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Superior Reactivity of Thiosemicarbazides in the Synthesis of 2-Amino-1,3,4-oxadiazoles

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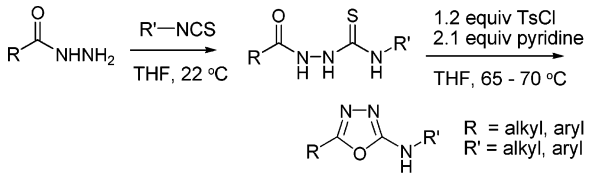


A facile and general protocol for the preparation of 2-amino-1,3,4-oxadiazoles is reported. This method relies on a tosyl chloride/pyridine-mediated cyclization of a thiosemicarbazide, which is readily prepared by acylation of a given hydrazide with the appropriate isothiocyanate. Cyclization of the thiosemicarbazide consistently outperforms the analogous semicarbazide cyclization under these conditions, for 18 distinct examples. Utilizing this protocol, we have prepared 5-alkyl- and 5-aryl-2-amino-1,3,4-oxadiazoles in 78−99% yield.

1,3,4-Oxadiazoles are commonly utilized pharmacophores due to their metabolic profile and ability to engage in hydrogen bonding. In particular, marketed antihypertensive agents such as tiodazosin[1] and nesapidil[2] as well as antibiotics such as furamizole[3] contain the oxadiazole nucleus (Figure 1). 2-Amino-1,3,4-oxadiazoles have demonstrated biological activity as muscle relaxants[4] and antiomitotics,[5] while 2,5-diaryl-1,3,4-oxadiazoles are known to be platelet aggregation inhibitors.[6] 5-Aryl-2-hydroxymethyl-1,3,4-oxadiazoles have shown diuretic, analgesic, antiinflammatory, anticonvulsive, and antiemetic properties,[7] and 2-hydroxyphenyl-1,3,4-oxadiazoles behave as hypnotics and sedatives.[8] The widespread use of 1,3,4-oxadiazoles as a scaffold in medicinal chemistry as demonstrated by these examples establishes this moiety as a member of the privileged structures class. However, despite their common use, most reported methods to prepare 1,3,4-oxadiazoles suffer from harsh conditions or stoichiometric formation of an intractable byproduct. Typically, 2-amino-1,3,4-oxadiazoles are prepared by cyclization of the corresponding acyclic semicarbazide or thiosemicarbazide derivatives (Scheme 1). As part of an ongoing research program, we were interested in the development of a robust and general method to access functionalized 2-amino-1,3,4-oxadiazoles.

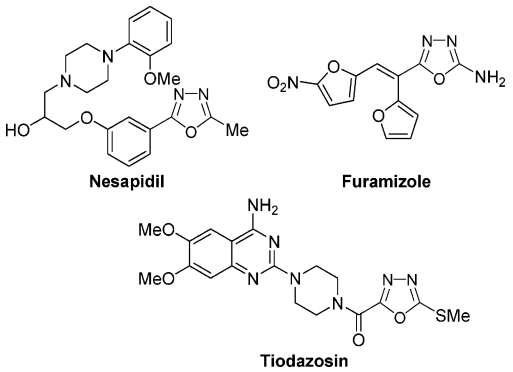
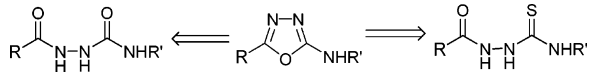


FIGURE 1. Some pharmaceutical products which contain the oxadiazole core.

SCHEME 1. 2-Amino-1,3,4-oxadiazoles Are Accessible from the Semicarbazide or Thiosemicarbazide



Approaches based on cyclo-dehydration of semicarbazides are generally used and typically require harsh reagents such as $POCl_3$[9] or concentrated sulfuric acid.[10] Alternatively, reagents that activate one carbonyl group to promote cyclization have been used. Such reagents include phosphonium salts[11] and Burgess-type reagents;[12] however, these reagents result in significant byproduct formation and have typically been restricted to use in solid-phase synthesis strategies. When thi-

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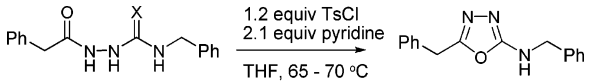
osemicarbazides are used as oxadiazole precursors, H_2S scavengers, such as stoichiometric mercuric[13] or lead oxide,[14] can be used to effect cyclization. A common, more environmentally benign alternative is activation of sulfur through iodine-mediated oxidation in the presence of base.[15] Selective activation of the sulfur moiety followed by cyclization has been achieved by coupling reagents such as DCC[16] and EDC[17] as well as highly reactive alkylating agents such as methyl iodide[18] and ethyl bromoacetate.[19]

Recently, the Boger group reported an intriguing method to prepare 2-amino-1,3,4-oxadiazoles via cyclo-dehydration of an ester semicarbazide mediated by tosyl chloride and base at room temperature.[20] We were attracted to this strategy due to the low cost of reagents and mild reaction conditions. However, when we used the reported conditions with semicarbazide **1a**, we observed less than 5% conversion to oxadiazole **2**, even after 48 h. After some modification, we were able to obtain a modest 23% conversion after 20 h at reflux in THF with pyridine as base (Scheme 2). In an effort to improve reactivity, we turned our attention to the thiosemicarbazide analogue. We envisioned that due to the polarizability of sulfur vs oxygen the related thiosemicarbazide could also be activated toward cyclization by tosyl chloride, affording an intermediate more predisposed to cyclization. Gratifyingly, when thiosemicarbazide **1b** was treated with tosyl chloride and pyridine in THF at reflux, >99% conversion to the desired oxadiazole was observed within 5 h. Encouraged by this result, we set out to examine the generality of this reaction. Thus, a variety of semicarbazides, and the related thio analogues, were prepared in order to directly compare their reactivity in the tosyl chloride/pyridine mediated cyclization protocol.

SCHEME 2. Cyclization of Semicarbazides 1a and 1b



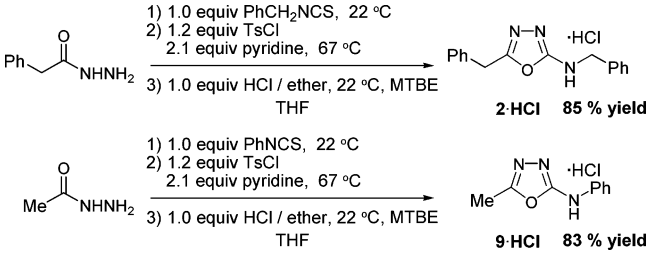
1a, X = O: 23 % conv after 20 h
1b, X = S: 99 % conv after 5 h

2

We found that for various semicarbazides and thiosemicarbazides higher reactivty of the thio analogue is a general trend, as shown in Table 1. 5-Benzyloxadiazoles with primary, secondary, and tertiary alkylamines in the 2-position (entries 1−6) were prepared in 78−89% yield from thiosemicarbazide precursors. In contrast, semicarbazide precursors showed significantly lower conversion under the same conditions for all examples. 2-Benzylamino-oxadiazoles with both linear and branched alkyl groups in the 5-position (entries 7−12) were readily prepared in 85−93% yield. Oxadiazoles with either electron-donating or electron-withdrawing alkyl groups in the 5-position were prepared in 95−99% yield from thiosemicarbazides; less than 30% conversion was observed for the corresponding semicarbazides (entries 13−18). A variety of 5-aryl- and 5-heteroaryloxadiazoles were also prepared in high yield, with 2-benzylamino (entries 19−26), 2-*tert*-butylamino (entries 27−32), and 2-phenylamino (entries 33−36) substituents. It is interesting to note that while semicarbazides in general afforded less than 30% conversion after 20 h, a few examples (entries 4, 10, and 26) did show greater than 50% conversion. However, in each of these cases, the analagous thiosemicarbazide (entries 3, 9, 25) proceeded to >95% conversion within 3.5 h.

Semicarbazides and thiosemicarbazides were readily prepared by acylation of commercially available hydrazides with the requisite isocyanate or isothiocyanate.[21] Although most thiosemicarbazides can be readily purified by precipitation from the crude acylation reaction mixture, this is unnecessary.[22] Thus, when the crude slurry from acylation of a given hydrazide with isothiocyanate was treated with tosyl chloride and pyridine at reflux in THF, the requisite oxadiazole was obtained in 83−85% yield after workup and HCl salt formation (Scheme 3). This two-step, one-pot procedure provides access to a variety of 2-amino-oxadiazoles in an efficient manner.

SCHEME 3. One-Pot Acylation/Cyclization



In summary, this work has established that tosyl chloride effectively activates thiosemicarbazides toward cyclization to afford the related 2-amino-1,3,4-oxadiazoles. Thiosemicarbazides have consistently exhibited a higher rate of cyclization than the corresponding semicarbazides. This methodology provides an efficient preparation for a variety of 5-alkyl- and 5-aryl-2-amino-1,3,4-oxadiazoles. As an additional feature, the parent thiosemicarbazides can be prepared in situ and used without purification in the subsequent cyclization step, thereby making the synthesis a convenient two-step, one-pot process. This process provides a means to rapidly prepare a wide variety of oxadiazoles as part of any high-throughput screening program or a robust method for use in development.

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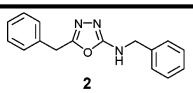
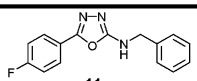
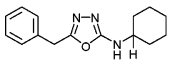
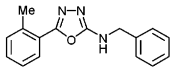
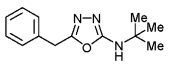
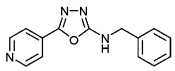
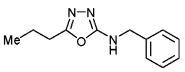
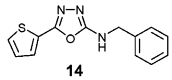
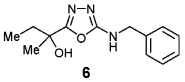
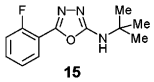
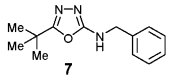
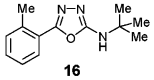
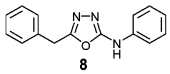
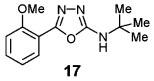
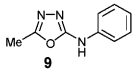
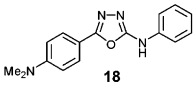
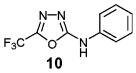
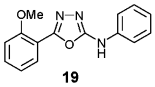
TABLE 1. Preparation of 2-Amino-oxadiazoles via Tosyl Chloride-Mediated Cyclization[a]

entry	X=	product	conv[b] (%)	yield[c] (%)	entry	X=	product	conv[b] (%)	yield[c] (%)
1	S	 **2**	99	89 (84)[e]	19	S	 **11**	99	82 (82)[d]
2	O		23	ND	20	O		19	ND
3	S	 **3**	99	79 (73)[e]	21	S	 **12**	99	99 (87)[d]
4	O		69	49	22	O		27	ND
5	S	 **4**	99	78 (58)[e]	23	S	 **13**	99	90 (85)[d]
6	O		28	ND	24	O		16	ND
7	S	 **5**	97	87 (*35*)[f]	25	S	 **14**	99	90 (82)[d]
8	O		43	31	26	O		61	43
9	S	 **6**	99	88 (64)[e]	27	S	 **15**	99	89 (88)[e]
10	O		61	45	28	O		13	ND
11	S	 **7**	99	93 (70)[e]	29	S	 **16**	99	78 (57)[e]
12	O		35	ND	30	O		27	ND
13	S	 **8**	99	95 (80)[e]	31	S	 **17**	99	93 (74)[e]
14	O		5	ND	32	O		0	ND
15	S	 **9**	99	99 (76)[e]	33	S	 **18**	99	85 (78)[d]
16	O		29	ND	34	O		0	ND
17	S	 **10**	99	99 (95)[e]	35	S	 **19**	99	96 (85)[e]
18	O		0	ND	36	O		0	ND

[a] Reaction conditions: substrate treated with 1.2 equiv of TsCl and 2.1 equiv of pyridine in THF at 65−70 °C for 20 h. [b] Conversion determined by relative HPLC (A%) vs authentic standard. [c] Assay yield determined by HPLC vs authentic standard. [d] Isolated yield after trituration in THF/MTBE. [e] Isolated yield of HCl salt after treatment of THF solution of free base with 1 equiv of ethereal HCl and addition of MTBE. [f] Isolated yield after purification via column chromatography on silica gel.

Experimental Section

Representative Procedure for Stepwise Oxadiazole Preparation. *N*-Benzylphenylacetic Acid Thiosemicarbazide (1b). Phenyl acetic acid hydrazide (2.0 g, 13.3 mmol) and benzyl isothiocyanate (1.77 mL, 13.3 mmol) were combined in THF (50 mL) at room temperature. The resultant solution was stirred for 18 h, and then volatiles were removed in vacuo to afford an off-white solid. The solid was suspended and triturated in MTBE (50 mL) for 1 h and then filtered to afford 3.80 g (95% yield) of the desired thiosemicarbazide; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.0 (s, 1H) 9.35 (s, 1H) 8.51 (s (br), 1H) 7.25 (m, 10H) 4.73 (d, J = 6.0 Hz, 2H) 3.47 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.9 139.2 135.4 129.3 128.1 128.0 127.0 126.5 46.7; HPLC t_R 6.78 min; mp 170.1−171.0 °C; IR 3336.3 (s), 3201.9 (s), 3030.4 (s), 1948.5 (w), 1683.2 (s), 1653.5 (s), 1604.6 (m), 1555.2 (s), 1492.8 (s), 1378.1 (s), 1292.5 (s), 1186.8 (s), 1074.5 (s); HRMS calcd for $C_{16}H_{17}N_3OS$ 300.1171, found 300.1174.

Benzyl(5-benzyl[1,3,4]oxadiazol-2-yl)amine·HCl (2). *N*-Benzylphenylacetic acid thiosemicarbazide **1b** (2.05 g, 6.85 mmol), tosyl chloride (1.57 g, 8.22 mmol), and pyridine (1.16 mL, 14.4 mmol) were combined in THF (30 mL) in a 100 mL round-bottom flask fitted with a magnetic stir bar, reflux condenser, and nitrogen inlet. The solution was heated in a 70 °C oil bath to bring the mixture to reflux for 20 h and then cooled to room temperature. An aliquot of the crude reaction mixture indicated complete conversion (no thiosemicarbazide visible by LC) to the oxadiazole, with 97% assay yield. EtOAc (20 mL) and 1 N HCl (20 mL) were added; the mixture was vigorously stirred for 5 min, and then the aqueous layer was removed. The aqueous layer was back-extracted with EtOAc (20 mL), and then the combined organic layers were flushed with heptane (2 × 75 mL) and the material was concentrated to an orange slurry. The material was dissolved in ∼10 mL of THF and filtered over Solka-Floc. HCl (3.43 mL, 2.0 M in diethyl ether) was added to the solution. After the mixture was stirred for 30 min at room temperature, a thin slurry was obtained. MTBE was added dropwise to the slurry (25 mL) and the resultant mixture stirred for an additional 25 min. The slurry was filtered to afford 1.74 g of shiny white powder (84% yield): ^{1}H NMR (400 MHz,

DMSO-d_6) δ 7.99 (t, J = 6.0 Hz, 1H) 7.30 (m, 10H) 4.31 (d, J = 6.0 Hz, 2H) 4.04 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.7 158.5 138.8 135.1 128.7 128.3 127.3 127.1 127.0 46.0 30.9; HPLC t_R 7.79 min; mp 157.0 − 157.5 °C; IR 2948.7 (m), 2550.5 (m), 1734.8 (s), 1714.7 (s), 1638.3 (s), 1496.8 (m), 1453.8 (m), 1415.1 (w), 1214.4 (w), 1011.0 (m); HRMS calcd for $C_{16}H_{15}N_3O$ 266.1293, found 266.1290.

Representative Procedure for One-Pot Oxadiazole Preparation. Benzyl(5-benzyl[1,3,4]oxadiazol-2-yl)amine·HCl (2). Phenylacetic acid hydrazide (2.17 g, 14.4 mmol) and benzyl isothiocyanate (1.92 mL, 14.4 mmol) were combined in THF (50 mL) in a 100-mL round-bottom flask at room temperature and stirred for 18 h. Tosyl chloride (3.30 g, 17.3 mmol) and pyridine (2.45 mL, 30.3 mmol) were added to the reaction mixture. The flask was fitted with a reflux condenser and nitrogen inlet and submerged into a 70 °C oil bath. The solution was heated to reflux in an oil bath for 20 h and then cooled to room temperature. An aliquot of the crude reaction mixture indicated complete conversion (no thiosemicarbazide visible by LC) to the oxadiazole, with 97% assay yield. EtOAc (50 mL) and 1 N HCl (50 mL) were added; the mixture was vigorously stirred for 5 min, and then the aqueous layer was removed. The aqueous layer was back-extracted with EtOAc (50 mL), and then the combined organic layers were flushed with heptane (2 × 150 mL) and the material was concentrated to an orange slurry. The material was dissolved in ∼35 mL of THF and filtered over Solka-Floc. HCl (14.4 mL, 1.0 M in diethyl ether) was added to the solution. After the mixture was stirred 30 min at room temperature, a thin slurry was obtained. MTBE was added dropwise to the slurry (70 mL) and the resultant mixture stirred an additional 25 min. The slurry was filtered to afford 3.70 g of shiny white powder (85% yield). Spectral data matched that found for material prepared via a stepwise procedure.

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Supporting Information Available: Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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