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Copper catalyzed arylsulfenylation of thiohydantoin using elemental sulfur and arylhalide: C-S coupling

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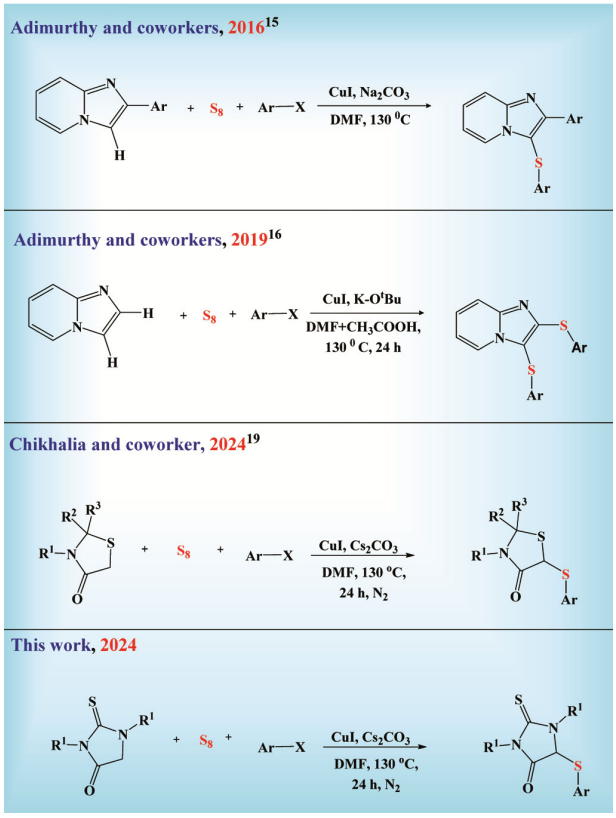
The generation and applications of carbon-sulfur (C-S) bonds in numerous natural and medicinal products have led to the development of efficient techniques for C-S bond creation. Thiohydantoin is a privileged scaffold for biological activities, which has aroused our interest in developing the C-S bond formation by clubbing it with another nucleus. Herein, we have developed a C-S bond between thiohydantoin and phenyl nucleus with elemental sulfur and aryl halides using copper(I) iodide as catalyst. Optimization has been carried out using various catalyst loadings, base, temperature and solvent. The reaction is highly effective with broad functional group tolerance and affords yield in good to better range.

Keywords: Thiohydantoin, Elemental sulfur, Copper(I) iodide, C-S-C bond formation, Arylsulfenylation

Organosulfur chemistry has seen a tremendous development due to the vital auxiliary role played by sulfur-containing groups[1,2]. They are of greater importance used as ubiquitous molecules in ligand design[3], pharmaceuticals[4] and material science[5]. Over few decades, considerable work has been investigated for creating novel techniques in the formation of C–S bonds. Recently, we have witnessed an enormous rise in the pursuit of transition metal-mediated C-S bond formation methodologies because of their great effectiveness in the transformation reactions[6]. Various sulfenylating agents like thiols, thiophenols, thioamides, potassium xanthate, potassium thiocyanate, elemental sulfur, sodium thiomethoxide, sodium sulfide, carbon disulphide, disulfides, sulfonyl hydrazides, $AgSCF_3$, $CuSCF_3$ plays vital role in these transformations[4].

Elemental sulfur is one of the primary source of sulfur implemented to sulfenylate organic moieties[7]. It is reactive, non-volatile, stable, non-hygroscopic, inexpensive, and easily obtainable, which makes it an effective sulfur source in organic synthesis[8]. Transition metal-catalyzed arylsulfenylation provides a wide range of functional group tolerance which suffice it a widely equipped technique[9]. Copper is considered a greener catalyst due to its low price, lower catalyst loading, mild reaction conditions and encouraging results[10-13]. Various research groups have developed different synthetic pathways for C-S bond formation using different sulfur sources to achieve a wide range of substrate scopes[5]. These various successful work includes Cu(II)-mediated C-S/N-S bond formation *via* C-H activation: access to benzoisothiazolones using elemental sulfur[14], copper-catalyzed three-component system for arylsulfenylation of imidazopyridines with elemental sulfur[15], copper-catalyzed multicomponent reactions (MCRs) for disulfenylation of imidazo[1,2-a]pyridines using elemental sulfur and arylhalides[16], annulation of 1-(2-aminoaryl)pyrroles, ethers with elemental sulfur[17], assembly of 3-sulfenylbenzofurans and 3-sulfenylindoles by palladium-catalyzed cascade annulation/arylthiolation[18], arylsulfenylation of 4-thiazolidinone with elemental sulfur and aryl halide: thioether linkage (C–S–C) [19], *etc*. (Scheme 1).

Thiohydantoin analogues are regarded as a significant class of bioactive heterocyclic compounds[20]. Its broad-spectrum applications lead to the development and functionalization of bioactive pharmacophores[21,22]. These make it widely recognized as an anticarcinogenic, antimutagenic, hypolipidemic, antimicrobial, antiviral, anti-inflammatory, antifungal, and anti-ulcer agent (Fig. 1)[23]. It also holds applications in synthesizing resins and plastics, textile printing, materials, pesticides, and polymerization catalysis[24]. Due to its broad range of applications, our research group has selected this moiety and explored various functionalities. Some of these include the



Scheme 1 — Arylsulfenylation of thiohydantoin

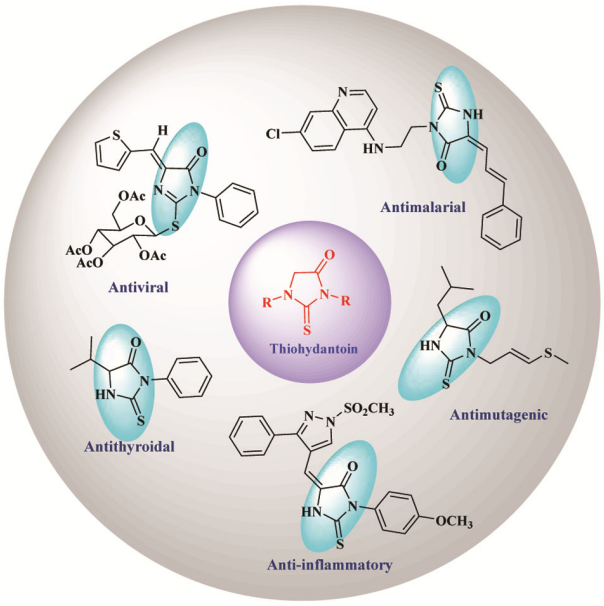


Fig. 1 — Bioactive scaffolds of thiohydantoin

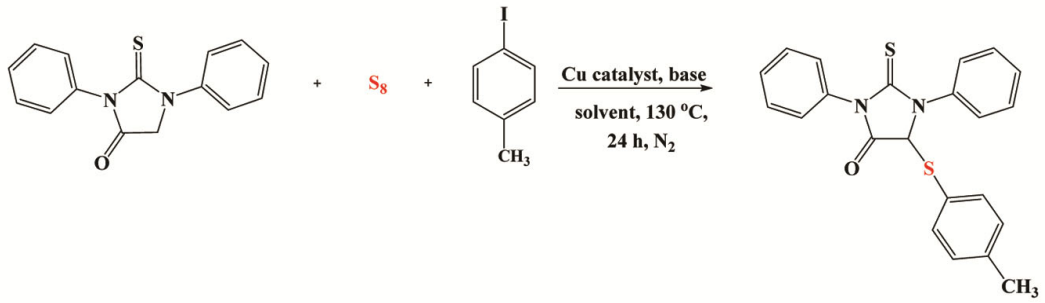
iron-catalyzed construction of cyanomethylated thiohydantoins by cross-dehydrogenative C(sp^3)-C(sp^3) coupling[25], iron-catalyzed alkynylation of thiohydantoins with terminal alkyne *via* cross-dehydrogenative coupling (CDC)[26], iron-catalyzed cross-dehydrogenative C-N coupling of thiohydantoins with various amines[27], *etc*. Herein, we have been reporting the development of a novel C-S bond formation on thiohydantoin using an environmentally benign technique with elemental sulfur. Also, we envisioned our studies on thioether linkage formation[28] and sp^3(C-H)-sp^2(C-H) linkage formation[29,19].

Results and Discussion

To confirm our present work, we initially performed a reaction of thiohydantoin[30] (0.25 mmol), elemental sulfur (0.75 mmol), *p*-methyl iodobenzene (0.75 mmol) in the presence of CuI (20 mol%) as a catalyst, Na_2CO_3 as a base under N_2 atmosphere in DMF at 130°C (Table 1, entry 1). Under these conditions, considerable yield, *i.e.* 23%, was observed. Then, the reaction was performed using various catalysts like CuBr, CuCl, $Cu(OAc)_2$, $CuCl_2$, $FeCl_2$, and $FeCl_3$, but no improvement in yield was observed (Table 1, entries 2-7). Further, various solvents were employed, including polar solvents like DMF, DMSO, CH_2Cl_2, NMP, and dioxane which results an increase in yield (Table 1, entries 13 to 16). In contrast, nonpolar solvents like toluene and xylene showed decrease in yields (Table 1, entries 17, 18). Among all, better yield was observed with DMF, which may be due to the coordination of DMF with the in-situ formation of the thiol derivative. When the catalyst loading was increased to 20%, gratifyingly, the yield was increased to 79% (Table 1, entry 11) and further increased to 30%, results in lowering of yield (Table 1, entry 12). Surprisingly, the yield increased to 79% (Table 1, entry 11) when Cs_2CO_3 was employed as a base. Notably, no significant yield was observed in the presence of other bases like K_2CO_3, KOH, Al_2CO_3. (Table 1, entry 8-10). Elevation or demotion in temperature was not so effective in getting yield, perhaps decrease in yield was observed. Based on the above result obtained, the optimized conditions were set as 0.25 mmol of thiohydantoin, 0.75 mmol of elemental sulfur, 0.75 mmol of *p*-methyl iodobenzene in 1 mL DMF at 130℃ for 24 hr to get arylsulfenylated product.

With the optimized condition (Table 1, entry 11), we investigated the substrate scope for arylsulfenylation of thiohydantoin using various aryl halide and S_8. Initially, the reaction was observed for unsubstituted thiohydantoin with iodobenzene, which gives only trace amount of yield (Table 2, **3a**). When unsubstituted thiohydantoin was reacted with *p*-methyl iodobenzene, an increase in the yield was

Table 1 — Optimization of reaction condition[a]



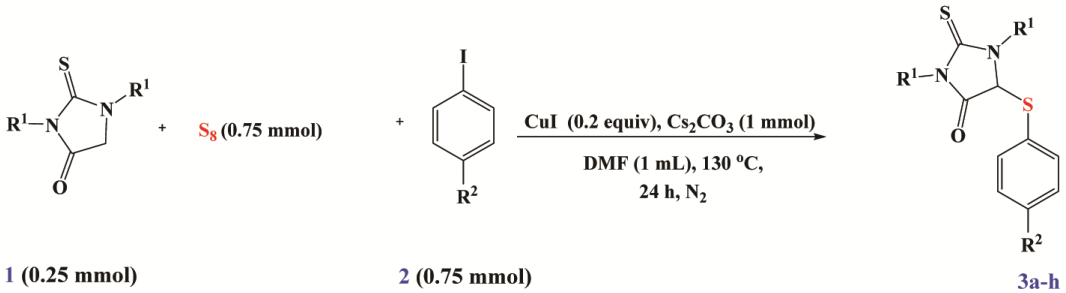
1 2 3

S. No.	Catalyst (mol %)	Base	Solvent	Temp (°C)	Yield (%)[b]
1	CuI (10)	Na_2CO_3	DMF	130	23
2	CuBr (10)	Na_2CO_3	DMF	130	20
3	CuCl (10)	Na_2CO_3	DMF	130	15
4	$Cu(OAc)_2$ (10)	Na_2CO_3	DMF	130	13
5	$CuCl_2$ (10)	Na_2CO_3	DMF	130	10
6	$FeCl_2$ (10)	Na_2CO_3	DMF	130	Trace
7	$FeCl_3$ (10)	Na_2CO_3	DMF	130	Trace
8	CuI (10)	K_2CO_3	DMF	130	21
9	CuI (10)	KOH	DMF	130	19
10	CuI (10)	Al_2CO_3	DMF	130	14
11	CuI (20)	Cs_2CO_3	DMF	130	79
12	CuI (30)	Cs_2CO_3	DMF	130	65
13	CuI (20)	Cs_2CO_3	DMSO	150	56
14	CuI (20)	Cs_2CO_3	CH_2Cl_2	40	45
15	CuI (20)	Cs_2CO_3	NMP	100	63
16	CuI (20)	Cs_2CO_3	Dioxane	100	51
17	CuI (20)	Cs_2CO_3	Toluene	110	34
18	CuI (20)	Cs_2CO_3	Xylene	130	29
19	CuI (20)	Cs_2CO_3	DMF	140	72
20	CuI (20)	Cs_2CO_3	DMF	150	69
21	CuI (20)	Cs_2CO_3	DMF	120	57

[a] Reaction conditions: Thiohydantoin (0.25 mmol), 4-methyl iodobenzene (0.75 mmol), elemental sulfur (0.75 mmol), catalyst, base in solvent (1 mL) for 24 h at 130°C in nitrogen atmosphere

[b] Isolated yield after column chromatography

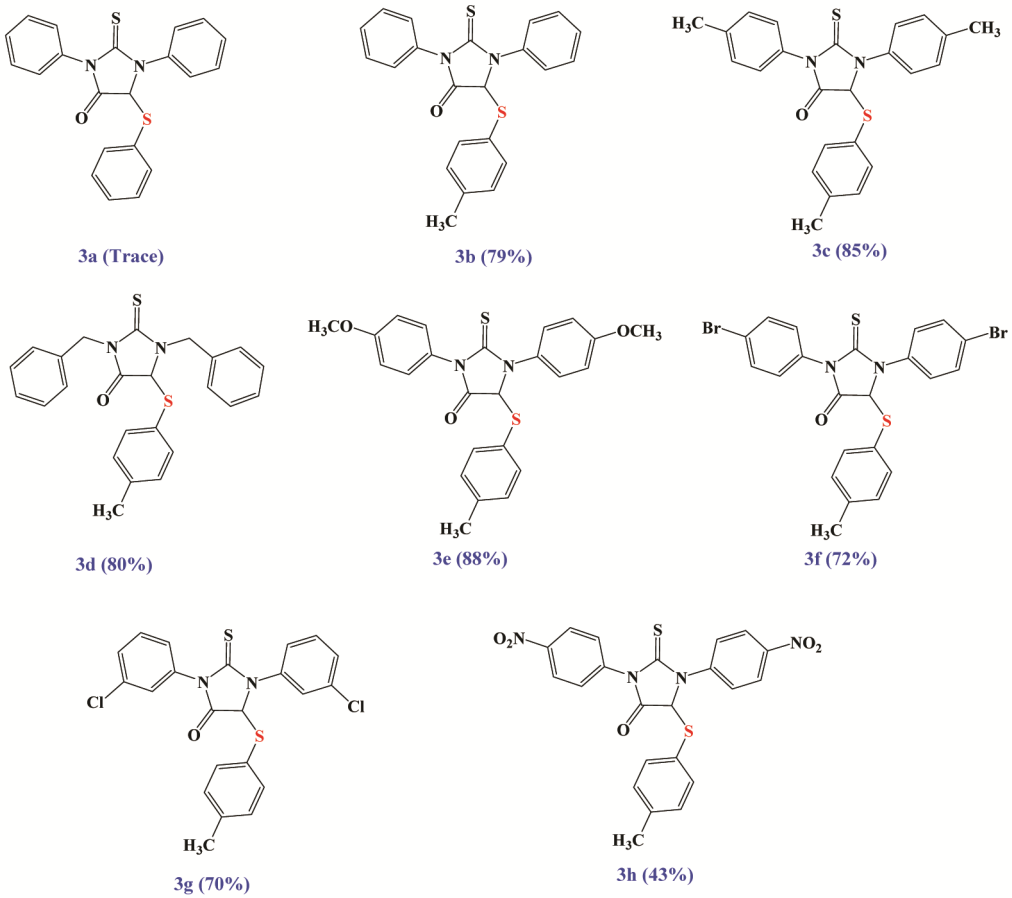
Table 2 — Substrate scopes for thiohydantoin



1 (0.25 mmol) **2 (0.75 mmol)** **3a-h**

(*Contd.*)

Table 2 — Substrate scopes for thiohydantoin (*Contd*.)



observed, which indicates the importance of the presence of the methyl group at *p*-position on iodobenzene (Table 2, **3b**). This can be attributed due to hyperconjugation effect resulting in the ring activation. The presence of electron-rich and electron-deficient groups on thiohydantoin reacted efficiently under the optimized conditions and gave good to better yield in the range of 43% to 88%. When *p*-methyl iodobenzene was reacted with thiohydantoin containing electron-donating groups such as alkyl, alkoxy, unsubstituted benzyl resulted in improved yields between 80% to 88% (Table 2, **3c-3e**) respectively. Similarly, when electron withdrawing groups such as halogen, nitro, were substituted, it yields in the range of 43 to 72% (Table 2, **3f-3h**) respectively. Similarly, presence of electron donating and electron withdrawing groups on iodobenzene was subjected for study.

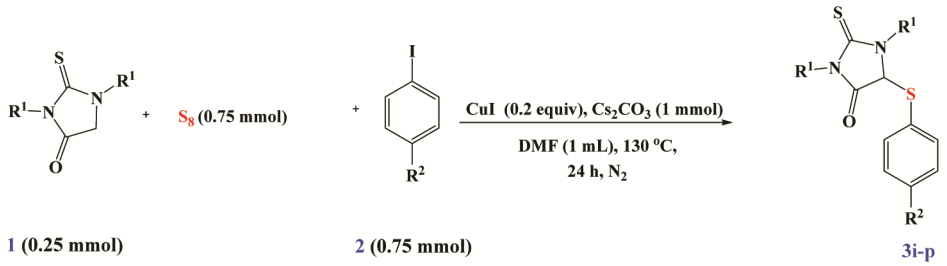
When thiohydantoin containing electron donating groups like -alkoxy, -unsubstituted benzyl were reacted with electron-withdrawing group containing iodobenzene, resulted in good yield (Table 3, 75%, 70%, **3l-3m**) respectively, whereas when thiohydantoin containing electron withdrawing group were subjected with electron donating iodobenzene, comparatively lower yield was recorded (Table 3, 40%-72%, **3n-3p**). Employment of the haloarenes like chloro, bromo was carried out but the reactions were not proceeded. So, substituted iodobenzene was subjected to entire reactions.[15]

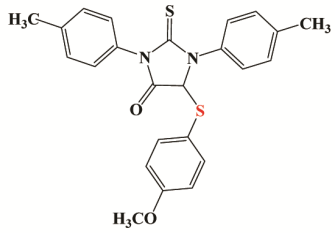
Control Experiment

Control experiment has been carried out for the better understanding of reaction mechanism. For instance, the product **3** was obtained with 60% yield when 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added to the reaction of thiohydantoin **1** and substituted iodoarene **2**, at the standard optimum conditions for 24 hrs. Hence, it is concluded that the reaction does not follow a radical pathway (Scheme 2).

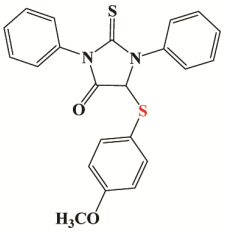
Based on above experimental results and previous literature survey, a plausible mechanism has been

Table 3 — Substrate scopes for *p*-substituted iodobenzenes

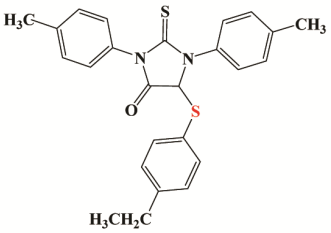




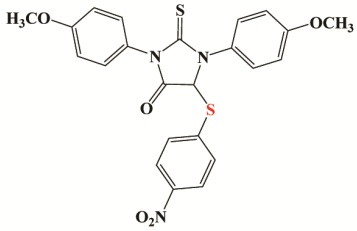
3i (87%)



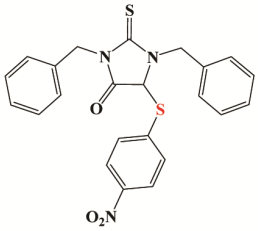
3j (81%)



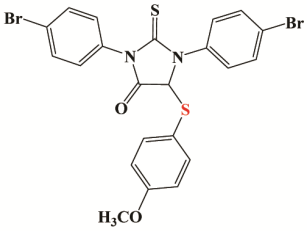
3k (75%)



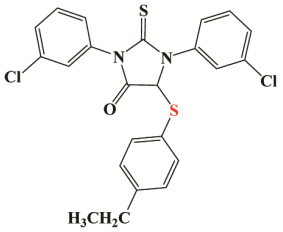
3l (75%)



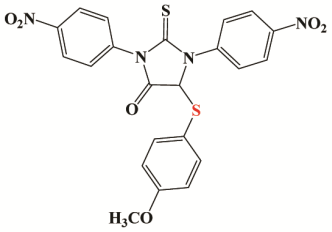
3m (70%)



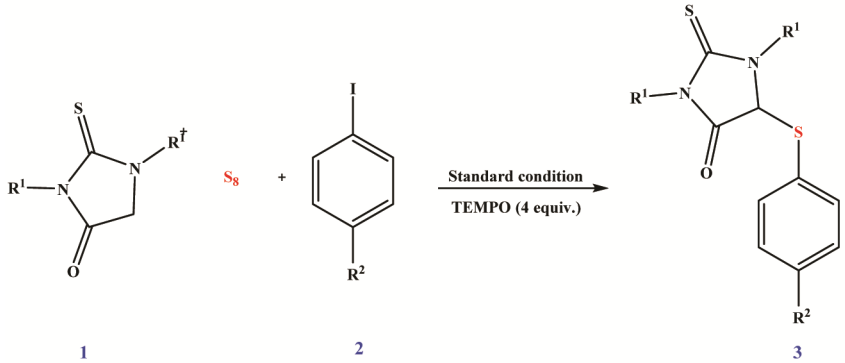
3n (71%)



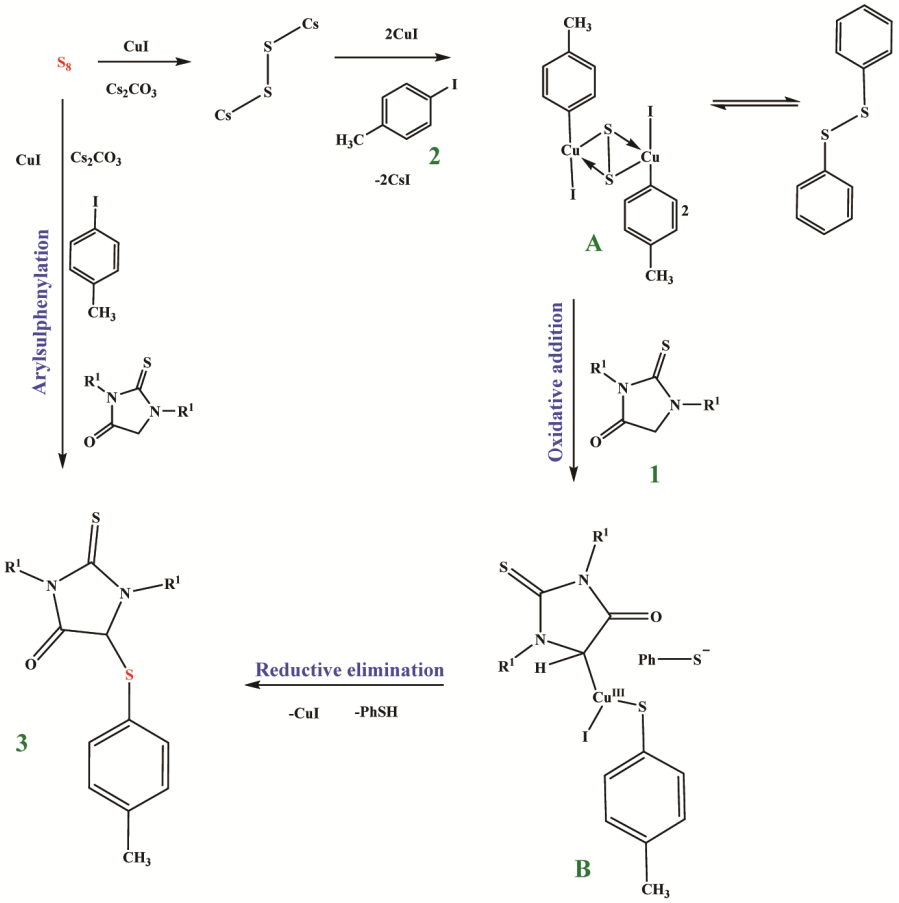
3o (72%)



3p (40%)



Scheme 2 — Control experiment



Scheme 3 — Plausible mechanism for arylsulfenylation of thiohydantoin

proposed for the formation of desired product (Scheme 3). Initially, the reaction of elemental sulfur with base and CuI generates a sulfur dimer, which upon further reaction with iodoarene **2** results in the formation of complex **A**. Thiohydantoin **1** is oxidatively added to complex A gives intermediate **B** with formation of Cu(III) and thiol ion. Further on reductive elimination the desired product **3** is formed with simultaneous removal of thiophenol and copper(I) iodide.

Experimental Section

General information

All the basic chemicals and solvents were procured from university-identified suppliers. Commercial reagents and solvents were used without purification. ^{1}H NMR, ^{13}C NMR and mass spectral analysis characterized the prepared compounds. Melting points were determined in open capillaries on a Veego electronic apparatus VMP-D (Veego Instrument Corporation, Mumbai, India) and are uncorrected. ^{1}H NMR and ^{13}C NMR spectras were recorded on a 400 MHz FT NMR, Advance III Bruker model spectrometer using DMSO-d_6 as a solvent and TMS as internal standard. ESI mass spectras were recorded on a Bruker Daltonics MicroTof. NMR chemical shifts are reported as parts per million (ppm) downfield from TMS. The splitting patterns are designated: s, singlet; d, doublet; t, triplet; m, multiplet.

General procedure for the synthesis of compound 3

To a solution of thiohydantoin **1** (Ref. 30) (0.25 mmol) in DMF (1 mL), iodobenzene **2** (0.75 mmol), elemental sulfur (0.75 mmol) was added along with copper iodide (20 mol%) and Cs_2CO_3 (1 mmol) in a reaction glass tube. The resulting mixture was stirred at 130°C temperature for 24h in nitrogen atmosphere. The completion of reaction was confirmed by TLC. After the completion of reaction, it was poured into 10 mL sodium carbonate solution. The resultant product was extracted with ethyl acetate (10 mL × 3) and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure left out the crude

residue. Finally, the crude residue was purified by column chromatography to get the desired product **3**.

Conclusion

Herein, we have developed an effective and tandem arylsulfenylation of thiohydantoin with elemental sulfur and iodoarene using Cu(I) as catalyst. This technique demonstrates the C-H activation reaction between sp^3(C-H) of thiohydantoin with sp^2(C-H) of iodoarene by employing CuI catalyst, Cs_2CO_3 base and DMF solvent. One pot synthesis, functional group tolerance and formation of thioether linkage make this protocol more engrossing and optimistic. This strategy tolerates a wide range of functional groups and provides new insight into organic synthesis. Also, it will build new hopes for the synthesis of building blocks having C-S-C linkage or thioether linkage.

Supplementary Information

Supplementary information is available in the website
http://nopr.niscpr.res.in/handle/123456789/58776.

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