



Synthesis of novel thiadiazoles and bis-thiadiazoles from carbonothioic dihydrazide

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ABSTRACT

Efficient syntheses of 1,3,4-thiadiazoles and bis-thiadiazoles by the reaction of hydrazonoyl halides with carbonothioic dihydrazide are reported. In addition, 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole is obtained via oxidative cyclization of bis-(substituted methylene)carbonothioic dihydrazone.

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1,3,4-Thiadiazoles have been screened for their antibacterial and antifungal,^{1–4} anti-inflammatory,⁵ and anti-tuberculosis activities,⁶ as well as for their activity against cancer.⁷ They have also been applied in the areas of pharmaceutical, agricultural, industrial, and polymer chemistry.^{8–17} The 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole ring system was first reported by Kanaoka,¹⁸ and much attention has been devoted to the chemistry of 3,6-disubstituted derivatives of this class of heterocycles as many of them possess biological activity. For example, some of these derivatives were reported to possess antibacterial,^{19–21} analgesic,²² and fungicidal activities²³ as well as interesting CNS depressant action,²⁴ whereas others exhibited moderate antimalarial and antitumor activity.²⁵ Herein the synthesis of 1,3,4-thiadiazole, bis(1,3,4-thiadiazole), and triazole[3,4-*b*][1,3,4]thiadiazole derivatives is reported.

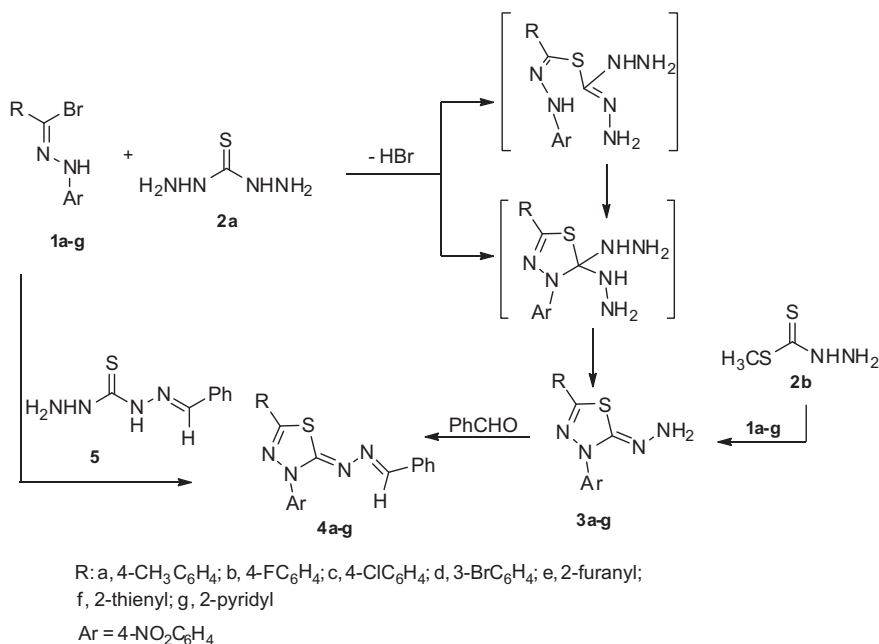
Treatment of carbonothioic dihydrazide^{26a} (**2a**) with the appropriate hydrazonoyl halide²⁷ **1** in ethanol under heating gave a single isolated product in each case. For example, the reaction of **1a** with **2a** in boiling ethanol afforded product **3a** via the elimination of HBr and hydrazine. The IR spectrum of **3a** revealed absorption bands at 3300 and 3200 cm⁻¹ due to the NH₂ group. The ¹H NMR spectrum showed signals at δ 2.51 (s, 3H, CH₃), δ 5.70 (s, 2H, NH₂, exchangeable with D₂O), and at δ 7.35–8.46 (m, 8H, ArH). Compound **3a** was also obtained via the reaction of **1a** with methyl hydrazine carbodithioate^{26b} (**2b**) in ethanolic triethylamine and was an identical product in all respects (mp, mixed mp, and spectra) with that obtained from **2a**. Similarly, compounds **1b–g**

reacted with **2a** or **2b** to afford 1,3,4-thiadiazoles **3b–g** as shown in Scheme 1.

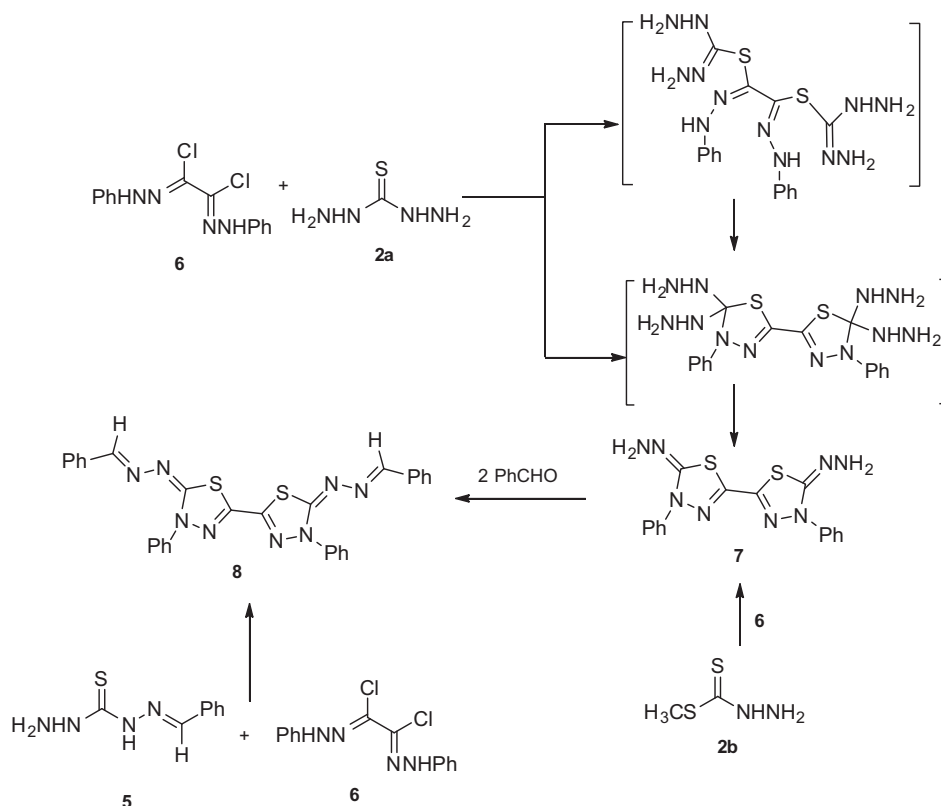
Compound **3a** reacted with benzaldehyde to give the corresponding hydrazone **4a**. The ¹H NMR spectrum of **4a** exhibited resonances at δ 2.52 (s, 3H, CH₃), and δ 7.49–8.51 (m, 14H, ArH, vinyl CH=) and its ¹³C NMR spectrum showed signals at appropriate chemical shifts. Compound **4a** was also obtained via the reaction of **1a** with 2-(phenylmethylene)carbonothioic dihydrazide²⁸ (**5**) in ethanolic triethylamine and was identical in all respects (mp, mixed mp, and spectra) with that obtained from **3a**. Similarly, reactions of **1b–g** with **5** afforded hydrazones **4b–g** as shown in Scheme 1.

Also, the reaction of **2a** with *N,N*-diphenylethane(bis-hydrazonoyl dichloride)²⁹ (**6**) in ethanol gave bis-thiadiazole **7** as the only product. The molecular formula of **7**, C₁₆H₁₄N₈S₂, was consistent with the elimination of 2HCl and 2NH₂NH₂. The structure of **7** was elucidated by elemental analysis and spectroscopy. The IR spectrum of **7** revealed absorption bands at 3290 and 3274 cm⁻¹ due to the NH₂ group. The ¹H NMR spectrum showed signals at δ 5.73 (s, 2H, NH₂, exchangeable with D₂O) and δ 7.23–7.91 (m, 10H, ArH). Compound **7** was also obtained via the reaction of **6** with hydrazine carbodithioate **2b** in ethanolic triethylamine and was identical in all respects (mp, mixed mp, and spectra) with that obtained from **2a** (Scheme 2). Bis-thiadiazole **7** reacted with benzaldehyde to give the corresponding bis-hydrazone **8**, the structure of which was confirmed by elemental analysis and spectral data. The ¹H NMR spectrum of **8** exhibited a multiplet resonance at δ 7.32–8.52 (m, 22H, ArH, and vinyl CH=). Compound **8** was also obtained via the reaction of **6** with 2-(phenylmethylene)carbon-

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Scheme 1. Synthesis of 1,3,4-thiadiazole derivatives **3a–g** and **4a–g**.

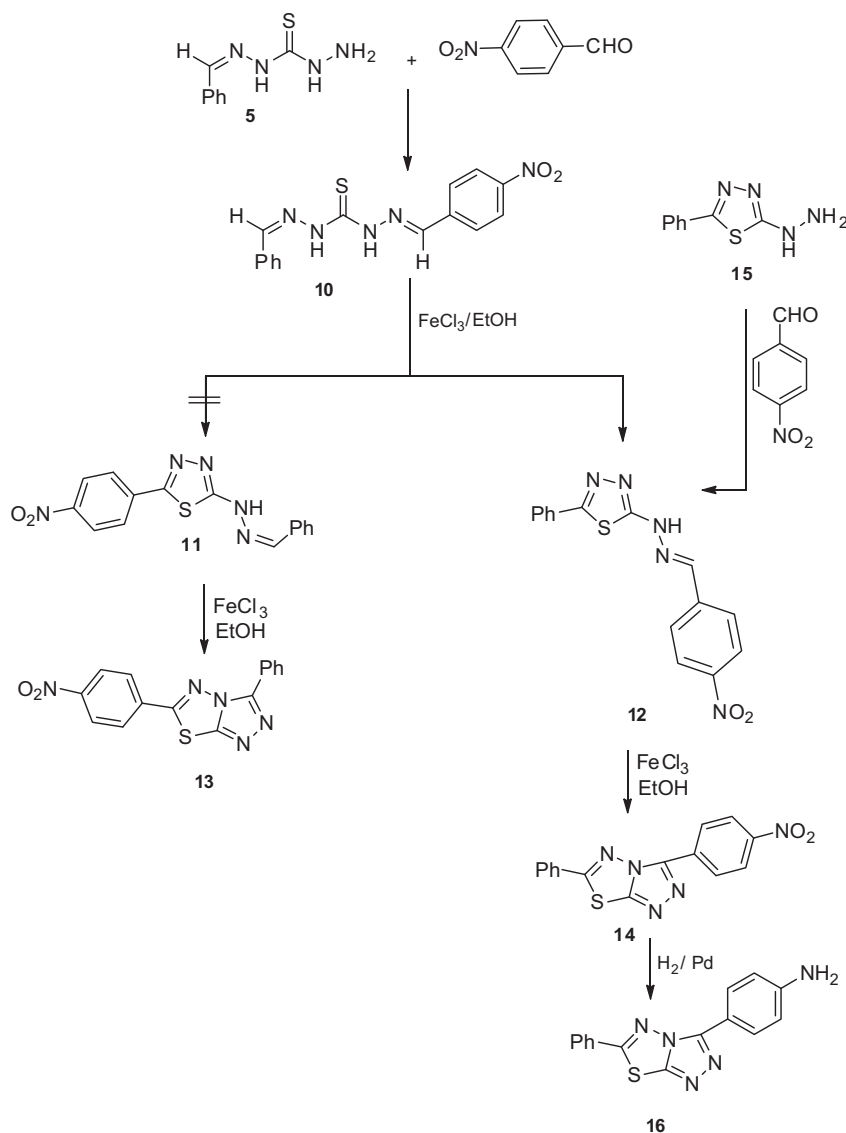


Scheme 2. Synthesis of bis(1,3,4-thiadiazole) derivatives **7** and **8**.

othioic dihydrazide (**5**) in ethanolic triethylamine and was identical (mp, mixed mp, and spectra) with that obtained from **7**.

We previously reported the synthesis of 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole³⁰ via oxidative cyclization of an asymmetric bis-hydrazone. These principles were extended to the synthesis of the new amine **16** as shown in Scheme 3. Compound **10** is also

novel and was prepared by the condensation of **5** with 4-nitrobenzaldehyde as shown in Scheme 3. Treatment of the bis-hydrazone **10** with ferric chloride in ethanol yielded a single crystalline product that was identified as **12** and not the anticipated thiadiazole **11**. The structure of **12** was confirmed by an alternative synthesis involving the reaction of **15** with 4-nitrobenz-



Scheme 3. Synthesis of 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole derivatives **10**, **14** and **16**.

aldehyde.^{31,32} Elemental analysis and the mass spectrum revealed that the product **12** had two hydrogen atoms less than the precursor bis-hydrazone **10**. Its ¹H NMR spectra showed the presence of one methine proton –N=CH– and one hydrazone (–NHN=C). Further oxidation of **12** with ferric chloride led to 6-phenyl-3-(4-nitrophenyl)-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole (**14**).

The structure of **14** was confirmed by elemental analysis and from spectral data (MS, IR and ¹H NMR). The ¹H NMR spectrum of **14** was devoid of the signal characteristic of the –NH–N=CH–proton that appeared in the spectra of precursors **10** and **12**. Isomeric compound **13** was prepared according to the literature.³³ Compounds **13** and **14** have similar structures which are almost identical according to spectral analysis. Thus the structure of compound **14** was confirmed by an unambiguous alternative synthesis starting from **15**. Reduction of compound **14** with H₂/Pd gave the aniline derivative **16** (molecular formula C₁₅H₁₁N₅S). The IR spectrum revealed absorption bands at 3359 and 3205 cm⁻¹ due to the NH₂ group. Its ¹H NMR spectrum showed signals at δ 4.65 (s, 2H, NH₂) and δ 7.25–8.40 (m, 9H, ArH).

In summary, new and efficient syntheses of 1,3,4-thiadiazoles, bis-thiadiazoles, and an aniline derivative have been reported.

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Supplementary data

Supplementary data (experimental details for the synthesis and characterization for all the new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.06.060.

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