HETEROCYCLES, Vol. 24, No. 8, 1986

HETEROCYCLIC STUDIES - PART 1[1].
SYNTHESIS OF THIENO[2,3-*d*]TRIAZOLES

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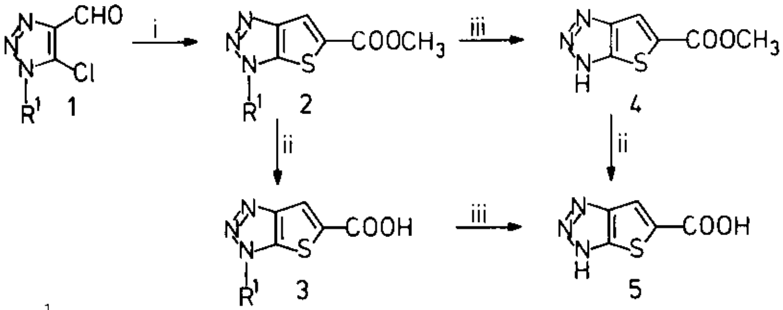
Abstract - The thieno[2,3-*d*]triazole-5-carboxylic acid was synthesized from a 5-chloro-4-formyltriazole. Attempted decarboxylation led to decomposition of the ring system.

In general heterocyclic β-chloroaldehydes can be used[2,3] for the preparation of annelated thiophenes. As there currently is interest [4] in the chemistry of fused thienoazoles and as we previously have synthesized 5-chloro-4-formyltriazoles[1] we have investigated the preparation of the hitherto unknown thieno[2,3-*d*]triazole ring system which is of interest as a potential source of thienyl nitrenes.

RESULTS AND DISCUSSION

Reaction of the 5-chloro-4-formyltriazoles 1 with methyl mercaptoacetate in methanol and sodium carbonate gave the thieno[2,3-*d*]triazoles 2. It appeared of interest to prepare the hitherto unknown parent thieno[2,3-*d*]triazole ring system. Thus hydrolyses of ester 2c with sodium hydroxide gave the carboxylic acid 3c. Debenzylation[5] of the 4-methoxybenzyl derivative 2c with trifluoroacetic acid gave the carboxylic ester 4. Hydrolyses of either this ester 4 in sodium hydroxide or debenzylation of the acid 3c gave in both cases the 1*H*-thieno[2,3-*d*]triazole-5-carboxylic acid 5.



1a, 2a: R^1 = benzyl
1b, 2b: R^1 = 4-chlorphenyl
1c, 2c, 3c: R^1 = 4-methoxybenzyl
1d, 2d: R^1 = phenyl

i: mercaptoacetic acid methylester, sodium carbonate. ii: sodium hydroxide (2M). iii: trifluoro acetic acid, 65 °C. (For compounds 4 and 5 only one tautomer shown).

As the thieno[2,3-d]triazole ring system was found to be relatively unstable at elevated temperatures the yields of this compound were not high and attempted decarboxylation reactions either at compound 3c or of the acid 5 did not give the desired unsubstituted thieno[2,3-d]triazole system due to extensive decomposition under the reaction conditions used.

Structures of the new compounds described here were all in agreement with the spectroscopic and analytical values. The ^{13}C NMR spectra of the new thieno[2,3-d]-triazoles 2 were in agreement with the structure, thus 2c showed aliphatic ^{13}C signals at δ = 52 and 54 ppm due to benzylic and methoxy carbons. The fused carbon atoms give signals at δ = 135 and 153 ppm, the signal at 153 ppm can be ascribed to the N-C-S carbon. Carbon atom 4 and 5 are located at 120 resp. 139 ppm. All compounds 2-5 showed a carbonyl carbon signal in the ^{13}C spectra at δ = 162 ppm.

Table. ^{13}C NMR decoupled spectra of 1H-thieno[3,2-d]triazoles (δ values; internal standard TMS; solvent DMSO-d_6.

Compound	C-4	C-5	C-6	C-8	Other carbons	Aryl carbons
2a	120.56	139.17	153.58	135.04	162.84(CO) 54.26(CH_3) 52.57(CH_2)	132.15, 129.39, 129.13
2b	120.46	138.65	152.87	134.26	168.22(CO) 52.70(CH_2) 52.24(CH)	153.68, 131.05, 129.04
2c	120.50	139.10	153.42	135.01	162.90(CO) 55.33(OCH) 53.74(CH_3) 52.54(CH_2)	160.47, 130.73 123.97, 114.68
2d	120.75	138.10	153.15	135.62	162.02(CO) 52.82(CH_3)	134.12, 130.29 128.68, 118.93
3c	119.58	137.89	152.79	136.49	163.41(CO) 55.12(OCH_3) 52.56(CH_2)	159.68, 130.97 124.99, 114.32
4	118.41	137.24	148.64	147.12	162.31(CO) 52.75(CH_3)	
5	117.66	139.64	148.77	147.12	163.54(CO)	

EXPERIMENTAL

Microanalyses were carried out by Mr. Preben Amsler at NOVO A/S Bagsvaerd, Denmark. The instrumentation was: ^{1}H NMR, Jeol JNM-PMX60; ^{13}C NMR, Jeol FX60; mp, Büchi aparatus (uncorrected); IR, Perkin Elmer 580.

5-Carbomethoxy-1(3)H-thieno[2,3-d]triazoles 2a-2d:

General Procedure:

Anhydrous sodium carbonate (0.5 g, 5 mmol) was added to a solution of the appropriate 4-formyl-5-chlorotriazole (1) (2.5 mmol) and 2-mercaptomethylacetate (3.5 mmol, 0.04 g) in 10 ml of methanol. The reaction mixture was heated under reflux for 2 h. After cooling the mixture was poured slowly on 25 ml of ice water. The precipitated crystals were filtered and recrystallized from 2-propanol.

5-Carbomethoxy-1-benzyl-1H-thieno[2,3-d]triazole 2a:

The general method was used for compound 2a, yield 63%, mp 134-135 °C (2-propanol). IR: 1730 cm^{-1} (C=O). ^1H NMR ($CDCl_3$): δ 2.86 (s, CH_3), 5.67 (s, CH_2), 7.41 (s, 5H), 7.89 (s, 1H). MS **m/z** 273 (M^+, 13), 91 (100). $C_{13}H_{11}N_3O_2S$ (273.3) Calcd. C, 57.13; H, 4.06; N, 15.37. Found C, 56.94; H, 4.07; N, 15.35.

5-Carbomethoxy-1-(4-chlorobenzyl)-1H-thieno[3,2-d]triazole 2b:

The general method was used for compound 2b, yield 59%, mp 160-161 °C (2-propanol). IR: 1730 cm^{-1} (C=O). ^1H NMR ($CDCl_3$): δ 3.85 (s, CH_3), 5.90 (s, CH_2), 7.51 (s, 5H), 8.11 (s, 1H). MS: m/z 307 (M^+, 20), 125 (100). $C_{13}H_{10}ClN_3O_2S$ (307.8) Calcd. C, 50.74; H, 3.28; N, 13.65. Found C, 50.93; H, 3.31; N, 13.65.

5-Carbomethoxy-1-(4-methoxybenzyl)-1H-thieno[3,2-d]triazole 2c:

The general method was used for compound 2c, yield 57%, mp 143-144 °C (2-propanol). IR= 1725 cm^{-1} (C=O). ^1H NMR ($CDCl_3$): δ 3.48 (s, CH_3), 3.65 (s, CH_3), 5.60 (s, CH_2), 6.92 (d, 2H), 7.35 (d, 2H), 7.88 (s, 1H). MS: m/z 303 (M^+, 3.2), 121 (100). $C_{14}H_{13}N_3O_3S$ (303.3) Calcd. C, 55.44; H, 4.32; N, 13.85. Found C, 55.48; H, 4.30; N, 13.71.

5-Carbomethoxy-1-phenyl-1H-thieno[3,2-d]triazole 2d:

The general method was used for compound 2d, yield 64%, mp 145-146 °C (2-propanol). IR: 1710 cm^{-1} (C=O). ^1H NMR ($CDCl_3$): δ 3.92 (s, CH_3), 7.5-8.0 (m, 5H), (s, 1H). MS: m/z 259 (M^+, 21), 128 (100). $C_{12}H_9N_3O_2S$ (259.3) Calcd. C, 55.59; H, 3.50; N, 16.21. Found C, 55.72; H, 3.53; N, 16.18.

5-Carboxy-1-(4-methoxy benzyl)-1H-thieno[2,3-d]triazole 3c:

The methyl ester 2c (5 g, 0.0165 mol) was refluxed in sodium hydroxide (2M, 100 ml) for 10 min, the reaction mixture was cooled and the precipitated crystals filtered to give 3c (4.3 g) in 90% yield, mp 206-208 °C (dec.) (water). IR: 1695 cm^{-1} (C=O). ^1H NMR DMSO-d_6: δ 5.80 (s, CH_2), 7.5 (d, 2H, J = 9Hz), 7.1 (d, 2H, J = 9Hz), 8.05 (s, 1H). MS: m/z 289 (12), 121 (100). $C_{13}H_{11}N_3O_3S$ (289.3) Calcd. C, 53.97; H, 3.83; N, 14.52. Found C, 53.45; H, 3.71; N, 14.27.

5-Carboxymethyl-1(3)H-thieno[3,2-d]triazole 4:

The ester 2c (1.0 g, 0.0035 mol) was dissolved in trifluoroacetic acid (100 ml) and heated with stirring at 65 °C for 7 h. The dark reaction mixture was concentrated *in vacuo* and the resulting product recrystallized from water to give 4 (0.3 g) (47%), mp 208-210 °C (dec.). IR: 3100 (NH), 1730 cm^{-1} (C=O). UV (abs. ethanol) $\lambda_{max} = 272$ ($\log\varepsilon = 3.11$). ^1H NMR (DMSO-d_6): δ 3.9 (s, CH_3), 8.1 (s, 1H). MS m/z 183 (M^+, 90), 152 (100). $C_6H_5N_3O_2S$ (183.) Calcd. C, 39.35; H, 2.75; N, 22.94. Found C, 39.94; H, 2.90; N, 22.27.

1(3)-*H*-Thieno[2,3-*d*]triazolo-5-carboxylic acid **5**:

The thieno[3,2-*d*]triazole **3c** (5.0 g, 0.0173 mol) was deanisylated by reflux in trifluoroacetic acid (100 ml) for 7 h, followed by concentration *in vacuo*. Yield 1.1 g (38%), mp 207-208 ^{o}C. IR: 1700 cm^{-1} (C=O). UV (abs. ethanol) λ_{max} = 272 (log ε = 309). ^{1}H NMR (DMSO-d$_{6}$): δ 8.1 (s, 1H). MS: m/z 169 (M^{+}, 100), 86 (19), 52 (26). Peak match: Calcd. 168.9946, Found 168.9947. $C_5H_3N_3O_2S$ (168.99) Calcd. C, 35.50; H, 1.79; N, 24.83. Found C, 35.88; H, 1.84; N, 24.27.

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Received, 2nd May, 1986