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Oxidative cyclization of aldazines with bis(trifluoroacetoxy)iodobenzene

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Abstract—Symmetrical and unsymmetrical aldazines are efficiently converted to 2,5-disubstituted-1,3,4-oxadiazoles by oxidation with bis(trifluoroacetoxy)iodobenzene (BTI).
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1. Introduction

Symmetrical and unsymmetrical 1,3,4-oxadiazoles have been reported to be biologically versatile compounds displaying a variety of biological effects, which include antiinflammatory,[1] antifungal,[2] antiparasitic,[3] and antimicrobial[4] activities. In addition, they have been utilized as bioisosteres of the carboxamide moiety in benzodiazepine receptor agonists,[5a] muscarinic receptor agonists,[5b] NK1 receptor antagonists,[5c] and Phe-Gly peptidomimetics.[5d] Moreover, oxadiazole derivatives have been widely used as electron conducting and hole blocking materials in molecule-based as well as polymeric light-emitting devices (LEDs) due to the electron deficient and favorable electron transport properties of oxadiazole rings.[6]

The most common synthetic approach to 1,3,4-oxadiazoles involves cyclodehydration of 1,2-diacylhydrazines **1** (Scheme 1). Typically, this reaction is carried out by using thionyl chloride,[7] phosphorous oxychloride,[8] phosphorous pentoxide,[9] triphenylphosphine,[10] or trifluoromethane–sulfonic anhydride as the dehydrating agent.[11] Related preparations of oxadiazoles include the reaction of hydrazides with ketenylidene triphenylphosphorane,[12] base promoted cyclization of trichloroacetyl hydrazones,[13] and condensation of hydrazine with 2-acyl-4,5-dichloropyrid-azin-3-ones in polyphosphoric acid (PPA) or $BF_3{\cdot}OEt_2$.[14] Although these methods are very useful for the preparation of large quantities of materials due to the ready availability of diacylhydrazines, hydrazides, and hydrazones as starting materials, the reaction conditions tend to be harsh and long reaction times are generally needed.

An alternative route to 1,3,4-oxadiazoles **2** by oxidative cyclization from the corresponding aldehyde *N*-acylhydrazones **3** proceeds with lead tetraacetate,[15a] lead(IV) oxide,[15b] potassium permanganate,[15c] electro-chemical methods,[15d] iodobenzene diacetate (IBD),[15e] or chloramine T.[15f] The use of azines as oxidative cyclization precursors, however, is limited to a single example of Gillis and Lamontagne who reported that benzalazine can be oxidized to 2,5-diphenyl-1,3,4-oxadiazole with 2 equiv of lead tetraacetate in benzene.[16]

Herein we report that aldazines **4** react smoothly with the organic iodine(III) reagent, bis(trifluoroacetoxy)iodobenzene (BTI), at room temperature to efficiently afford 2,5-disubstituted 1,3,4-oxadiazoles **5** in good yields (Scheme 2). Initial studies indicated that, among the solvents that were surveyed, DMSO is the best solvent for this oxidation (Table 1). Symmetrical and unsymmetrical aldazines are oxidized to symmetrical and unsymmetrical 1,3,4-oxadiazoles with equal facility (Table 2). The use of DMSO as solvent and BTI as oxidant gave good results in most of the cases examined (products **5a**–**f**, **j**, and **k**). When the aldazine **4** contains a hydroxyl group (product **5g**), the reaction proceeded rapidly, but the yield was lower than for other examples. Generally, molecules **4** with electron-donating moieties on the aromatic rings (product **5e**) gave better yields and required shorter reaction times than those with

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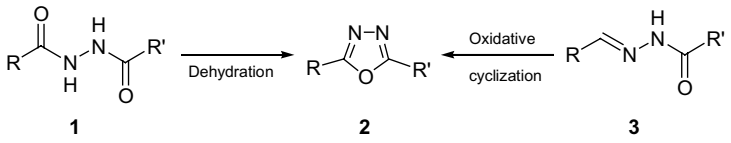
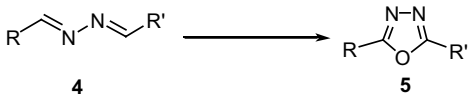


Scheme 1.



Scheme 2.

electron-withdrawing moieties (product **5h**) possibly due to resonance stabilization by the methoxy group on the proposed nitrenium ion intermediate (Scheme 3). The reaction also proceeded well with heteroaromatic aldazines such as furfuralazine (product **5f**) and 2-furfural-*p*-tolylazine (product **5k**) to yield the oxadiazoles in 69% and 80%, respectively. Substrates such as 4,4′-dibromobenzalazine, 4,4′-dinitrobenzalazine, and 2,2′,4,4′-tetrachlorobenzalazine failed to cyclize probably due to their poor solubility in DMSO. Isobutyraldehyde and propionaldehyde azine derivatives also failed to give the oxadiazole products.

Commercially available BTI is commonly used as an efficient oxidizing reagent in organic synthesis. Many applications of BTI have been reported[17] a reflection both of its mild reactivity along with a low side-product profile. In the current report, similar advantages of this reagent, mild reactivity and cleanly prepared products, were observed. A related oxidant, iodobenzene diacetate has been used to convert an aldazine to an aldehyde dimethylacetal in alcohol;[18] however, a change of solvent from alcohol to $CHCl_3$ in this reaction did not yield any oxidative cyclization product even after 12 h at room temperature (unreported results).

A proposal for the reaction mechanism is shown in Scheme 3. The imine moiety of **4** can be oxidized to nitrenium ion **6** (Scheme 3), which in turn may react with the trifluoroacetate counter ion to afford after elimination of iodobenzene and trifluoroacetic acid, iminoanhydride **8**. This intermediate can then cyclize to **10**, which after reaction with a second equivalent of BTI, and elimination of iodobenzene, trifluoroacetic acid, and rearrangement byproduct **15** (pathway A) or trifluoroacetic anhydride (pathway B), would give the product **5**. When the reaction is carried out in DMSO, pathway A may be preferred; pathway B may operate in non-nucleophilic solvents. In support of pathway B, trifluoroacetic anhydride formation was indirectly studied by adding 3,4,5-trimethoxy-phenylamine to the reaction mixture resulting in the formation of 2,2,2-trifluoro-*N*-(3,4,5-trimethoxy-phenyl)-acetamide (unreported results).

The reported method of preparing 2,5-diaryl-1,3,4-oxadiazoles is operationally simple, rapid, and gives good yields. As the reaction conditions are extremely mild, it could be a generally useful method for the synthesis of a wide variety of oxadiazole containing compounds.

2. General procedure

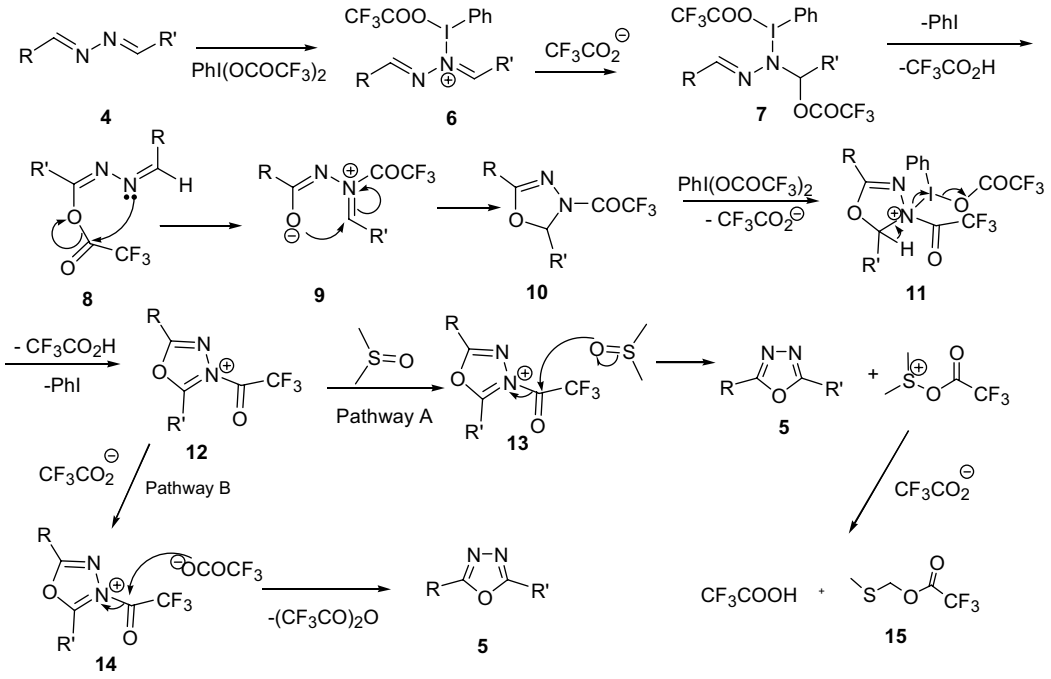
A dried round-bottomed flask was charged with aldazine (0.5 mmol),[19] bis(trifluoroacetoxy)iodobenzene (BTI, 1.1 mmol), and anhydrous DMSO (10 mL). This

Table 1. Solvent effect on oxidation of benzalazine with BTI

Solvents	DMSO	$CHCl_3$	CH_2Cl_2	THF	Dioxane	MeCN
Reaction time (min)	5	90	100	240	300	30
Yield (%)	69	40	35	—	—	20

Table 2. Oxidative cyclization of aldazines with bis(trifluoroacetoxy)iodobenzene

Product	R	R′	Reaction time (min)	Isolated Yield (%)
5a	Ph	Ph	5	69
5b	*p*-MeC_6H_4	*p*-MeC_6H_4	10	83
5c	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	10	71
5d	*o*-$MeOC_6H_4$	*o*-$MeOC_6H_4$	13	77
5e	3,4-$(MeO)_2C_6H_3$	3,4-$(MeO)_2C_6H_3$	35	85
5f	2-Furyl	2-Furyl	4	65
5g	*p*-OHC_6H_4	*p*-OHC_6H_4	3	49
5h	4,5-$(MeO)_2$-2-nitroC_6H_2	4,5-$(MeO)_2$-2-nitroC_6H_2	65	53
5i	Ph	*p*-$MeOC_6H_4$	10	68
5j	*p*-MeC_6H_4	*p*-$MeOC_6H_4$	7	76
5k	*p*-MeC_6H_4	2-Furyl	6	80



Scheme 3.

mixture was stirred at room temperature (above 30 °C) and monitored by TLC. When the reaction was complete, purification of the product directly by flash chromatography (silica gel, ethyl acetate–petroleum ether) afforded 2,5-disubstituted 1,3,4-oxadiazoles as solids.

^{1}H NMR (400 MHz, $CDCl_3$) compound **5a**: 7.51–8.14 (m, 10H), 137–138 °C (lit.[8b] mp 138 °C; lit.[14] mp 132–133 °C); **5b**: 2.41 (s, 6H), 7.29–7.31 (d, 4H, J = 8.0 Hz), 7.98–8.00 (d, 4H, J = 8.0 Hz) 179–180 °C (lit.[8b] mp 175 °C; lit.[15c] mp 187 °C in ethanol); **5c**: 3.86 (s, 6H), 6.99–7.01 (m, 4H), 8.02–8.05 (dd, 4H, J = 1.6 Hz, J = 7.2 Hz) 159–161 °C (lit.[8b] mp 161.5 °C); compound **5d**: 3.95 (s, 6H), 7.03–7.07 (m, 4H), 7.45–7.49 (m, 2H), 7.97–7.99 (dd, 2H, J = 1.6 Hz, J = 1.6 Hz) 115–116 °C (lit.[8b] 99.5 °C); **5e**: 3.95 (s, 6H), 3.98 (s, 6H), 6.96 (d, 2H, J = 8.4 Hz), 7.63–7.68 (m, 4H) ^{13}C NMR 56.0, 56.2, 109.5, 111.1, 116.6, 120.3, 149.4, 151.9, 164.2; 179–181 °C; compound **5f**: 6.59–6.60 (dd, 2H, J = 1.6 Hz, J = 3.6 Hz), 7.21–7.22 (dd, 2H, J = 0.8 Hz, J = 3.6 Hz), 7.64–7.65 (dd, 2H, J = 0.8 Hz, J = 1.6 Hz) 143–144 °C (lit.[14] mp 136–138 °C); compound **5h**: 3.84 (s, 6H), 3.90 (s, 6H), 7.38 (s, 2H), 7.65 (s, 2H); ^{13}C NMR 56.4, 56.4, 62.8, 108.2, 111.0, 132.3, 139.8, 148.0, 153.9; 205–207 °C; compound **5i**: 3.86 (s, 3H), 6.99–7.02 (dd, 2H, J = 2.0 Hz, J = 2.8 Hz), 7.49–7.52 (m, 3H), 8.04–8.06 (dd, 2H, J = 2.0 Hz, J = 2.8 Hz), 8.09–8.11 (m, 2H) 148–149 °C (lit.[15b] mp 150 °C); compound **5j**: 2.41 (s, 3H), 3.86 (s, 3H), 6.99–7.02 (m, 2H), 7.29–7.31 (d, 2H, J = 8.0 Hz), 7.97–7.99 (d, 2H, J = 8.4 Hz), 8.03–8.06 (m, 2H) 148–150 °C (lit.[15c] mp 150 °C in methanol); compound **5k**: 2.40 (s, 3H), 6.58–6.60 (m, 1H), 7.18–7.19 (d, 1H, J = 3.6 Hz), 7.28–7.30 (d, 2H, J = 8.4 Hz), 7.63–7.64 (m, 1H), 7.96–7.98 (d, 2H, J = 8.0 Hz) 131–132 °C (lit.[15f] mp 137–138 °C); ^{1}H NMR (400 MHz, DMSO); compound **5g**: 6.94–6.97 (d, 4H, J = 8.8 Hz), 7.90–7.92 (d, 4H, J = 8.8 Hz), 10.25 (s, 2H) >340 °C (lit.[8b] mp 350 °C).

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