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Hypervalent iodine(V) mediated mild and convenient synthesis of substituted 2-amino-1,3,4-oxadiazoles

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ABSTRACT

A simple protocol for the synthesis of 2-amino-1,3,4-oxadiazoles starting from the corresponding acylhydrazides by cyclodesulfurization of intermediate acylthiosemicarbazides mediated by *o*-iodoxybenzoic acid in good yields has been described. The protocol is mild with wide substrate scope, and thus a range of 2-amino-1,3,4-oxadiazoles have been prepared.

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1,3,4-Oxadiazoles have found extensive use as pharmacophores due to their metabolic profile and ability to engage in hydrogen bonding. 2-Amino-1,3,4-oxadiazoles have a wide range of biological activities such as antimicrobial agents, anti-inflammatory agents, anticancer agents, muscle relaxants, and antimitotics,[1] the 2,5-diaryl-1,3,4-oxadiazoles are known to be platelet aggregation inhibitors.[2] Due to myriad of biological applications of 1,3,4-oxadiazole scaffolds, efficient and mild methods to synthesize these moieties have attracted considerable interest. Our research group has recently reported simple access to 2-amino-1,3,4-oxadiazole peptidomimetics using *p*-TsCl mediated cyclization of amino acid derived thiosemicarbazides.[3] The most commonly followed strategy involves cyclization of the corresponding acyclic semicarbazide[4] (X = O) or thiosemicarbazide derivatives[5] (X = S), (Scheme 1). The reported protocols in the literature involve two steps, wherein semicarbazide/acylthiosemicarbazides were synthesized by reaction of hydrazides with the requisite isocyanate/isothiocyanate, which is typically isolated and purified. In the following step, cyclization was carried out using an appropriate reagent. Most of these methods have several disadvantages such as handling of harsh and toxic reagents, elevated temperatures, long reaction time etc. Xie et al. has recently described an efficient cyclodeselenization by heating selenosemicarbazides (X = Se) in DMF in one-pot from isoselenocyanates and hydrazides,[6] resulting in high yields of 2-amino-1,3,4-oxadiazoles. This protocol is devoid of the usage of any deselenizing reagent. Also there are a few reports wherein one pot strategy was explored starting from acylhydrazides using *p*-TsCl/pyridine[5a] and PS-carbodiimide[7] and both these methods suffer from harsh conditions which require heating for long hours for the cyclization of the acylthiosemicarbazide intermediate. Thus newer and mild protocols for this privileged class of molecules are continuously sought. In quest of novel methodologies for heterocycles, we have now focused on a simple and efficient protocol for the synthesis of 2-amino-1,3,4-oxadiazoles.

Hypervalent iodine reagents have been extensively used in various organic transformations because of their mild oxidizing and environmentally benign nature. The iodine atom in hypervalent iodine(V) reagents has strong electrophilic character and with the leaving ability of the phenyliodino group makes them reagents of choice for various oxidative transformations.[8] In addition, their affinity for sulfur has made these reagents attractive alternatives for desulfurization instead of heavy metal reagents.[9] Recently, an efficient synthesis of carbodiimides has been reported by desulfurization of thioureas using a variety of hypervalent iodine reagents.[9d,e] We envisaged the use of *o*-iodoxybenzoic acid[10] (IBX) as oxidative cyclization agent in the synthesis of 2-amino-1,3,4-oxadiazoles through a possible carbodiimide intermediate. On reviewing the mechanism of IBX oxidations, we presumed that cyclization of semicarbazide would generate water as possible side product, in which case the carbodiimide intermediate will revert back to the starting semicarbazide. Whereas in case of thiosemicarbazide it may result in efficient cyclization with precipitation of elemental sulfur.[9] Similar would be the case for selenosemicarbazide, wherein cyclodeselenization using IBX may result in 2-amino-1,3,4-oxadiazole with the precipitation of elemental selenium.

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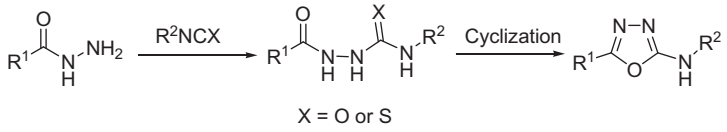
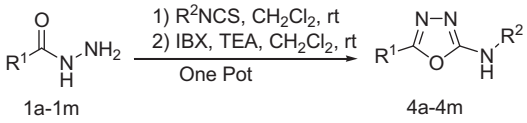
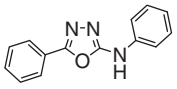
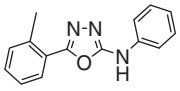
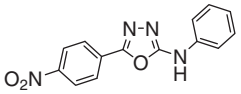
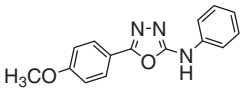
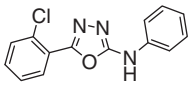
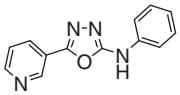
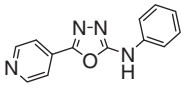
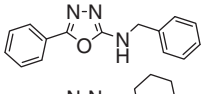
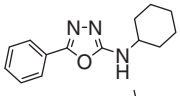
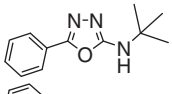
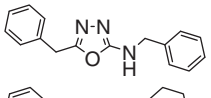
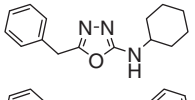
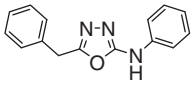


Scheme 1. Two step strategies for the preparation of 2-amino-1,3,4-oxadiazoles.



Scheme 2. One pot synthesis of 2-amino-1,3,4-oxadiazoles.

Table 1
List of 2-amino-1,3,4-oxadiazoles prepared

Entry	Hydrazide (**1**) R^1	Isothiocyanate (**2**) R^2	Product (**4**)	Yield[a] (%)
a	C_6H_5	C_6H_5		92
b	2-$CH_3C_6H_4$	C_6H_5		86
c	3-$NO_2C_6H_4$	C_6H_5		85
d	4-$CH_3OC_6H_4$	C_6H_5		83
e	2-ClC_6H_4	C_6H_5		84
f	3-C_4H_4N	C_6H_5		83
g	4-C_4H_4N	C_6H_5		86
h	C_6H_5	$C_6H_5CH_2$		84
i	C_6H_5	C_6H_{11}		82
j	C_6H_5	C_4H_9		80
k	$C_6H_5CH_2$	$C_6H_5CH_2$		86
l	$C_6H_5CH_2$	C_6H_{11}		84
m	$C_6H_5CH_2$	C_6H_5		88

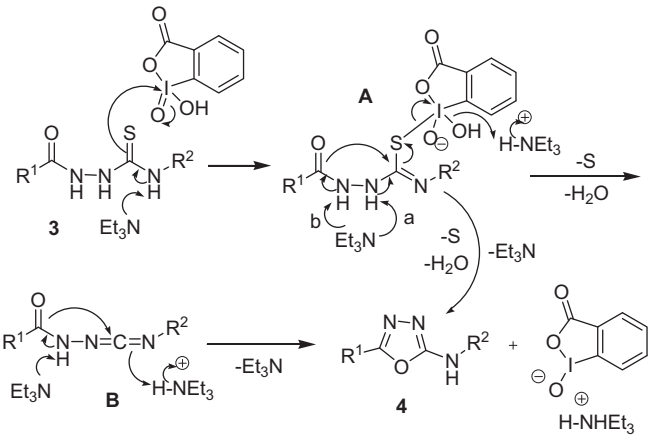
[a] Isolated yield.

Thus, we tried to explore IBX for dehydrothiolative cyclization of acylthiosemicarbazide, to obtain 2-amino-1,3,4-oxadiazoles. We envisioned that due to the polarizability of sulfur and thiophilic nature of hypervalent iodine reagents, thiosemicarbazide could be activated by IBX affording an intermediate which is more prone toward cyclization (Scheme 2) and consequently we employed this strategy for one pot synthesis of 2-amino-1,3,4-oxadiazoles directly from acylhydrazides.

In a typical reaction, phenylisothiocyanate **1b** was treated with benzoylhydrazide **1a** in CH_2Cl_2 at rt. After completion of reaction (by TLC), the intermediate acylthiosemicarbazide was directly treated with triethylamine (TEA, 2 equiv) and IBX (1 equiv) added portion wise with continued stirring. Gratifyingly, within 15 min the required oxadiazole was formed in 92% isolated yield.[11] The reaction conditions were optimized with respect to solvents such as DMF, MeCN, EtOAc, THF, and equivalents of IBX and TEA. However, molar ratio of 1:1:2 for substrate/IBX/TEA in CH_2Cl_2 as solvent was found to be efficient and cleaner. Lesser equivalents of TEA resulted in lower yield of final product. These results encouraged us to examine the generality of this protocol. Thus, a variety of acylhydrazides and isothiocyanates were subjected to the afore-mentioned protocol (Table 1). In all cases complete conversion to amino oxadiazoles in good yields and purity was obtained under very mild conditions (Table 1, entries a–m).

In analogy with the literature reports of desulfurization by hypervalent iodine reagents,[9] the following mechanism (Scheme 3) was proposed for the cyclodesulfurization of acylthiosemicarbazides by IBX. Initially the nucleophilic attack of S on the electrophilic iodine of IBX will form intermediate **A**. Then TEA assisted desulfurization (path **a**) leads to carbodiimide intermediate **B** and subsequent cyclization resulting in 2-amino-1,3,4-oxadiazole. In a second pathway **b**, cyclization may be effected by direct nucleophilic attack by carbonyl oxygen assisted by TEA. The precipitation of elemental sulfur supports the proposed mechanism.

The generality of methodology has further been demonstrated by an example of cyclodeselenization of intermediate acylselenosemicarbazide, wherein the optimized conditions were tested for *N*-phenylisoselenocyanate and benzoylhydrazide **1a** in CH_2Cl_2 at rt in one pot. As expected, cyclodeselenization was found to be



Scheme 3. Plausible mechanism for the formation of 2-amino-1,3,4-oxadiazole **4** from thiosemicarbazide **3**.

complete within 10 min of the addition of IBX, giving same product **4a**. The yield was comparable to that of cyclodesulfurization at 91% and thus, this protocol can be extended to other substrates as well. Hence, it was evident that the IBX reagent works efficiently for cyclodelfurization/cyclodeselenization resulting in required 2-amino-1,3,4-oxadizoles in good yields and purity.

In summary, the present methodology provides a robust one-pot approach for efficient preparation of a variety of 2-amino-1,3,4-oxadiazoles in good yields. Important feature of this methodology is that the acylthiosemicarbazides were prepared in situ and subjected to subsequent cyclization without purification using IBX within a short duration of time, thus resulting in a hassle-free and convenient one-pot synthesis. Thus, this strategy provides rapid access to a wide variety of 2-amino-1,3,4-oxadiazoles under mild conditions at room temperature.

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11. Typical experimental procedure for the synthesis of 2-amino-1,3,4-oxadiazoles **4**. Benzoyl hydrazide **1a** (1.0 mmol) and phenylisothiocyanate **1b** (1.0 mmol) were combined in CH_2Cl_2 (5 mL) at room temperature and the resultant solution was stirred for 3 h. Completion of the reaction was checked by TLC, then TEA (2.0 mmol) was added under stirring, followed by addition of IBX (1.0 mmol) portion wise and stirring was continued further for 15 min. After completion of the reaction by TLC, the crude reaction mass was quenched with 10% $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 (2×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, which was then admixed with silica gel and subjected to column chromatography using EtOAc:hexane mixture as eluent to isolate the analytically pure compound. Spectroscopic data for representative compounds: *N*,5-Diphenyl-1,3,4-oxadiazol-2-amine[6] (**4a**): Yield 92%; white solid; mp 218 °C (lit. 218–220 °C); IR (KBr, thin film) ν_{max} (cm^{-1}): 3386, 3060, 1562, 1498, 1442; ^1H NMR (300 MHz, DMSO-d_6): δ 7.02 (t, J = 7.4 Hz, 1H), 7.35 (t, J = 7.6 Hz, 2H), 7.56–7.65 (m, 5H), 7.89–7.92 (m, 2H), 10.66 (br, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 117.1, 121.9, 123.9, 125.5, 129.1, 129.4, 131.0, 138.6, 159.9, 157.7; HRMS calcd for $C_{14}H_{11}N_3O$ m/z 237.0902, found 260.1174 $[M+Na]^+$. *N*,5-Dibenzyl-1,3,4-oxadiazole-2-amine[5a] (**4k**): Yield 86%; white solid; mp 122–123 °C (lit. 120–122 °C); IR (KBr, thin film) ν_{max} (cm^{-1}): 3334, 3032, 1548, 1468, 1422; ^1H NMR (300 MHz, DMSO-d_6): δ 4.03 (s, 2H), 4.35 (s, 2H), 7.24 (dd, J = 7.6, 8.4 Hz, 2H), 7.28–7.30 (dd, J = 7.6, 8.4 Hz, 2H), 7.36–7.39 (m, 3H), 7.54 (m, 3H), 8.04 (t, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.8, 157.8, 138.9, 130.7, 129.4, 128.5, 127.6, 127.2, 125.3, 124.4, 46.1, 34.5; HRMS calcd for $C_{16}H_{15}N_3O$ m/z 265.1215, found 288.1411 $[M+Na]^+$.