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A convenient method for synthesis of bis-2,2′-(1,3,4-thiadiazole) and bis-3,3′-(1,2,4-triazole) derivatives

Ahmad S. Shawali [a] , Abdelwahed R. Sayed [a] & Mohie M. Zayed [a]
[a] Department of Chemistry, Faculty of Science , University of Cairo , Giza, Egypt

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A convenient method for synthesis of bis-2,2′-(1,3,4-thiadiazole) and bis-3,3′-(1,2,4-triazole) derivatives

Ahmad S. Shawali*, Abdelwahed R. Sayed and Mohie M. Zayed

Department of Chemistry, Faculty of Science, University of Cairo, Giza, Egypt

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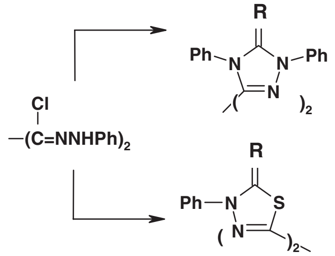
Reactions of the bis-hydrazonoyl chloride **1** with ketene *N*,*S*-acetal **2** and the active methine thioanilides **4** and **6** provide a new convenient site-selective synthetic strategy to functionalized bis-3,3′-(1,2,4-triazoles) **3** and bis-2,2′-(1,2,4-thiadiazoles) **5** and **7**.



Keywords: ketene *N*,*S*-acetal; hydrazonoyl chlorides; thioanilides; heterocycles; dithiocarbamates

1. Introduction

In continuation of our research in the chemistry of nitrilimines and their precursors (*1–5*) and our recent study of the reaction of hydrazonoyl halides with acyclic ketene aminals (*6*), it was thought worthwhile to study the reactions of the bis-hydrazonoyl chloride **1** with ketene *N*, *S*-acetal **2** and the active methine thioanilides **4** and **6** which have not been reported hitherto (Scheme 1) to shed light on their site selectivity and to explore their utility in the synthesis of the title ring systems. As outlined below, the studied reactions proved to be site-selective and appear to develop a new convenient synthetic strategy to functionalized *n*, *n*′-bis(azoles) namely 3,3′-bis(1,2,4-triazoles) **3** and 2,2′-bis(1,2,4-thiadiazoles) **5** and **7** (Schemes 1 and 2).

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*Corresponding author. Email: as_shawali@mail.com; as_shawali@yahoo.com

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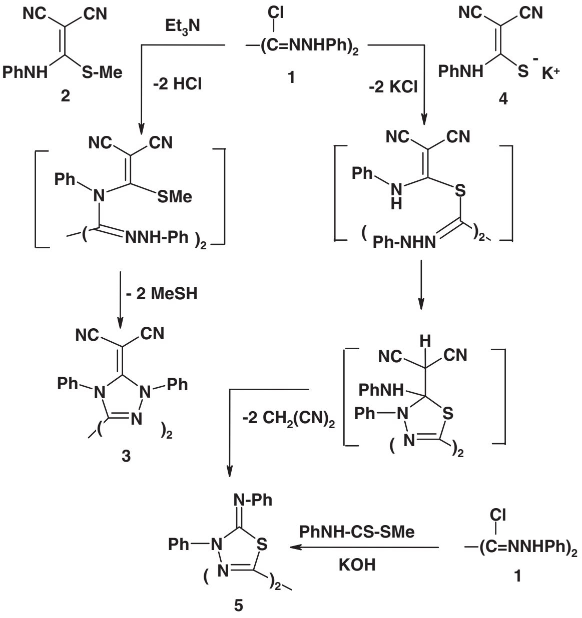
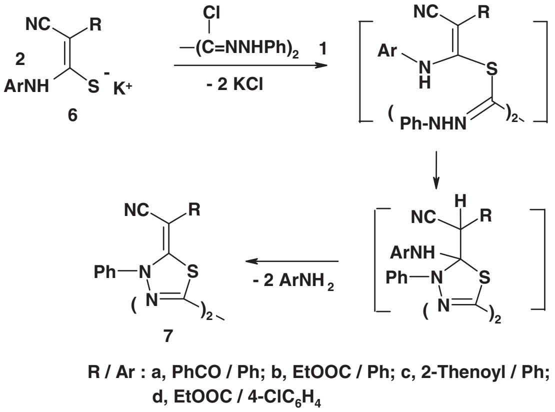


Scheme 1. Reaction of bis-hydrazonoyl chloride with N, S-acetals.



Scheme 2. Synthesis of bis-2,2′-(1,2,4-thiadiazoles).

2. Results and discussion

The required precursors namely the bis-hydrazonoyl chloride **1** (*7*) and 2-cyano-3-methylthio-3-phenylaminoacrylonitrile **2** (*8*) were prepared in this work by literature methods. In our hands, treatment of **1** with two mole equivalents of **2** in refluxing ethanol in the presence of triethylamine proceeded smoothly to give a product that was identified as 3,3′-bis(1,2,4-triazole) derivative **3** (Scheme 1). The structure of the latter product was elucidated on the basis of its microanalysis and spectra (see Section 3). On the other hand, treatment of **1** with two equivalents of the potassium salt of dicyanothioacetanilide **4** in dimethylformamide (DMF) in the presence of potassium hydroxide gave 2,2′-bis(1,3,4-thiadiazole) derivative **5** (Scheme 1). The IR spectrum of the latter product showed the absence of absorption bands due to $-C \equiv N$ and NH groups. Its structure was further evidenced by its alternate synthesis. Thus, reaction of **1** with methyl N-phenyldithiocarbamate in ethanol in the presence of triethylamine yielded **5** identical in all respects with that one obtained above from **1** and **4** (Scheme 1).

Similar reactions of **1** with potassium salts of the other active methine thioanilides **6a**–**c** were found to give the respective bis(1,3,4-thiadiazole) derivatives **7a**–**c** (Scheme 2). In these cases, it seems that the initially formed thiohydrazonate intermediates cyclized with concurrent elimination of aniline to give **7** as end products. This suggestion was evidenced by our finding that reaction of **1** with N-(p-chlorophenyl)-2-cyano-2-ethoxycarbonyl-thioacetanilide **6d** in DMF in the presence of potassium hydroxide yielded also **7b** (Scheme 2).

3. Experimental

The melting points (mp's) were measured on an electrothermal Gallenkamp mp apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 with tetramethylsilane as an internal standard using 300 MHz Varian Gemini spectrometer. The IR spectra were measured on a Fourier transform and Pye Unicam infrared spectrophotometers using potassium bromide wafer. Mass spectra were recorded on a GCMS-QP 1000 EX spectrometer at an ionizing potential of 70 eV. Elemental microanalyses were carried out at the microanalytical laboratory of Cairo University, Giza, Egypt. The identification of compounds from different experiments was secured by mixed mp's and superimposable IR spectra. The bis-hydrazonoyl chloride **1** (*7*), 2-cyano-3-methylthio-3-phenylaminoacrylonitrile **2** (*8*) and methyl N-phenyldithiocarbamate (*9*) were prepared as previously described.

3.1. *3,3′-Bis(1,4-diphenyl)-5-dicyanomethylene-1,2,4-triazole) (3)*

To a mixture of the bis-hydrazonoyl chloride **1** (0.005 mol) and the ketene N,S-acetal **2** (0.010 mol) in ethanol (40 ml) was added triethylamine (1.4 ml, 0.010 mol) and the mixture was refluxed till methanethiol ceased to evolve (1–1.5 h). The precipitate that was formed was filtered off and crystallized from DMF–ethanol (EtOH) mixture to give the 3,3′-bis(1,2,4-triazole) derivative **3** as brown solid (1.14 g, 40%), mp $>$ 300 °C. IR (KBr) ν 2197, 2189 cm^{-1}; ^{1}H NMR δ 7.38–8.52 (m); MS m/z (%) 569 (M$^+$ + 1, 11), 568 (M$^+$, 25), 401 (12), 310 (11), 283 (7), 235 (4), 168 (18), 177 (5), 121 (8), 91 (67), 77 (93), 64 (100). Anal. Calcd. $C_{34}H_{20}N_{10}$ (568.6): C, 71.82; H, 3.55; N, 24.63; Found: C, 71.50; H, 3.30; N, 24.41%.

3.2. *Reactions of the bis-hydrazonoyl chloride with potassium salts of thioanilides 6a–c*

General method: To a stirred suspension of potassium hydroxide (0.56 g, 0.01 mol) in DMF (30 ml), malonitrile (0.01 mol) was added. To the resulting solution was added phenyl isothiocyanate (0.01 mol) and the reaction mixture was stirred at room temperature. After stirring for 3 h, bis-hydrazonoyl chloride **1** (1.50 g, 0.005 mol) was added and the reaction mixture was refluxed for 5 h, then cooled and poured onto ice-cold hydrochloric acid solution. The solid that precipitated was filtered, washed with water, dried and finally crystallized from the proper solvent to give **5**.

When the above procedure was repeated using benzoylacetonitrile, ethyl cyanoacetate and 2-theonylacetonitrile each in place of malonitrile, the bis(1,3,4-thiadiazole) derivatives **7a**–**c** were produced, respectively.

Also, repetition of the above procedure using p-chlorophenyl isothiocyanate in place of phenyl isothiocyanate in the reaction with ethyl cyanoacetate yielded **7b**. The physical constants of the products **5** and **7a**–**c** are listed below.

3.2.1. *2,2′-Bis-(4-phenyl-5-phenylimino-1,3,4-thiadiazole) (**5**)*

Yellow brown solid (1.26 g, 50%), mp 310 °C. IR (KBr) ν 1600, 1560 cm^{-1}; ^{1}H NMR δ 7.07–7.79 (m); MS m/z (%) 505 (M$^+$ + 1, 7), 504 (M$^+$, 19), 252 (3), 135 (10), 91 (100), 77 (57). Anal. Calcd. $C_{28}H_{20}N_6S_2$ (504.6): C, 66.64; H, 3.99; N, 16.65; found: C, 66.54; H, 3.84; N, 16.53%.

3.2.2. *2,2′-Bis-[4-phenyl-5-(cyanobenzoylmethylene)-1,3,4-thiadiazole] (**7a**)*

Brown solid (1.22 g, 40%), mp. 170 °C (EtOH). IR (KBr) ν 2191, 1640 cm^{-1}; ^{1}H NMR δ 6.72–7.65 (m); MS m/z (%) 609 (M$^+$ + 1, 5), 608 (M$^+$, 7), 278 (2), 143 (2), 105 (100), 77 (98). Anal. Calcd. $C_{34}H_{20}N_6O_2S_2$ (608.7): C, 67.09; H, 3.31; N, 13.81; found: C, 67.20; H, 3.41; N, 13.75%.

3.2.3. *2,2′-Bis-[4-phenyl-5-(ethoxycarbonylcyanomethylene)-1,3,4-thiadiazole] (**7b**)*

Brown solid (1.36 g, 50%), mp. 195°C (EtOH). IR (KBr) ν 2206, 1659 cm^{-1}; ^{1}H NMR δ 1.24 (t, $J = 7$ Hz, 6H), 4.23 (q, $J = 7$ Hz, 4H), 7.03–7.97 (m, 10H); ^{13}C NMR δ 14.9, 15.0, 62.1, 62.2, 113.6, 120.9, 123.6, 125.4, 128.1, 128.4, 128.5, 129.7, 129.9, 130.1, 130.6, 131.8, 132.0, 138.2, 139.0, 147.7, 167.3, 167.4; MS m/z (%) 545 (M$^+$ + 1, 52), 544 (M$^+$, 100), 271 (2), 246 (2), 155 (2), 91 (16, 77 (43). Anal. Calcd. $C_{26}H_{20}N_6O_4S_2$ (544.6): C, 57.41; H, 3.82; N, 15.38; found: C, 57.34; H, 3.70; N, 15.43%.

3.2.4. *2,2′-Bis-[4-phenyl-5-(2-thenoylcyanomethylene)-1,3,4-thiadiazole] (**7c**)*

Brown solid (1.39 g, 45%), mp. 215 °C (EtOH). IR (KBr) ν 2207, 1660 cm^{-1}; ^{1}H NMR δ 7.42–8.99 (m); MS m/z (%) 621 (M$^+$ + 1, 3), 620 (M$^+$, 12), 310 (14), 284 (15), 207 (100), 110 (13). Anal. Calcd. $C_{30}H_{16}N_6O_2S_4$ (620.7): C, 57.05; H, 2.60; N, 13.54; found: C, 58.34; H, 2.41; N, 13.50%.

3.3. *Alternate synthesis of (5)*

To a stirred solution of methyl N-phenyldithiocarbamate (3.20 g, 0.02 mol) in ethanol (60 ml) containing triethylamine (2.8 ml, 0.02 mol), the bis-hydrazonoyl chloride **1** (3.07 g, 0.01 mol) was added and the mixture was stirred for 7 h at room temperature. The precipitated solid was filtered off, washed with water, dried and finally crystallized from EtOH–DMF to give **5** (1.89 g, 75%) as yellow brown solid which proved identical in all respects with that one obtained above from **1** and **2**.

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