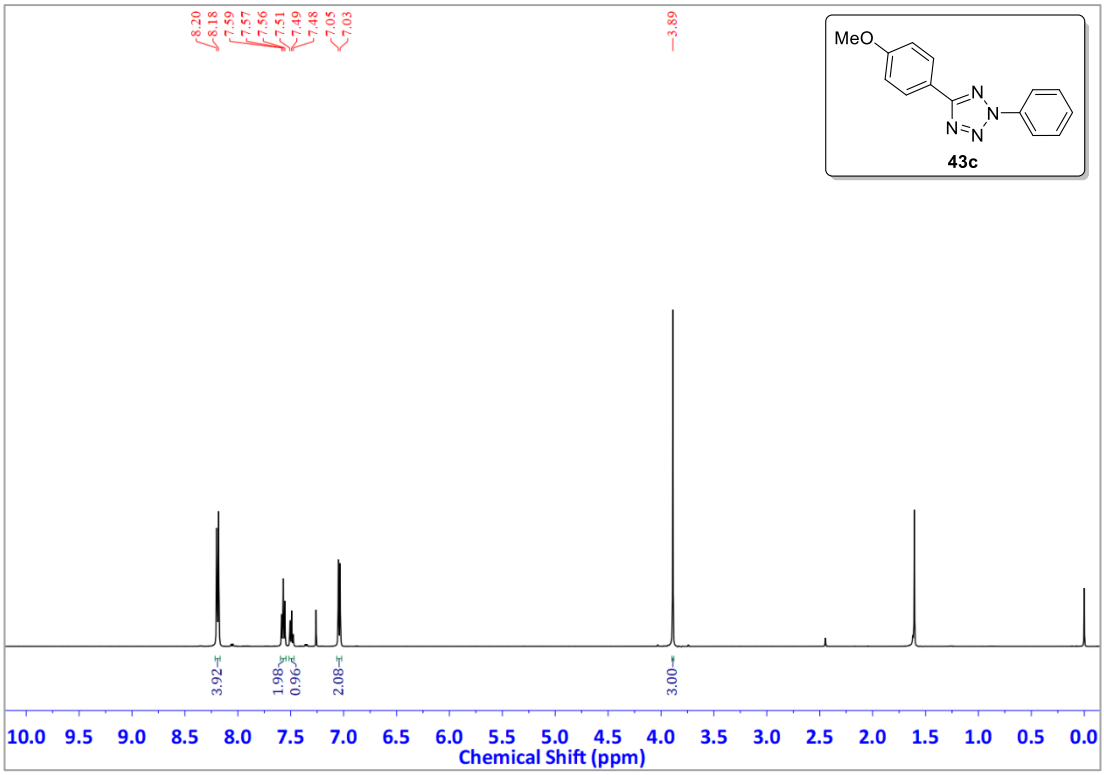


Figure 2.3 ^{1}H NMR spectrum of **43c** ($CDCl_3$, 400 MHz, 298 K)

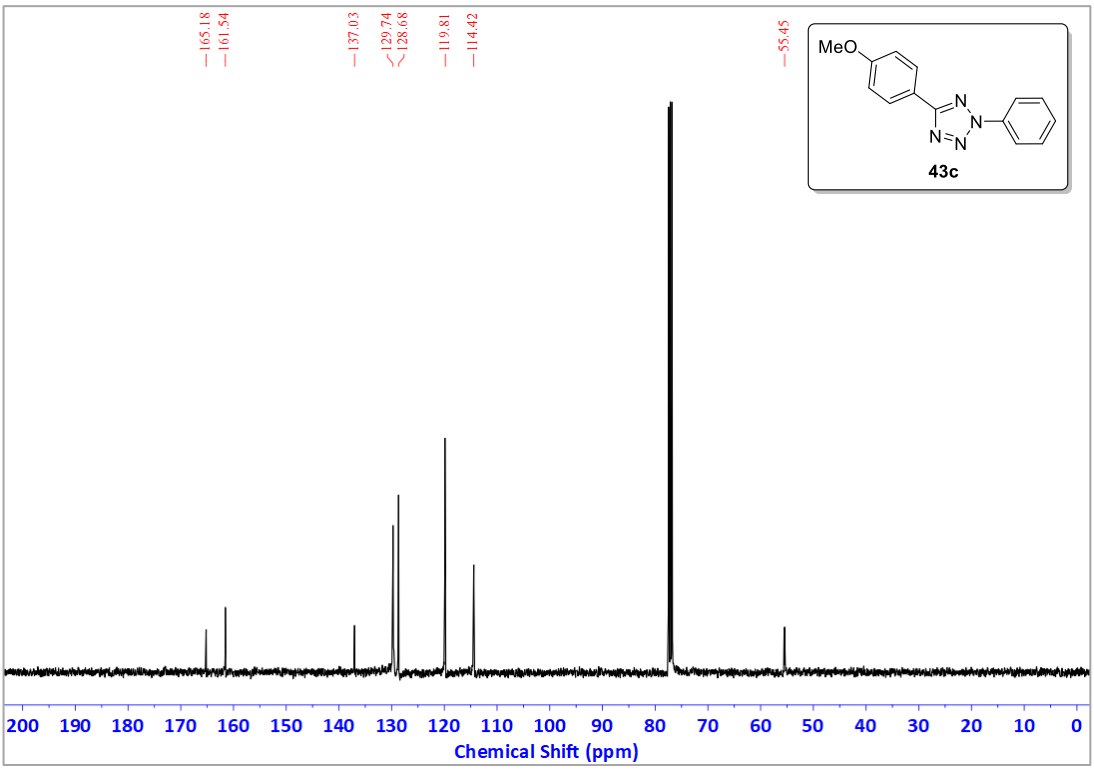


Figure 2.4 ^{13}C NMR spectrum of **43c** ($CDCl_3$, 100 MHz, 298 K)

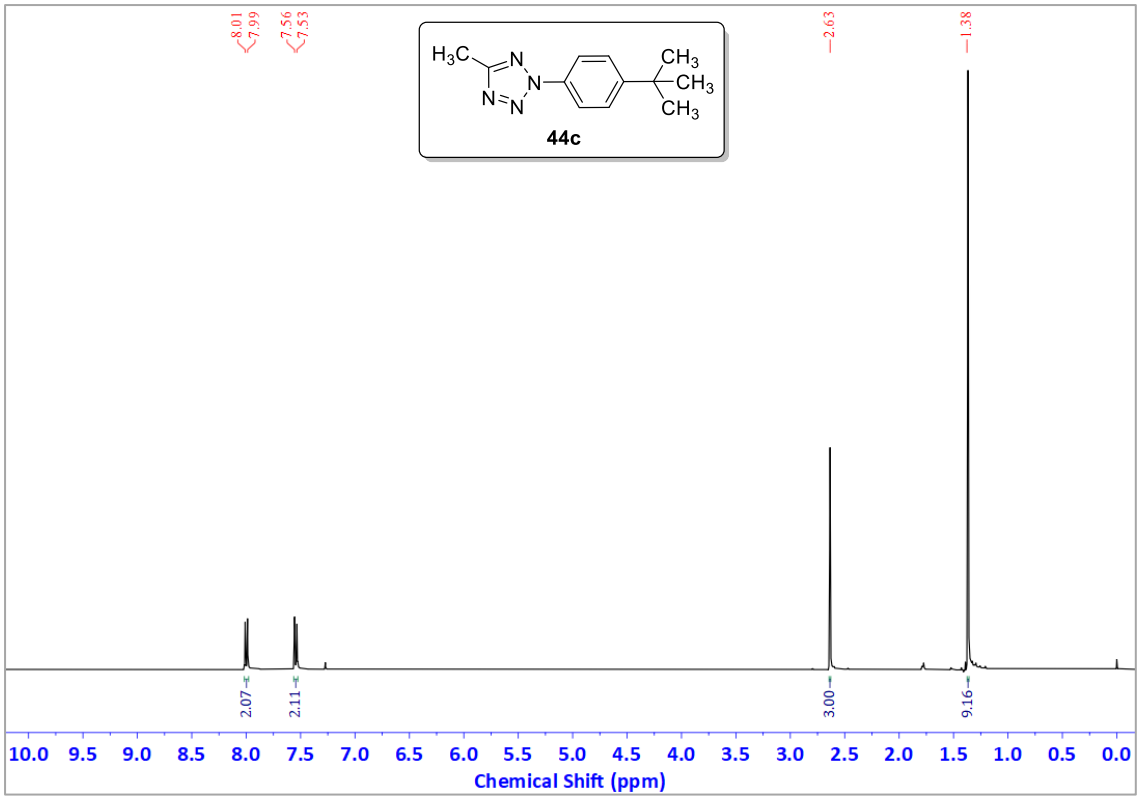


Figure 2.5 ^{1}H NMR spectrum of **44c** ($CDCl_3$, 400 MHz, 298 K)

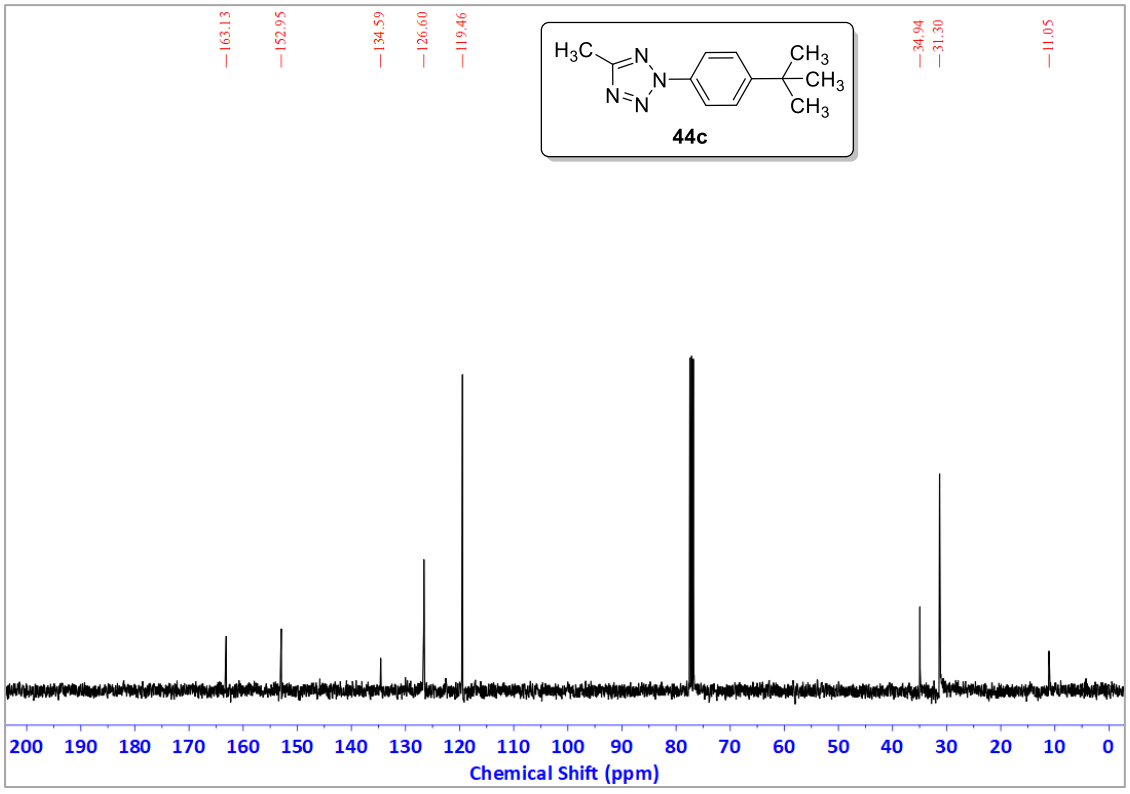


Figure 2.6 ^{13}C NMR spectrum of **44c** ($CDCl_3$, 100 MHz, 298 K)

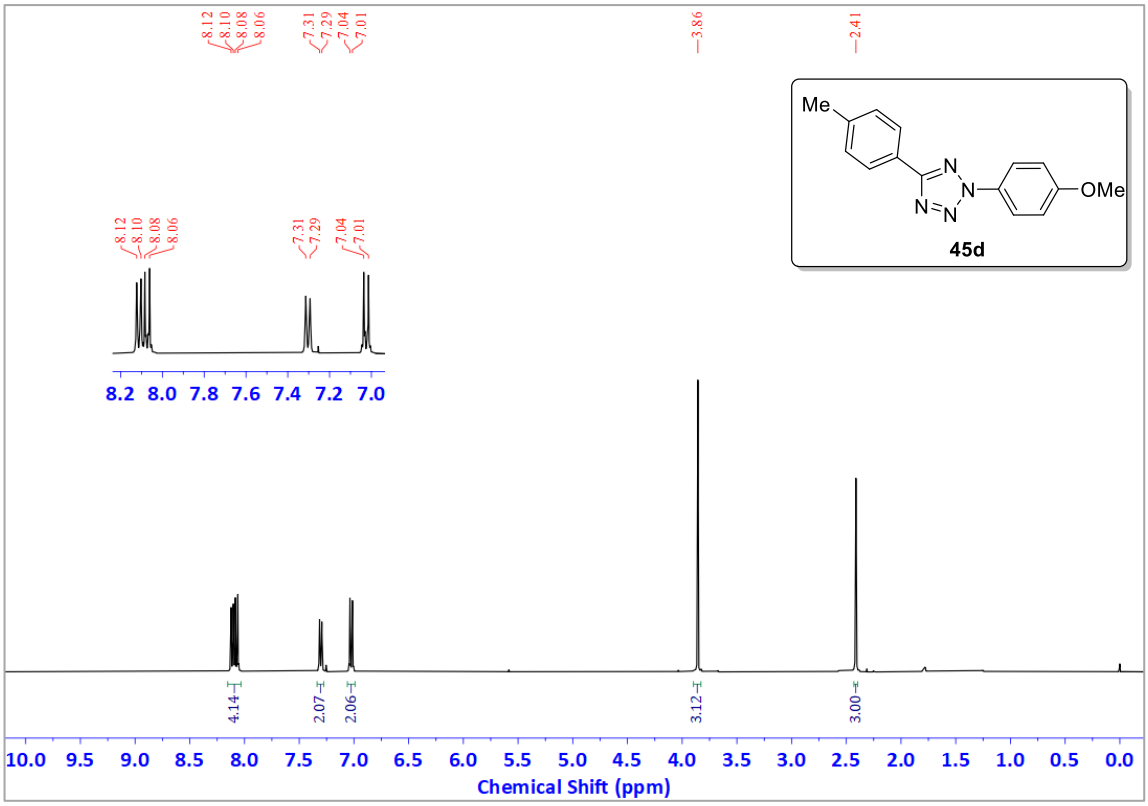


Figure 2.7 ^{1}H NMR spectrum of **45d** ($CDCl_3$, 400 MHz, 298 K)

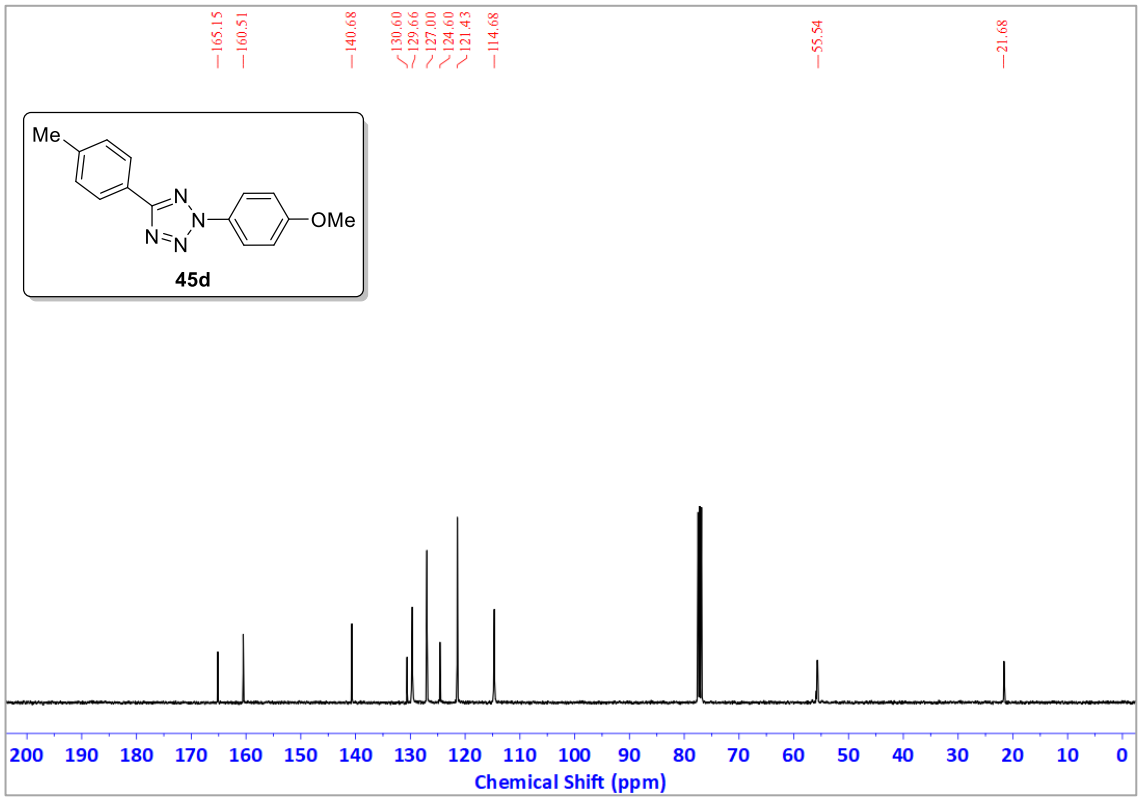


Figure 2.8 ^{13}C NMR spectrum of **45d** ($CDCl_3$, 100 MHz, 298 K)

2.12 Bibliography

[1] Neochoritis, C. G., Zhao, T., and Dömling, A. Tetrazoles *via* multicomponent reactions. *Chemical Reviews*, 119(3):1970–2042, 2019.

[2] Popova, E. A., Trifonov, R. E., and Ostrovskii, V. A. Tetrazoles for biomedicine. *Russian Chemical Reviews*, 88(6):644, 2019.

[3] Popova, E. A., Protas, A. V., and Trifonov, R. E. Tetrazole derivatives as promising anticancer agents. *Anti-Cancer Agents in Medicinal Chemistry*, 17(14):1856–1868, 2017.

[4] Nasrollahzadeh, M., Nezafat, Z., Bidgoli, N. S. S., and Shafiei, N. Use of tetrazoles in catalysis and energetic applications: Recent developments. *Molecular Catalysis*, 513:111788, 2021.

[5] Kang, X. M., Tang, M. H., Yang, G. L., and Zhao, B. Cluster/cage-based coordination polymers with tetrazole derivatives. *Coordination Chemistry Reviews*, 422:213424, 2020.

[6] Lv, F., Liu, Y., Zou, J., Zhang, D., and Yao, Z. Synthesis of the novel photographic DIAR couplers. *Dyes & Pigments*, 68(2-3):211–216, 2006.

[7] Li, Y. T., Yao, W. Q., Zhou, S., Xu, J. X., Lu, H., Lin, J., Hu, X. Y., and Zhang, S. K. Synthesis, fungicidal activity, and 3D-QSAR of tetrazole derivatives containing phenyloxadiazole moieties. *Bioorganic & Medicinal Chemistry Letters*, 34:127762, 2021.

[8] Özkan, H. and Demirci, B. Synthesis and antimicrobial and antioxidant activities of sulfonamide derivatives containing tetrazole and oxadiazole rings. *Journal of Heterocyclic Chemistry*, 56(9):2528–2535, 2019.

[9] Fischer, N., Karaghiosoff, K., Klapötke, T. M., Stierstorfer, J. New Energetic Materials Featuring Tetrazoles and Nitramines Synthesis, Characterization and Properties. *Zeitschrift für Anorganische und Allgemeine Chemie*, 636:735–749, 2010.

[10] Vitaku, E., Smith, D. T., and Njardarson, J. T. Analysis of the structural diversity, substitution patterns, and frequency of nitrogen heterocycles among US FDA approved pharmaceuticals: miniperspective. *Journal of Medicinal Chemistry*, 57(24):10257–10274, 2014.

[11] Zhang, J., Wang, S., Ba, Y., and Xu, Z. Tetrazole hybrids with potential anticancer activity. *European Journal of Medicinal Chemistry*, 178:341-351, 2019.

[12] Zhang, L. H., Zhang, Z. H., Li, M. Y., Wei, Z. Y., Jin, X. J., and Piao, H. R. Synthesis and evaluation of the HIF-1α inhibitory activities of novel ursolic acid tetrazole derivatives. *Bioorganic & Medicinal Chemistry Letters*, 29(12):1440–1445, 2019.

[13] Subramanian, V., Knight, J. S., Parelkar, S., Anguish, L., Coonrod, S. A., Kaplan, M. J., and Thompson, P. R. Design, synthesis, and biological evaluation of tetrazole analogs of Cl-amidine as protein arginine deiminase inhibitors. *Journal of Medicinal Chemistry*, 58(3):1337–1344, 2015.

[14] Gao, C., Chang, L., Xu, Z., Yan, X. F., Ding, C., Zhao, F., Wu, X., and Feng, L. S. Recent advances of tetrazole derivatives as potential anti-tubercular and anti-malarial agents. *European Journal of Medicinal Chemistry*, 163:404–412, 2019.

[15] Black, H. R., Bailey, J., Zappe, D., and Samuel, R. Valsartan. *Drugs*, 69(17):2393–2414, 2009.

[16] Sörgel, F., Kinzig, M., Abdel-Tawab, M., Bidmon, C., Schreiber, A., Ermel, S., Wohlfart, J., Besa, A., Scherf-Clavel, O., and Holzgrabe, U. The contamination of valsartan and other sartans, part 1: New findings. *Journal of Pharmaceutical and Biomedical Analysis*, 172:395–405, 2019.

[17] Zhang, Y., Lee, J. C. H., Reese, M. R., Boscoe, B. P., Humphrey, J. M., and Helal, C. J. 5-Aryltetrazoles from Direct C–H Arylation with Aryl Bromides. *The Journal of Organic Chemistry*, 85(8):5718–5723, 2020.

[18] Chauhan, K., Sharma, M., Trivedi, P., Chaturvedi, V., and Chauhan, P. M. New class of methyl tetrazole based hybrid of (Z)-5-benzylidene-2-(piperazin-1-yl) thiazol-4 (%H)-one as potent antitubercular agents. *Bioorganic & Medicinal Chemistry Letters*, 24(17):4166–4170, 2014.

[19] Arshad, M., Bhat, A. R., Pokharel, S., Kim, J.-E., Lee, E. J., Athar, F., and Choi, I. Synthesis, characterization, and anticancer screening of some novel piperonyl–tetrazole derivatives. *European Journal of Medicinal Chemistry*, 71:229–236, 2014.

[20] Łukowska-Chojnacka, E., Mierzejewska, J., Milner-Krawczyk, M., Bondaryk, M., and Staniszewska, M. Synthesis of novel tetrazole derivatives and evaluation

of their antifungal activity. *Bioorganic & Medicinal Chemistry*, 24(22):6058–6065, 2016.

[21] Köhler, S. C. and Wiese, M. HM30181 derivatives as novel potent and selective inhibitors of the breast cancer resistance protein (BCRP/ABCG2). *Journal of Medicinal Chemistry*, 58(9):3910–3921, 2015.

[22] Sprachman, M. M., Laughney, A. M., Kohler, R. H., and Weissleder, R. In vivo imaging of multidrug resistance using a third generation MDR1 inhibitor. *Bioconjugate Chemistry*, 25(6):1137–1142, 2014.

[23] Wang, Y., Hu, W. J., Song, W., Lim, R., and Lin, Q. Discovery of long-wavelength photoactivatable diaryltetrazoles for bio-orthogonal 1,3-dipolar cycloaddition reactions. *Organic Letters*, 10(17):3725–3728, 2008.

[24] Wang, Y. and Lin, Q. Synthesis, and evaluation of photoreactive tetrazole amino acids. *Organic Letters*, 11(16):3570–3573, 2009.

[25] Ito, S., Tanaka, Y., and Kakehi, A. Synthesis of 2,5-diaryltetrazoles from *N*-phenylsulfonylbenzhydrazidoyl chlorides and arylhydrazines. *Bulletin of the Chemical Society of Japan*, 49(3):762–766, 1976.

[26] Ramanathan, M., Wang, Y. H., and Liu, S. T. One-pot reactions for synthesis of 2,5-substituted tetrazoles from aryldiazonium salts and amidines. *Organic Letters*, 17(23):5886–5889, 2015.

[27] Livingstone, K., Bertrand, S., and Jamieson, C. One-Pot Suzuki-Hydrogenolysis Protocol for the Modular Synthesis of 2,5-Diaryltetrazoles. *The Journal of Organic Chemistry*, 85(11):7413–7423, 2020.

[28] Berzina, B., Sokolovs, I., and Suna, E. Copper-catalyzed *para*-selective C–H amination of electron-rich arenes. *ACS Catalysis*, 5(11):7008-7014, 2015.

[29] Rajamanickam, S., Sah, C., Mir, B. A., Ghosh, S., Sethi, G., Yadav, V., Venkataramani, S., and Patel, B. K. Bu_4NI-catalyzed, radical-induced regioselective *N*-alkylations and arylations of tetrazoles using organic peroxides/peresters. *The Journal of Organic Chemistry*, 85(4):2118–2141, 2020.

[30] Lam, P. Y., Clark, C. G., Saubern, S., Adams, J., Winters, M. P., Chan, D. M., and Combs, A. New aryl/heteroaryl C–N bond cross-coupling reactions *via* arylboronic acid/cupric acetate arylation. *Tetrahedron Letters*, 39(19):2941–2944, 1998.

[31] Fedorov, A. Y. and Finet, J. P. *N*-Phenylation of azole derivatives by triphenylbismuth derivatives/cupric acetate. *Tetrahedron Letters*, 40(14):2747–2748, 1999.

[32] Beletskaya, I. P., Davydov, D. V., and Gorovoy, M. S. Palladium-and copper-catalyzed selective arylation of 5-aryltetrazoles by diaryliodonium salts. *Tetrahedron Letters*, 43(35):6221–6223, 2002.

[33] Davydov, D. V., Beletskaya, I. P., Semenov, B. B., and Smushkevich, Y. I. Regioselective arylation of *N*-tributylstannylated 5-substituted tetrazoles by diaryliodonium salts in the presence of $Cu(OAc)_2$. *Tetrahedron Letters*, 43(35):6217–6219, 2002.

[34] Zhou, T. and Chen, Z. C. Hypervalent iodine in synthesis 87: The synthesis of 2,5-diaryl-2*H*-tetrazoles. *Journal of Chemical Research*, 2004(6):404–405, 2004.

[35] Li, Y., Gao, L. X., and Han, F. S. Efficient synthesis of 2,5-disubstituted tetrazoles *via* the Cu_2O-catalyzed aerobic oxidative direct cross-coupling of N–H free tetrazoles with boronic acids. *Chemical Communications*, 48(21):2719–2721, 2012.

[36] Onaka, T., Umemoto, H., Miki, Y., Nakamura, A., and Maegawa, T. $[Cu(OH)(TMEDA)]_2Cl_2$-catalyzed regioselective 2-arylation of 5-substituted tetrazoles with boronic acids under mild conditions. *The Journal of Organic Chemistry*, 79(14):6703–6707, 2014.

[37] Rajamanickam, S., Saraswat, M., Venkataramani, S., and Patel, B. K. Intermolecular CDC amination of remote and proximal unactivated Csp^3–H bonds through intrinsic substrate reactivity–expanding towards a traceless directing group. *Chemical Science*, 12(46):15318–15328, 2021.

[38] Ruan, Z., Huang, Z., Xu, Z., Zeng, S., Feng, P., and Sun, P.-H. Late-stage azolation of benzylic C–H bonds enabled by electrooxidation. *Science China Chemistry*, 64(5):800–807, 2021.

[39] Ghosh, R. and Olofsson, B. Metal-free synthesis of *N*-aryloxyimides and aryloxyamines. *Organic Letters*, 16(6):1830-1832, 2014.

[40] Gigant, N., Chausset-Boissarie, L., Belhomme, M. C., Poisson, T., Pannecoucke, X., and Gillaizeau, I. Copper-catalyzed direct arylation of cyclic enamides using diaryliodonium salts. *Organic Letters*, 15(2):278–281, 2013.

[41] Virant, M. and Košmrlj, J. Arylation of click triazoles with diaryliodonium salts. *The Journal of Organic Chemistry*, 84(21):14030–14044, 2019.

[42] Malmgren, J., Santoro, S., Jalalian, N., Himo, F., and Olofsson, B. Arylation with unsymmetrical diaryliodonium salts: a chemoselectivity study. *Chemistry–A European Journal*, 19(31):10334–10342, 2013.

[43] Kumar, S., Dubey, S., Saxena, N., and Awasthi, S. K. $(NH_4)_2Ce(NO_3)_6$ as an inexpensive, eco-friendly, efficient catalyst for the synthesis of 5-substituted 1*H*-tetrazoles from nitriles. *Tetrahedron Letters*, 55(44):6034–6038, 2014.

[44] Demko, Z. P. and Sharpless, K. B. Preparation of 5-substituted 1*H*-tetrazoles from nitriles in water. *The Journal of Organic Chemistry*, 66(24):7945–7950, 2001.

[45] Chrétien, J. M., Kerric, G., Zammattio, F., Galland, N., Paris, M., Quintard, J. P., and Le Grognec, E. Tin-catalyzed synthesis of 5-substituted 1*H*-tetrazoles from nitriles: homogeneous and heterogeneous procedures. *Advanced Synthesis & Catalysis*, 361(4):747–757, 2019.

[46] Lucchetti, N., Scalone, M., Fantasia, S., and Muniz, K. Sterically congested 2,6-disubstituted anilines from direct C–N Bond Formation at an iodine(III) centre. *Angewandte Chemie International Edition*, 55(42):13335–13339, 2016.

[47] Vogel, A. I., Furniss, B. S., Hannaford, A. J., Rogers, V., Smith, P. W. G. and Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry*, 4th Edition, ELBS & Longman, London, 1978.

[48] Huy, P. H. and Mbouhom, C. Formamide catalyzed activation of carboxylic acids–versatile and cost-efficient amidation and esterification. *Chemical Science*, 10(31):7399–7406, 2019.