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Note

A facile synthesis of new [1,2,4]triazolo[3,4-*d*][1,3,5]dithiazines involving acid-labile methanesulphinyl leaving group

L D S Yadav*, Anjum Vaish & Sangeeta Sharma
Department of Chemistry, University of Allahabad,
Allahabad 211 002, India
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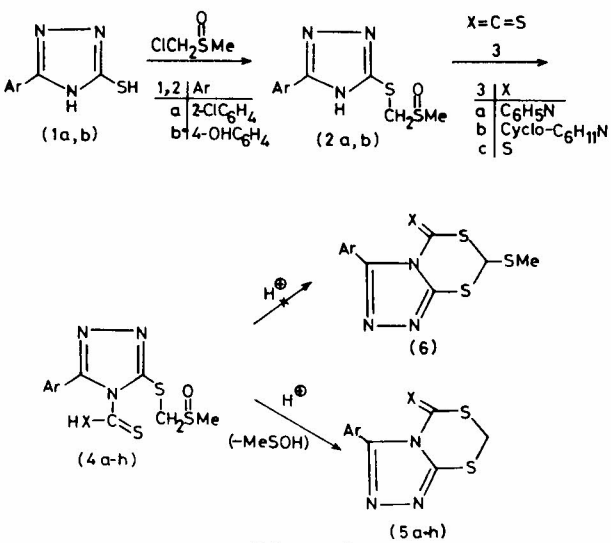
Nucleophilic addition of the amine function of 5-aryl-3-methanesulphinylmethylthio-1, 2, 4-triazoles **2a, b** to carbon disulphide and aryl/cyclohexyl isothiocyanates furnishes adducts **4a-h** which undergo a facile intramolecular cyclisation via a nucleophilic displacement to yield the corresponding [1, 2, 4]triazolo[3,4-*d*][1,3,5]dithiazines **5a-h** with the loss of the acid-labile methanesulphinyl leaving group as methanesulphenic acid.



Scheme I

Cyclic isothioureas bearing an effective leaving group on the sulphur atom undergo nucleophilic addition to heterocumulenes followed by cyclisation to cyclic disulphides[1-4]. In view of our continued interest in widening the synthetic scope of isothioureas[3-5], we report herein the synthesis of hitherto unknown compounds **5a-h** which, apart from their chemical interest, could also be a subject of study as pharmacological agents and agrochemicals owing to the presence of biolabile [1,2,4]triazole and [1,3,5]dithiazine moieties fused together.

The synthetic route to compounds **5a-h** is outlined in Scheme I. Nucleophilic addition of the amine function of 5-aryl-3-methanesulphinylmethylthio-1,2,4-triazoles **2a,b** to heterocumulenes **2** (X = S, ArN or cyclo-$C_6H_{11}N$) furnished the adducts **4a-h** in 65-80% yield which underwent a facile intramolecular cyclisation via a nucleophilic displacement to new [1, 2, 4]triazolo[3,4-*d*] [1,3,5]dithiazines **5a-h** in 68-80% yield with the loss of the acid-labile methanesulphinyl group as methanesulphenic acid. Whereas the methylene transfer works with chloromethyl methyl sulphoxide, it does not work with CH_2Cl_2, CH_2Br_2, $CH_2(OMe)_2$ or HCHO. It is noteworthy that products **6**, which would be expected to be formed via a Pummerer rearrangement, were not obtained in the present experimental conditions.

The structural assignments of the products were based on their elemental anaylses (C, H and N) and IR, ^{1}H NMR and mass spectral data. All the compounds gave satisfactory elemental analyses (C, H and N). The spectral data of only representative compounds are given in the Experimental Section. The IR spectra of compound **2** and **4** exhibited a sharp band around 1035 cm^{-1} due to S = O function, whereas their successors **5** were devoid of this band. The compounds **5a-c** and **5e-g**, revealed a characteristic IR band around 1685 cm^{-1} attributable to the exocyclic C = N function, whereas their thione analogues **5d** and **5h** exhibited a sharp band around 1100 cm^{-1} due to C = S group. The ^{1}H NMR spectra of compounds **2** and **4** revealed expected singlets in the range of δ 2.50-2.64 and 3.73-3.83 attributable to MeSO and SCH_2SO protons, respectively. Similarly, compounds **5** exhibited a singlet in the region δ 3.98-4.08 due to SCH_2S protons. In addition, all compounds **2,4** and **5** revealed expected PMR signals for cyclohexyl, Me, NH and OH protons present in them (cf. Experimental Section).

The easy and wide availability of isothioureas[6] and heterocumulenes[7], combined with the simplicity of the operations performed under mild conditions make the present cyclisation a general route for the synthesis of a variety of cyclic systems such as triazolo-thiadiazine, benzimidazo-dithiazine, benzimidazo-thiadiazine, etc. Various syntheses using chloromethyl methyl sulphoxide

as a methylene transfer reagent are now being developed.

Experimental Section

Melting points were determined in open glass capillaries and are uncorrected. IR spectra in KBr were recorded on a Perkin-Elmer 577 infrared spectrophotometer (ν_{max} in cm^{-1}), ^1H NMR spectra on a Perkin-Elmer R-32 (90 MHz) spectrometer in DMSO-d_6 using TMS as internal standard (chemical shifts are expressed in δ, ppm) and mass spectra on a JEOL D-300 mass spectrometer.

The starting compounds 5-aryl-3-mercapto-1,2,4-triazoles **1a,b** and chloromethyl methyl sulphoxide were prepared by the known procedures[8,9].

5-Aryl-3-methanesulphinylmethylthio-1,2,4-triazoles (2a,b). To a suspension of 5-aryl-3-mercapto-1,2,4-triazole (1) (11 mmole) in ethanol (30 mL) was added NaOH (11 mmole) and the reaction mixture was stirred at room temp for 15 min. Then, chloromethyl methyl sulphoxide (11 mmole) was added and the reaction mixture was heated at reflux for 5 hr. After the reaction mixture had been cooled to room temp, it was poured into water (60 mL) and the desired product thus precipitated was filtered, washed with water and recrystallised from ethanol.

2a. Yield 83%; m.p. 200-02°C (Found: C, 41.5; H, 3.4; N, 14.7. $C_{10}H_{10}ClN_3OS_2$ requires C, 41.7; H, 3.5; N, 14.6%); IR : 3265 (NH), 1035 (S=O); ^1H NMR : 2.60 (s, 3H, MeSO), 3.76 (s, 2H, SCH_2SO), 7.40-8.18 (m, 4H, ArH), 14.16 (br s, 1H, NH, exchangeable with D_2O); MS : m/z (M^+) = 287.

2b. Yield 80%; m.p. 217-19°C (Found : C, 44.3; H, 4.2; N, 15.4. $C_{10}H_{11}N_3O_2S_2$ requires C, 44.6; H, 4.1; N, 15.6%); IR : 3260 (NH), 1030 (S=O); ^1H NMR : 2.62 (s, 3H, MeSO), 3.73 (s, 2H, SCH_2SO), 4.46 (s, 1H, OH), 7.38-8.12 (m, 4H, ArH), 14.14 (br s, 1H, NH, exchangeable with D_2O); MS : m/z (M^+) = 269.

5-Aryl-3-methanesulphinylmethylthio-4-thiocarboxamido-1, 2, 4-triazoles (4a-h). A mixture of **2a** (6 mmole) and phenyl isothiocyanate **3a** (6 mmole) in ethanol (20 mL) was refluxed for 6 hr, then cooled to room temp and poured into water. The product thus obtained was filtered off, washed with water and recrystallised from ethanol to give an analytical sample of **4a**. According to the same procedure compounds **4b, 4c, 4e, 4f** and **4g** were prepared and recrystallized from ethanol. For **4d** and **4h** by the above method, carbon disulphide was employed in place of phenyl isothiocyanate. Yields, melting points, molecular formulae and elemental analyses of compounds **4a-h** are recorded in Table I.

Table I—Yields and melting points of compounds **4** and **5**

Compd	Ar	X	Yield (%)	m.p. (°C)
4a	2-ClC_6H_4	PhN	80	201-03
4b	2-ClC_6H_4	2-MeC_6H_4N	74	236-38
4c	2-ClC_6H_4	cyclo-$C_6H_{11}N$	78	216-18
4d	2-ClC_6H_4	S	72	226-28
4e	4-OHC_6H_4	PhN	76	118-19
4f	4-OHC_6H_4	2-MeC_6H_4N	65	116
4g	4-OHC_6H_4	cyclo-$C_6H_{11}N$	73	114
4h	4-OHC_6H_4	S	79	105
5a	2-ClC_6H_4	PhN	80	184-85
5b	2-ClC_6H_4	2-MeC_6H_4N	74	197-98
5c	2-ClC_6H_4	cyclo-$C_6H_{11}N$	70	186-88
5d	2-ClC_6H_4	S	77	174-75
5e	4-OHC_6H_4	PhN	75	109
5f	4-OHC_6H_4	2-MeC_6H_4N	68	110-11
5g	4-OHC_6H_4	cyclo-$C_6H_{11}N$	73	106
5h	4-OHC_6H_4	S	76	99

4a. IR : 3315 (NH), 1035 (S=O); ^1H NMR : 2.64 (s, 3H, MeSO), 3.83 (s, 2H, SCH_2SO), 7.33-8.21 (m, 9H, ArH), 8.90 (br s, 1H, NH, exchangeable with D_2O); MS : m/z (M^+) = 422.

4c. IR : 3320 (NH), 1035 (S=O); ^1H NMR : 1.34-1.68 (br s, 11H, cyclohexyl), 2.58 (s, 3H, MeSO), 3.81 (s, 2H, SCH_2SO), 7.48-8.18 (m, 4H, ArH), 8.88 (br s, 1H, NH, exchangeable with D_2O); MS : m/z (M^+) = 428.

4f. IR : 3310 (NH), 1030 (S=O); ^1H NMR : 2.26 (s, 3H, Me), 2.57 (s, 3H, MeSO), 3.77 (s, 2H, SCH_2SO), 4.51 (s, 1H, OH), 7.27-8.00 (m, 8H, ArH), 8.84 (br s, 1H, NH, exchangeable with D_2O); MS : m/z (M^+) = 418.

4h. IR : 1030 (S=O); ^1H NMR : 2.58 (s, 3H, MeSO), 3.76 (s, 2H, SCH_2SO), 4.49 (s, 1H, OH), 7.27-8.08 (m, 4H, ArH), 10.12 (br s, 1H, SH, exchangeable with D_2O); MS : m/z (M^+) = 345.

3-(2-Chlorophenyl)-5-phenylimino-5*H*,7*H*-[1,2,4]-triazolo[3-4-*d*][1,3,5]dithiazine 5a. Compound **4a** (3 mmole) was dissolved in 90% H_2SO_4 (5 mL) under ice-cooling (maintaining the temperature of the reaction mixture < 5°C) and allowed to stand in an ice bath for 30 min. The product was isolated by pouring the reaction mixture in

water (30 mL) followed by basification with concentrated NH_4OH (4 mL; d 0.91). It was filtered off, washed with water and recrystallized from ethanol to furnish an analytical sample. Similarly, compounds **5b-h** were obtained by intramolecular cyclisation of the respective compounds **4b-h** and were recrystallized from ethanol. Yields, melting points, molecular formulae and elemental analyses of compounds **5a-h** are recorded in Table I.

5a. IR : 1690 (C=N) (exocyclic); ^{1}H NMR : 4.08 (s, 2H, SCH_2S), 7.34-8.20 (m, 9H, ArH); MS : m/z (M^+) = 358.

5c. IR : 1685 (C=N) (exocyclic); ^{1}H NMR : 1.57 (br s, 11H, cyclohexyl), 4.02 (s, 2H, SCH_2S), 7.33-8.12 (m, 5H, ArH); MS : m/z (M^+) = 364.

5f. IR : 1680 (C=N) (exocyclic); ^{1}H NMR : 2.28 (s, 3H, Me), 4.02 (s, 2H, SCH_2S), 4.47 (s, 1H, ArOH), 7.27-7.99 (m, 8H, ArH); MS : m/z (M^+) = 354.

5h. IR : 1095 (C=S); ^{1}H NMR : 3.98 (s, 2H, SCH_2S), 4.50 (s, 1H, ArOH), 7.26-8.02 (m, 4H, ArH).

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