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SYNTHESIS AND REARRANGEMENT OF 3-AMINO-2-BENZYL[1,2,4]TRIAZOLO[4,3-*a*]PYRIMIDINIUM SALTS

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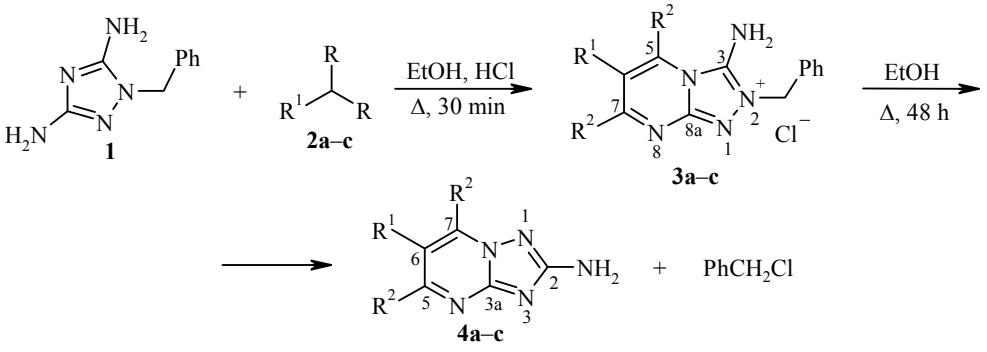
It has previously been shown that the reaction of 1-phenyl[1,2,4]triazole-3,5-diamine perchlorate with 1,3-diketones or 1,1,3,3-tetraethoxypropane yields 2-amino-1-phenyl[1,2,4]triazolo[1,5-*a*]pyrimidinium perchlorates [1]. According to the authors [1], these compounds are the products of a Dimroth rearrangement of the initially formed [4,3-*a*]-isomers, which could not be separated.

We have shown that brief heating of 1-benzyl[1,2,4]triazole-3,5-diamine (**1**) with the 1,3-diketones **2a**,**b** or 1,1,3,3-tetramethoxypropane (**2c**) in ethanol in the presence of HCl gives the 2-R-3-amino[1,2,4]triazolo-[4,3-*a*]pyrimidinium chlorides **3a-c**, i.e. condensation proceeds similarly to the reaction of 1-substituted [1,2,4]triazole-3,5-diamines with β-ketoesters [2].



2 a,**b** R = Ac, **c** R = $CH(OMe)_2$; **2**–**4 a**,**c** R^1 = H; **b** R^1 = Cl; **3**, **4 a**,**b** R^2 = Me, **c** R^2 = H

The structure of compounds **3a-c** was confirmed using spectroscopic methods including the NOESY spectra of compounds **3a**,**c** in which correlated peaks were observed for the protons of the amino group with the signals for both the CH_2Ph group and the substituent at the position 5. The chemical shift values for the C-3 and C-8a atoms in compounds **3a-c** (signal assignments were made with the help of the HSQC and HMBC spectra) were close to analogous signals in the spectra of the mesoionic 2-R-3-amino[1,2,4]triazolo[4,3-*a*]pyrimidin-5-ones [2, 3].

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Prolonged refluxing of salts **3a-c** in ethanol solutions gives the 2-amino[1,2,4]triazolo[1,5-*a*]pyrimidines **4a-c**. Hence, in contrast to the mesoionic triazolopyrimidin-5-ones (which rearrange to 1-R-3-amino-[1,2,4]triazolo[4,3-*a*]pyrimidin-5-ones [2]), compounds **3a-c** undergo a Dimroth rearrangement with loss of the benzyl group under mild conditions. Using gas chromato-mass spectrometry it was established that the benzyl group is lost as benzyl chloride, which undergoes gradual solvolysis.

The properties of compounds **4a-c** are identical to those reported in the literature [4-6], and their structure was additionally confirmed by a counter synthesis from [1,2,4]triazole-3,5-diamine and compounds **2a-c** using a known method [4].

The results presented here and previously published data show that the primary route of cyclocondensation of 1-substituted [1,2,4]triazole-3,5-diamines with a variety of 1,3-carbonyl compounds is apparently the same and yields 2-substituted 3-amino[1,2,4]triazolo[4,3-*a*]pyrimidines. However, the route of subsequent recyclizations of these compounds depends markedly on their structural features.

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 600 instrument (600 and 150 MHz, respectively) using DMSO-d_6 with TMS as internal standard. Mass spectra (EI, 70 eV) were registered on a Finnigan MAT Incos 50 spectrometer with direct introduction of the sample into the ion source. Gas chromato-mass spectrometry experiments were performed on an Agilent 7890A chromatograph fitted with an Agilent 5975C (EI, 70 eV) mass selective detector and HP-5MS capillary column. Elemental analysis was carried out on a Perkin Elmer 2400 analyzer. Melting points were determined in sealed capillaries on a PTP apparatus.

Preparation of Compounds 3a-c (General Method). 36% HCl (390 mg, 3.71 mmol) in EtOH (1 ml) was added to a solution of compound **1** (539 mg, 2.85 mmol) and compound **2a-c** (3.71 mmol) in EtOH (2 ml). The mixture was refluxed for 30 min, cooled to 0-5°C, and the precipitate formed was filtered off and crystallized from MeCN.

3-Amino-2-benzyl-5,7-dimethyl[1,2,4]triazolo[4,3-*a*]pyrimidin-2-ium Chloride (3a). Yield 297 mg (36%). Colorless prisms, mp 215-217°C. ^{1}H NMR spectrum, δ, ppm: 2.45 (3H, s, CH_3); 2.83 (3H, s, CH_3); 5.64 (2H, s, CH_2); 6.82 (1H, s, H-6); 7.34-7.45 (5H, m, H Ph); 8.82 (2H, s, NH_2). ^{13}C NMR spectrum, δ, ppm: 18.2 (5-CH_3); 25.0 (7-CH_3); 51.1 (CH_2); 111.8 (C-6); 128.2, 128.4, 128.6, 134.4 (C Ph); 144.3 (C-3); 146.2 (C-5); 147.9 (C-8a); 169.9 (C-7). Mass spectrum, *m/z* (I_{rel}, %): 254 $[M\text{-}Cl]^+$ (6), 253 $[M\text{-}HCl]^+$ (36), 162 (11), 107 (100), 91 (58), 67 (55), 65 (32), 36 (30). Found, %: C 58.31; H 5.41; N 23.89. $C_{14}H_{16}ClN_5$. Calculated, %: C 58.03; H 5.57; N 24.17.

3-Amino-2-benzyl-6-chloro-5,7-dimethyl[1,2,4]triazolo[4,3-*a*]pyrimidin-2-ium Chloride (3b). Yield 286 mg (31%). Colorless prisms, mp 211-214°C. ^{1}H NMR spectrum, δ, ppm: 2.56 (3H, s, CH_3); 2.99 (3H, s, CH_3); 5.74 (2H, s, CH_2); 7.32-7.47 (5H, m, H Ph); 9.24 (2H, s, NH_2). ^{13}C NMR spectrum, δ, ppm: 15.9 (5-CH_3); 24.8 (7-CH_3); 51.3 (CH_2); 118.2 (C-6); 128.2, 128.3, 128.5, 134.0 (C Ph); 143.2 (C-5); 144.4 (C-3); 145.5 (C-8a); 166.9 (C-7). Mass spectrum, *m/z* (I_{rel}, %): 289 $[M\text{-}Cl]^+$ (6), 287 $[M\text{-}HCl]^+$ (18), 141 (50), 91 (100), 67 (40), 36 (30). Found, %: C 52.08; H 4.53; N 21.47. $C_{14}H_{15}Cl_2N_5$. Calculated, %: C 51.86; H 4.66; N 21.60.

3-Amino-2-benzyl[1,2,4]triazolo[4,3-*a*]pyrimidin-2-ium Chloride (3c). Yield 330 mg (44%). Colorless prisms, mp 206-207°C. ^{1}H NMR spectrum, δ, ppm: 5.59 (2H, s, CH_2); 7.14-7.16 (1H, m, H-6); 7.33-7.46 (5H, m, H Ph); 8.78-8.79 (1H, m, H-7); 9.28-9.29 (1H, m, H-5); 10.03 (2H, s, NH_2). ^{13}C NMR spectrum, δ, ppm: 51.2 (CH_2); 110.2 (C-6); 128.2, 128.3, 128.5 (C Ph); 133.7 (C-5); 134.0 (C Ph); 143.7 (C-3); 146.4 (C-8a); 160.4 (C-7). Mass spectrum, *m/z* (I_{rel}, %): 226 $[M\text{-}Cl]^+$ (1), 225 $[M\text{-}HCl]^+$ (20), 91 (100), 79 (38), 65 (37), 53 (28), 36 (23). Found, %: C 55.32; H 4.53; N 26.49. $C_{12}H_{12}ClN_5$. Calculated, %: C 55.07; H 4.62; N 26.76.

Preparation of Compounds 4a-c (General Method). A solution of compound **3a-c** (1.15 mmol) in EtOH (3 ml) was refluxed for 48 h, cooled, and the precipitate formed was filtered off and crystallized.

5,7-Dimethyl[1,2,4]triazolo[1,5-*a*]pyrimidin-2-amine (4a). Yield 244 mg (84%); mp 354-357°C (DMF–EtOH) (mp 355-357°C [4]). The material did not give a depression in melting point when mixed with a sample obtained by method [4]. ^{1}H NMR spectrum, δ, ppm: 2.45 (3H, s, CH_3); 2.52 (3H, s, CH_3); 6.22 (2H, s,

NH_2); 6.80 (1H, s, H-6). ^{13}C NMR spectrum, δ, ppm: 16.6 (CH_3); 24.1 (CH_3); 108.1 (C-6); 144.6 (C-7); 161.0 (C-3a); 166.9 (C-2,5). Mass spectrum, *m/z* (I_{rel}, %): 163 $[M]^+$ (100), 124 (17), 108 (11), 67 (10), 39 (14).

6-Chloro-5,7-dimethyl[1,2,4]triazolo[1,5-*a*]pyrimidin-2-amine (4b). Yield 180 mg (79%); mp 328°C (decomp., DMF–EtOH). The material did not give a depression in melting point when mixed with a sample obtained by condensation of [1,2,4]triazole-3,5-diamine with compound **2b** in AcOH by using method [4]. ^1H NMR spectrum, δ, ppm: 2.54 (3H, s, CH_3); 2.70 (3H, s, CH_3); 6.31 (2H, s, NH_2). Mass spectrum, *m/z* (I_{rel}, %): 197 $[M]^+$ (100), 142 (10), 124 (12), 65 (9). Found, %: C 42.21; H 3.91; N 35.19. $C_7H_8ClN_5$. Calculated, %: C 42.54; H 4.08; N 35.44.

[1,2,4]Triazolo[1,5-*a*]pyrimidin-2-amine (4c). Yield 70 mg (45%); mp 205-206°C (EtOH) (mp 202-203°C (BuOH) [5]). The UV and ^1H NMR spectra were identical with those reported in [5, 6]. Mass spectrum, *m/z* (I_{rel}, %): 135 $[M]^+$ (100), 95 (6), 80 (7), 68 (5), 53 (22), 39 (10).

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