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A simple and efficient procedure for synthesis of symmetrical bis(4-amino-4*H*-1,2,4-triazole-5-thiols)

Abstract: A series of bis(1,2,4-triazole-3-thiols) **3a–d** were prepared by condensation reactions of arylbis(carboxymethylthio)methanes **2a–d** with thiocarbohydrazide. The starting diacids **2a–d** were prepared by reactions of aromatic aldehydes **1a–d** with thioglycolic acid. The structures of these newly synthesized compounds are characterized by elemental analysis, IR, and NMR spectroscopy.

Keywords: 4-amino-4*H*-1,2,4-triazole-3-thiol; thioacetal; thiocarbohydrazide.

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Introduction

The 1,2,4-triazole system is an important recognition element in many biologically active molecules including potent agonist or antagonist receptor ligands [1, 2]. 1,2,4-Triazole derivatives have been used as mimics [3, 4] or isosteres [5] of the amide bond in attempts to increase bioavailability of the parent bioactive molecules. They have also been incorporated into peptides as surrogates for *cis* amide bonds [6]. A variety of approaches have been reported for the preparation 4-amino-1,2,4-triazol-3-thioles including the reactions of carboxylic acids [7] and 1,3,4-oxadiazol-5-thiones [8]. The amino and thiol groups are nucleophilic centers for the synthesis of condensed nitrogen and sulfur heterocyclic systems, such as triazolothiadiazoles [9–12], triazolothiadiazines [13, 14], macrocycles [15–17], and triazolothiadiazepines [18]. As part of our ongoing studies on the synthesis of triazole derivatives, we report here the synthesis of novel symmetrical bis(4-amino-4*H*-1,2,4-triazole-3-thiols).

Results and discussion

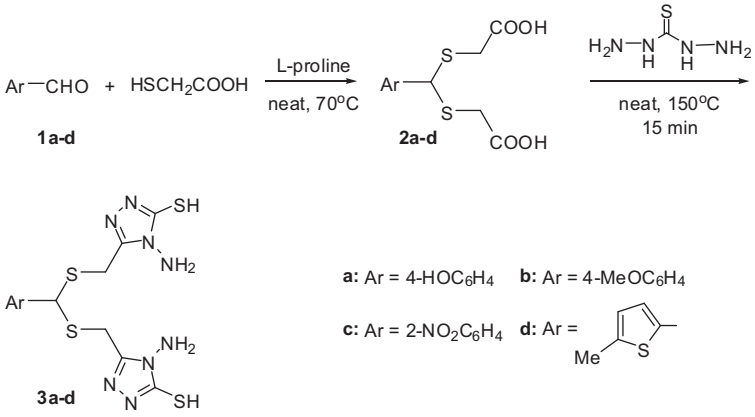
The synthesis of compounds **2a–d** and **3a–d** is outlined in Scheme 1. The substrates **2a–d** were obtained by reaction of various substituted benzaldehydes and thioglycolic acid using L-proline as an organocatalyst at 70°C under solvent-free conditions. The desired compounds were obtained in excellent yields.

The ^{1}H NMR spectra showed a singlet signal in the region of 5.18–5.88 ppm attributed to the resonance of the methine proton (S-CH-S). The IR absorptions and ^{13}C NMR signals due to the presence of carbonyl groups clearly confirmed the formation of products **2a–d**.

The final bis-triazole derivatives **3a–d** were prepared by heating compounds **2a–d** with two equivalents of thiocarbohydrazide in an oil bath at 150°C. These compounds were obtained in reasonable yields. The structures of new compounds **3a–d** were supported by NMR and IR spectra, and elemental analyses. The IR spectrum of compounds **2a–d** showed two absorption bands, at 2500–3500 cm^{-1} and 1700 cm^{-1}, due to OH and C=O groups, respectively, that are absent in the IR spectra of products **3a–d**. Similarly, the ^{1}H NMR spectrum of compounds **2a–d** showed a broad singlet peak at δ ~12.60 ppm for the COOH groups, which disappear upon the formation of bis(aminotriazole) derivatives **3a–d**. The corresponding IR absorptions and ^{1}H NMR signals for the SH and NH_2 groups in compounds **3a–d** clearly confirm the formation of the bis(aminotriazole) system.

Conclusion

A rapid and highly efficient method for the synthesis of a new series of symmetrical bis(aminotriazoles) is described. This protocol is characterized by a short reaction time, good to excellent yield, and simple purification.



Scheme 1

Experimental

Melting points were determined using an electrothermal digital apparatus and are uncorrected. Purity of the compounds were checked by thin layer chromatography (TLC) using EtOH/*n*-hexane (1:1, v/v) as an eluent. IR spectra were recorded on a Galaxy series FT-IR 5000 spectrophotometer using KBr discs. NMR spectra were recorded in DMSO-d_6 on a Bruker spectrophotometer (300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR). Elemental analyses were performed on a Vario EL III elemental analyzer.

General procedure for preparation of compounds 2a–d

A mixture of an aldehyde **1a–d** (5 mmol), thioglycolic acid (12 mmol), and L-proline (5% mol) was magnetically stirred at 70°C. After completion of the reaction (monitored by TLC), the mixture was poured slowly onto crushed ice with stirring. The resultant precipitate of **2a–d** was filtered, washed with water, and dried.

4-Hydroxyphenyl-bis(carboxymethylthio)methane (2a) Reaction time 15 min; yield 99%; mp 160–161°C (lit mp 155–156°C; [19]); IR: 2540–3430, 1700, 1200 cm^{-1}; ^{1}H NMR: δ 12.63 (br, 2H), 9.59 (s, 1H), 7.19 (d, 2H, *J* = 7.7 Hz), 6.73 (d, 2H, *J* = 7.7 Hz), 5.18 (s, 1H), 3.35 (d, 2H *J* = 15 Hz), 3.18 (d, 2H, *J* = 15 Hz); ^{13}C NMR: δ 34.4, 52.8, 115.7, 129.3, 129.4, 157.7, 171.3. Anal. Calcd for $C_{11}H_{12}O_5S_2$: C, 45.82; H, 4.19; S, 22.24. Found: C, 45.70; H, 4.14; S, 22.16.

4-Methoxyphenyl-bis(carboxymethylthio)methane (2b) Reaction time 15 min; yield 99%; mp 122–123°C (lit mp 121.5–122.5°C; [20]); IR: 2520–3400, 1705, 1205, 1185 cm^{-1}; ^{1}H NMR: δ 12.60 (br, 2H), 7.31 (d, 2H, *J* = 8.4 Hz), 6.73 (d, 2H, *J* = 8.4 Hz), 5.24 (s, 1H), 3.75 (s, 3H), 3.37 (d, 2H, *J* = 15 Hz), 3.20 (d, 2H, *J* = 15 Hz). Anal. Calcd for $C_{12}H_{14}O_5S_2$: C, 47.67; H, 4.67; S, 21.21. Found: C, 47.59; H, 4.63; S, 21.15.

2-Nitrophenyl-bis(carboxymethylthio)methane (2c) Reaction time 15 min; yield 99%; mp 124°C (lit mp 122–123°C; [21]); IR: 2500–3385, 1711, 1532, 1362, 1201 cm^{-1}; ^{1}H NMR: δ 12.65 (br, 2H), 7.93 (m, 1H), 7.81 (m, 1H), 7.74 (m, 1H), 7.53 (m, 1H), 5.88 (s, 1H), 3.47 (d, 2H, *J* = 15 Hz), 3.30 (d, 2H, *J* = 15 Hz). Anal. Calcd for: $C_{11}H_{11}NO_6S_2$: C, 41.63; H, 3.49; N, 4.41; S, 20.21. Found: C, 41.50; H, 3.42; N, 4.37; S, 20.14.

5-Methyl-2-thienyl-bis(carboxymethylthio)methane (2d) Reaction time 20 min; yield 85%; mp 96–98°C; IR: 2425–3417, 1704, 1203 cm^{-1}; ^{1}H NMR: δ 12.71 (br, 2H), 6.88 (s, 1H), 6.63 (s, 1H), 5.52 (s, 1H), 3.45 (d, 2H, *J* = 15 Hz), 3.29 (d, 2H, *J* = 15 Hz), 2.39 (s, 3H); ^{13}C NMR: δ 15.5, 34.5, 48.6, 125.2, 127.1, 140.6, 140.7, 171.1. Anal. Calcd for $C_{10}H_{12}O_4S_3$: C, 41.08; H, 4.14; S, 32.90. Found: C, 40.95; H, 4.08; S, 32.78.

General procedure for synthesis of bis(aminotriazoles) 3a–d

A mixture of diacid **2a–d** (10 mmol) and thiocarbohydrazide (20 mmol) was fused at 150°C in an oil bath for 15 min. After cooling, the reaction mixture was triturated with ethanol. The precipitate was dried and crystallized from ethanol to give pure product **3a–d**.

4-Hydroxyphenyl-bis[(4-amino-5-mercapto-4*H*-1,2,4-triazol-3-yl)methylthio]methane (3a) Reaction time 15 min; yield 80%; mp 228–230°C; IR: 3285, 3142, 2752, 1605, 1490 cm^{-1}; ^{1}H NMR: δ 13.38 (s, 2H), 9.56 (s, 1H), 7.18 (d, 2H, *J* = 7.6 Hz), 6.75 (d, 2H, *J* = 7.6 Hz), 5.50 (s, 4H), 5.21 (s, 1H), 3.85 (d, 2H, *J* = 14 Hz), 3.66 (d, 2H, *J* = 14 Hz); ^{13}C NMR: δ 25.2, 52.8, 115.8, 129.1, 129.6, 150.0, 157.7, 166.5. Anal. Calcd for $C_{13}H_{16}N_8OS_4$: C, 36.43; H, 3.76; N, 26.15; S, 29.93. Found: C, 36.21; H, 3.65; N, 26.02; S, 29.76.

4-Methoxyphenyl-bis[(4-amino-5-mercapto-4*H*-1,2,4-triazol-3-yl)methylthio]methane (3b) Reaction time 15 min; yield 77%; mp 215–218°C; reaction time 15 min; yield 99%; mp 160–161°C; IR: 3245, 3150, 2761, 1600 cm^{-1}; ^{1}H NMR: δ 13.35 (s, 2H), 7.31 (d, 2H, *J* = 8.0 Hz), 6.92 (d, 2H, *J* = 8 Hz), 5.52 (s, 4H), 5.23 (s, 1H), 3.82 (d, 2H, *J* = 14 Hz), 3.65 (d, 2H, *J* = 14 Hz); ^{13}C NMR: δ 25.3, 52.7, 55.7, 114.4, 129.3, 130.9, 149.9, 161.0, 166.8. Anal. Calcd for $C_{14}H_{18}N_8OS_4$: C, 37.99; H, 4.10; N, 25.32; S, 28.98. Found: C, 37.75; H, 3.99; N, 25.17; S, 28.83.

2-Nitrophenyl-bis[(4-amino-5-mercapto-4*H*-1,2,4-triazol-3-yl) methylthio]methane (3c) Reaction time 15 min; yield 80%; mp 208–210°C; IR: 3268, 3162, 2770, 1612, 1550, 1325 cm^{-1}; ^{1}H NMR: δ 13.45 (s, 2H), 7.93 (d, 1H *J* = 7.9 Hz), 7.74–7.82 (m, 2H), 7.56 (m, 1H), 5.86

(s, 1H), 5.54 (s, 4H), 4.00 (d, 2H, J = 14 Hz), 3.73 (d, 2H, J = 14 Hz); ^{13}C NMR: δ 25.7, 52.5, 125.6, 127.9, 128.2, 130.2, 131.6, 135.3, 147.6, 149.8, 166.9. Anal. Calcd for $C_{13}H_{15}N_9O_2S_4$: C, 34.12; H, 3.30; N, 27.55; S, 28.03. Found: C, 33.91; H, 3.22; N, 27.42; S, 27.89.

5-Methyl-2-thienyl-bis[(4-amino-4*H*-1,2,4-triazol-3-yl)methylthio] methane (3d) Reaction time 15 min; yield 68%; mp 180–183°C; IR: 3381, 3153, 2760, 1599 cm^{-1}; ^{1}H NMR: δ 13.41 (s, 2H), 6.87 (s, 1H), 6.65 (s, 1H), 5.52 (m, 5H), 3.88 (d, 2H, J = 14 Hz), 3.68 (d, 2H, J = 14 Hz), 2.41 (s, 3H); ^{13}C NMR: δ 15.6, 25.4, 48.8, 125.2, 127.0, 140.5, 140.7, 150.0, 166.3. Anal. Calcd for $C_{12}H_{16}N_8S_5$: C, 33.31; H, 3.73; N, 25.90; S, 37.06. Found: C, 33.15; H, 3.65; N, 25.81; S, 37.19.

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