Notes

Novel Nucleophilic 5-Substitution Route to 1,2,3-Thiadiazoles

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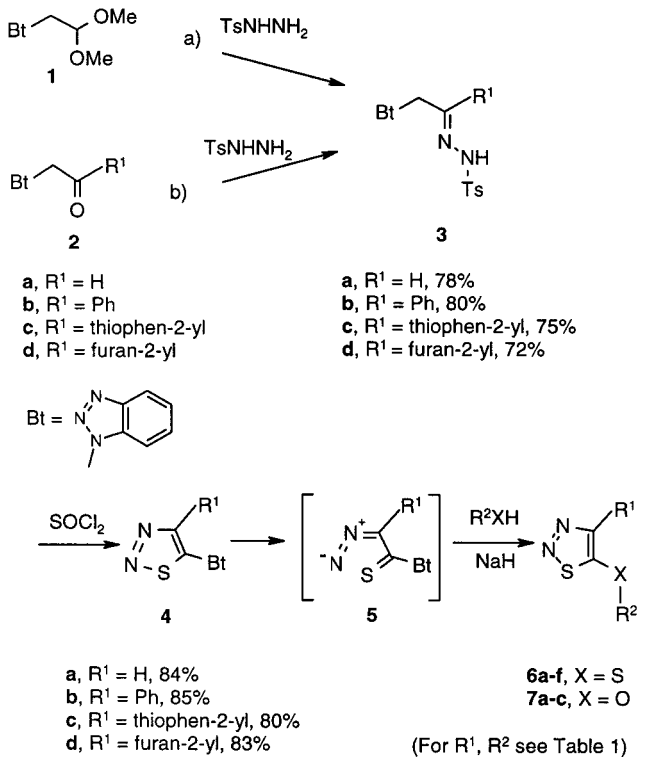
Introduction

1,2,3-Thiadiazoles are useful pharmacophores: their cephalosporin derivatives exhibit antimicrobial activity,[1] and compounds with a terminal 1,2,3-thiadiazole moiety are antipsychotic agents,[2] platelet-activating factors,[3] and angiotensin II receptor antagonists.[4] 1,2,3-Thiadiazoles are valuable as synthetic intermediates for substituted thioacetylenes,[5a,b] thioketenes,[6a−d] and substituted thioamides.[6b,7]

1,2,3-Thiadiazoles are generally prepared by thionyl chloride induced cyclizations of tosylhydrazones,[8] alkyl 1-hydrazonecarboxylates,[5b,9] or semicarbazones.[10] The rearrangement of 5-mercapto-1,2,3-triazoles to 5-amino-1,2,3-thiadiazoles[11] is of a narrow scope. 5-Substituted 1,2,3-thiadiazoles are frequently obtained by reactions of the 5-chloro derivatives with nucleophiles,[12] but this method is limited by the availability of α-chloroketones and low yields of intermediate 5-chloro-1,2,3-thiadiazoles.[9]

Scheme 1



Readily accessible[13a−e] α-benzotriazolylalkyl ketones are useful synthons for the preparation of 3,5-disubstituted phenols,[14] 2,4,6-trisubstituted pyridines,[15] and benzannelated- and 1-(2-arylethenyl)-thiazoles, -indolizines, and -imidazo[1,2-*a*]pyridines.[16] We now describe a two-step synthetic approach to 1,2,3-thiadiazoles from α-benzotriazolylalkyl ketone tosylhydrazones **3a**−**d** (Scheme 1) via key intermediates **4a**−**d**, which allow facile nucleophilic introduction of 5-substituents.

Results and Discussion

Tosylhydrazones **3** (prepared as shown in Scheme 1, **3a** from **1** and **3a**−**d** from **2a**−**d**) with thionyl chloride afforded the 1,2,3-thiadiazoles **4a**−**d** in good yields. Further reactions of **4a**−**d** with *S*- and *O*-nucleophiles gave final products **6a**−**f** and **7a**−**c** (Table 1). Optimization of the conditions for displacement was needed; treatment with thiophenols (NaH in DMF, room tem-

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Table 1. Preparation of 5-Substituted 1,2,3-Thiadiazoles 6 and 7

product	X	R^1	R^2	yields, %
6a	S	H	*p*-CH_3-C_6H_4	42
6b	S	Ph	*p*-CH_3-C_6H_4	68
6c	S	Ph	2-naphthyl	30
6d	S	Ph	Bn	24
6e	S	thiophen-2-yl	*p*-CH_3-C_6H_4	70
6f	S	Ph	*p*-Cl-C_6H_4	57
7a	O	Ph	Ph	45
7b	O	Ph	2-naphthyl	11
7c	O	furan-2-yl	*p*-CH_3O-C_6H_4	76

perature) gives products **6a**−**f** in good to moderate yields and satisfactory conversion of the starting benzotriazole derivative **4**. Displacement with the anion generated from an aliphatic thiol afforded 1,2,3-thiadiazole **6d** in lower yield. The use of *O*-nucleophiles required harsher conditions (NaH in DMF, 100 °C) and gave variable yields of 5-aryloxy substituted products **7a**−**c**.

The mechanism for the displacement reactions **4** → **6**,**7** likely involves the known ring-chain tautomerism of substituted 1,2,3-thiadiazoles involving cleavage of the 1,2-bond to afford 2-diazoethanethione tautomers **5**. Intermediates **5** undergo a direct nucleophilic substitution of benzotriazole moiety and sequential ring closure to yield 5-substituted 1,2,3-thiadiazoles **6**,**7**.

Conclusion

In conclusion, a new method for the preparation of 5-substituted 1,2,3-thiadiazoles is presented. The easy availability of starting materials and mild reaction conditions for both the cyclization and the *O*- and *S*-nucleophilic substitution steps make this route a useful complement to previous synthetic approaches.

Experimental Section

Compounds **2a,b** were synthesized according to the published procedure.[13a] Synthesis of **3b** has been previously described.[13e]

2-(1*H*-1,2,3-Benzotriazol-1-yl)-1-(2-thienyl)-1-ethanone (2c). A mixture of 1-[(trimethylsilyl)methyl]-1*H*-1,2,3-benzotriazole (0.615 g, 3 mmol) and 2-thiophenecarbonyl chloride (0.32 mL, 3 mmol) was heated at 50 °C for 0.5 h, dissolved in chloroform (20 mL), and refluxed for an additional 2 h. The solvent was removed, and the obtained semisolid was recrystallized from chloroform/hexanes: pale-yellow needles, yield 81%, mp 121−122 °C; ^{1}H NMR δ 5.98 (s, 2H), 7.18 (t, J = 3.6 Hz, 1H), 7.35−7.39 (m, 1H), 7.46−7.47 (m, 2H), 7.75 (d, J = 4.8 Hz, 1H), 7.90 (d, J = 3.6 Hz, 1H), 8.06 (d, J = 8.1 Hz, 1H); ^{13}C NMR δ 53.9, 109.6, 120.0, 124.1, 127.9, 128.7, 133.3, 133.6, 135.6, 140.3, 145.9, 183.4. Anal. Calcd for $C_{12}H_9N_5OS$: C, 59.24; H, 3.74; N, 17.28. Found: C, 59.20; H, 3.67; N, 17.17.

2-(1*H*-1,2,3-Benzotriazol-1-yl)-1-(2-furyl)-1-ethanone (2d). 1-[(Trimethylsilyl)methyl]-1*H*-1,2,3-benzotriazole (0.615 g, 3 mmol) was dissolved in 2-furoyl chloride (0.30 mL, 3 mmol) at room temperature. The reaction mixture was heated at 50 °C for 0.5 h, dissolved in chloroform (20 mL), and refluxed for an additional 2 h. The solvent was removed, and the obtained semisolid was recrystallized from chloroform/hexanes: white microcrystals, yield 68%, mp 132−133 °C; ^{1}H NMR δ 5.94 (s, 2H), 6.61 (d, J = 2.4 Hz, 1H), 7.35−7.48 (m, 4H), 7.68 (s, 1H), 8.07 (d, J = 8.1 Hz, 1H); ^{13}C NMR δ 53.2, 109.5, 112.9, 119.0, 120.0, 124.0, 127.8, 133.7, 145.9, 147.5, 150.4, 179.6. Anal. Calcd for $C_{11}H_9N_5O_2$: C, 63.43; H, 4.00; N, 18.50. Found: C, 63.04; H, 3.89; N, 18.48.

General Procedure for the Preparation of Compounds 3a−d. Method A. 1-(2,2-Dimethoxyethyl)-1*H*-1,2,3-benzotriazole (**1**) (0.67 g, 3.3 mmol) or the corresponding 2-(1*H*-1,2,3-benzotriazol-1-yl)-1-R^1-ethanone **2** (3.3 mmol), 4-*p*-toluensulfonhydrazide (0.614 g, 3.3 mmol), and 1 mL of HCl (concentrated) in ethanol (50 mL) were refluxed during 12 h. The solution was diluted with water (50 mL), and the precipitate was recrystallized from methanol.

Method B. A mixture of the corresponding 2-(1*H*-1,2,3-benzotriazol-1-yl)-1-R^1-ethanone **2** (4.12 mmol) and 4-*p*-toluensulfonhydrazide (4.12 mmol) in benzene (50 mL) was refluxed overnight. The reaction mixture was cooled to room temperature, and the obtained crystalline product was filtered off and recrystallized from benzene.

***N′*-[2-(1*H*-1,2,3-Benzotriazol-1-yl)ethylidene]-4-methylbenzenesulfonhydrazide (3a).** White needles, yield 84%, mp 173 °C; ^{1}H NMR δ 2.30 (s, 3H), 5.39 (d, J = 4.5 Hz, 2H), 7.22 (d, J = 8.1 Hz, 2H), 7.30−7.34 (m, 4H), 7.43 (d, J = 8.1 Hz, 2H), 7.95−7.97 (m, 1H), 11.33 (s, 1H); ^{13}C NMR δ 21.1, 48.7, 110.5, 119.1, 124.0, 127.1, 127.3, 129.6, 132.9, 135.7, 143.4, 144.0, 145.2. Anal. Calcd for $C_{15}H_{15}N_5O_2S$: C, 54.69; H, 4.60; N, 21.27. Found: C, 54.80; H, 4.61; N, 21.04.

General Procedure for the Preparation of Compounds 4a−d. The corresponding 4-*p*-toluensulfonhydrazide **3** (1 mmol) and thionyl chloride (10 mL) were stirred at room temperature for 12 h. An excess of thionyl chloride was removed, the reaction mixture was diluted with ether (20 mL) or acetone, and the obtained crystalline precipitate was filtered off and washed with ether (3 × 20 mL) or recrystallized from acetone to give compounds **4**.

1-(1,2,3-Thiadiazol-5-yl)-1*H*-1,2,3-benzotriazole (4a). White microcrystals, yield 72%, mp 169 °C; ^{1}H NMR δ 7.61 (t, J = 8.1 Hz, 1H), 7.82 (t, J = 8.1 Hz, 1H), 8.21 (d, J = 8.3 Hz, 1H), 8.27 (d, J = 8.3 Hz, 1H), 9.71 (s, 1H); ^{13}C NMR δ 109.4, 118.7, 124.2, 128.7, 128.9, 134.9, 144.3, 149.6. Anal. Calcd for $C_8H_5N_5S$: C, 47.28; H, 2.48; N, 34.47. Found: C, 47.31; H, 2.44; N, 34.43.

General Procedure for the Preparation of Compounds 6 and 7. The corresponding 1-(1,2,3-thiadiazol-5-yl)-1*H*-1,2,3-benzotriazole **4** (2 mmol), thiol, or phenol (2 mmol) and sodium hydride (0.08 g, 2 mmol, 60% suspension in mineral oil) in DMF (10 mL) were stirred at room temperature for 6 h (for **6**) or heated for 30 min at 110 °C (for **7**). The reaction mixture was diluted with chloroform (25 mL), poured into a separatory funnel, and washed with water, saturated sodium hydrocarbonate solution (2 × 20 mL), and water (3 times). After drying over magnesium sulfate and evaporation of the solvent, the residue was purified by column chromatography (silica gel, ethyl acetate/hexanes 2:1 for **6** and ether/hexanes for **7** as the eluents) and recrystallized from ethyl acetate (**6a,b,e,f** and **7a,b**) or ether (**6c,d** and **7c**).

5-[(4-Methylphenyl)thio]-1,2,3-thiadiazole (6a). White microcrystals, yield 42%, mp 152−153 °C; ^{1}H NMR δ 2.40 (s, 3H), 7.25 (d, J = 7.9 Hz, 2H), 7.47 (d, J = 7.9 Hz, 2H), 8.29 (s, 1H); ^{13}C NMR δ 21.3, 128.1, 130.9, 133.4, 140.8, 145.0, 156.5. Anal. Calcd for $C_9H_8N_2S_2$: N, 12.38. Found: N, 12.30. Anal. HRMS (FAB) Calcd for $C_9H_8N_2S_2$: 209.0207. Found: 209.0216.

5-Phenoxy-4-phenyl-1,2,3-thiadiazole (7a). White microcrystals (from acetone), yield 45%, mp 101−102 °C; ^{1}H NMR δ 7.21−7.52 (m, 8H), 8.18 (d, J = 7.0 Hz, 2H); ^{13}C NMR δ 119.0, 127.3, 127.5, 129.1, 129.3, 130.6, 131.1, 146.8, 159.7, 172.3. Anal. Calcd for $C_{14}H_{10}N_2OS$: C, 66.12; H, 3.97; N, 11.02. Found: C, 65.98; H, 3.93; N, 10.95.

Supporting Information Available: The procedures for the preparation of compounds **2b**, **3a**−**c**, **4a**−**c**, **6** and **7**, and their characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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