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N^1- and N^3-Arylations of Hydantoins Employing Diaryliodonium Salts *via* Copper(I) Catalysis at Room Temperature

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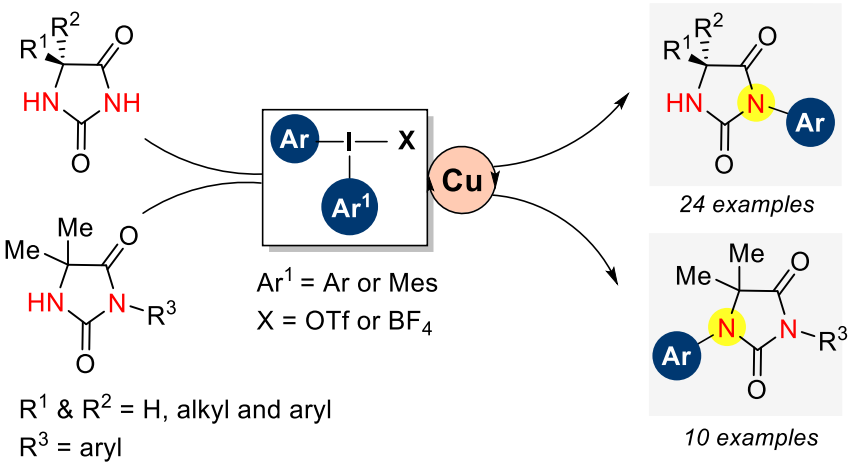
Chapter 4

N-Arylations of Hydantoins under Copper(I) Catalysis

Abstract: Copper(I)-catalyzed *N*-arylation (both N^1- and N^3-) of hydantoins with diaryliodonium salts as aryl partners at room temperature is reported. The transformation allows diverse scopes on both hydantoins and diaryliodonium salts delivering functionalized N^3-arylated products under mild reaction conditions. The robustness of the protocol is tested with the varied examples of hydantoins including C5-H and N1-H unprotected hydantoins. Chiral hydantoins can also be synthesised *via* this methodology. Sterically-complicated *ortho*-substituted diaryliodonium salts are tolerated under the reaction condtions and challenging *ortho*-arylated products are delivered. In addition, this strategy can also be effectively extended to N^1-arylation of hydantoins.



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4.1 Introduction

4.1.1 Importance of *N*-arylated hydantoins

Biologically active arylated hydantoin **1** (also known as imidazolidine-2,4-diones) derivatives [1–2] have marked skeletal appearances in a wide array of natural [3–7] and synthetic products [8–13]. This motif is effectively used in medicinal chemistry [14–17], coordination chemistry [18–19], agrochemistry [20–21], and polymer science [22–24]. Though, structurally simple and first synthesized [25] in 1861, intense research efforts have been devoted to synthetic developments and studies of this class of five-membered compounds [1]. Hydantoin based drugs such as Nilutamide **2** [26] and Enzalutamide **3** [27] have been used as *anti*-androgen and *anti*-prostate cancer agents respectively; while GLGP-0492 **4**, BMS-564929 **5**, BMS-587101 **6**, and BMS-688621 **7** are candidates under clinical development [28] (Figure 4.1).

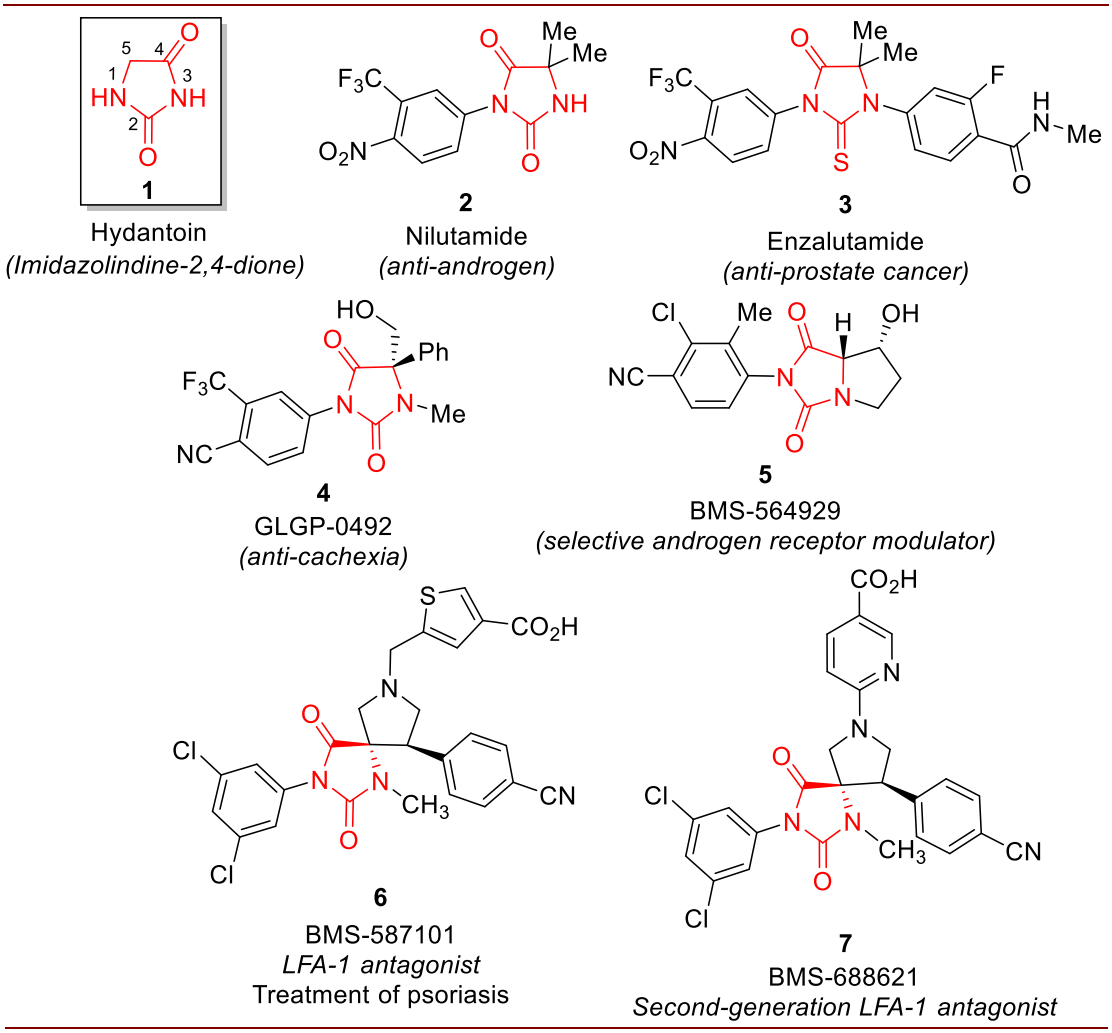
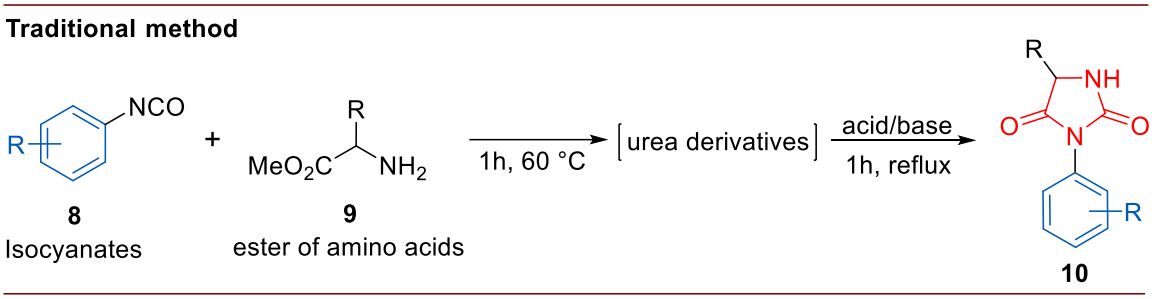


Figure 4.1 Important *N*-arylated hydantoin based drugs and clinical candidates

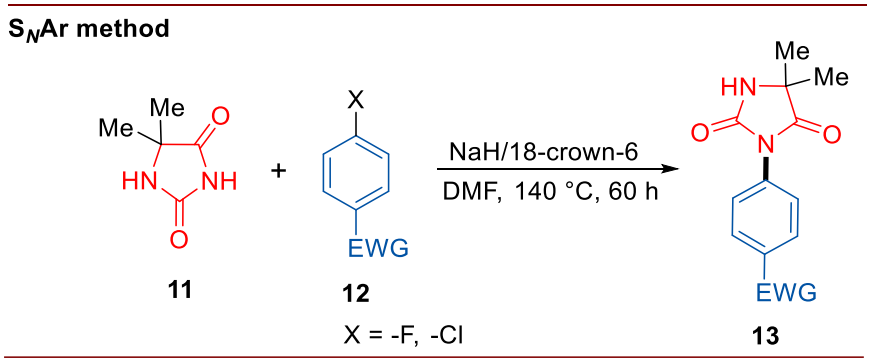
4.1.2 Previous methods for the synthesis of *N*-arylated hydantoins

In traditional approach, condensation of aryl isocyanates with amino acid derivatives affords N^3-arylated hydantoins (Scheme 4.1) [29]. This cyclisation and indirect strategy requires strong acidic or basic condition during the cyclisation of ureido derivatives. Moreover, substituted aryl isocyanates needed extra steps for their syntheses. Also, isocyantes are often toxic and unstable under ambient conditions [30–31].



Scheme 4.1 Traditional approach to access N^3-arylated hydantoins

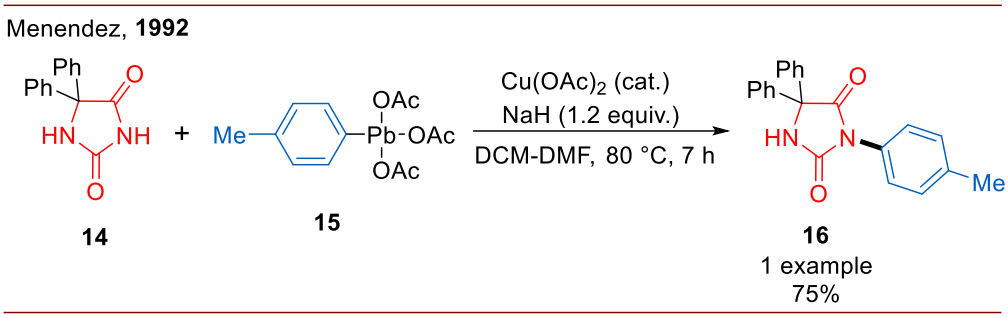
Featuring an amidic and imidic N-H group on the hydantoin core, these heterocyclic molecules have participated in the *N*-arylation reactions. Therefore, another complementary approach to access N^3-aryl hydantoins is the direct functionalization in the N^3-H position of the hydantoin with an applicable arylating source. The conventional nucleophilic aromatic substitution method (S_NAr) requires high temperature and yields of the reactions are generally low (Scheme 4.2) [32].



Scheme 4.2 Synthesis of N^3-aryl hydantoins *via* S_NAr approach

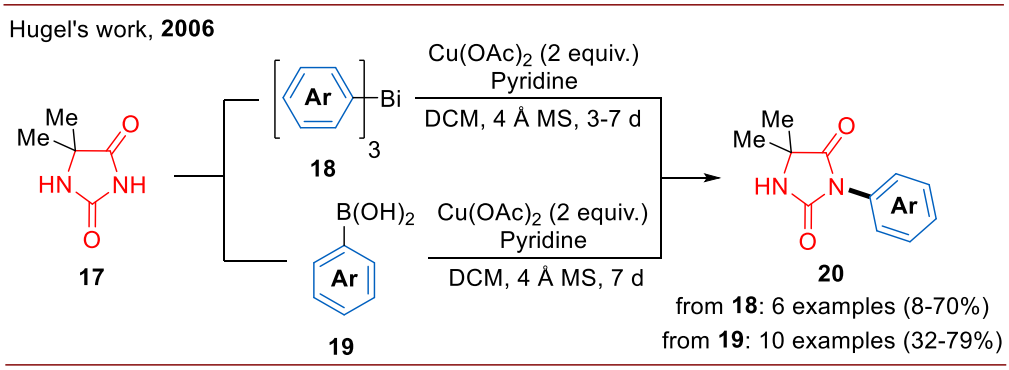
In 1992, Menendez and co-workers pioneered Cu-catalysed N^3-arylation of hydantoins with *p*-tolyllead triacetate as a arylating source (Scheme 4.3) [33]. A series of amidic and imidic nitrogen sources such as phthalimides, sulfonamides, and

carboxylic acid imides were employed in this study and one example of hydantoin was explored too.



Scheme 4.3 *N*-arylation with aryl lead reagents

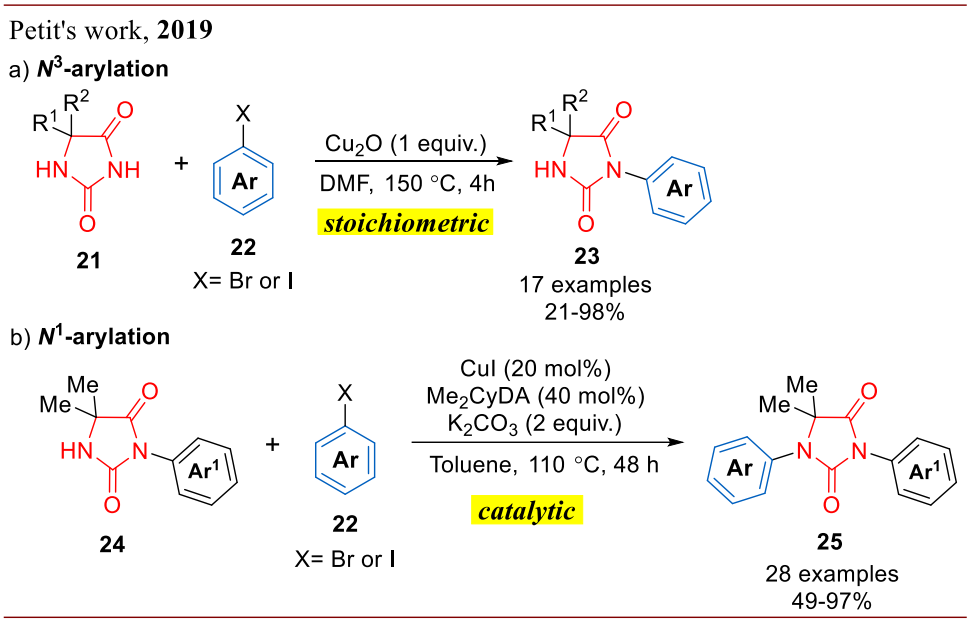
Subsequently, many arylation methodologies were developed with other arylating precursors such as triarylbismuthanes, arylboronic acids and aryl iodides under both Cu-mediated and copper-catalytic protocols. In 2006, Hügel and co-workers introduced a common copper-mediated approach with triarylbismuthanes and arylboronic acids (Scheme 4.4) [32]. The protocols utilized excess amount of arylating precursors and the arylation step required much longer reaction duration affording poor to moderate yields.



Scheme 4.4 N^3-arylation methods with triarylbismuthanes and arylboronic acids

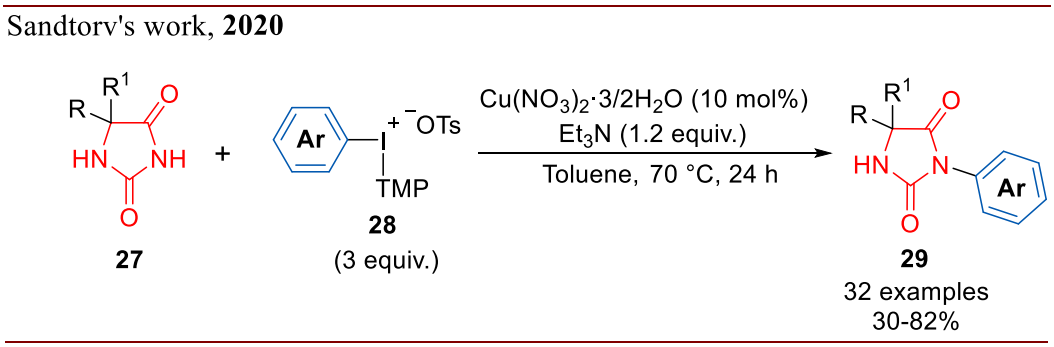
Aryl halides, another arylating source was extensively utilized in the synthesis of bio-active hydantoin scaffolds over the last decade [34-36]. Of late, Petit's group re-established aryl halides based N^3-arylation method with a Cu-mediated approach and subsequently, they developed Cu-catalysed N^1-arylayion technique of N^3-arylated hydantoins (Scheme 4.5) [37]. The methodology highlighted a broad range of substrates scope of the aryl halides and a larger scale applicabilty of the N^1-arylation condition was demonstrated. Although the method highlighted broad substrate scopes, *ortho*-substituted aryl groups failed to tolerate the reaction

condition. Also, N^3-arylation of hydantoins containing both acidic C^5–H and N^1–H exhibited poor selectivity and hence limited hydantoins were studied.



Scheme 4.5 *N*-arylations of hydantoins with aryl halides as coupling partners

Coincident to our work in this chapter, Sandtorv and co-workers published a report on Cu-catalysed N^3-arylation of hydantoin by utilising unsymmetrical iodonium salt, aryl(TMP)OTs (Scheme 4.6) [38]. In that Cu-catalysed protocol, the methodology highlighted the efficiency of regioselective arylation without epimerization at C^5- and N^1- position of hydantoins. The protocol required excess amount of iodonium salts and trace amounts of both N^1-regiomer and N^1,N^3-biarylated side products were observed. Wide ranges of both hydantoin derivatives and functionalized aryl groups were studied under the protocol; however, highly congested *ortho*-substituents were not mentioned.



Scheme 4.6 N^3-arylation with unsymmetrical TMP-iodonium salts

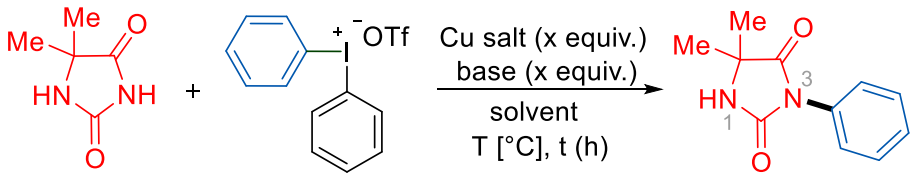
Considering the limitations of existing methodologies for the arylation of hydantoins (excluding Sandtorv's work, as this particular report was not known in the literature when we started our objective for *N*-arylation of hydantoins), this chapter aimed to search a methodology for the *N*-arylation (both N^1- and N^3-) of hydantoins with diaryliodonium salts as the arylating partner. In addition, the major objective of this chapter to emphasize on extension of scope of the aryl substrates (from diaryliodonium salts) possessing electronically and sterically diverse functional groups.

4.2 Optimization

4.2.1 Initial screening of the reaction conditions

We embarked the initial optimisation of the reaction conditions employing 5,5-dimethylhydantoin (**30a**) as the model hydantoin substrate and diphenyliodonium triflate (**31a-OTf**) as the aryl precursor (Table 4.1). No arylation was observed under base-mediated condition (metal-free arylation conditions) (entries 1-9). The first positive indication of arylation was obtained when the reaction was conducted utilising stoichiometric amount of CuI and Na_2CO_3 (1 equiv.) at room temperature (30 °C) affording the desired product (**32a**) in 74% yield (entry 10). The *N*-arylation step was regio-selective (as confirmed by ^{1}H NMR analysis) and occured at the N^3-position of the hydantoin without showing any N^1-arylated and N^1,N^3-diarylated side products. Decreasing the amount of CuI to a catalytic scale (entry 11) took a longer reaction duration and the yield came down to 45%.

Table 4.1 Optimization with diphenyliodonium triflate 31a-OTf[a]



30a **31a-OTf** **32a**

Entry	30a (equiv.)	31a-OTf (equiv.)	solvent	base (equiv.)	Cu (equiv.)	T (°C)	t (h)	yield[b] (%)
1	1	1	Toluene	-	-	rt	24	ND
2	1	1	Toluene	-	-	110	24	ND
3	1	1	Toluene	Na_2CO_3 (1.0)	-	110	48	ND

4	1	1	Toluene	Cs_2CO_3 (1.0)	-	110	24	ND
5	1	1	Toluene	NaH (1.0)	-	110	24	ND
6	1	1	Toluene	NaOH (1.0)	-	110	24	ND
7	1	1	Toluene	KO^{t}Bu (1.0)	-	110	24	ND
8	1	1	Toluene	DABCO (1.0)	-	110	24	ND
9	1	1	Toluene	Et_3N (1.0)	-	110	24	ND
10	**1**	**1**	**DCE**	**Na_2CO_3 (1.0)**	**CuI (1.0)**	**rt**	**5**	**74 (76)[c]**
11	1	1.2	DCE	Na_2CO_3 (1.0)	CuI (0.2)	rt	24	45 (51)[d]
12	1	1.5	DCE	Na_2CO_3 (2)	CuI (0.2)	rt	24	54

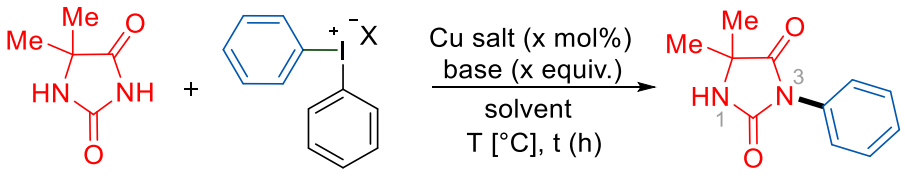
[a]Reaction conditions: Diphenyliodonium salt **31a-OTf** (0.2 mmol), hydantoin **30a** (0.2 mmol), base and copper sources were added into a Schlenk tube. Anhydrous and degassed toluene (2 mL) was added. Anhydrous DCE was used (2 mL). [b]Isolated yield. [c]1.2 equiv. Of **31a-OTf**. [d]80 °C. ND i.e., not detected.

4.2.2 Further optimization of catalytic conditions

Different types of bases and solvents were screened to optimize the reaction conditions for the best catalytic conditions. Moreover, various copper salts and diphenyliodonium salts having various counter-anions were checked too (Table 4.2). Surprisingly, utilizing K_3PO_4 as base, the reaction conditions delivered comparitively higher yield (77%) of **32a** (entry 4) and the reaction completion required shorter time. The yield of **32a** did not show any variation while changing equivalents of **30a** and **31a-OTf** (entries 6-7). Similarly, by increasing the equivalents of base (K_3PO_4), we mostly observed decomposition of **31a-OTf** and lower yield of product formation (45%) was noticed (entry 8). Furthermore, the optimization for bases and solvents was examined; but yield of **32a** did not improve and instead, other side products were observed (entries 9-16). Both Cu^I and Cu^{II} catalysts such as $Cu(OTf)_2$, $Cu(OAc)_2$, CuCl etc. were evaluated, but CuI was found to be the superior catalyst (entries 17-21). Finally, the impact of anion in iodonium salts was optimised; where

tetraflouroborate salt showed better yield in comparison to other salts (entries 22-25).

Table 4.2 Further optimization[a]



30a **31a-X** **32a**

Entry	30a/31a-X (equiv.)	X	Solvent	Base (equiv.)	Cu (x mol%)	T (°C)	t (h)	Yield[b] (%)
1	1/1.2	OTf	DCE	Cs_2CO_3 (1)	CuI (20)	50	24	34
2	1/1.2	OTf	DCE	K_3PO_4 (1.0)	CuI (20)	50	24	72
3	1/1.2	OTf	DCE	K_3PO_4 (1.0)	CuI (20)	rt	24	76
4	**1/1.2**	**OTf**	**DCE**	**K_3PO_4 (1.0)**	**CuI (20)**	**rt**	**5**	**77**
5	1/1.2	OTf	DCE	no base	CuI (20)	rt	24	ND
6	1/**1.5**	OTf	DCE	K_3PO_4 (1.0)	CuI (20)	rt	5	76
7	1.5/1	OTf	DCE	K_3PO_4 (1.0)	CuI (20)	rt	5	42
8	1/1.2	OTf	DCE	K_3PO_4 (**1.5**)	CuI (20)	rt	5	45
9	1/1.2	OTf	DCE	NaH (1.2)	CuI (20)	rt	24	23
10	1/1.2	OTf	DCE	KO^{t}Bu (1.0)	CuI (20)	RT	5	trace
11	1/1.2	OTf	DCE	DABCO (1.0)	CuI (20)	rt	24	ND
12	1/1.2	OTf	DCE	Et_3N (1.0)	CuI (20)	rt	24	trace
13	1/1.2	OTf	Toluene	K_3PO_4 (1.0)	CuI (20)	rt	24	44
14	1/1.2	OTf	DMF	K_3PO_4 (1.0)	CuI (20)	rt	12	23
15	1/1.2	OTf	DMSO	K_3PO_4 (1.0)	CuI (20)	rt	24	ND

16	1/1.2	OTf	ACN	K_3PO_4 (1.0)	CuI (20)	rt	18	54
17	1/1.2	OTf	DCE	K_3PO_4 (1.0)	CuI (10)	rt	12	52
18	1/1.2	OTf	DCE	K_3PO_4 (1.0)	CuCl (20)	rt	12	65
19	1/1.2	OTf	DCE	K_3PO_4 (1.0)	$Cu(OTf)_2$ (20)	rt	5	trace
20	1/1.2	OTf	DCE	K_3PO_4 (1.0)	Cu_2O (20)	rt	5	56
21	1/1.2	OTf	DCE	K_3PO_4 (1.0)	$Cu(OAc)_2$ (20)	rt	5	trace
22	1/1.2	BF_4	DCE	K_3PO_4 (1.0)	CuI (20)	rt	5	67
23	1/1.2	OTs	DCE	K_3PO_4 (1.0)	CuI (20)	rt	5	ND
24	1/1.2	Br	DCE	K_3PO_4 (1.0)	CuI (20)	rt	5	34
25	1/1.2	TFA	DCE	K_3PO_4 (1.0)	CuI (20)	rt	5	trace

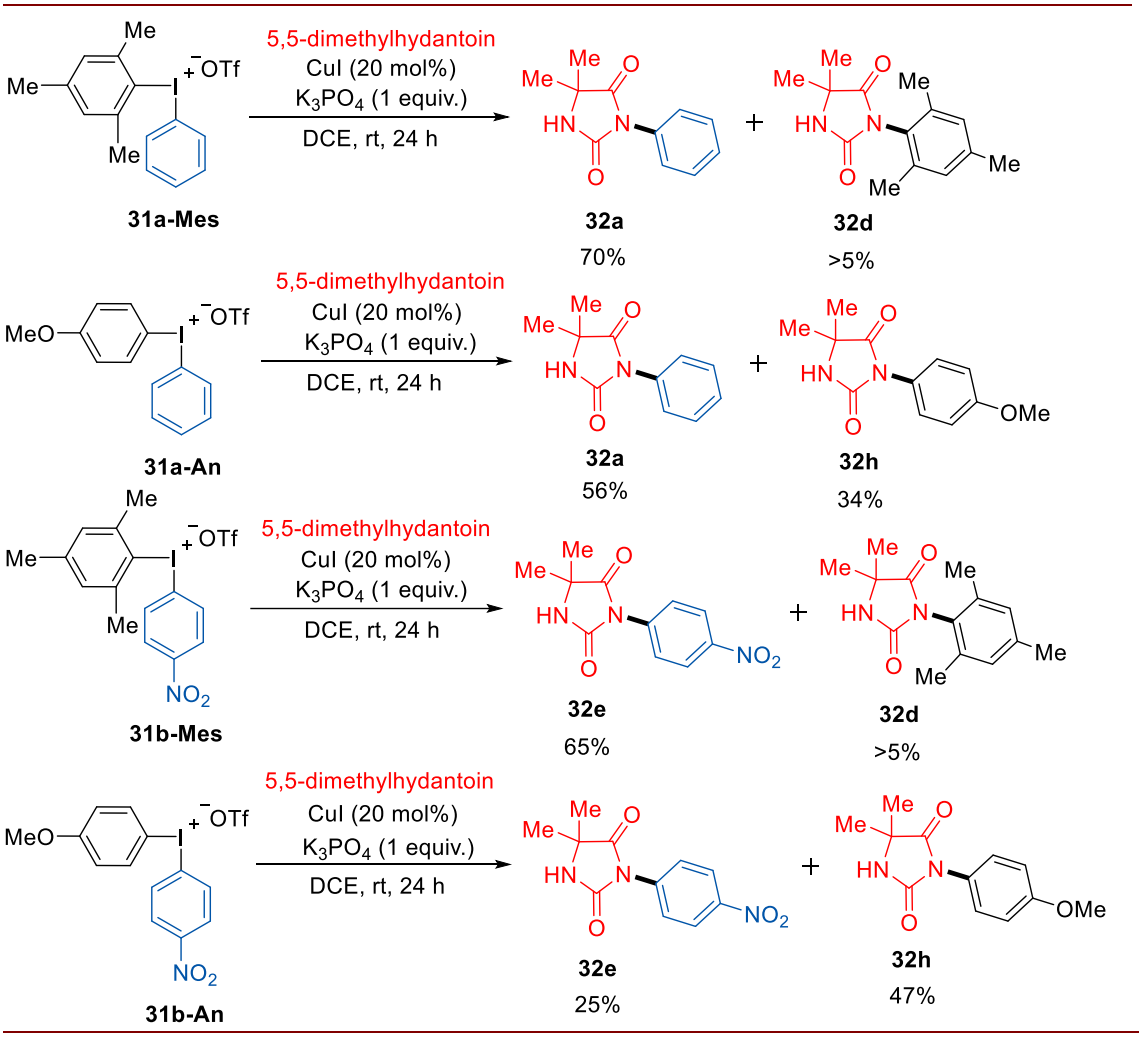
[a]Reaction conditions: Hydantoin **30a** (0.2 mmol), diphenyliodonium salt **31a-X** (0.2 mmol), base (x equiv) and copper salt (x equiv.) were added into a Schlenk tube. [b]Isolated yield.

Synthetic routes for iodonium salts vary depeding on the counter-anions, therefore; information of the compatible counter-anion for the reaction condition is very much necessary prior to establishing substrate scope of iodonium salts. Other anions (BF_4, OTs, Br and TFA) were also investigated. Iodonium salts with –BF_4 and –Br counter-anion showed the formation of **32a**, but the yield of product formation was lesser than –OTf salt. In case of -OTs iodonium salt, *O*-arylation at the tosyl group was primarily observed which is contrary to Sandtorv's work [38]. Although, *O*-arylation is possible with iodonium salt having -OTs anion in some cases [40], but -OTs acts as non-interferring counter anion in many metal-free and metal-catalyzed arylation reactions [41]. In this chapter, Cu-catalysed version of *N*-arylation of hydantoins was achieved because of the lesser nucleophilicity of diaryliodonium triflate.

4.2.3 Chemoselective study of unsymmetrical iodonium salts

Chemoselectivity of the iodonium salts with the optimized reaction conditions is very necessary before planning the scope of iodonium salts having both electron donating and electron withdrawing groups (as discussed in chapter 1) [42]. In general,

symmetrical iodonium salts show no chemoselectivity problem and one of the aryl groups easily participates in the arylation reaction. But in case of the unsymmetrical iodonium salts, both aryl groups have possibility to undergo arylation and selective arylation is not easily feasible. Good atom economy of the reaction can be considered only when one aryl group exclusively takes part in arylation and the other aryl group leaves as "dummy" iodoarene. According to previous literature, unsymmetrical aryl(Mes)iodonium salts were employed as effective choice under copper-catalyzed reactions and mesityl group behaved as an excellent dummy group.



Scheme 4.7 Chemoselectivity pattern of the unsymmetrical iodonium salts

The chemoselectivity study (Scheme 4.7) was performed under optimised reaction condition between hydantoin (**30a**) and four selected auxiliary-iodonium salts (**31a-Mes**, **31a-An**, **31b-Mes** and **31b-An**). The model reaction selected was phenylation and 4-nitrophenylation from iodonium salts with anisyl- and mesityl- auxiliaries.

Mixture of products was observed in the case of anisyl-iodonium salts (**31a-An** and **31b-An**) and the electron-deficient group relative to anisyl was found to get transferred to furnish **32a** and **32e**, as the major product. In comparison to anisyl as dummy ligand, mesityl containing iodonium salts showed higher selectivity in both the cases (**31a-Mes** and **31b-Mes**). The observed trend matches with previous studies under metal-catalyzed conditions which implies "mesityl" is more reliable as dummy group due to steric factor.

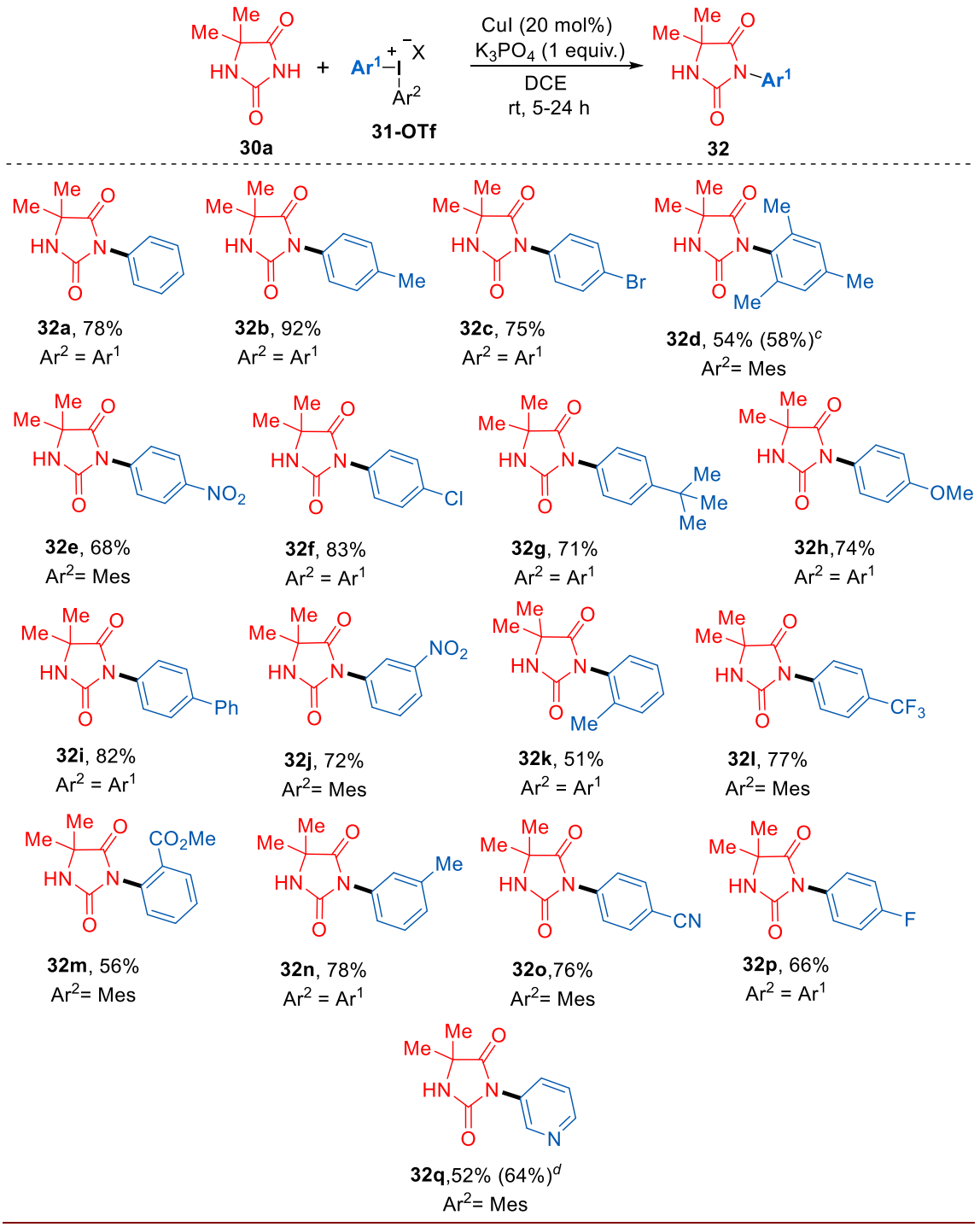
4.3 *N*^{3}-arylation of hydantoins

4.3.1 Scope of diaryliodonium salts

With the optimized reaction conditions and chemoselective studies in hand, the scope of the Cu-catalysed *N*^{3}-arylation of hydantoins was studied (Table 4.3). Various symmetrical and unsymmetrical iodonium salts were employed as the coupling partner. The use of 5,5-dimethylhydantoin (**30a**) and diaryliodonium salts containing electron-donating, electron-withdrawing and electron-neutral groups afforded the desired products (**32a-32q**) in moderate to good yields. Halide substituents such as –F, –Cl and –Br were easily transferred from its corresponding symmetrical iodonium salts and products **32c**, **32f** and **32p** were obtained in good yields in less than 10 hrs, which is a rather difficult to accomplish in metal-catalysed reactions with other aryl sources [43]. *Ortho*-substituted groups such as mesityl, –Me, and –CO_2Me were found to be well tolerated under this protocol and furnished the products **32d**, **32k** and **32m**. As found in chemoselectivity study, electron-withdrawing groups such as –NO_2, –CF_3, –CO_2Me and –CN was selectively transferred to the hydantoin core affording **32e**, **32l**, **32m** and **32o** respectively in moderate yields. Similarly, bis-(*tert*-butyl(phenyl)iodonium) salt, **32g** underwent arylation at room temperature, though it took longer time for completion of the reaction. Very few reports are found on the transfer of electron-donating groups to hydantoins in metal-catalysed reaction with aryl halides; but, in our protocol a *p*-methoxyphenyl group, **32h** is easily used as the arylating partner from bis-(4-methoxyphenyl)iodonium salt, in 74% yield. Biphenyl group from (biphenyl)mesityl iodonium salt was also selectively induced in the hydantoin core, **32i** with excellent yields. **32j** and **32n** are the examples for *meta*-substituted hydantoins from mesityl-(3-nitrolphenyl)iodonium triflate (**31o-Mes**) and bis-(3-methylphentyl)iodonium

tertrafluoroborate (**31k-BF$_4$**), respectively. Heterocyclic moiety containing iodonium salts were also employed in this protocol and pyridine ring containing **32q** was isolated along with the formation of **32d** as side product.

Table 4.3 Application of diverse symmetrical and aryl(Mes)iodonium salts[a,b]

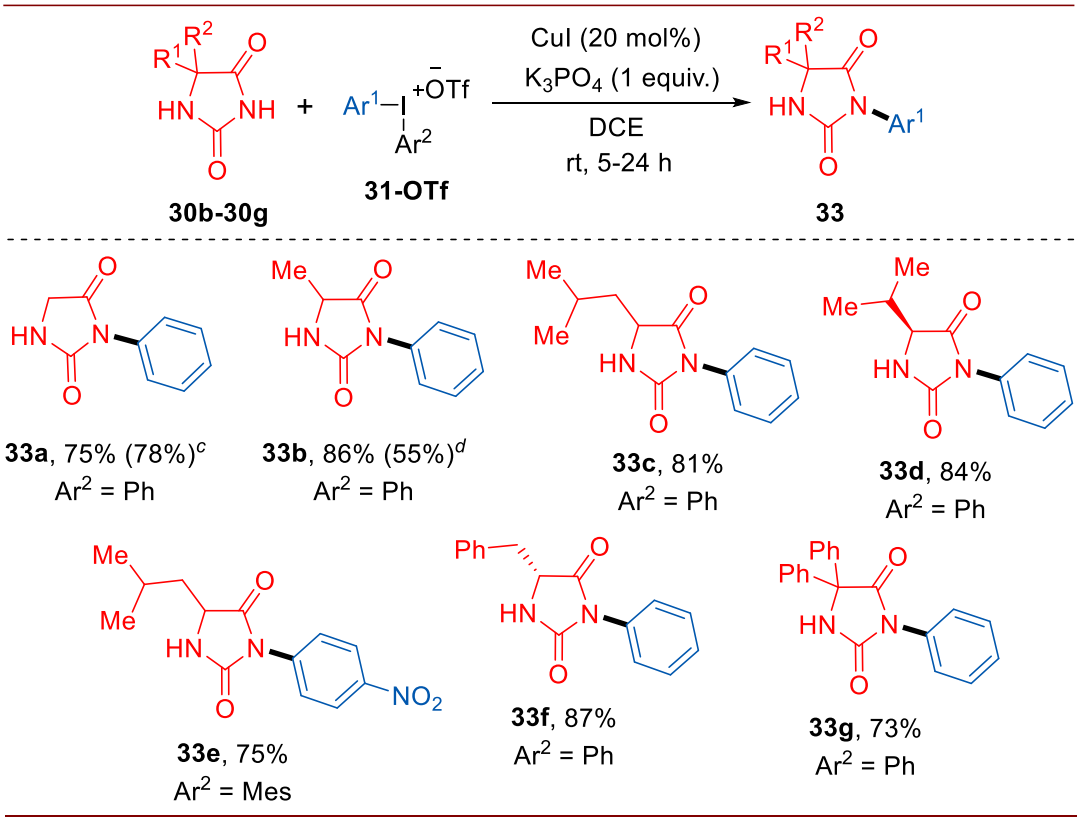


[a]Reaction conditions: 5,5-dimethylhydantoin **30a** (0.25 mmol), iodonium salt **31-OTf** (0.3 mmol), CuI (20 mol%), K_3PO_4 (0.25 mmol), DCE (0.1 M). [b]Isolated yields. [c]2 equiv. of iodonium salt. [d]80 °C.

4.3.2 Scope of hydantoins

After conducting the arylation scope with diaryliodonium salts, the scope of the reaction was first examined for the arylation of hydantoins with iodonium salt (**31a-OTf**) (Table 4.4). Simple hydantoin (**30a**) was arylated selectively at N^3-position without showing any traces of by-product(s). Presence of one α-hydrogen in compounds (**33a-33f**) did not hinder the selective arylation at N^3-position of these hydantoins without showing any mixture of C^5- and N^1-arylation. Alanine-derived hydantoin, **33b** was less reactive than other bulky amino acid-derived hydantoins (**33c** and **33d**). Nitro-phenylation of leucine-derived hydantoin **33e** also showed good conversion (75% isolated yield) and we successfully observed regioselective arylation. D-valine (**33d**) and L-phenylalanine derived hydantoin (**33f**) reacted without affecting the chirality yielding 84% and 87%, respectively. Bulky hydantoin (**33g**) also tolerated the reaction condition and showed arylation in a similar pattern.

Table 4.4 Application of substituted hydantions[a,b]



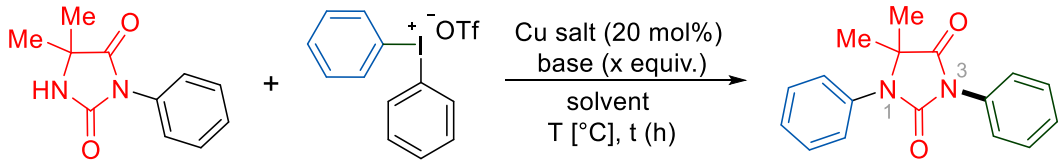
[a]Reaction conditions: 5-substituted-hydantoin **30b-30g** (0.25 mmol), iodonium salt **31-OTf** (0.3 mmol), CuI (20 mol%) and K_3PO_4 (0.25 mmol) in DCE (0.1 M). [b]Isolated yields. [c]2 equiv. of **31a-OTf**. [d]2 equiv. of **30b**.

4.4 N^1-Arylation of hydantoins with diaryliodonium salts

4.4.1 Optimization of the reaction conditions

After the comprehensive study on N^3-arylation of hydantoins, we next focused on a more challenging aspect, i.e. N^1-arylation of the hydantoin moiety [44]. The initial attempt to obtain N^1,N^3-arylated product was one-pot double arylation from **31a-OTf** by utilising the eliminated aryl iodide under Ullmann-type coupling. The strategy was screened in presence of ligand and elevated temperature, but the reaction didn't proceed beyond N^3-arylation and the eliminated iodobenzene from **31a-OTf** remained unreacted. Later, a step-wise manner was planned using the N^3-phenylated hydantoin (**32a**) as starting compound for the N^1-arylation (Table 4.5). However, yield of the reaction was low with DCE as solvent. Temperature and solvents were optimized further for the reaction between **32a** and **31a-OTf**, while keeping other parameters constant. Gratifyingly, 1,4-dioxane exhibited better yield of **34a** (82%) at room temperature and K_3PO_4 still remained best choice of base. Other Cu^I and Cu^{II} sources and different bases were tested too, but the yield did not improve.

Table 4.5 Optimization for N^1-arylation with N^3-phenyl-5,5-dimethyl-hydantoin (33a)[a]



32a **31a-OTf** **34a**

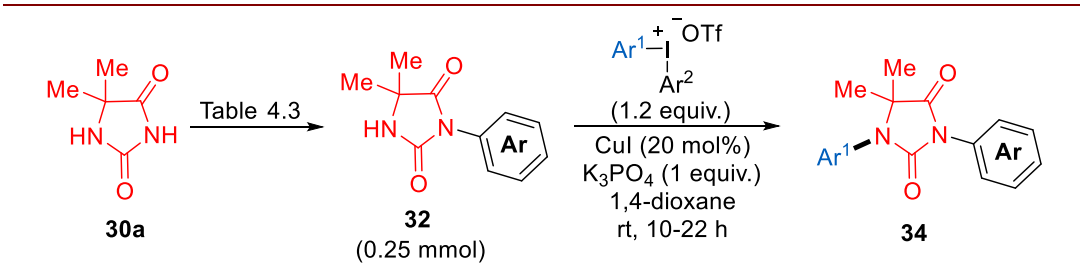
Entry	Cu salt	base	solvent	T (°C)	t (h)	yield[b] (%)
1	CuI	K_3PO_4	DCE	rt	10	54
2	CuI	K_3PO_4	DCE	80	8	58
3	**CuI**	**K_3PO_4**	**1,4-dioxane**	**rt**	**12**	**82**
4	CuI	*t*-BuOK	1,4-dioxane	rt	48	trace
5	$Cu(OTf)_2$	K_3PO_4	1,4-dioxane	rt	48	trace
6	CuI	Et_3N	1,4-dioxane	rt	12	36
7	$Cu(OTf)_2$	Et_3N	1,4-dioxane	rt	48	ND

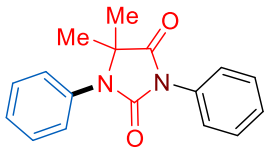
[a]Reaction conditions: All reactions were performed with **32a** (0.2 mmol), **31a-OTf** (0.3 mmol), Cu (20 mol%), base (1 equiv.), and solvent (0.1 M). [b]Isolated yields.

4.4.2 Substrate scope

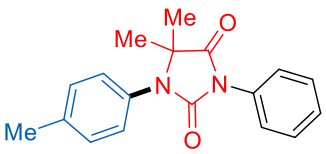
The synthesis of N^1,N^3-arylated compounds (**34a-34j)** proceeded smoothly under the optimized condition in moderate to good yields (Table 4.6). Symmetrical iodonium salts containing electron-neutral (**34a**, **34f** and **34h**), and weakly electron-donating and electron-withdrawing (**34b**, **34d**, **34e**, **34g** and **34j**) groups were discussed in this study. In addition, unsymmetrical iodonium salts containing electron-deficient groups (**34c** and **34i**) were easily tolerated with the methodology.

Table 4.6 Application of diverse symmetrical and aryl(Mes)iodonium salts[a,b]

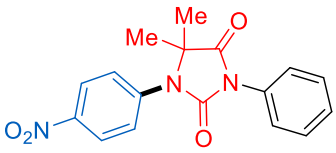




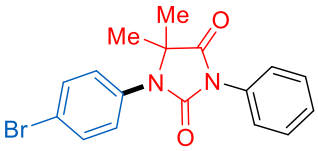
34a, 82%
$Ar^2 = Ar^1$



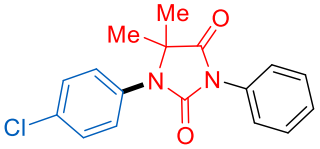
34b, 90%
$Ar^2 = Ar^1$



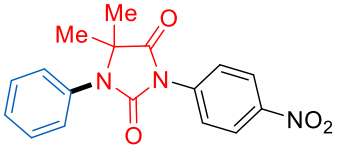
34c, 68%
Ar^2= Mes



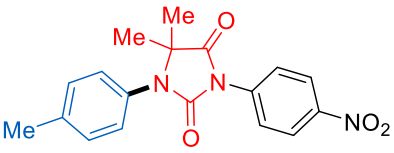
34d, 78%
$Ar^2 = Ar^1$



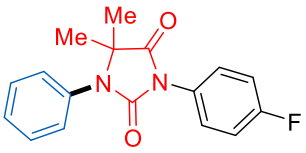
34e, 82%
$Ar^2 = Ar^1$



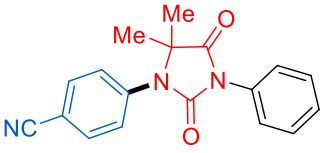
34f, 77%
$Ar^2 = Ar^1$



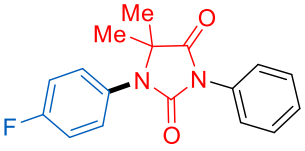
34g, 84%
$Ar^2 = Ar^1$



34h, 54%
$Ar^2 = Ar^1$



34i, 62%
Ar^2= Mes



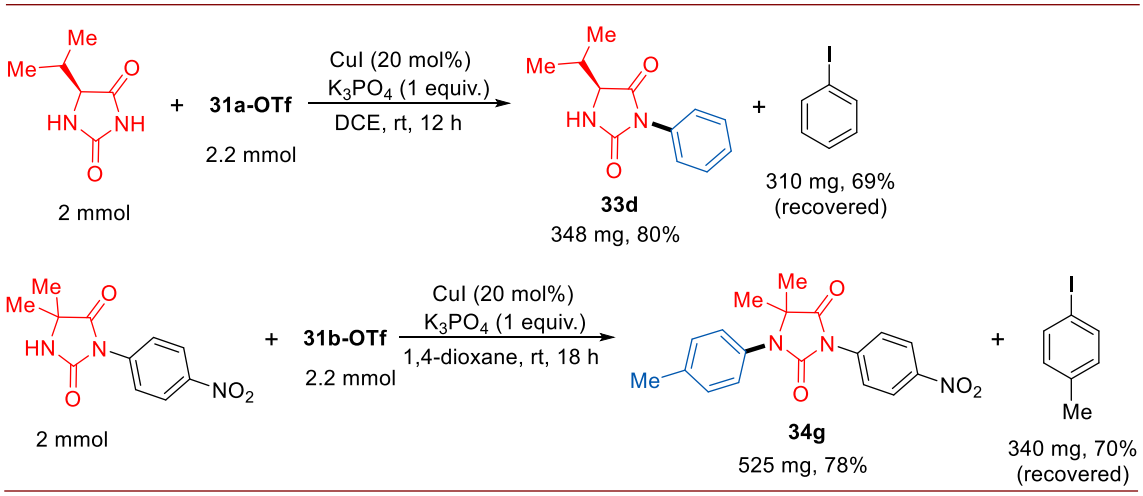
34j, 68%
$Ar^2 = Ar^1$

[a]Reaction conditions: 3-aryl-5,5-dimethylhydantoin **32** (0.25 mmol), iodonium salt (0.3 mmol), CuI (20 mol%) and K_3PO_4 (0.25 mmol) in 1,4-dioxane (0.1 M). [b]Isolated yields.

Hereby, we demonstrated *N*-arylations and their wide scope on both the nitrogen atoms of the hydantoin motif.

4.5 Scalability of the protocol

The protocol was extended successfully to a larger scale (Scheme 4.8) for **33d** and **34g** showcasing the gram-scale applicability of this method. In both cases, the eliminated aryl iodide after *N*-arylation from its corresponding symmetrical iodonium salts were recovered and utilized in the next-batch synthesis of iodonium salts.

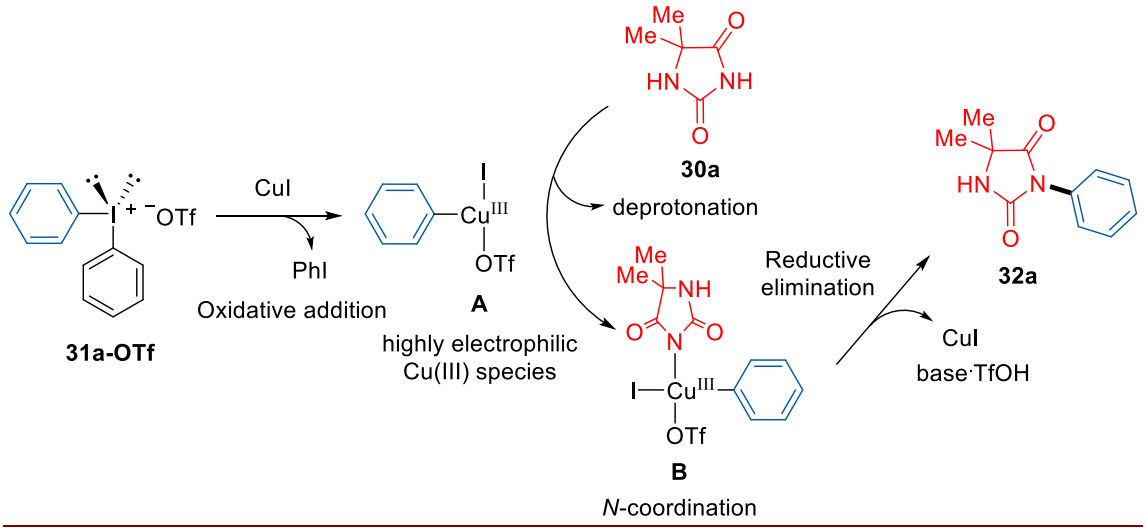


Scheme 4.8 Larger-scale synthesis of **33d** and **34g**

4.6 Plausible mechanism of the reaction

To gain mechanistic insight of the reaction, the model reaction of the work was performed in the presence of 2 equiv. of TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) as a radical scavenger. In that condition, the N^3-arylated product was obtained in 65% yield which indicated that radical pathway of the reaction was not more likely [45]. The plausble mechanism of the *N*-arylation reaction can be expected to begin with reaction between the copper(I) catalyst and the diaryliodonium salt to generate species **A** (Scheme 4.9). Ph–Cu(III) species **A**, a highly electrophilic copper centre is generated after the oxidative addition of iodonium salts to CuI. The N^3-atom of the hydantoin undergoes co-oridination with the species **A** and forms species **B**, from which reductive elimination delivers the arylated product, while making the copper source available for the next cycle. The mechanism for the arylation of the N^1-position can also be proposed in the same line. This similar pattern of mechanism can be found

in the literature for the known arylation reaction of carbon and heteroatomic nucleophile with diaryliodonium salts [46].



Scheme 4.9 Plausible mechanism for the formation of **32a**

4.7 Summary of the chapter

In conclusion, this chapter demostrated a mild and robust Cu-catalyzed *N*-arylation of hydantoins at room temperature with diaryliodonium salts. Broad substrate scopes of hydantoins was achieved for N^3-arylation including chiral hydantoins. The protocol delivered moderate to good yields of *N*-arylated hydantoins. Electron-neutral, electron-donating and electron-withdrawing groups from both symmetrical and unsymmetrical iodonium salts worked well under the method. *Ortho*-substituted arylating partners were employed too and successful transformation with moderate yields was obtained. Our methodology was also extended to N^1-arylation and substantial scopes of diaryliodonium salts were discussed. We believe this methodology could be of interest to organic chemists and afford many medicinally active scaffolds.

4.8 Experimental section

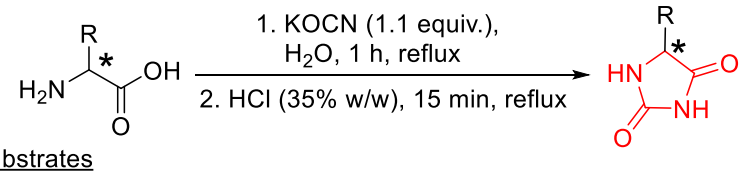
All reactions were performed in oven-dried Schlenk-tubes or round bottom flasks under nitrogen condition, unless otherwise stated. Dichloromethane (DCM), dichloroethane (DCE) and acetonitrile (ACN) were dried by refluxing over CaH_2 under nitrogen condition and stored over 4 Å molecular sieves. Toluene and 1,4-dioxane were dried utilising conventional drying procedures using sodium/

benzophenone as indicator and stored over 4 Å molecular sieves. All chemicals were purchased from commercial suppliers and used as received, unless otherwise stated. NaOH, Cs_2CO_3, K_3PO_4 and KO^{t}Bu were stored in a desiccator. For experimental details, see the reference for each method used. *m*-CPBA (Aldrich, 77% active oxidant) was dried at room temperature over high vacuum for 1 hour and titrated by iodometric titration prior to use in the synthesis of diaryliodonium salts. Thin Layer Chromatography (TLC) analysis was performed on pre-coated Merck silica gel 60 F_{254} plates using UV (λ= 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 at 400 MHz 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, and app = apparent), coupling constants (in Hz) and integration. Chemical shifts for ^{19}F-NMR are given in ppm relative to monofluorobenzene (-113.15 ppm) used as internal standard. The raw data of NMR were processed by MestReNova software.

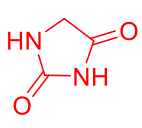
4.8.1 Synthesis of hydantoins (30b-30g)

5,5'-dimethylhydantoin (**30a**) is commercially available. Other hydantoins (**30b–30f**) are known compounds and were prepared by method 1 [47] and compound **30g** was prepared by method 2 [48] according to literature procedure.

Method 1: From amino acids

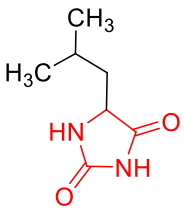


Synthesized substrates

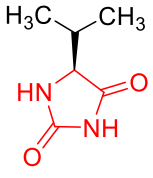


30b

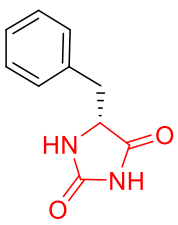
30c



30d

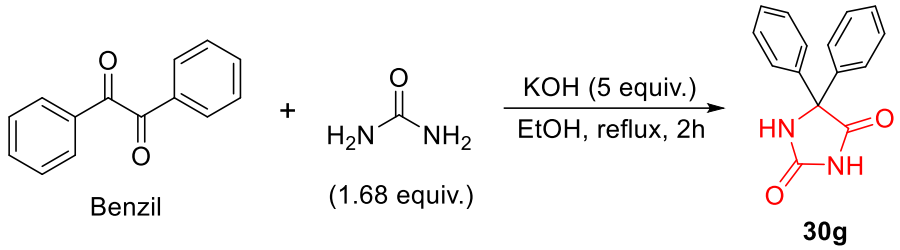


30e



30f

Method 2: For synthesis of 5,5-diphenylhydantoin

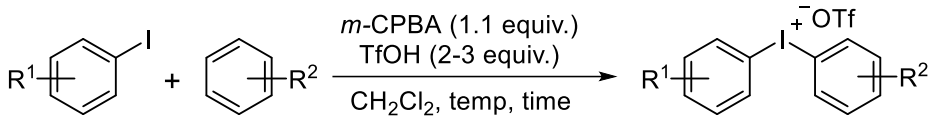


4.8.2 Synthesis of diaryliodonium salts

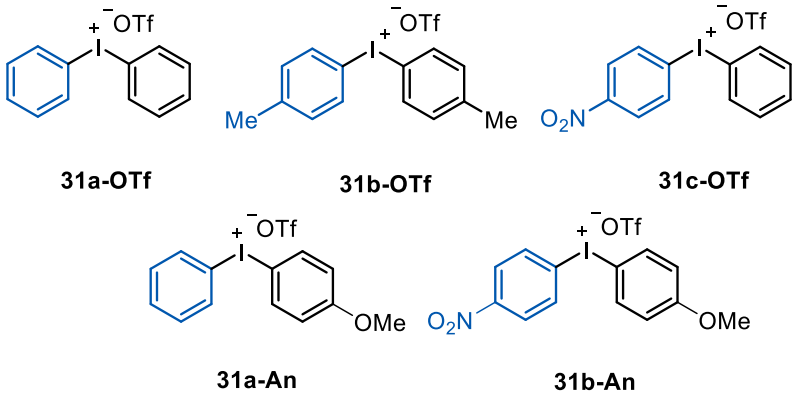
All the diaryliodonium salts are previously well-explored and the analytical data (especially ^{1}H NMR spectroscopy) of the synthesized diaryliodonium salts in this work were matched with literature (Table 4.7).

Table 4.7 Synthesized diaryliodonium salts in this chapter

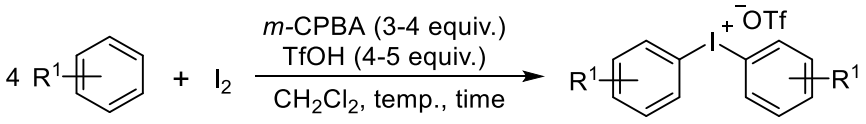
Method I [71, chapter 1]



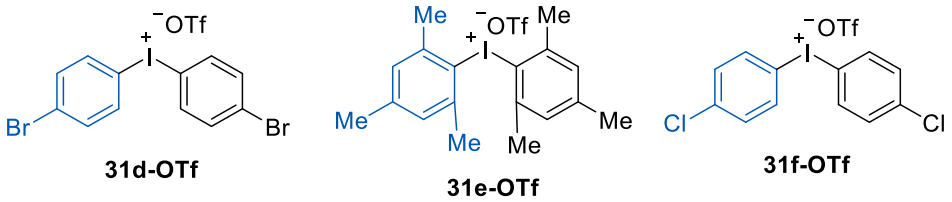
Synthesized diaryliodonium salts:

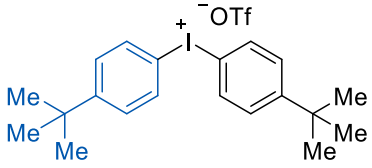


Method II [72, chapter 1]

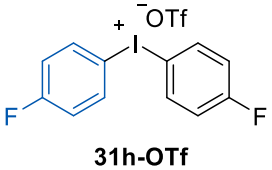


Synthesized diaryliodonium salts:



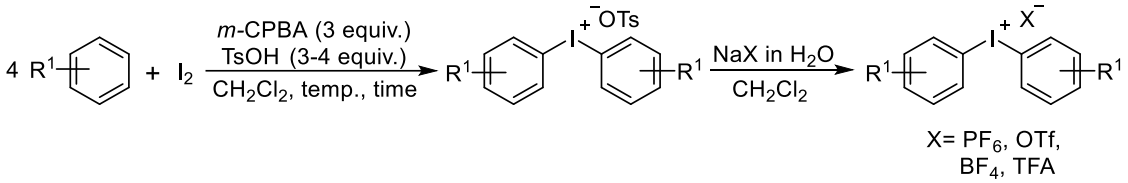


31g-OTf

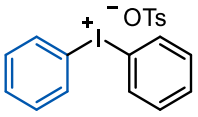


31h-OTf

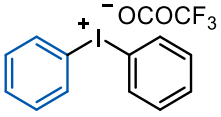
Method III [73, chapter 1]



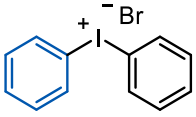
Synthesized diaryliodonium salts:



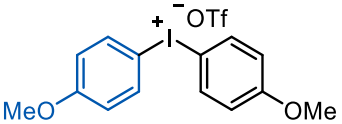
31a-OTs



31a-TFA

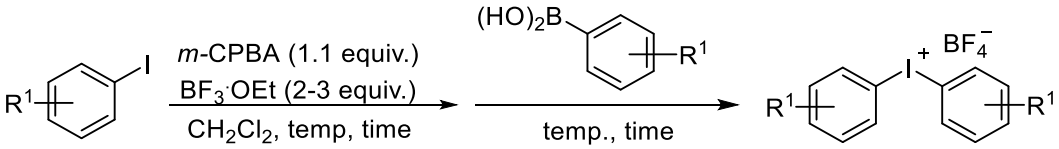


31a-TFA

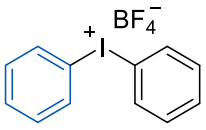


31c-An

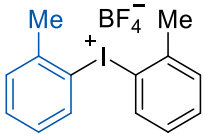
Method IV [74, chapter 1]



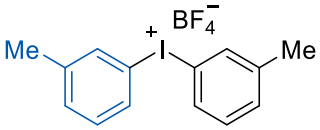
Synthesized diaryliodonium salts:



31a-BF$_4$

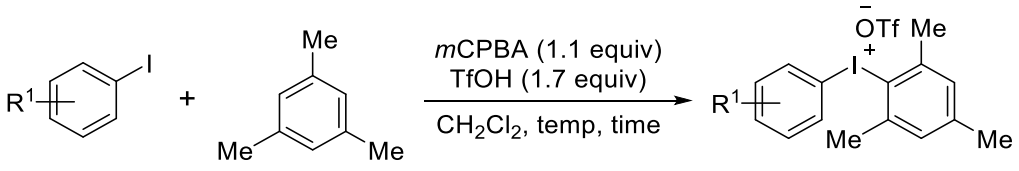


31b-BF$_4$

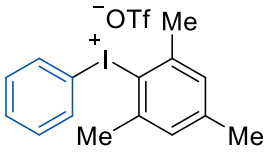


31c-BF$_4$

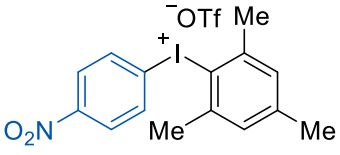
Method V [65, chapter 1]



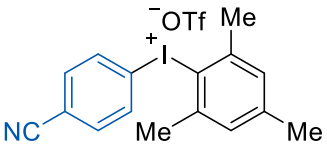
Synthesized diaryliodonium salts:



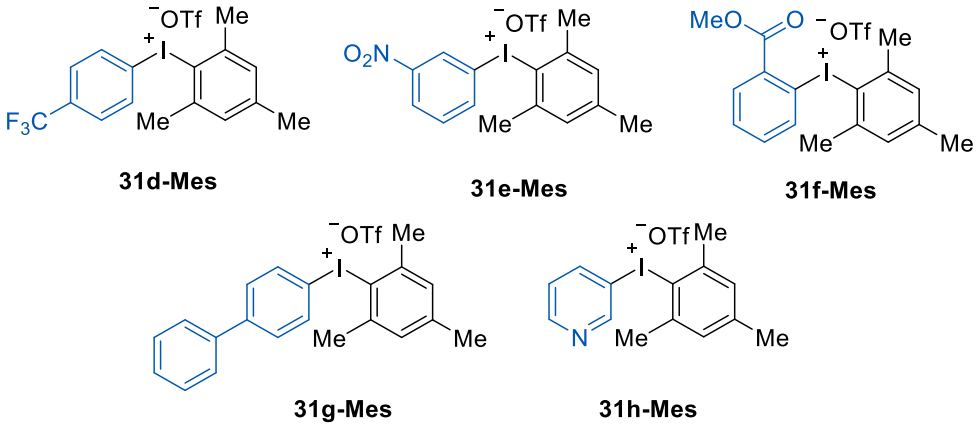
31a-Mes



31b-Mes

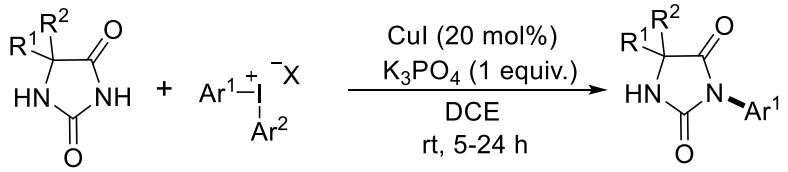


31c-Mes



4.9 Synthetic procedures and characterization data for the products

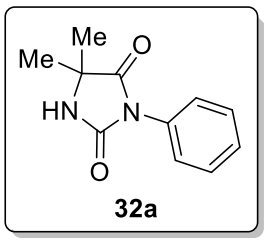
4.9.1 General procedure A (GP-A): *N*^{3}-arylation of hydantoins



30(a-g) (1 equiv.) | **31-OTf** (1.2 equiv.) | **32(a-q)** or **33(a-g)**

To an oven-dried Schlenck-tube, hydantoin **30** (0.25 mmol), diaryliodonium salt **31** (0.3 mmol), CuI (50 µmol, 0.2 equiv.) and K_3PO_4 (0.25 mmol) was added under N_2 atmosphere. The tube was sealed and DCE (3 mL) was added under N_2 atmosphere. The reaction mixture was stirred at room temperature for indicated time. The reaction was filtered through celite and concentrated *in vacuo*. The crude product was purified as described.

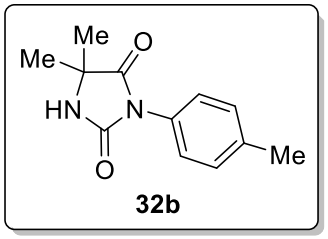
***5,5-Dimethyl-3-phenylhydantoin* (32a)** [49]



Synthesized following **GP-A** starting from *5,5*-dimethylhydantoin (**30a**) (32 mg, 0.25 mmol, 1 equiv.), diphenyliodonium triflate (**31a-OTf**) (129 mg, 0.3 mmol, 1.2 equiv.), CuI (9.5 mg, 0.05 mmol, 0.2 equiv.) and K_3PO_4 (53 mg, 0.25 mmol). The reaction mixture was stirred at room temperature for 5 h. The crude was purified by column chromatography (AcOEt/Hexane: 30/70) to afford **32a** (42 mg, 0.205 mmol, 78%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.38 (m, 2H), 7.34-7.28 (m, 3H), 6.82 (bs, 1H), 1.43 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.4, 155.7, 131.5, 128.6, 127.9, 126.1, 58.3, 25.12.

IR (ν_{max}, cm^{-1}): 3217 (b), 3101 (s), 1728 (s), 1427 (s), 1295 (s), 1148 (s), 861 (s), 765 (m), 708 (s), 604 (s). HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{11}H_{13}N_2O_2$ 205.0977; found 205.0998.

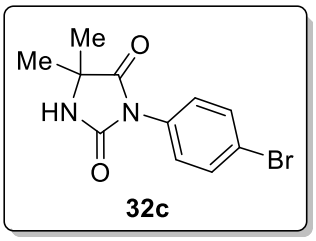
5,5-dimethyl-3-(p-tolyl)imidazolidine-2,4-dione **(32b)**



32b

Synthesized following **GP-A** starting from *5,5*-dimethylhydantoin (**30a**) (32 mg, 0.25 mmol) and bis(4-methylphenyl)iodonium triflate (**31b-OTf**) (138 mg, 0.30 mmol). The reaction was stirred for 7 h. The reaction mixture was purified by column chromatography (AcOEt/Hexane: 20/80) to afford **32b** (49 mg, 0.225 mmol, 92%) as a light-yellow solid. ^1H NMR (400 MHz, $CDCl_3$): δ 7.19 (s, 4H), 6.84 (bs, 1H), 2.30 (s, 3H), 1.42 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.7, 156.4, 138.5, 129.9, 129.1, 126.1, 58.9, 25,1, 21.3. IR (ν_{max}, cm^{-1}): 3217 (b), 2911 (m), 1720 (s), 1421 (s), 1387 (s), 1260 (s), 818 (s), 792 (s). HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{15}N_2O_2$ 219.1134; found 219.1159.

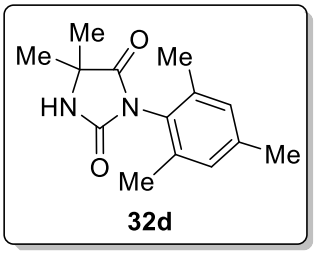
3-(4-bromophenyl)-5,5-dimethylimidazolidine-2,4-dione **(32c)**



32c

Synthesized following **GP-A** starting from *5,5*-dimethylhydantoin (**30a**) (32 mg, 0.25 mmol) and bis(4-bromophenyl)iodonium triflate (**31d-OTf**) (176 mg, 0.30 mmol). The reaction was stirred for 12 h. The reaction mixture was purified by column chromatography (AcOEt/Hexane: 20/80) to afford **32c** (53 mg, 0.187 mmol, 75%) as a brown solid. ^1H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, J = 8 Hz, 2H), 7.26 (d, J = 8 Hz, 2H), 6.82 (bs, 1H), 1.44 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.1, 155.6, 132.5, 130.8, 128.1, 122.3, 58.6, 25.1. IR (ν_{max}, cm^{-1}): 3241 (b), 3110 (m), 2089 (m), 2929 (s), 1706 (m), 1492 (s), 1427 (s), 821 (m), 732 (m), 604 (m). HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{11}H_{12}N_2O_2Br$ 283.0082; found 283.0091.

3-mesityl-5,5-dimethylimidazolidine-2,4-dione **(32d)**

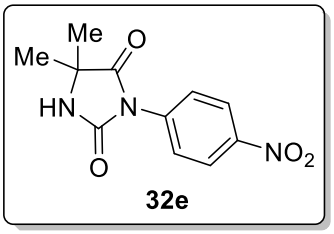


32d

Synthesized following **GP-A** starting from *5,5*-dimethylhydantoin (**30a**) (32 mg, 0.25 mmol) and bis(2,4,6-trimethylphenyl))iodonium triflate (**31e-OTf**) (154 mg, 0.30 mmol). The reaction was stirred for 16 h. The reaction mixture was purified by column chromatography (AcOEt/Hexane: 20/80) to afford **32d** (33.21 mg, 0.135 mmol, 54%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.97 (s, 2H), 6.80 (bs, 1H), 2.30 (s, 3H), 2.14 (s, 6H) 1.44 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.2, 155.5, 139.2, 136.5, 129.1, 126.4, 59.4, 25.5, 21.1, 17.4. IR (ν_{max}, cm^{-1}): 3227 (b), 3106 (m), 2918 (s), 2860 (s), 1746 (s), 1724 (s), 1603 (s), 1468 (m), 1283 (s), 1253 (s), 835 (m), 674 (s). HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{19}N_2O_2$ 247.1446; found 247.1475.

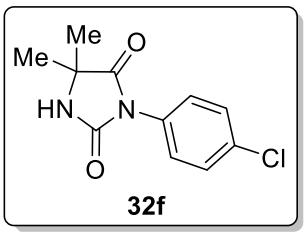
5,5-dimethyl-3-(4-nitrophenyl)imidazolidine-2,4-dione **(32e)** [37]



32e

Synthesized following **GP-A** starting from *5,5*-dimethylhydantoin (**30a**) (32 mg, 0.25 mmol) and (4-nitrophenyl)(2,4,6-trimethylphenyl)iodonium triflate (**31b-Mes**) (155 mg, 0.30 mmol). The reaction was stirred for 12 h. The reaction mixture was purified by column chromatography (AcOEt/Hexane: 30/70) to afford **32e** (43 mg, 0.172 mmol, 68%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (d, J = 8 Hz 2H), 7.77 (d, J = 8 Hz, 2H), 6.00 (bs, 1H), 1.58 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.3, 154.2, 146.4, 137.6, 125.6, 124.2, 58.6, 25.0. IR (ν_{max}, cm^{-1}): 3261 (b), 2920 (s), 2852 (s), 1731 (s), 1521 (s), 1337 (s), 1135 (s), 831 (s), 725 (s). HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{11}H_{11}N_3O_4$ 250.0822; found 250.0847.

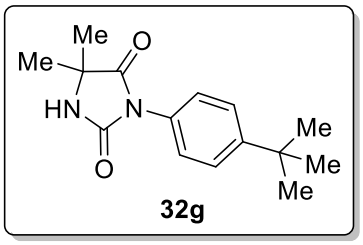
3-(4-chlorophenyl)-5,5-dimethylimidazolidine-2,4-dione **(32f)**



32f

Synthesized following **GP-A** starting from *5,5*-dimethylhydantoin (**30a**) (32 mg, 0.25 mmol) and bis(4-chlorophenyl)iodonium triflate (**31f-OTf**) (149.7 mg, 0.30 mmol). The reaction was stirred for 6 h. The reaction mixture was purified by column chromatography (AcOEt/Hexane: 20/80) to afford **32f** (49 mg, 0.205 mmol, 83%) as a brownish solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45-7.38 (m, 4H), 6.19 (bs, 1H), 1.54 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.5, 155.7, 139.2, 134.7, 130.4, 129.6, 127.7, 58.8, 25.4. IR (ν_{max}, cm^{-1}): 3298 (s), 2915 (s), 2849 (s), 1715 (s), 1497 (s), 1426 (s), 1309 (s), 1148 (s), 1089 (s), 819 (s), 740 (s). HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{11}H_{12}N_2O_2Cl$ 239.0587; found 239.0591.

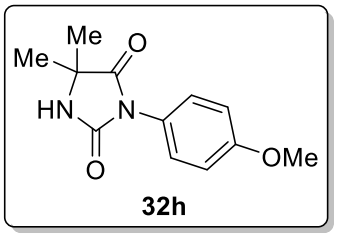
***3-(4-(tert-butyl)phenyl)-5,5-dimethylimidazolidine-2,4-dione* (32g)** [37]



32g

Synthesized following **GP-A** starting from *5,5*-dimethylhydantoin (**30a**) (32 mg, 0.25 mmol) and bis(4-*tert*-butylphenyl)iodonium triflate (**31g-OTf**) (162.72 mg, 0.30 mmol). The reaction was stirred for 24 h. The reaction mixture was purified by column chromatography (AcOEt/Hexane: 20/70) to afford **32g** (46 mg, 0.177 mmol, 71%) as a brownish solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, J = 8 Hz, 2H), 7.32 (d, J = 8 Hz, 2H), 6.71 (bs, 1H), 1.51 (s, 6H), 1.33 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.1, 156.1, 151.2, 128.5, 126.0, 58.3, 34.7, 30.9, 25.1. IR (ν_{max}, cm^{-1}): 3277 (s), 2972 (s), 1717 (s), 1528 (s), 1420 (s), 1141 (s), 846 (s). HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{21}N_2O_2$ 261.1681; found 261.1683.

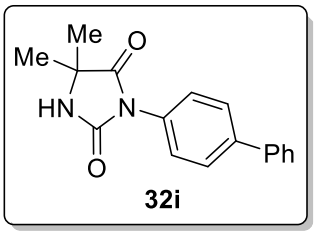
***3-(4-methoxyphenyl)-5,5-dimethylimidazolidine-2,4-dione* (32h)**



32h

Synthesized following **GP-A** starting from *5,5*-dimethylhydantoin (**30a**) (32 mg, 0.25 mmol) and bis(4-methoxyphenyl)iodonium triflate (**31c-An**) (147.06 mg, 0.30 mmol). The reaction was stirred for 8 h. The reaction mixture was purified by column chromatography (AcOEt/Hexane: 20/80) to afford **32h** (44 mg, 0.185 mmol, 74%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (d, J = 8 Hz, 2H), 6.97 (d, J = 8 Hz, 2H), 6.28 (bs, 1H), 3.28 (s, 3H), 1.55 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.5, 159.1, 155.7, 127.4, 124.0, 114.2, 58.2, 55.5, 24.8. IR (ν_{max}, cm^{-1}): 3268 (s), 2942 (s), 1731 (s), 1707 (s) 1460 (m), 1283 (s), 1228 (s), 1086 (s), 867 (m), 741 (s), 674 (s). HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{15}N_2O_3$ 235.1107; found 235.1109.

***3-([1,1'-biphenyl]-4-yl)-5,5-dimethylimidazolidine-2,4-dione* (32i)** [37]

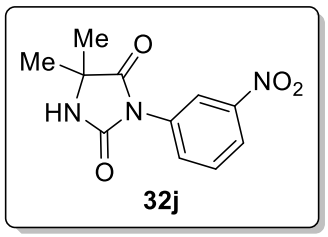


32i

Synthesized following **GP-A** starting from *5,5*-dimethylhydantoin (**30a**) (32 mg, 0.25 mmol) and (biphenyl)(2,4,6-trimethylphenyl)iodonium triflate (**31g-Mes**) (164 mg, 0.30 mmol). The reaction was stirred for 16 h. The reaction mixture was purified by column chromatography (AcOEt/Hexane: 30/70) to afford **32i** (58 mg, 0.205 mmol, 82%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 8 Hz), 7.60 (d, J = 8 Hz, 2H), 7.52-7.44 (m, 4H), 7.38 (t, J = 8 Hz, 1H), 6.75 (bs, 1H), 1.55 (s, 6H). ^{13}C NMR (100 MHz,

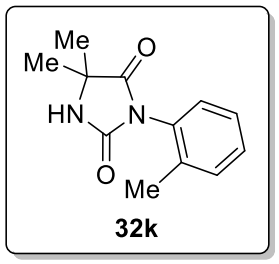
$CDCl_3$) δ 175.8, 155.1, 141, 139.3, 130.1, 128.4, 127.4, 126.7, 126, 58.4, 24.8. IR (ν_{max}, cm^{-1}): 3221 (b), 2908 (s), 1755 (s), 1489 (s), 1318 (s), 1156 (s), 810 (s), 743 (s). HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{17}H_{17}N_2O_2$ 281.1285; found 281.1308.

5,5-dimethyl-3-(3-nitrophenyl)imidazolidine-2,4-dione **(32j)**



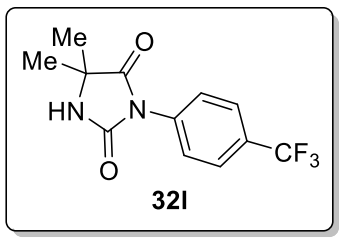
Synthesized following **GP-A** starting from *5,5*-dimethylhydantoin (**30a**) (32 mg, 0.25 mmol) and (3-nitrophenyl)(2,4,6-trimethylphenyl)iodonium triflate (**31e-Mes**) (155 mg, 0.30 mmol). The reaction was stirred for 18 h. The reaction mixture was purified by column chromatography (AcOEt/Hexane: 40/60) to afford **32j** (44 mg, 0.176 mmol, 72%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.72 (bs, 1H), 8.37 (s, 1H), 8.25 (d, *J* = 8 Hz, 1H), 7.87 (d, *J* = 8 Hz, 1H), 7.75 (d, *J* = 8 Hz, 1H), 1.43 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 176.3, 154, 148.1, 133.8, 133.4, 130.5, 122.8, 121.7, 58.1, 24.6. IR (ν_{max}, cm^{-1}): 3223 (b), 2933 (s), 1732 (s), 1509 (s), 1321 (s), 1176 (s), 866 (s), 790 (s). HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{11}H_{12}N_3O_4$ 250.9113; found 250.9121.

5,5-dimethyl-3-(o-tolyl)imidazolidine-2,4-dione **(32k)**



Synthesized following **GP-A** starting from *5,5*-dimethylhydantoin (**30a**) (32 mg, 0.25 mmol) and bis(2-methylphenyl)iodonium tetrafluoroborate (**31b-BF_4**) (118 mg, 0.30 mmol). The reaction was stirred for 12 h. The reaction mixture was purified by column chromatography (AcOEt/Hexane: 30/70) to afford **32k** (28 mg, 0.128 mmol, 51%) as a pink solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.26 (m, 4H), 7.17 (d, *J* = 8 Hz, 1H), 6.57 (bs, 1H), 2.21 (s, 3H), 1.53 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.3, 154, 148.1, 133.8, 133.4, 130.5, 122.8, 121.7, 58.1, 24.6. IR (ν_{max}, cm^{-1}): 3205 (b), 2943 (m), 1744 (s), 1440 (s), 1345 (s), 1225 (s), 867 (s), 765 (s). HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{15}N_2O_2$ 219.1128; found 219.1154.

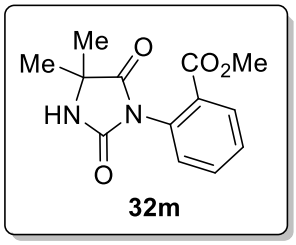
5,5-dimethyl-3-(4-(trifluoromethyl)phenyl)imidazolidine-2,4-dione **(32l)** [37]



Synthesized following **GP-A** starting from *5,5*-dimethylhydantoin (**30a**) (32 mg, 0.25 mmol) and mesityl(4-trifluoromethylphenyl)iodonium triflate (**31d-Mes**) (162 mg, 0.30 mmol). The reaction was stirred for 16 h. The reaction mixture was purified by

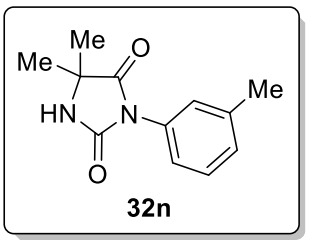
column chromatography (AcOEt/Hexane: 30/80) to afford **32l** (54 mg, 0.212 mmol, 77%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, J = 8 Hz, 2H), 7.30 (d, J = 8 Hz 2H), 6.57 (bs, 1H), 1.53 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176, 154.8, 148.8, 130.1, 127.5, 121.7, 121.6, 58.7, 25.3. ^{19}F (376 MHz, $CDCl_3$): δ -57.4. IR (ν_{max}, cm^{-1}): 3217 (b), 2949 (m), 2377 (m), 1743 (s), 1739 (s), 1408 (s), 1332 (s), 1164 (s), 1121 (s), 1038 (s), 843 (s), 713 (s). HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{13}N_2O_2F_3$ 273.1748; found 273.1756.

***Methyl 2-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)benzoate* (32m)**



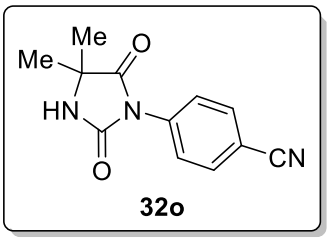
Synthesized following **GP-A** starting from *5,5*-dimethylhydantoin (**30a**) (32 mg, 0.25 mmol) and mesityl(2-(methoxycarbonyl)phenyl)iodonium triflate (**31f-OTf**) (159 mg, 0.30 mmol). The reaction was stirred for 12 h. The reaction mixture was purified by column chromatography (AcOEt/Hexane: 20/80) to afford **32m** (36 mg, 0.140 mmol, 56%) as a brown liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, J = 8 Hz, 1H), 7.68 (dt, J = 8 Hz & 1.3 Hz, 1H), 7.53 (dt, J = 8 Hz & 1.3 Hz, 1H), 7.37 (d, J = 8 Hz, 1H), 6.36 (bs, 1H), 3.85 (s, 3H), 1.53 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.3, 165.1, 155.6, 133.3, 131.6, 131.5, 130.0, 129.2, 128.0, 58.7, 52.07, 25.3. IR (ν_{max}, cm^{-1}): 3215 (b), 2918 (m), 1777 (s), 1729 (s), 1715 (s), 1434 (s), 1263 (s), 1107 (s), 710 (s), 678 (s). HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{15}N_2O_4$ 263.1026; found 263.1031.

***5,5-dimethyl-3-(m-tolyl)imidazolidine-2,4-dione* (32n)**



Synthesized following **GP-A** starting from *5,5*-dimethylhydantoin (**30a**) (32 mg, 0.25 mmol) and bis(*m*-tolyl)iodonium tetrafluoroborate (**31c-BF$_4$**) (119 mg, 0.30 mmol). The reaction was stirred for 10 h. The reaction mixture was purified by column chromatography (AcOEt/Hexane: 20/80) to afford **32n** (42 mg, 0.195 mmol, 78%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (t, J = 8 Hz, 1H), 7.22-7.20 (m, 3H), 6.33 (bs, 1H), 2.42 (s, 3H), 1.55 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.7, 156.0, 139.4, 131.4, 129.4, 129.1, 127.2, 123.4, 58.8, 25.3, 21.4. IR (ν_{max}, cm^{-1}): 3212 (b), 2955 (m), 1734 (s), 1438 (s), 1342 (s), 1228 (s), 865 (s), 769 (s). HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{15}N_2O_2$ 219.1128; found 219.1159.

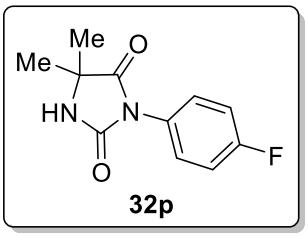
***4-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)benzonitrile* (32o)**



32o

Synthesized following **GP-A** starting from *5,5*-dimethylhydantoin (**30a**) (32 mg, 0.25 mmol) and (4-cyanophenyl)(mesityl)iodonium triflate (**31c-Mes**) (149 mg, 0.30 mmol). The reaction was stirred for 15 h. The reaction mixture was purified by column chromatography (AcOEt/Hexane: 20/80) to afford **32o** (43 mg, 0.1 mmol, 76%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, J = 8 Hz, 2H), 7.69 (d, J = 8 Hz, 2H), 6.47 (bs, 1H), 1.56 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.5, 154.4, 135.4, 132.4, 125.6, 118.2, 111.1, 58.3, 24.8. IR (ν_{max}, cm^{-1}): 3214 (b), 2948 (s), 2270 (s), 1766 (s), 1643 (s), 1532 (s), 1406 (s), 1141 (s), 894 (s), 776 (s), 684 (s). HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{12}N_3O_2$ 230.0924; found 230.0934.

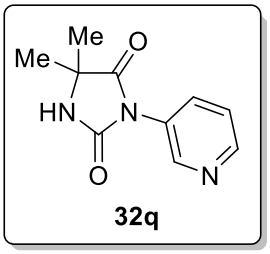
***3-(4-fluorophenyl)-5,5-dimethylimidazolidine-2,4-dione* (32p)**



32p

Synthesized following **GP-A** starting from *5,5*-dimethylhydantoin (**30a**) (32 mg, 0.25 mmol) and bis(4-fluorophenyl)iodonium triflate (**31h-OTf**) (139 mg, 0.30 mmol). The reaction was stirred for 9 h. The reaction mixture was purified by column chromatography (AcOEt/Hexane: 30/80) to afford **32p** (36 mg, 0.165 mmol, 66%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.39 (m, 2H), 7.16 (t, J = 8 Hz, 2H), 6.36 (bs, 1H), 1.54 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.7, 162.4, 161.56 (d, $J_{C\text{-}F}$ = 247 Hz), 155.2, 127.69 (d, $J_{C\text{-}F}$ = 9 Hz), 127.15 (d, $J_{C\text{-}F}$ = 3 Hz), 115.69 (d, $J_{C\text{-}F}$ = 15 Hz), 58.3, 24.5; ^{19}F (376 MHz, Chloroform-*d*): δ -112.9. IR (ν_{max}, cm^{-1}): 3218 (b), 2908 (s), 1765 (s), 1711 (s), 1530 (s), 1258 (s), 1130 (s), 884 (s), 712 (s). HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{11}H_{11}N_2O_2F$ 223.0877; found 223.0891.

***5,5-dimethyl-3-(pyridin-3-yl)imidazolidine-2,4-dione* (32q)**

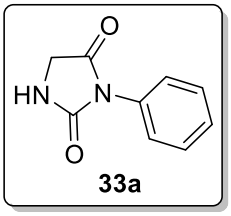


32q

Synthesized following **GP-A** starting from *5,5*-dimethylhydantoin (**30a**) (32 mg, 0.25 mmol) and mesityl(pyridin-3-yl)iodonium triflate (**31h-Mes**) (141 mg, 0.30 mmol). The reaction was stirred for 18 h. The reaction mixture was purified by column chromatography (AcOEt/Hexane: 30/80) to afford **32q** (29 mg, 0.165 mmol, 52%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.79 (s, 1H), 8.62 (d, J = 8 Hz, 1H), 7.84 (d, J = 9.5 Hz, 1H),

7.45-7.42 (m, 1H), 6.69 (bs, 1H), 1.57 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.9, 154.6, 148.9, 146.8, 133.4, 129.3, 123.5, 59.1, 25.3. IR (ν_{max}, cm^{-1}): 3209 (b), 2920 (s), 1762 (s), 1712 (s), 1534 (s), 1354 (s), 1347 (s), 1076 (s), 862 (s). HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{10}H_{11}N_3O_2$ 206.0924; found 206.0949.

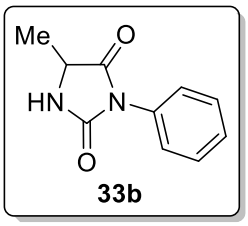
3-phenylimidazolidine-2,4-dione **(33a)** [50]



33a

Synthesized following **GP-A** starting from imidazolidine-2,4-dione (**30b**) (25 mg, 0.25 mmol, 1 equiv.), diphenyliodonium triflate (**31a-OTf**) (129 mg, 0.3 mmol, 1.2 equiv.), CuI (9.5 mg, 0.05 mmol, 0.2 equiv.) and K_3PO_4 (53 mg, 0.25 mmol). The reaction mixture was stirred at room temperature for 10 h. The mixture was purified by column chromatography (AcOEt/Hexane: 40/60) to afford **33a** (33 mg, 0.187 mmol, 75%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51-7.49 (m, 2H), 7.41-7.38 (m, 3H), 6.91 (bs, 1H), 4.07 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 157.8, 131.3, 129.0, 128.4, 126.0, 46.2. IR (ν_{max}, cm^{-1}): 3173 (b), 3056 (m), 2932 (s), 1835 (s), 1744 (s), 1595 (s), 1503 (s), 1449 (s), 1405 (s). HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_9H_9N_2O_2$ 177.0664; found 177.0688.

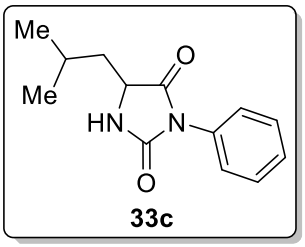
5-methyl-3-phenylimidazolidine-2,4-dione **(33b)** [51]



33b

Synthesized following **GP-A** starting from 5-methylimidazolidine-2,4-dione (**30c**) (29 mg, 0.25 mmol), diphenyliodonium triflate (**31a-OTf**) (129 mg, 0.3 mmol), CuI (9.5 mg, 0.05 mmol, 0.2 equiv.) and K_3PO_4 (53 mg, 0.25 mmol). The reaction was stirred for 12 h. The reaction mixture was purified by column chromatography (AcOEt/Hexane: 20/80) to afford **33b** (41 mg, 0.215 mmol, 86%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50-7.47 (m, 2H), 7.41-7.37 (m, 3H), 6.58 (bs, 1H), 4.22 (qd, J = 6.9 & 1.3 Hz, 1H), 1.52 (d, J = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.1, 156.2, 131.5, 129.1, 128.3, 126.1, 52.3, 17.4. IR (ν_{max}, cm^{-1}): 3216 (b), 3080 (b), 3311 (m), 1780 (s), 1720 (s), 1404 (s), 1377 (s), 1240 (s), 1041 (s), 916 (s) 818 (s), 639 (s). HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{10}H_{11}N_2O_2$ 191.0820; found 191.0866.

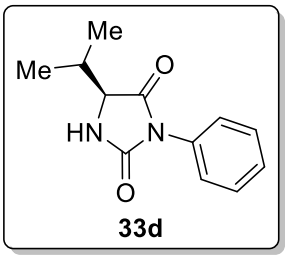
***5-isobutyl-3-phenylimidazolidine-2,4-dione* (33c)**



33c

Synthesized following **GP-A** starting from 5-isobutylimidazolidine-2,4-dione (**30d**) (39 mg, 0.25 mmol), diphenyliodonium triflate (**31a-OTf**) (129 mg, 0.3 mmol) CuI (9.5 mg, 0.05 mmol, 0.2 equiv.) and K_3PO_4 (53 mg, 0.25 mmol). The reaction was stirred for 12 h. The reaction mixture was purified by column chromatography (AcOEt/Hexane: 40/60) to afford **33c** (47 mg, 0.202 mmol, 81%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49-7.45 (m, 2H), 7.41-7.36 (m, 3H), 6.49 (bs, 1H), 4.20-4.17 (m, 1H), 1.92-1.82 (m, 2H), 1.69-1.64 (m, 1H), 1.01-0.98 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.1, 156.2, 131.5, 129.1, 128.3, 126.1, 52.3, 17.4. IR (ν_{max}, cm^{-1}): 3255 (b), 3112 (m), 3311 (m), 1776 (s), 1726 (s), 1430 (s), 1402 (s), 1160 (s), 860 (s), 712 (s), 648 (s). HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{17}N_2O_2$ 233.1290; found 233.1294.

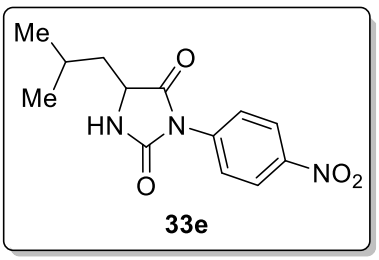
***(S)-5-isopropyl-3-phenylimidazolidine-2,4-dione* (33d)**



33d

Synthesized following **GP-A** starting from 5-isopropylimidazolidine-2,4-dione (**30e**) (36 mg, 0.25 mmol) and diphenyliodonium triflate (**31a-OTf)** (129 mg, 0.3 mmol). The reaction was stirred for 12 h. The reaction mixture was purified by column chromatography (AcOEt/Hexane: 40/60) to afford **33d** (47 mg, 0.202 mmol, 84%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50-7.46 (m, 2H), 7.40-7.37 (m, 3H), 6.69 (bs, 1H), 4.06-4.07 (m, 1H), 2.37-2.29 (m, 1H), 1.09 (d, J = 7 Hz, 3H), 1.01 (d, J = 7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.6, 157.4, 131.1, 129.3, 127.9, 126.1, 62.1, 30.4, 18.2, 15.6. IR (ν_{max}, cm^{-1}): 3273 (b), 3116 (m), 3311 (m), 2966 (s), 1720 (s), 1429 (s), 1171 (s), 762 (s), 633 (s). HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{15}N_2O_2$ 219.1133; found 219.1131.

***5-isobutyl-3-(4-nitrophenyl)imidazolidine-2,4-dione* (33e)**

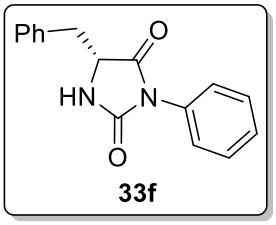


33e

Synthesized following **GP-A** starting from 5-isobutylimidazolidine-2,4-dione (**30d**) (39 mg, 0.25 mmol) and (4-nitrophenyl)(mesityl)iodonium triflate (**31b-Mes**) (155 mg, 0.30 mmol). The reaction was stirred for 12 h. The reaction mixture was purified by column chromatography (AcOEt/Hexane: 40/60) to afford **33e** (51 mg, 0.187 mmol,

75%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.81 (bs, 1H), 8.34 (d, *J* = 8 Hz, 2H), 7.73 (d, *J*= 8 Hz, 2H), 4.27 (t, *J* = 4 Hz, 1H), 1.90-1.82 (m, 1H), 1.64-1.58 (m, 2H), 0.93 (d, *J* = 7 Hz, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.6, 155.3, 146.2, 138.1, 127.2, 124.5, 55.1, 24.6, 23.2, 21.3. IR (ν_{max}, cm^{-1}): 3258 (b), 2955 (s), 2840 (s), 1756 (s), 1540 (s), 1310 (s), 1135 (s), 848 (s), 768 (s), 667 (s). HRMS (ESI) *m/z*: [M+H]$^+$ calcd for $C_{13}H_{16}N_3O_4$ 279.1219; found 279.1220.

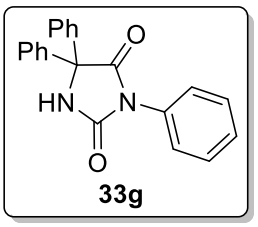
(R)-5-benzyl-3-phenylimidazolidine-2,4-dione **(33f)**



33f

Synthesized following **GP-A** starting from *(R)*-5-benzylimidazolidine-2,4-dione (**30e**) (47 mg, 0.25 mmol) and diphenyliodonium triflate (**31a-OTf**) (129 mg, 0.3 mmol). The reaction was stirred for 12 h. The reaction mixture was purified by column chromatography (AcOEt/Hexane: 40/60) to afford **33f** (57 mg, 0.214 mmol, 87%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.46-7.42 (m, 2H), 7.38-7.31 (m, 2H), 7.26-7.22 (m, 2H), 5.81 (bs, 1H), 4.22 (qd, *J*= 7 and 1.3 Hz, 1H), 3.33 (dd, *J* = 7 and 1.3 Hz, 1H), 3.03 (dd, *J* = 7 and 1.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 171.7, 155.8, 134.7, 131, 129.4, 129.0, 128.8, 128.3, 127.5, 126.2, 57.7, 37.7. IR (ν_{max}, cm^{-1}): 3205 (b), 3110 (m), 2944 (m), 1743 (s), 1402 (s), 1317 (s), 1139 (s), 746 (s). HRMS (ESI) *m/z*: [M+H]$^+$ calcd for $C_{16}H_{15}N_2O_2$ 267.1133; found 267.1134.

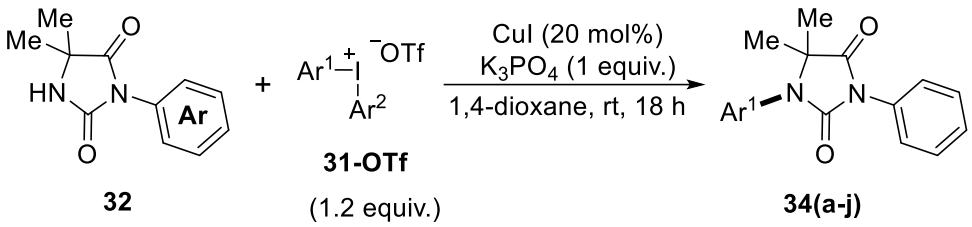
3,5,5-triphenylimidazolidine-2,4-dione **(33g) [CAS: 52461-02-6]** [51]



33g

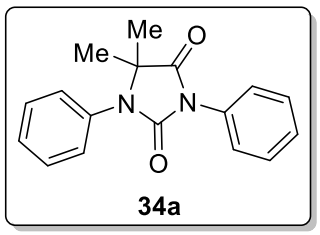
Synthesized following **GP-A** starting from 5,5-diphenylimidazolidine-2,4-dione (**30f**) (63 mg, 0.25 mmol) and diphenyliodonium triflate (**31a-OTf)** (129 mg, 0.3 mmol). The reaction was stirred for 12 h. The reaction mixture was purified by column chromatography (AcOEt/Hexane: 30/70) to afford **33g** (59 mg, 0.182 mmol, 73%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.50-7.42 (m, 15H), 6.83 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 172.2, 155.8, 139.1, 131.4, 129.1, 127.1, 126.3, 70.07. IR (ν_{max}, cm^{-1}): 3237 (b), 3105 (m), 3311 (m), 2931 (m), 1715 (s), 1431 (s), 1350 (s), 1169 (s), 689 (s). HRMS (ESI) *m/z*: [M+H]$^+$ calcd for $C_{21}H_{17}N_2O_2$ 329.1290; found 329.1295.

4.9.2 General procedure B (GP-B): *N*[1]-arylation of *N*[3]-arylated hydantoin



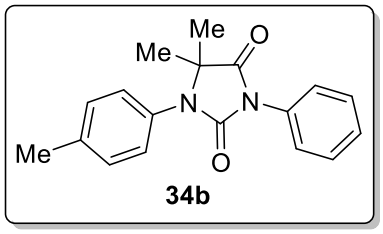
To an oven-dried Schlenck-tube, 3-arylated-hydantoin **32** (0.25 mmol), diaryliodonium salt **31-OTf** (0.3 mmol), CuI (50 μmol, 0.2 equiv.) and K_3PO_4 (0.25 mmol) was added under N_2 atmosphere. The tube was sealed and 1,4-dioxane (3 mL) was added under N_2 atmosphere. The reaction mixture was stirred at room temperature for indicated time. The reaction was filtered through celite and concentrated *in vacuo*. The crude product was purified as described.

***5,5-dimethyl-1,3-diphenylhydantoin* (34a)** [52]



Synthesized following **GP-B** starting from 3-phenyl-5,5-dimethylhydantoin (**32a**) (51 mg, 0.25 mmol), diphenyliodonium triflate (**31a-OTf**) (129 mg, 0.3 mmol, 1.2 equiv.), CuI (9.5 mg, 0.05 mmol, 0.2 equiv.) and K_3PO_4 (53 mg, 0.25 mmol). The reaction mixture was stirred at room temperature for 10 h. The crude was purified by column chromatography (AcOEt/Hexane: 20/80) to afford **34a** (57 mg, 0.205 mmol, 82%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52-7.32 (m, 10H), 1.43 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.9, 153.8, 134.1, 131.9, 129.6, 129.0, 128.7, 128.1, 126.1, 63.2, 23.6. IR (ν_{max}, cm^{-1}): 2976 (s), 2929 (s), 1780 (s), 1714 (s), 1496 (s), 1412 (s), 1366 (s), 1200 (s) 878 (m), 755 (s), 692 (s). HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{17}H_{17}N_2O_2$ 281.1290; found 281.1302.

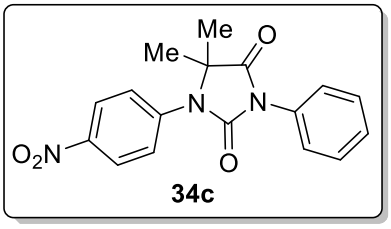
***5,5-dimethyl-3-phenyl-1-(p-tolyl)hydantoin* (34b)**



Synthesized following **GP-B** starting from 3-phenyl-5,5-dimethylhydantoin (**32a**) (51 mg, 0.25 mmol), bis(4-methylphenyl)iodonium triflate (**31b-OTf**) (138 mg, 0.30 mmol), CuI (9.5 mg, 0.05 mmol, 0.2 equiv.) and K_3PO_4 (53 mg, 0.25 mmol). The reaction was stirred for 12 h. The reaction mixture was purified by column chromatography (AcOEt/Hexane: 20/80) to afford **34b** (66 mg, 0.225 mmol, 90%) as a white solid. ^{1}H

NMR (400 MHz, $CDCl_3$): δ 7.50-7.44 (m, 4H), 7.35-7.33 (m, 1H), 7.26 (d, J = 8 Hz, 2H), 7.19 (d, J = 8 Hz, 2H), 2.39 (s, 3H), 1.52 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.2, 154.0, 138.5, 131.8, 130.0, 128.8, 127.9, 126.4, 63.3, 23.7, 21.1. IR (ν_{max}, cm^{-1}): 2975 (s), 2930 (s), 1779 (s), 1713 (s), 1493 (s), 1406 (s), 1198 (s), 1143, 767 (s), 687 (s), 517 (s). HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{18}H_{19}N_2O_2$ 295.1446; found 295.1468.

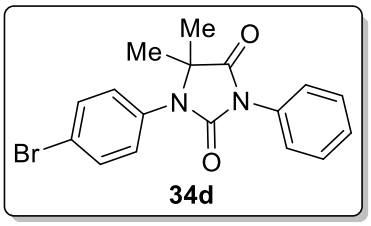
***5,5-dimethyl-1-(4-nitrophenyl)-3-phenylhydantoin* (34c)** [37]



34c

Synthesized following **GP-B** starting from 3-phenyl-5,5-dimethylhydantoin (**32a**) (51 mg, 0.25 mmol), (4-nitrophenyl)(mesityl)iodonium triflate (**32b-Mes**) (155 mg, 0.30 mmol), CuI (9.5 mg, 0.05 mmol, 0.2 equiv.) and K_3PO_4 (53 mg, 0.25 mmol). The reaction was stirred for 12 h. The reaction mixture was purified by column chromatography (AcOEt/Hexane: 20/80) to afford **34c** (55 mg, 0.170 mmol, 68%) as a pale-yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (d, J = 8 Hz, 2H), 7.62 (d, J = 8 Hz, 2H), 7.52-7.41 (m, 5H), 1.66 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.3, 153.5, 146.2, 141.0, 131.3, 129.0, 127.4, 126.4, 124.7, 64.0, 24.5. IR (ν_{max}, cm^{-1}): 2923 (m), 1776 (s), 1724 (s), 1522 (s), 1497 (s), 1403 (s), 1333 (s), 1194, 854 (s), 751 (s), 619 (s). HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{17}H_{16}N_3O_4$ 326.1140; found 326.1175.

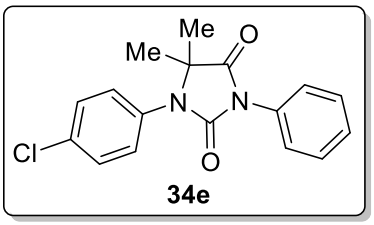
***1-(4-bromophenyl)-5,5-dimethyl-3-phenylhydantoin* (34d)**



34d

Synthesized following **GP-B** starting from 3-phenyl-5,5-dimethylhydantoin (**32a**) (51 mg, 0.25 mmol), bis(4-bromophenyl)iodonium triflate (**31d-OTf**) (176 mg, 0.30 mmol), CuI (9.5 mg, 0.05 mmol, 0.2 equiv.) and K_3PO_4 (53 mg, 0.25 mmol). The reaction was stirred for 12 h. The reaction mixture was purified by column chromatography (AcOEt/Hexane: 20/80) to afford **34d** (69 mg, 0.170 mmol, 78%) as a beige solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, J = 8 Hz, 2H), 7.40-7.39 (m, 4H), 7.32-7.28 (m, 1H), 7.13 (d, J = 8 Hz, 2H), 1.46 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.7, 152.5, 132.1, 131.8, 130.5, 129.4, 128.1, 127.2, 125.1, 121.5, 62.5, 23.0; IR (ν_{max}, cm^{-1}): 2927 (s), 2856 (s), 1772 (s), 1715 (s), 1494 (s), 1416 (s), 1203 (s), 1154 (s), 1069 (s), 879 (s), 804 (s), 767 (s), 687 (s), 518 (s); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{17}H_{16}N_2O_2Br$ 359.0395; found 359.0399.

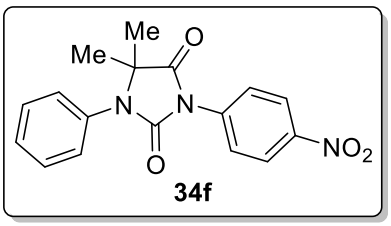
***1-(4-chlorophenyl)-5,5-dimethyl-3-phenylhydantoin* (34e)**



34e

Synthesized following **GP-B** starting from 3-phenyl-5,5-dimethylhydantoin (**32a**) (51 mg, 0.25 mmol), bis(4-chlorophenyl)iodonium triflate (**32f-OTf**) (149.7 mg, 0.30 mmol), CuI (9.5 mg, 0.05 mmol, 0.2 equiv.) and K_3PO_4 (53 mg, 0.25 mmol). The reaction was stirred for 12 h. The reaction mixture was purified by column chromatography (AcOEt/Hexane: 20/80) to afford **34e** (63 mg, 0.2 mmol, 82%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, J = 8 Hz, 2H), 7.46-7.45 (m, 4H), 7.34-7.33 (m, 1H), 7.19 (d, J = 8 Hz, 2H), 1.52 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.6, 153.6, 133, 132.7 131.4, 130.3, 130.2, 128.9, 128.1, 125.9, 122.3, 63.5, 23.7. IR (ν_{max}, cm^{-1}): 2981 (s), 2917 (s), 1768 (s), 1707 (s), 1491 (s), 1416 (s), 1206 (s), 1150 (s), 1088 (s), 878 (s), 697 (s), 519 (s). HRMS (ESI) *m/z*: $[M+K]^+$ calcd for $C_{17}H_{16}N_2O_2Cl$ 315.0900; found 315.0908.

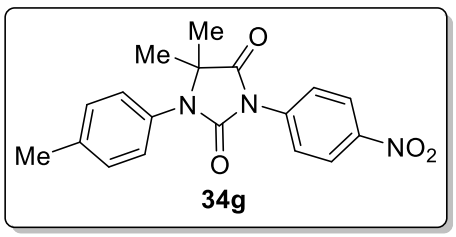
***5,5-dimethyl-3-(4-nitrophenyl)-1-phenylhydantoin* (34f)** [14]



34f

Synthesized following **GP-B** starting from 5,5-dimethyl-3-(4-nitrophenyl)hydantoin (**32e**) (62 mg, 0.25 mmol), diphenyliodonium triflate (**31a-OTf**) (129 mg, 0.3 mmol), CuI (9.5 mg, 0.05 mmol, 0.2 equiv.) and K_3PO_4 (53 mg, 0.25 mmol). The reaction was stirred for 12 h. The reaction mixture was purified by column chromatography (AcOEt/Hexane: 30/70) to afford **34f** (62 mg, 0.192 mmol, 77%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (d, J = 8 Hz, 2H), 7.86 (d, J = 8 Hz, 2H), 7.51-7.47 (m, 3H), 7.33-7.31 (m, 2H), 1.58 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.9, 153, 146.1, 137.7, 133.1, 129.8, 128.9, 125.8, 124.5, 63.4, 23.8. IR (ν_{max}, cm^{-1}): 2973 (b), 2923 (m), 1780 (s), 1722 (s), 1515 (s), 1416 (s), 1343 (s), 1200 (s), 847 (s), 764 (s), 695 (s). HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{17}H_{16}N_3O_4$ 326.1140; found 326.1172.

***5,5-dimethyl-3-(4-nitrophenyl)-1-(p-tolyl)hydantoin* (34g)**

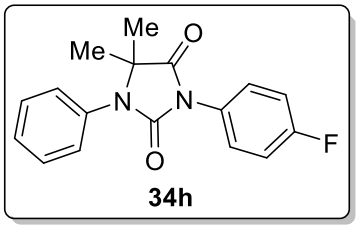


34g

Synthesized following **GP-B** starting from 5,5-dimethyl-3-(4-nitrophenyl)hydantoin (**32e**) (62 mg, 0.25 mmol), bis(4-methylphenyl)iodonium triflate (**31b-OTf**) (138 mg, 0.30 mmol), CuI (9.5 mg, 0.05 mmol, 0.2 equiv.) and K_3PO_4 (53 mg,

0.25 mmol). The reaction was stirred for 10 h. The reaction mixture was purified by column chromatography (AcOEt/Hexane: 30/70) to afford **34g** (71 mg, 0.21 mmol, 84%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (d, J = 8 Hz, 2H), 7.28 (d, J = 8 Hz, 2H), 7.84 (d, J = 8 Hz, 2H), 7.17 (d, J = 8 Hz, 2H), 2.42 (s, 3H), 1.58 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.6, 152.6, 145.8, 139.1, 137.7, 130.2, 128.9, 126.2, 124.1, 63.3, 23.6, 21.3. IR (ν_{max}, cm^{-1}): 31125 (m), 2920 (b), 2923 (m), 1768 (s), 1723 (s), 1524 (s), 1411 (s), 1340 (s), 1203 (s), 849 (s), 762 (s). HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{18}H_{18}N_3O_4$ 340.1297; found 340.1306.

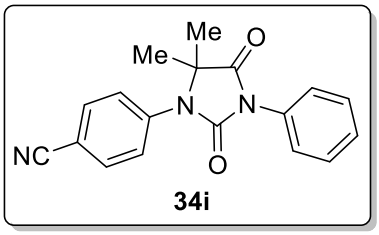
3-(4-fluorophenyl)-5,5-dimethyl-1-phenylhydantoin **(34h)**



34h

Synthesized following **GP-B** starting from 3-(4-fluorophenyl)-5,5-dimethylhydantoin (**32p**) (51 mg, 0.25 mmol), diphenyliodonium triflate (**31a-OTf**) (129 mg, 0.3 mmol), CuI (9.5 mg, 0.05 mmol, 0.2 equiv.) and K_3PO_4 (53 mg, 0.25 mmol). The reaction was stirred for 12 h. The reaction mixture was purified by column chromatography (AcOEt/Hexane: 30/70) to afford **34h** (40 mg, 0.135 mmol, 54%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51-7.43 (m, 5H), 7.33-7.31 (m, 2H), 7.19-7.14 (m, 2H), 1.55 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.3, 161.8 (d, J_{C-F} = 271 Hz), 153.6, 133.7, 129.6, 129.0, 128.8, 128.0, 127.7, 116.0 (d, J_{C-F} = 7 Hz), 63.5, 24.0. ^{19}F (376 MHz, $CDCl_3$): δ -112.16. IR (ν_{max}, cm^{-1}): 3076 (m), 2987 (b), 1760 (s), 1710 (s), 1516 (s), 1417 (s), 1366 (s), 1204 (s), 1147 (s), 830 (s), 757 (s), 701 (s). HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{17}H_{16}N_2O_2F$ 299.1195; found 299.1204.

4-(5,5-dimethyl-2,4-dioxo-3-phenylimidazolidin-1-yl)benzonitrile **(34i)** [37]

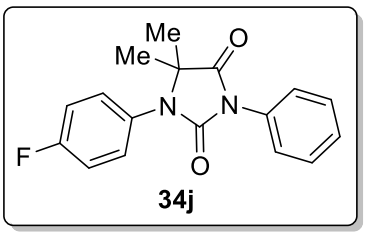


34i

Synthesized following **GP-B** starting from 3-phenyl-5,5-dimethylhydantoin (**32a**) (51 mg, 0.25 mmol) and (4-cyanophenyl)(mesityl)iodonium triflate (**31c-OTf**) (149 mg, 0.30 mmol). The reaction was stirred for 12 h. The reaction mixture was purified by column chromatography (AcOEt/Hexane: 30/70) to afford **34i** (47 mg, 0.153 mmol, 62%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, J = 8 Hz, 2H), 7.55 (d, J = 8 Hz, 2H), 7.50-7.46 (m, 4H), 7.43-7.39 (m, 1H), 1.63 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.4, 153.6, 138.9, 133.3, 131.2, 129.0, 127.8, 126.1, 118.0, 111.5, 63.8, 24.4. IR (ν_{max}, cm^{-}

[1]): 2220 (s) 1777 (s), 1727 (s), 1497 (s), 1415 (s), 1345 (s), 1202 (s), 833 (s), 749 (s). HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{18}H_{16}N_3O_2$ 306.1242; found 306.1276.

***1-(4-fluorophenyl)-5,5-dimethyl-3-phenylhydantoin* (34j)**



34j

Synthesized following **GP-B** starting from 3-phenyl-5,5-dimethylhydantoin (**32a**) (51 mg, 0.25 mmol) and bis(4-fluorophenyl)iodonium triflate (**31h-OTf**) (139 mg, 0.30 mmol). The reaction was stirred for 12 h. The reaction mixture was purified by column chromatography (AcOEt/Hexane: 30/70) to afford **34j** (55 mg, 0.140 mmol, 68%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50-7.47 (m, 4H), 7.40-7.35 (m, 1H), 7.32-7.28 (m, 2H), 7.19-7.14 (m, 2H), 1.54 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.8, 162.4 (d, $J_{C\text{-}F}$ = 273 Hz), 154.0, 131.7, 131.0, 129.8, 129.0, 128.1, 126.1, 116.5 (d, $J_{C\text{-}F}$ = 3 Hz), 63.5, 23.8. ^{19}F (376 MHz, $CDCl_3$): δ -112.5. IR (ν_{max}, cm^{-1}): 2994 (m) 1788 (s), 1729 (s), 1510 (s), 1417 (s), 1214 (s), 1202 (s), 1147 (s) 691 (s). HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{17}H_{16}N_2O_2F$ 299.1195; found 299.1210.

4.9.3 Larger Scale Synthesis Procedure

i) *(S)-5-isopropyl-3-phenylimidazolidine-2,4-dione* (33d)

(*S*)-5-isopropylimidazolidine-2,4-dione (**30e**) (284 mg, 2 mmol) and diphenyliodonium triflate (**31a-OTf)** (1.032 g, 2.4 mmol), CuI (38 mg, 0.2 mmol) and K_3PO_4 (424 mg, 2 mmol) were added under N_2 atmosphere to a dried 50 mL round-flask. The flask was equipped with a rubber septum, evacuated, and backfilled with nitrogen three times. Dry DCE (20 mL) was added to the flask and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was filtered through celite and concentrated *in vacuo*. The mixture was purified by column chromatography (AcOEt/Hexane: 40/60) to afford **33d** (348 mg, 1.6 mmol, 80%) as white solid.

ii) *5,5-dimethyl-3-(4-nitrophenyl)-1-(p-tolyl)hydantoin* (34g)

5,5-dimethyl-3-(4-nitrophenyl)hydantoin (**32e**) (498 mg, 2 mmol) and bis(4-methylphenyl)iodonium triflate (**31b-OTf**) (1.099 g, 2.4 mmol), CuI (38 mg, 0.2 mmol) and K_3PO_4 (424 mg, 2 mmol) were added under N_2 atmosphere to a dried 50 mL round-flask. The flask was equipped with a rubber septum, evacuated, and backfilled with nitrogen three times. Dry DCE (20 mL) was added to the flask and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was

filtered through celite and concentrated *in vacuo*. The mixture was purified by column chromatography (AcOEt/Hexane: 20/80) to afford **34g** (525 mg, 1.56 mmol, 78%) as white solid.

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

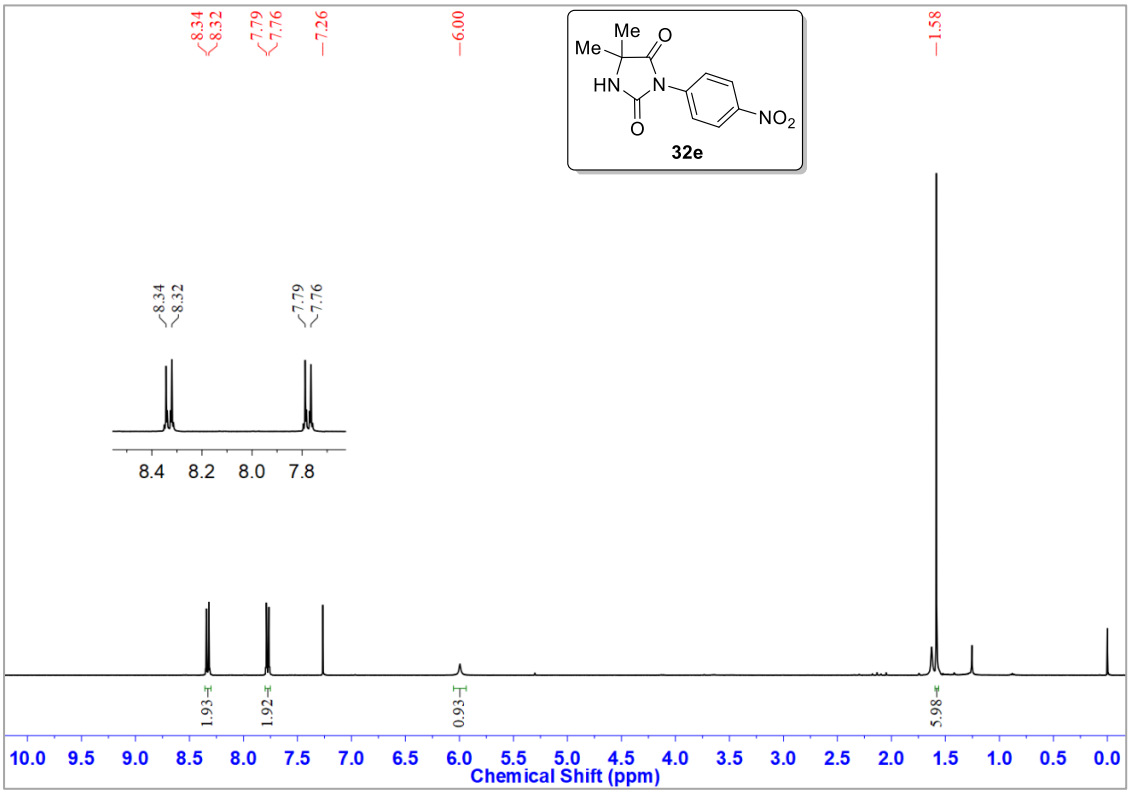


Figure 4.2 ^{1}H NMR spectrum of **32e** ($CDCl_3$, 400 MHz, 298 K)

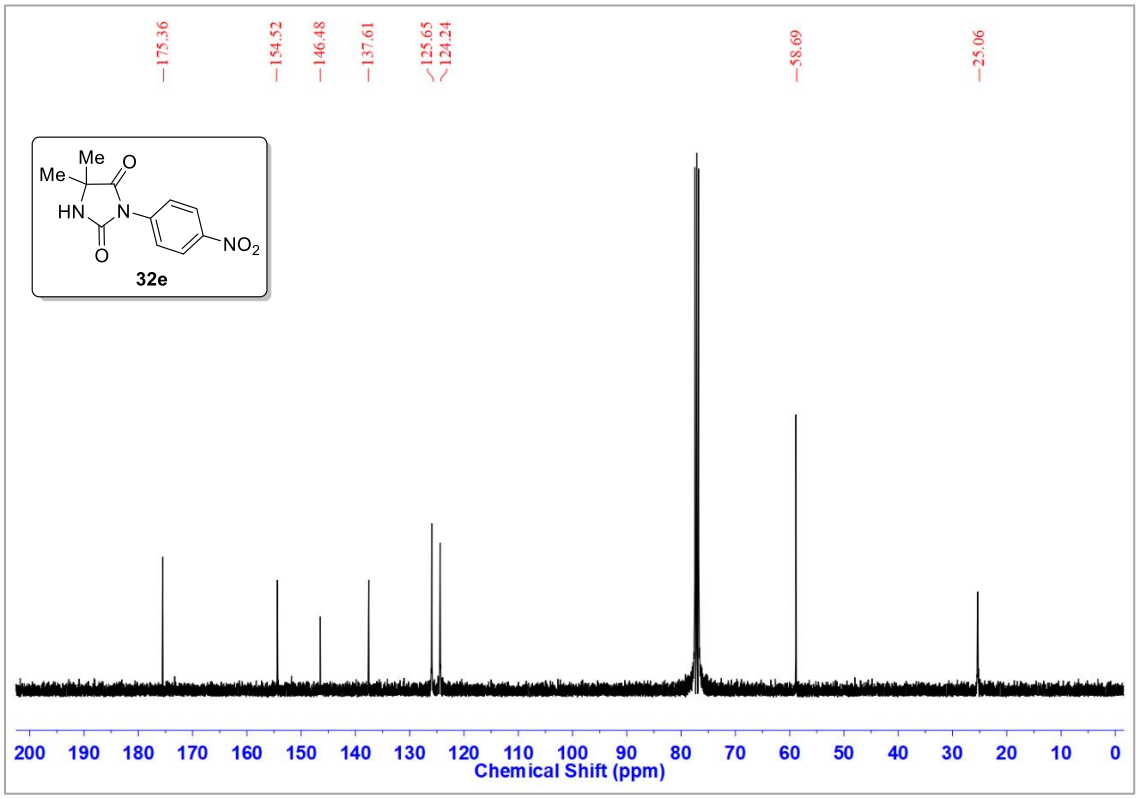


Figure 4.3 ^{13}C NMR spectrum of **32e** ($CDCl_3$, 100 MHz, 298 K)

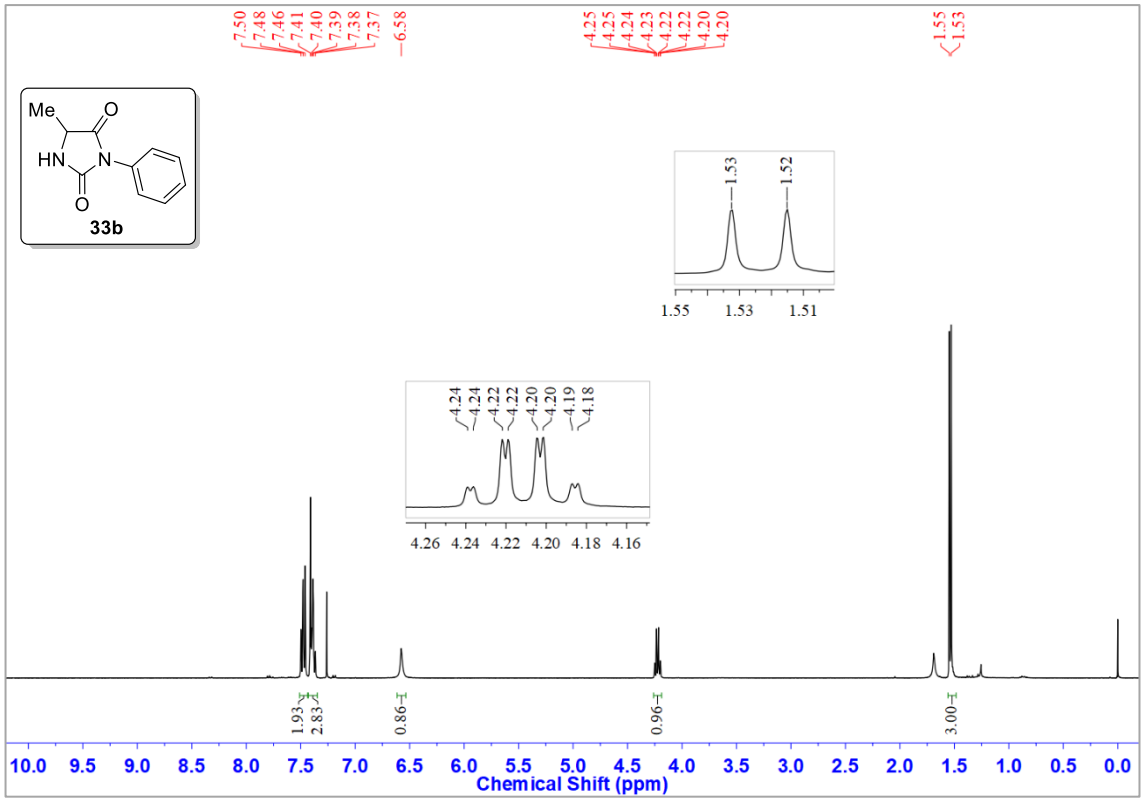


Figure 4.4 ^{1}H NMR spectrum of **33b** ($CDCl_3$, 400 MHz, 298 K)

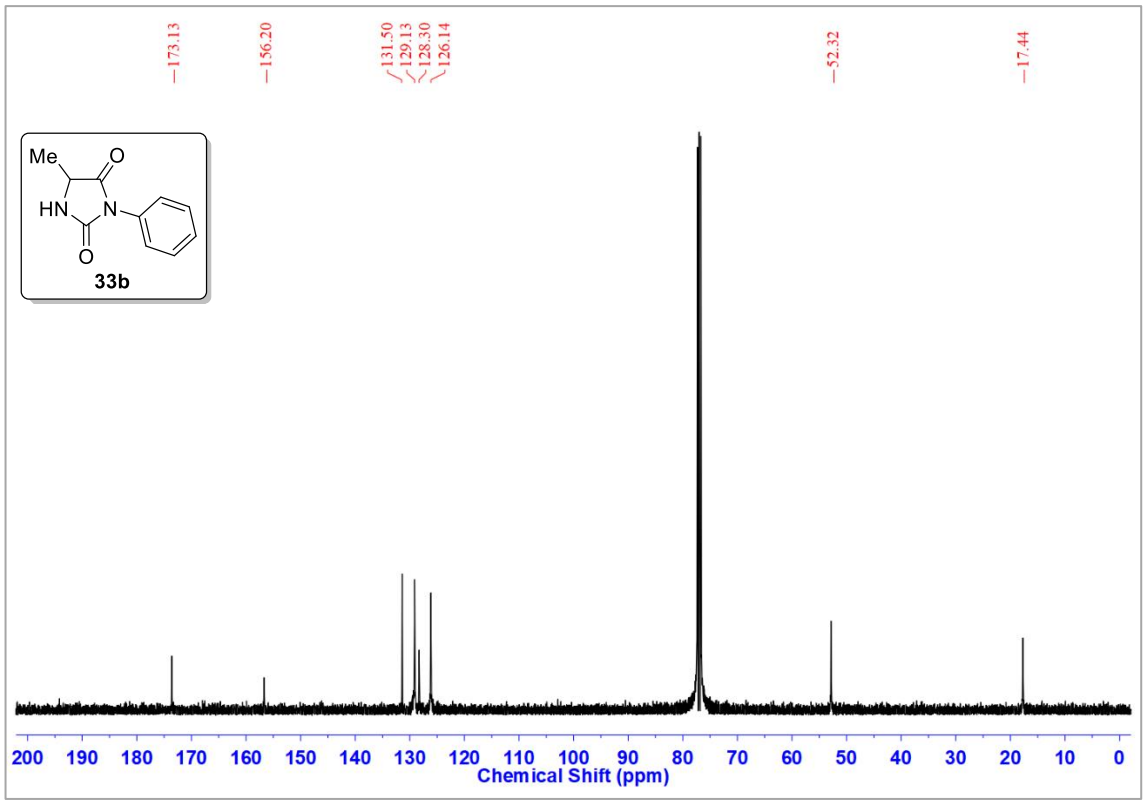


Figure 4.5 ^{13}C NMR spectrum of **33b** ($CDCl_3$, 100 MHz, 298 K)

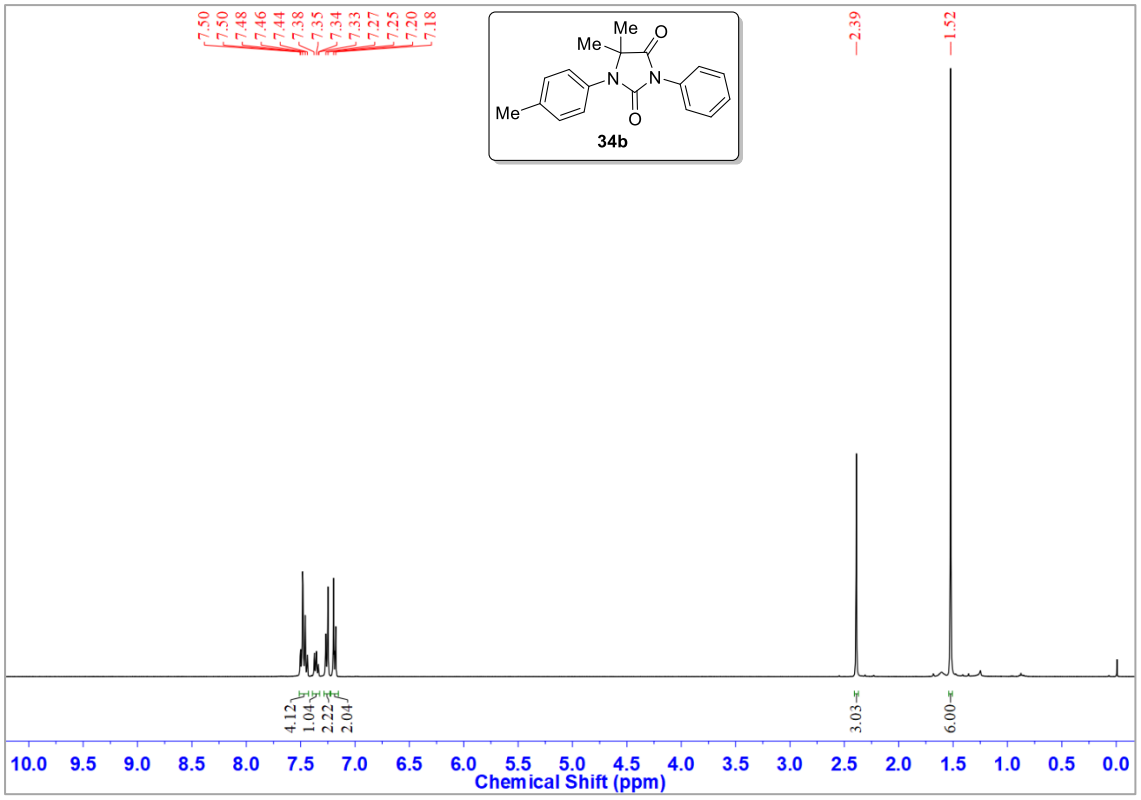


Figure 4.6 ^{1}H NMR spectrum of **34b** ($CDCl_3$, 400 MHz, 298 K)

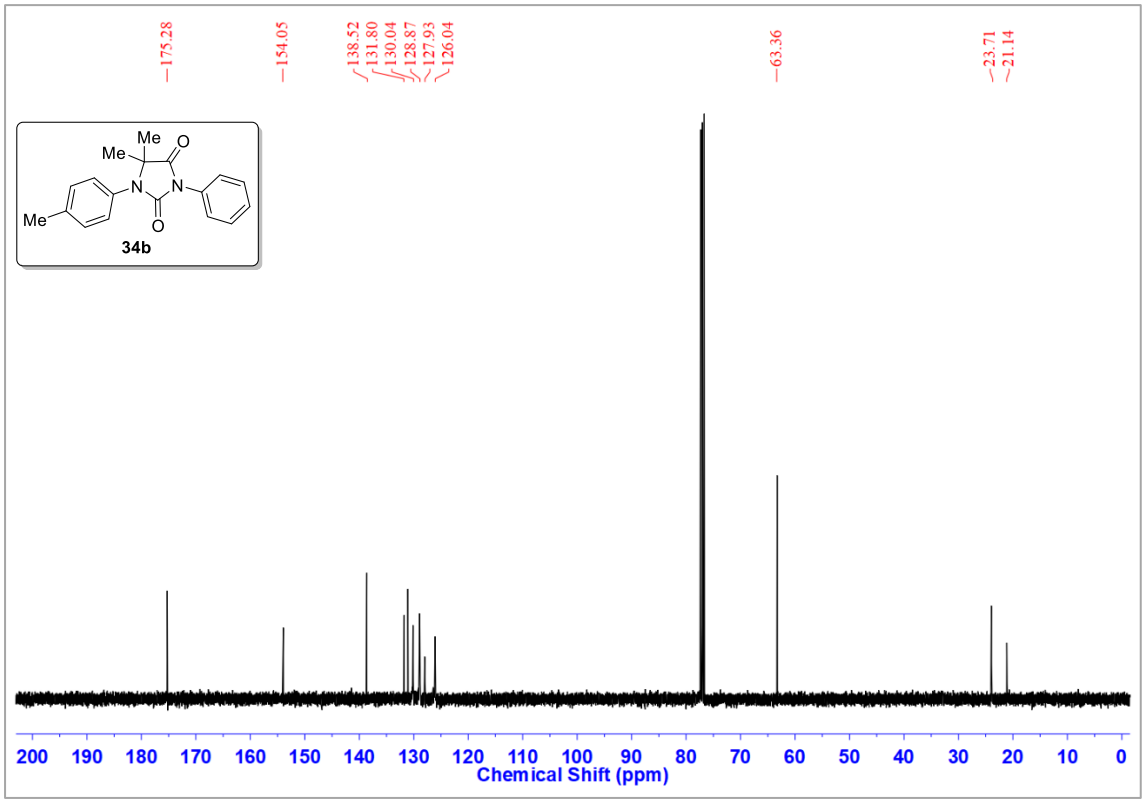


Figure 4.7 ^{13}C NMR spectrum of **34b** ($CDCl_3$, 100 MHz, 298 K)

4.11 Bibliography

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