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An efficient one-pot synthesis of 3-substituted-5-amino-1,2,4-thiadiazoles from isothiocyanates and amidines

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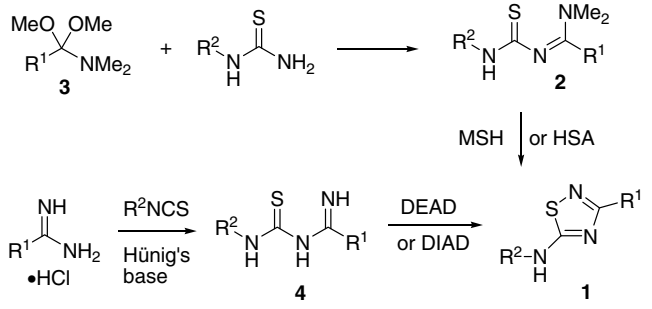
This Letter is dedicated to Professor E. J. Corey on the occasion of his 80th birthday

Abstract

An efficient one-pot synthesis of 3-substituted-5-amino-1,2,4-thiadiazoles from isothiocyanates and amidines is described.

In a recent medicinal chemistry program, we desired easy access to a series of 3-substituted-5-amino-1,2,4-thiadiazoles **1**. These compounds have been reported to have a broad spectrum of biological activity including antibacterial,[1] anti-inflammatory,[2] antiulcerative,[3] and antidiabetic.[4] Even though many methodologies exist for the preparation of thiadiazoles **1**,[5] only two of them meet our basic criteria for high speed analoging (Scheme 1). The first approach involves the amination of *N*′-carbamothioyl-*N*,*N*-dimethylamidines **2** with *O*-(mesitylenesulfonyl)hydroxylamine (MSH) or hydroxyamine-*O*-sulfonic acid (HSA) followed by cyclization.[6] Amidines **2** are made from thioureas and *N*,*N*-dimethylalkanamide dimethyl acetals **3** by condensation. As acetals **3** are not easily accessible with the exception of a few simple ones (R^1 = H, Me), this method has limited application for our purpose. The other route is based on the oxidative heterocyclization of thioacylguanidines **4**.[5] Typical oxidizing agents are bromine, NCS, NBS, iodine, nitric acid, acidic hydrogen peroxide, and arylsulfonyl halides in the presence of pyridine. Unfortunately, these reagents suffer from undesirable side reactions such as halogenation and oxidative degradation. More recently, Furukawa and co-workers carried out S–N heterocyclization using diethyl azodicarboxylate (DEAD) under mild and neutral conditions.[7] However, there are only three relatively simple 3-phenyl-*N*-aryl-1,2,4-thiadiazol-5-amines described in the report, and the yields are moderate (40–63%). To our knowledge, there have been no other reports applying this methodology to the synthesis of thiadiazoles. Therefore, in the outset of our medicinal chemistry program, we sought to investigate the scope of this DEAD-induced heterocyclization and also improve the yield of this reaction. This report describes the development of an efficient one-pot synthesis of 1,2,4-thiadiazoles **1** from isothiocyanates and amidines.



Scheme 1. Two representative approaches to 3-substituted-5-amino-1,2,4-thiadiazoles.

The orginal procedure for the thiadiazole formation from thioacylguanidines **4** requires 2 equiv of DEAD and

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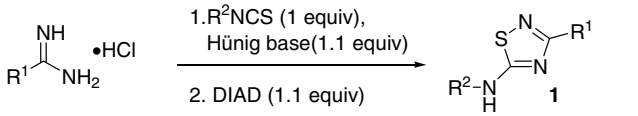
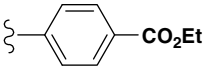
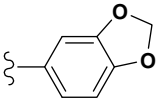
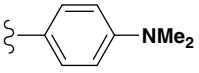
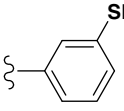
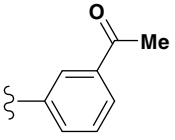
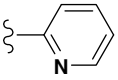
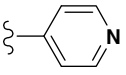
ethanol as a solvent.[7] We have recently re-examined this reaction by using both diisopropyl azodicarboxylate (DIAD) and DEAD, and by varying solvent, concentration, and the ratio of the reagent versus the substrate. Our studies showed that DMF is a more suitable solvent than ethanol because the solubility of some substrates in ethanol is limited. In addition, we obtained slightly improved yields with DIAD over DEAD (vide infra), and for this reason, we applied DIAD throughout this methodology. We also found that 1.1 equiv of DIAD is sufficient to bring about complete cyclization. In several instances where DIAD was added in large excess (e.g., 2 equiv), removal of the excessive reagent from the cyclized products proved to be difficult and tedious by silica gel chromatography. Thus, our optimized conditions include 1.1 equiv of DIAD, 0.80 M concentration, and DMF as a solvent. In all cases studied, the cyclization was complete within 5–30 min as shown by TLC or LC/MS analysis. As a rule of thumb, the disappearance of the orange color of DIAD indicates the completion of the cyclization.

With the conditions for the cyclization established, we turned our attention to the synthesis of the cyclization precursors, thioacylguanidines **4**. In most cases, the addition of isothiocyanates with amidine hydrochlorides in the presence of Hünig's base in DMF proceeded cleanly as shown by LC/MS and TLC analyses. However, the isolated yields of thioacylguanidines were moderate due to loss during work-up and subsequent purification as they are quite insoluble in many solvent systems. To this end, it was logical to determine if 1,2,4-thiadiazoles **1** can be prepared from isothiocyanates and amidines without the isolation of the intermediate thioacylguanidines **4**. Indeed, the treatment of isothiocyanatobenzene (1.0 equiv) with benzimidamide hydrochloride (1.0 equiv) and Hünig's base (1.1 equiv) in DMF at room temperature for 12 h followed by the addition of DEAD (1.1 equiv) generated *N*,3-diphenyl-1,2,4-thiadiazol-5-amine in 75% yield. When the same reaction was carried out using DIAD instead of DEAD, the yield was increased to 82% (entry 1). This is a significant improvement over the 63% yield obtained from *N*-(phenylcarbamothioyl)benzimidamide (**4**, $R^1 = R^2 = Ph$) using 2 equiv of DEAD in ethanol as disclosed in the original report. The one-pot conditions worked well for both aryl and alkyl isothiocyanates (entries 1–13). The steric hindrance of aryl isothiocyanates does not exert significant impact on the yield of this reaction. For example, 2-bromophenyl and 2,6-dichlorophenyl isothiocyanates gave good yields of thiadiazoles (entries 2 and 4). However, steric effects may be important in the case of alkyl isothiocyanates. Thus, cyclohexyl isothiocyanate gave an 86% yield of the cyclized product (entry 12), but in contrast, no thiadiazole formation was observed in the case of 1-adamantyl isothiocyanate (entry 14). The failure with the latter is due to the thioacylguanidine formation step as 1-adamantyl isothiocyanate is inert to the addition of benzimidamide hydrochloride under current conditions. The moderate yield obtained with *tert*-butyl 6-isothiocyanatohexylcarbamate (entry 13) is caused by the incomplete conversion in the thioacylguanidine formation step. Another feature of this reaction is that the nature of the substituents on the phenyl isothiocyanates has little influence on the overall yield. For example, good yields of thiadiazoles were obtained from phenyl isothiocyanates bearing both

Table 1
3-Substituted-5-amino-1,2,4-thiadiazoles from amidines and isothiocyanates[8]



Entry	R^1	R^2	Yield[a,b] (%)
1	Ph	Ph	82
2	Ph	2-Bromophenyl	79
3	Ph	4-Bromophenyl	93
4	Ph	2,6-Dichlorophenyl	88
5	Ph	4-Nitrophenyl	92
6	Ph	2-Naphthyl	97
7	Ph		86
8	Ph		92
9	Ph		68
10	Ph		96
11	Ph		74
12	Ph	Cyclohexyl	86
13	Ph	$BocNH(CH_2)_6$	52
14	Ph	1-Adamantyl	0
15		2-Bromophenyl	95
16		2-Bromophenyl	82
17		2-Bromophenyl	78
18	Cyclopropyl	2-Bromophenyl	56
19	*t*-Butyl	2-Bromophenyl	77
20	1-Adamantyl	2-Bromophenyl	42
21	Methyl	2-Bromophenyl	0
22	$CH_2C(O)NH_2$	2-Bromophenyl	0

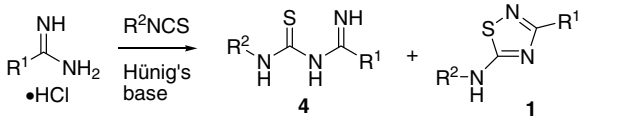
[a] Isolated yield.
[b] Yields not optimized.

electron-donating (entry 8 and 9) and electron-withdrawing groups (entries 7 and 11). Perhaps the most important feature is that ester (entry 7), ketone (entry 11), tertiary amine (entry 9), sulfide (entry 10), and even the acid-sensitive acetal (entry 8) and NHBoc (entry 13) functional groups remain intact during oxidative heterocyclization (entries 7 and 8) (Table 1).

In addition to benzimidamide, we also evaluated heteroaryl and alkyl amidines in the reaction with 1-bromo-2-isothiocyanatobenzene (entries 15–22). Both 2- and 4-pyridyl amidines gave excellent yields of thiadiazoles (entries 15–16). The steric impact from amidines appears to be less pronounced than that from the alkyl isothiocyanates. For example, both 1-phenylcyclopropanecarboximidamide (entry 17) and pivalimidamide (entry 19) furnished good yields of thiadiazoles. Of particular interest is that the reaction of 1-adamantane-carboximidamide with 1-bromo-2-isothiocyanatobenzene proceeded in 42% yield (entry 20), while 1-admantyl isothiocyanate failed to react with isothiocyanatobenzene (entry 14). The moderate yield obtained with 1-adamantane-carboximidamide results from the incomplete conversion in the thioacylguanidine step (ca. 50%). Also, an unidentified side product was observed during the addition of cyclopropylamidine with 1-bromo-2-isothiocyanatobenzene, and as a result, the yield was moderate (entry 18). Finally, acetimidamide (entry 21) and 3-amino-3-iminopropanamide (entry 22) did not work as both failed to produce the desired thioacylguanidines for cyclization.

In general, isothiocyanate reacts with amidine hydrochloride in the presence of Hünig's base to give thioacylguanidine **4** as the sole product. However, in three instances, we have observed the formation of the cyclized thiadiazoles in appreciable amounts even before the addition of DIAD. The ratio of the cyclized product **1** to adduct **4** ranges from 1:5 to 1:2 (Table 2). Since our reactions were carried out in the presence of air, thioacylguanidines **4** presumably underwent spontaneous oxygen-induced S–N heterocyclization. Future efforts will be directed toward understanding the mechanism of this novel reaction and exploring the feasibility of oxidative cyclization of thioacylguanidines **4** using oxygen.

Table 2
3-Substituted-5-amino-1,2,4-thiadiazoles from amidines and isothiocyanates without DIAD



Entry	R^1	R^2	**4** : **1**[a]
1	Ph	Ph	5 : 1
2	*t*-Bu	2-Bromophenyl	2 : 1
3	Ph	2-Naphthyl	4 : 1

[a] LC/MS ratio of the crude reaction mixture prior to the addition of DIAD.

In summary, we have developed an efficient one-pot synthesis of 3-substituted-5-amino-1,2,4-thiadiazoles from isothiocyanates and amidines. This method has been successfully applied to the synthesis of biologically active thiadiazoles bearing electron-rich phenyl and heterocycles, and these compounds will be reported in due course. Taking into account the wide variety of isothiocyanates and amidines either commercially available or easily accessible plus the compatibility of various functional groups with the current methodology, we anticipate widespread application of this operationally simple procedure to the synthesis of 3-substituted-5-amino-1,2,4-thiadiazoles.

Acknowledgments

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8. *Representative procedure*: To a solution of benzamidine hydrochloride (50 mg, 0.32 mmol) and 1-bromo-2-isothiocyanatobenzene (68 mg, 0.32 mmol) in DMF (0.40 mL) in an open vial at room temperature was added Hünig's base (0.35 mmol, 61 μL), the vial was capped, and the reaction mixture was stirred at room temperature for 12 h. DIAD (0.35 mmol, 69 μL) was added, and the reaction mixture was stirred at room temperature for 1 h. DMF was removed in vacuo, and the residue was purified by preparative TLC eluting with 50% ethyl acetate/50% hexanes to give *N*-(2-bromophenyl)-3-phenyl-1,2,4-thiadiazol-5-amine as a white solid (84 mg, 79%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.02 (1H, dt, $J = 1.2$, 7.6 Hz), 7.41–7.48 (4H, m), 7.63 (1H, dd, $J = 1.6$, 8.4 Hz), 7.78 (1H, dd, $J = 1.6$, 8.4 Hz), 8.16 (1H, br s), 8.20–8.25 (2H, m). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (attached H's) 179.62 (0), 169.74 (0), 137.04 (0), 133.28 (1), 132.84 (0), 130.27 (1), 128.99 (1), 128.60 (2C, 1), 128.10 (2C, 1), 124.92 (1), 118.20 (1), and 113.41 (0). Exact mass calcd for $C_{14}H_{11}N_3{}^{79}Br_{32}S$ (M+H): 331.9852; found: 331.9849; $C_{14}H_{11}N_3{}^{81}Br_{32}S$ (M+H): 333.9831; found: 333.9825.