A Novel Strategy for the Construction of Azole Heterocycles via an Oxidative Desulfurization Approach Using Iodobenzene and Oxone®

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Received: 18.05.2012; Accepted after revision: 18.06.2012

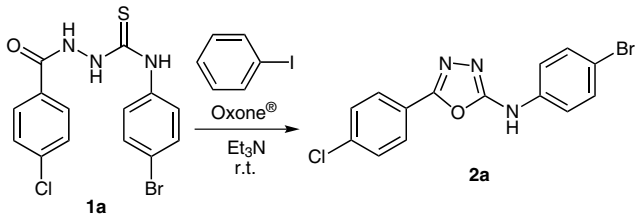
Abstract: The oxidative desulfurization approach has been utilized for the construction of oxadiazole and thiadiazole heterocycles using iodobenzene and Oxone®. The use of iodobenzene and the inexpensive readily available oxidant Oxone® makes the reaction system simple and versatile for desulfurization.

Key words: desulfurization, hypervalent iodine, iodobenzene, Oxone®, thiosemicarbazide, oxadiazole

Nitrogen-containing heterocycles are found ubiquitously in nature,[1a] and many synthetic bioactive compounds contain nitrogen heterocycles.[1b] Among these, azoles are an important class of heterocycles in medicinal chemistry. Within this group of heterocycles, 1,3,4-oxadiazole and 1,3,4-thiadiazole derivatives have been widely exploited for various properties anti-inflammatory,[1c] anticancer,[1d] and antimicrobial activity.[1e]

There are several methods described in the literature for the synthesis of 2-amino derivatives of 1,3,4-oxadiazole using cyclodehydration[2a] and cyclodesulfurization[2b] approaches. Similarly, synthesis of 2,5-diamino-1,3,4-thiadiazoles has been accomplished by cyclization of bisdiarylthioureas.[2a,b] These approaches suffer the disadvantages of requiring harsh reaction conditions, production of byproducts, and use of corrosive and toxic reagents.[2c–e] An iodine and K_2CO_3 combination has been used for desulfurization in the synthesis of oxadiazoles, but lower yields were observed.[3] Recently, IBX/triethylamine-mediated desulfurization has been reported for the synthesis of oxadiazoles and thiadiazoles from the corresponding thiosemicarbazides and bis(diarylthioureas).[4] However, the potentially explosive nature of IBX led us to consider desulfurization of thiosemicarbazide and bis(diarylthiourea) substrates using an iodine-based system.

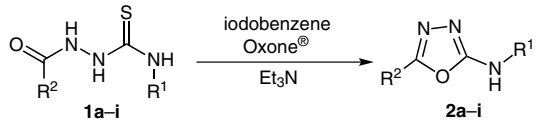
It has been reported that the hydroxy(phenyl)iodonium ion, which is an active iodine species, can be generated in situ using iodobenzene and Oxone® at room temperature.[5] As part of our studies on hypervalent iodine systems, we considered that this in situ generated species could be used for desulfurization. Thus for our initial study, *N*-(4-bromophenyl)-2-(4-chlorobenzoyl)hydrazine-carbothioamide **1a** was used as a model substrate (Scheme 1). We observed that thiosemicarbazide **1a** underwent oxidative desulfurization to form *N*-(4-bromophenyl)-5-(4-chlorophenyl)-2-amino-1,3,4-oxadiazole **2a** in the presence of iodobenzene and Oxone® in methanol as a solvent; but only a 50% yield was observed after prolonged reaction time. In the initial studies, we found that, on addition of 1 mol of triethylamine, the time for the reaction substantially decreased to 90 minutes but still with 50% yield. To increase the yield we studied different ratios of reagent and observed that a 90% yield could be achieved in 40 minutes with 2 mol of iodobenzene, 4 mol of Oxone®, and 2 mol of triethylamine in methanol. Acetonitrile and dichloromethane were also suitable solvents for this transformation, but the highest yield was observed with methanol.

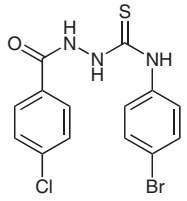


Scheme 1 Oxidative desulfurization of the thiosemicarbazide **1a** using iodobenzene/Oxone® in methanol

In order to study substrate scope, various thiosemicarbazides were surveyed, and the results are summarized in Table 1.[6]

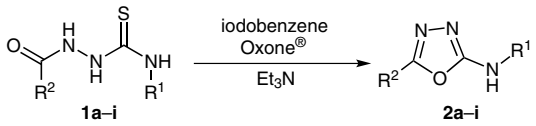
Table 1 Oxidative Desulfurization of the Thiosemicarbazide[a]



Entry	Substrate **1**	Product **2**	Yield (%)[b]
1	 **1a**	**2a**	91

SYNLETT 2012, 23, 1970–1972
Advanced online publication: 26.07.2012
DOI: 10.1055/s-0031-1290439; Art ID: ST-2012-D0435-L

Table 1 Oxidative Desulfurization of the Thiosemicarbazide[a] (continued)



1a–i **2a–i**

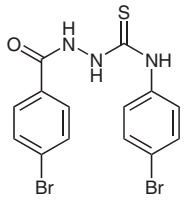
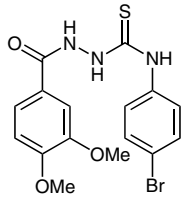
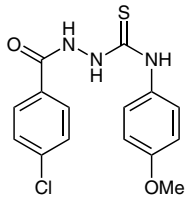
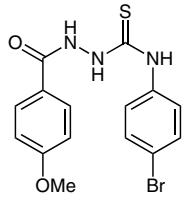
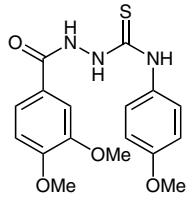
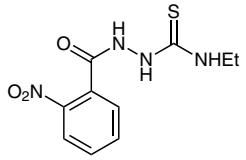
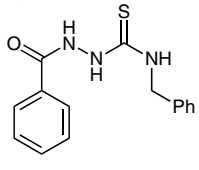
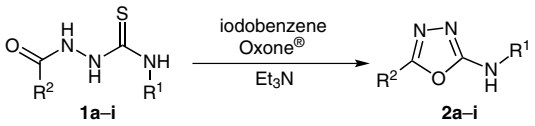
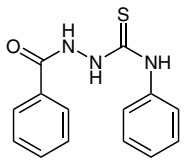
Entry	Substrate **1**	Product **2**	Yield (%)[b]
2	 **1b**	**2b**	85
3	 **1c**	**2c**	78
4	 **1d**	**2d**	76
5	 **1e**	**2e**	72
6	 **1f**	**2f**	84
7	 **1g**	**2g**	85
8	 **1h**	**2h**	81

Table 1 Oxidative Desulfurization of the Thiosemicarbazide[a] (continued)



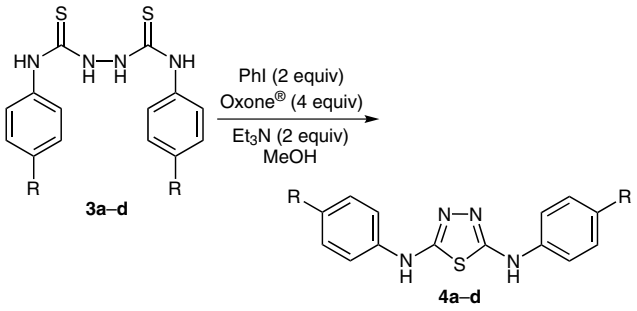
1a–i **2a–i**

Entry	Substrate **1**	Product **2**	Yield (%)[b]
9	 **1i**	**2i**	77

[a] Reaction conditions: Oxone® (4 mol), iodobenzene (2 mol), Et_3N (2 mol), MeOH, r.t.
[b] Isolated yields after column chromatography and structures were confirmed by comparison of IR, ^1H NMR, and mp with literature reports.

To extend the scope of this desulfurization protocol, the same reactant system was applied to bisdiarylthiourea **3a**, forming thiadiazole **4a** in good yield, and results with a range of substrates are summarized in Table 2. The yield and rate of reaction showed no notable correlation with the nature of substitution of the benzene rings.

Table 2 Oxidative Desulfurization of the Bisdiarylthiourea[a]



3a–d **4a–d**

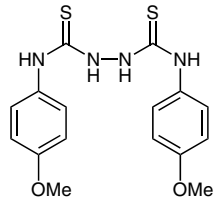
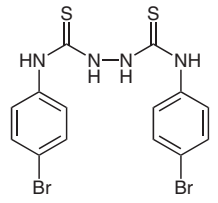
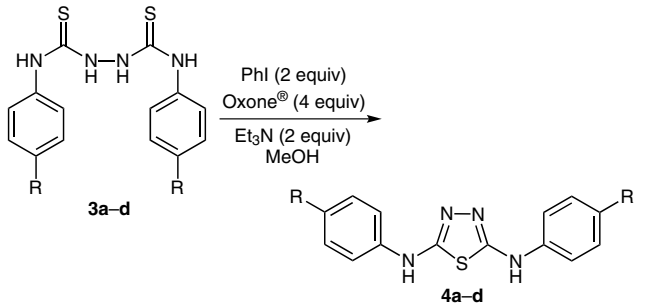
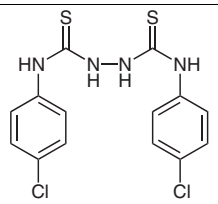
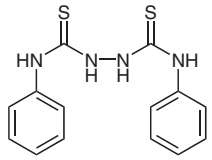
Entry	Substrate **3**	Product **4**	Yield (%)[b]
1	 **3a**	**4a**	90
2	 **3b**	**4b**	90

Table 2 Oxidative Desulfurization of the Bisdiarylthiourea[a] (continued)



3a–d → **4a–d**

Entry	Substrate **3**	Product **4**	Yield (%)[b]
3	 **3c**	**4c**	80
4	 **3d**	**4d**	78

[a] Reaction conditions: Oxone® (4 mol), iodobenzene (2 mol), Et_3N (2 mol), MeOH, r.t.
[b] Isolated yields after column chromatography and structures were confirmed by comparison of IR, ^1H NMR, and mp with literature reports.

In summary, we have utilized an in situ generated hypervalent iodine reagent system for the construction of the azole heterocycles.

Acknowledgment

We thank University Grant Commission, New Delhi, India for providing fellowships to KNP and NCJ under the Special Assistant Programme (UGC-SAP) and to PBJ under Rajiv Gandhi National Fellowship programme (UGC-RGNF).

References

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(6) **Typical Procedure for the Oxidative Desulfurization**
A mixture of Oxone® (4 equiv) and iodobenzene (2 equiv) in MeOH was stirred at r.t. for 20 min followed by addition of Et_3N (2 equiv) and substrate (1 equiv) at r.t. for 40 min. The reaction mixture was diluted with H_2O and then extracted twice with EtOAc. The organic layer was washed successively with 10% $NaHCO_3$ (2 × 20 mL), H_2O (2 × 20 mL) and dried over anhyd Na_2SO_4, filtered, and concen-trated under reduced pressure to give the crude product. The product was purified using silica gel column chromatography (30% EtOAc–hexane).
***N*-(4-Bromophenyl)-5-(4-chlorophenyl)-2-amino-1,3,4-oxadiazole (2a)**
White solid, mp273–274 °C (lit.[7a] 272–274 °C). IR (KBr): 3318, 3032, 1551, 1435 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.49–7.53 (m, 4 H),7.61 (d, 2 H), 7.89 (d, 2 H), 4.10 (s, 1 H).
***N*-5-Diphenyl-1,3,4-oxadiazole-2-amine (2i)**
White solid, mp 218–219 °C (lit.[7a] 217–219 °C). IR (KBr): 3371, 3043, 1549, 1452 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 6.92 (t, 1 H), 7.33 (dd, 2 H), 7.41 (m, 3 H), 7.58–7.62 (m, 2 H), 7.89 (m, 2 H), 8.91 (s, 1 H, NH).
***N*^{2},*N*^{5}-Bis(4-methoxyphenyl)-1,3,4-thiadiazole-2,5-diamine (4a)**
White solid, mp 234–236 °C (lit.[7b] 235–237 °C). IR (KBr): 3328, 1543, 1436, 1053 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 3.74 (s, 6 H), 7.04 (d, 4 H), 7.38 (d, 4 H), 8.21 (s, 2 H).
***N*^{2},*N*^{5}-Diphenyl-1,3,4-thiadiazole-2,5-diamine (4d)**
White solid, mp 238–240 °C (lit.[7c] 239–242 °C). IR (KBr): 3335, 1548, 1424, 1161 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 6.78 (d, 2 H), 7.15–7.47 (m, 6 H), 8.37 (s, 2 H).

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