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Synthesis of new triazepinethiones

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Abstract—We describe the first synthesis of 7-alkyl-5-aryl-1,2,4-triazepine-3-thiones using hydrazinediium dithiocyanate and α,β-unsaturated ketones as starting materials. Triazepine-3-thiones with this substitution pattern are not accessible by former reported methods. Those compounds may serve as black toning agents for laminated photographs or as starting materials for the synthesis of thiazolo[3,2-*b*][1,2,4]triazepines, which are supposed to have immunomodulating activities. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

The cyclisation of the β-isothiocyanatopentan-2-one **1** with hydrazine was first reported by Mathes and Stewart,[1] who claimed the product as mercapto pyrimidine. However, Zigeuner et al.[2] rectified the structure as 1,2,4-triazepin-3-thione **2**. This compound was used as black toning agent for laminated photographs[3] and as starting material for the synthesis of thiazolo-triazepinones.[4,5] All of the so far described 1,2,4-triazepin-3-thiones have been prepared from α,β-unsaturated ketones via their β-isothiocyanato derivatives, which were cyclised by the reaction with hydrazine or alkyl hydrazines.[4,6,7] They have either alkyl or aryl substitution in ring positions 5 and 7. Alkyl-aryl substituted 1,2,4-triazepine-3-thiones have not yet been reported. This paper deals with the syntheses of the latter from α,β-unsaturated ketones and hydrazinediium dithiocyanate.

2. Results and discussion

The cyclisation of 4-methyl-4-isothiocyanatopentan-2-one[8] (**1**) to 5,5,7-trimethyl-triazepine-3-thione (**2**) with hydrazine hydrate was carried out under alkaline conditions[4] or in refluxing benzene[2] (Scheme 1). The preparation of the 5,7-diphenyl analogue **3** from 3-isothiocyanato-1,3-diphenylpropan-1-one (**4**) succeeded in acidic medium.[7] But 4-isothiocyanato-4-phenylbutan-2-one[9] (**5**) gives no 1,2,4-triazepin-3-thione (**6**) by the above methods.

We synthesised **6** from benzylidene acetone (**7**) and hydrazinediium dithiocyanate. The starting materials were refluxed in dimethyl formamide at a water separator.

By the same procedure the α,β-unsaturated 3-arylketones **9**–**12** were cyclised with hydrazinediium dithiocyanate giving the alkyl-aryl substituted triazepine-thiones **13**–**16**. However, compound **2** was not formed from mesityloxide (**8**) by our method (Scheme 1).

Summing up it may be said that the so far known methods are suitable for the preparation of 5,7-dialkyl[2,4] and 5,7-diaryl-triazepine-3-thiones.[7] However, they fail in the synthesis of 7-alkyl-5-aryl-triazepine-3-thiones, which are available by our method. The structures of products **6** and **13**–**16** were elucidated by NMR spectroscopy.

3. Experimental

3.1. General

Melting points: digital melting point apparatus Electrothermal IA 9200, uncorrected. IR spectra: infrared spectrometer system 2000 FT (Perkin Elmer). UV–vis:

Keywords: triazepines; α,β-unsaturated ketones; hydrazinediium dithiocyanate; cyclisation.

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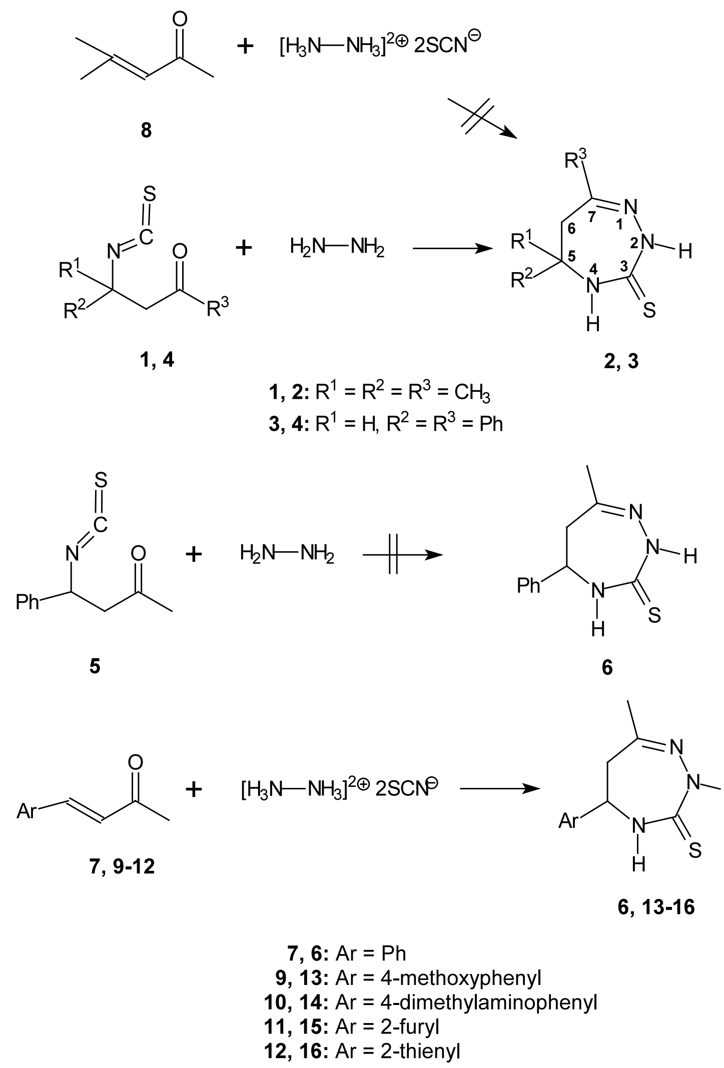

Scheme 1.

Lambda 17 UV–vis-spectrometer (Perkin Elmer). NMR spectra: Varian Inova 400 (300 K) 5 mm tubes, TMS resonance as internal standard. Assignments marked with an asterisk are interchangeable. MS: Varian MAT 711 spectrometer 70 eV electron impact. Microanalyses: EA 1108 CHNS-O apparatus (Carlo Erba).

3.2. Hydrazinediium dithiocyanate

Equimolar amounts of hydrazine hydrate and ammonium rhodanide were dissolved in the required volume of water and stirred for 1 h at room temperature. The solvent was evaporated and the residue was triturated with ethanol, filtered with suction and dried.

3.3. General procedure for 6, 13–16

Hydrazinediium dithiocyanate and the α,β-unsaturated ketones (**7**, **9**–**12**) were dissolved in dimethyl formamide and refluxed at a water separator for 4 h. The solvent was evaporated. The product crystallised partially from ethanol, was treated with charcoal in ethanol and recrystallised. Purification of the filtrate: CC (silica gel, eluent: CH_2Cl_2 for **6**, CH_2Cl_2:MeOH = 20:1 for **13**–**16**).

3.3.1. 5,6-Dihydro-7-methyl-5-phenyl-2*H*-1,2,4-triazepin-3(4*H*)-thione (6). Hydrazinediium dithiocyanate (12.7 g, 84.5 mmol) and 14 g (95.8 mmol) benzylidene acetone (**7**) in 200 ml of dimethyl formamide gave yellowish plates. Yield: 5 g (27%). Mp: 237°C; $R_f = 0.08$ (CH_2Cl_2); IR (KBr): $\tilde{\nu} = 3397$, 3252, 3149, 1592, 1498, 1421, 1380, 1364, 1326, 828, 756, 699 cm^{-1}; UV (CH_2Cl_2): λ ($\log \varepsilon$) = 276 (4.235), 235 (3.890) nm; ^1H NMR (400 MHz, δ, $CDCl_3$): 2.07 (s, 3H, CH_3), 2.73 (dd, 1H, 6-H), 3.46 (dd, 1H, 6-H), 5.87 (dd, 1H, 5-H), 5.95 (s, b, 1H, NH), 6.87 (s, b, 1H, NH), 7.15–7.35 (m, 5H, aromatic H) ppm; ^{13}C NMR (100 MHz, δ, $CDCl_3$): 16.14 (CH_3), 47.09 (C-6), 63.08 (C-5), 125.21, 127.48, 128.84, 141.80 (aromatic C), 158.11 (C-7), 176.40 (C-3) ppm; MS (EI+): *m*/*z* (%) = 220 (12.9) [M+H$^+$], 219 (93.9) [M^+]; $C_{11}H_{13}N_3S$ (219.31); calcd: C, 60.24; H, 5.97; N, 19.16; S, 14.62. Found: C, 59.96; H, 6.03; N, 19.14; S, 14.02.

3.3.2. 5,6-Dihydro-5-(4-methoxyphenyl)-7-methyl-2*H*-1,2,4-triazepin-3(4*H*)-thione (13). Hydrazinediium dithiocyanate (7.6 g, 50 mmol) and 14 g (50 mmol) 4-methoxybenzylidene acetone (**9**) in 80 ml of dimethyl formamide gave yellowish prisms. Yield: 4.9 g (40%).

Mp: 182°C; $R_f = 0.7$ (CH$_2$Cl$_2$:MeOH = 20:1); IR (KBr): $\tilde{\nu} = 3419$, 3254, 3149, 1596, 1514, 1491, 1455, 1385, 1361, 1324, 1308, 1287, 1252, 1184, 1034, 823 cm^{-1}; UV (CH$_2$Cl$_2$): λ (log ε) = 273 (4.257), 235 (4.065) nm; ^{1}H NMR (400 MHz, δ, DMSO-d_6): 2.02 (s, 3H, CH$_3$), 2.60 (dd, 1H, 6-H), 3.50 (dd, 1H, 6-H), 3.72 (s, 3H, OCH$_3$), 5.68 (dd, 1H, 5-H), 6.86, 7.02 (2d, 4H, aromatic H), 7.37 (s, b, 1H, NH), 7.70 (s, b, 1H, NH) ppm; ^{13}C NMR (100 MHz, δ, DMSO-d_6): 15.96 (CH$_3$), 46.59 (C-6), 55.22 (OCH$_3$), 61.93 (C-5), 113.88, 126.80, 135.33, 158.27 (aromatic C), 158.55 (C-7), 175.75 (C-3) ppm; MS (EI+): *m*/*z* (%) = 250 (8.8) [*M*+H$^+$], 249 (54.1) [*M*$^+$]; $C_{12}H_{15}N_3OS$ (249.34); calcd: C, 57.81; H, 6.06; N, 16.85; S, 12.86. Found: C, 57.71; H, 6.10; N, 16.89; S, 12.38.

3.3.3. 5-(4-Dimethylaminophenyl)-5,6-dihydro-7-methyl-2*H*-1,2,4-triazepin-3(4*H*)-thione (14). Hydrazinediium dithiocyanate (1.6 g, 11 mmol) and 2.0 g (11 mmol) 4-dimethylamino-benzylidene acetone (**10**) in 100 ml of dimethyl formamide gave white needles. Yield: 1.6 g (57%). Mp: 238°C; $R_f = 0.87$ (CH$_2$Cl$_2$:MeOH = 8:1); IR (KBr): $\tilde{\nu} = 3427$, 3261, 3153, 1621, 1592, 1529, 1488, 1381, 1363, 810 cm^{-1}; UV (CH$_2$Cl$_2$): λ (log ε) = 266 (4.458) nm; ^{1}H NMR (400 MHz, δ, DMSO-d_6): 2.02 (s, 3H, CH$_3$), 2.58 (dd, 1H, 6-H), 2.85 (s, 6H, (NCH$_3$)$_2$), 3.48 (dd, 1H, 6-H), 5.62 (dd, 1H, 5-H), 6.64, 6.92 (2d, 4H, aromatic H), 7.31 (s, b, 1H, NH), 7.63 (s, b, 1H, NH) ppm; ^{13}C NMR (100 MHz, δ, DMSO-d_6): 16.00 (CH$_3$), 40.42 (N(CH$_3$)$_2$), 46.58 (C-6), 62.00 (C-5), 112.50, 126.37, 130.93, 149.64 (aromatic C), 158.59 (C-7), 175.65 (C-3) ppm; $C_{13}H_{18}N_4S$ (262.38); calcd: C, 59.51; H, 6.92; N, 21.35; S, 12.22. Found: C, 59.50; H, 6.98; N, 21.38; S, 11.94.

3.3.4. 5-Furyl-5,6-dihydro-7-methyl-2*H*-1,2,4-triazepin-3(4*H*)-thione (15). Hydrazinediium dithiocyanate (7.7 g, 51 mmol) and 7 g (51 mmol) furfurylidene acetone (**11**) in 85 ml of dimethyl formamide gave grey plates. Yield: 2.7 g (25%). Mp: 220–222°C; $R_f = 0.6$ (CH$_2$Cl$_2$:MeOH = 20:1); IR (KBr): $\tilde{\nu} = 3406$, 3263, 3153, 1593, 1489, 1368, 815, 763 cm^{-1}; UV (CH$_2$Cl$_2$): λ (log ε) = 269 (4.222), 236 (3.985) nm; ^{1}H NMR (400 MHz, δ, DMSO-d_6): 2.04 (s, 3H, CH$_3$), 2.82 (dd, 1H, 6-H), 3.42 (dd, 1H, 6-H), 5.81 (dd, 1H, 5-H), 6.23 (d, 1H, 3′-H), 6.37 (m, 1H, 4′-H), 7.36 (s, b, 1H, NH), 7.53 (d, 1H, 5′-H), 7.77 (s, b, 1H, NH) ppm; ^{13}C NMR (100 MHz, δ, DMSO-d_6): 15.86 (CH$_3$), 42.82 (C-6), 56.30 (C-5), 107.22 (C-3′), 110.50 (C-4′), 142.02 (C-5′), 153.46 (C-2′), 158.52 (C-7), 175.80 (C-3) ppm; MS (EI+): *m*/*z* (%) = 210 (13.5) [*M*+H$^+$], 209 (100.0) [*M*$^+$]; $C_9H_{11}N_3OS$ (209.27); calcd: C, 51.66; H, 5.30; N, 20.08; S, 15.32. Found: C, 51.64; H, 5.33; N, 20.04; S, 15.18.

3.3.5. 5,6-Dihydro-7-methyl-5-(2-thienyl)-2*H*-1,2,4-triazepin-3(4*H*)-thione (16). Hydrazinediium dithiocyanate (5.2 g, 35 mmol) and 7 g (35 mmol) thenylidene acetone (**12**) in 60 ml of dimethyl formamide gave yellow needles. Yield: 2.3 g (29%). Mp: 220°C; $R_f = 0.7$ (CH$_2$Cl$_2$:MeOH = 20:1); IR (KBr): $\tilde{\nu} = 3389$, 3251, 3150, 1592, 1494, 1420, 1367, 1326, 1305, 825, 705 cm^{-1}; UV (CH$_2$Cl$_2$): λ (log ε) = 279 (3.714), 237 (3.576) nm; ^{1}H NMR (400 MHz, δ, CDCl$_3$): 2.11 (s, 3H, CH$_3$), 2.90 (dd, 1H, 6-H), 3.43 (dd, 1H, 6-H), 6.01 (s, b, 1H, NH), 6.19 (dd, 1H, 5-H), 6.81 (s, b, 1H, NH), 6.93 (dd, 1H, 4′-H), 7.02 (d, 1H, 5′-H*), 7.19 (d, 1H, 3′-H*) ppm; ^{13}C NMR (100 MHz, δ, CDCl$_3$): 16.15 (CH$_3$), 46.77 (C-6), 58.82 (C-5), 124.36 (C-3′*), 124.74 (C-5′*), 126.70 (C-4′), 144.23 (C-2′), 158.25 (C-7), 176.30 (C-3) ppm; MS (ES+): *m*/*z* (%) = 226 (11.5) [*M*+H$^+$], 225 (77.7) [*M*$^+$]; $C_9H_{11}N_3S_2$ (225.33); calcd: C, 47.97; H, 4.92; N, 18.65; S, 28.64. Found: C, 48.10; H, 4.95; N, 18.44; S, 28.50.

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