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SYNTHESIS OF *s*-TRIAZOLO[1,5-*c*]PYRIMIDINES

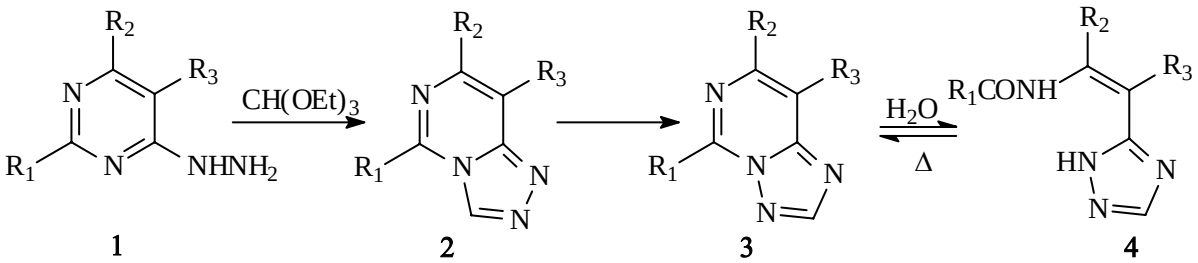
Ravi B. Shankar* and R. Garth Pews

Corporate Research and Development
The Dow Chemical Co.
Midland, MI 48674, U.S.A.

Abstract - A cyclization method for the synthesis of *s*-triazolo[1,5-*c*]pyrimidines is discussed.

s-Triazolo[1,5-*c*]pyrimidines (**3**) are very well known compounds. Their derivatives have been important in the areas of photochemistry, in medicinal chemistry as potential therapeutic agents[1] and in agricultural chemistry .[2] The synthesis of the *s*-triazolo[1,5-*c*]pyrimidines have been invariably from the Dimroth-like rearrangement of the isomeric *s*-triazolo[4,3-*c*]pyrimidines (**2**) .[3] The only exception to this has been the thermal recyclization of 1,2,4-triazoles (**4**) to yield the *s*-triazolo[1,5-*c*]pyrimidines. The 1,2,4-triazole (**4**) itself was obtained from the ring fission of the corresponding *s*-triazolo[1,5-*c*]pyrimidines as shown in Scheme 1.

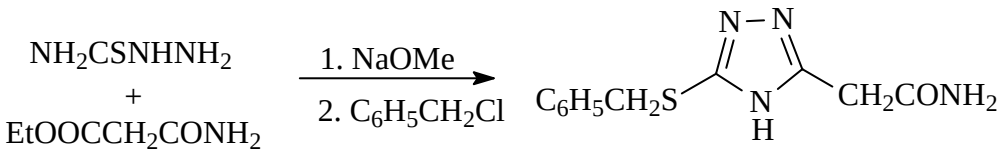
Scheme 1



1 **2** **3** **4**

In the present paper we wish to report the synthesis of the *s*-triazolo[1,5-*c*]pyrimidines (**3**) from a ring closure reaction of appropriately substituted 1,2,4-triazoles (**5**). The requisite 1,2,4-triazoles were assembled according to the method of Willems .[4] Base catalyzed condensation of thiosemicarbazide with ethyl malonamide followed by reaction with benzyl chloride yields the triazole (**5**) in 89% yield as shown in Scheme 2.

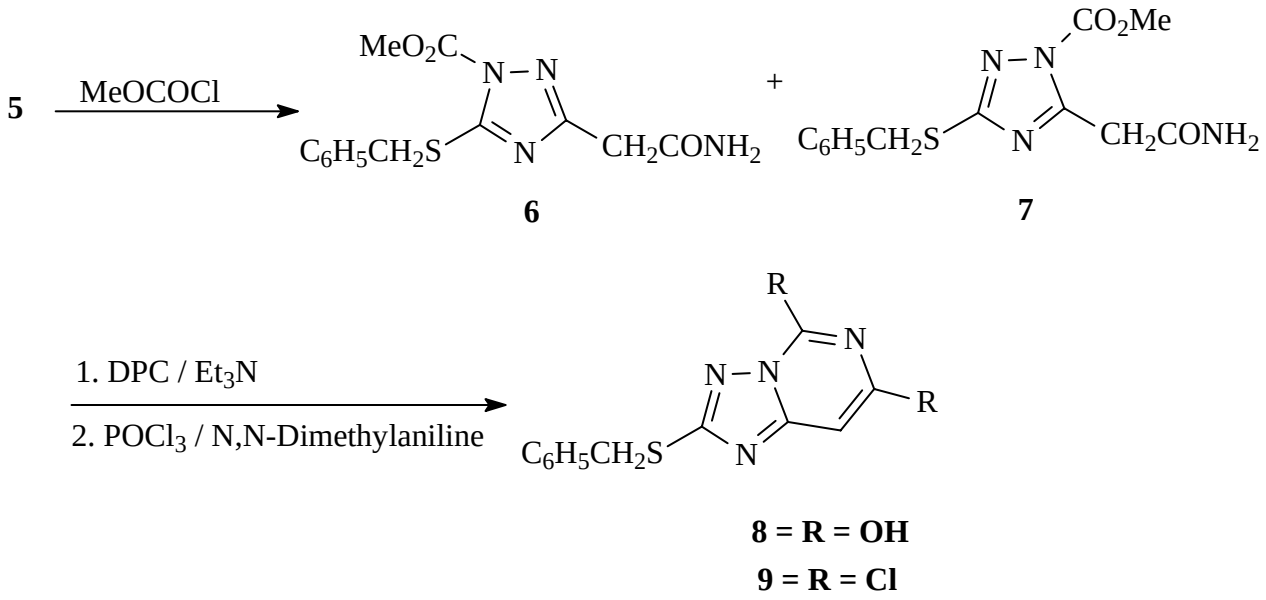
Scheme 2



5

Reaction of the triazole (**5**) with methyl chloroformate gave two compounds, both having the same MS. These are probably the regioisomers (**6**) and (**7**). Efforts to cyclize this mixture under acidic, basic and thermal conditions lead only to a mixture of products. Reaction of the triazole (**5**) with phenyl chloroformate in the presence of triethylamine gave the dihydroxy compound (**8**). The conversion of the triazole to the dihdroxy compound (**8**) was effected more efficiently by cyclizing with diphenyl carbonate in the presence of triethylamine The dihydroxy compound could be separated from the by product phenol by slurrying the reaction mixture with aqueous potassium hydroxide and filtering the potassium salt. The dihydroxy compound could be converted to the more useful dichloro derivative (**9**) by reaction with phosphorous oxychloride and dimethylaniline as shown in Scheme 3.

Scheme 3



In summary a cyclization method for the synthesis of *s*-triazolo[1,5-*c*]pyrimidines has been demonstrated.

EXPERIMENTAL

General Method

All melting points are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian XL-300 spectrometer. The ^{1}H and ^{13}C NMR chemical shifts are expressed as δ values (ppm) relative to a TMS standard. The HPLC samples were prepared in the eluant and analyzed on a HP 1090 system equipped with a HP ODS 200 x 2.1 mm column eluted with 35:65 water: acetonitrile buffered with 0.1 wt% sulfuric acid at a flow rate of 0.6 mL per minute and diode array detector with uv wavelength set at 240 nm and a bandwidth of 80 nm. The MS were recorded on a HP 5995 GC-MS *via* direct insertion probe method. In general the reactions were conducted under a positive pressure of nitrogen.

3-Benzylthio-1*H* -1,2,4-triazole-5-acetamide(**5**).

To a stirred suspension of 48 g (0.53 mol) of thiosemicarbazide in 170 mL of methanol was added sodium methoxide (125 g of 25 wt% solution in methanol) in methanol and the mixture was heated to reflux. To the resulting solution 85 g (0.63 mol) of ethyl malonamide was added and the mixture refluxed for a period of 3 h. The reaction mixture was cooled and filtered. Benzyl chloride (63 g, 0.5 mol) was added to the filtrate and stirred for 2 h. The reaction mixture was filtered and the filtrate concentrated. The residue was slurried in chloroform and filtered, washed with water and dried to yield 109 g (89%) of **5** as a white solid. A small portion was recrystallized from isopropanol and toluene (1:1), mp134-135°C; ^{1}H NMR (DMSO-d_6): δ 3.60(s, 2H), 4.33(s, 2H), 7.2-7.4(m, 4H), 7.65(s, 1H); ^{13}C NMR (DMSO-d_6): δ 33.87, 35.42, 127.59, 128.80, 129.25, 138.31, 154, 157, 169.50; MS *m/z* 248 (M^+). Anal. Calcd for $C_{11}H_{12}N_4OS$: C, 53.21; H, 4.87; N, 22.56. Found: C, 53.30; H, 4.72; N, 22.58.

5,7-Dihydroxy-2-benzylthio-1,2,4-triazolo[1,5-*c*]pyrimidine(**8**).
To a solution of 2.5 g (0.01 mol) of the amide (**5**) in triethylamine (4 g, 0.04 mol) and 25 mL of water was added 3.12 g (0.02 mol) of phenyl chloroformate and allowed to stir at vt for 14 h. The precipitate formed was filtered washed with water, methylene chloride and dried to yield 1.60 g (58%) of the dihydroxy compound (**8**), mp 283-286°C (decomp); ^{1}H NMR (DMSO-d_6): δ 2.51(br s, 2H), 4.35(s, 2H), 4.73(s, 1H), 7.24-7.43(m, 5H), 10.34(br s, 1H); ^{13}C NMR (DMSO-d_6): δ 34.31, 70.64, 126.88, 128.19, 128.64, 137.89, 145.88, 159.73, 162.20, 162.53.

5,7-Dichloro-2-benzylthio-1,2,4-triazolo[1,5-*c*]pyrimidine(**9**).
A solution of 35.4 g (0.17 mol) of the amide(**5**), triethylamine (33.4 g, 0.33 mol) and diphenyl carbonate (35.41 g, 0.17 mol) in 250 mL of acetonitrile was refluxed for 16 h. The reaction mixture was cooled, filtered and concentrated under reduced pressure. The residue was slurried in 200 mL of water and the resulting precipitate was filtered and dried. The solid (43.2 g) was slurried in 200 mL of phosphorus oxychloride and to it was added 16.6 g (0.14 mol) of N,N-dimethylaniline and the mixture was heated to 90°C for 16 h. The dark reaction mixture was concentrated and the residue dissolved in 200 mL of methylene chloride and washed with water. The organic layer was dried over anhydrous magnesium sulfate and filtered through a pad of silica gel (80 g). The yellow filtrate was concentrated to yield the dichloro compound (**9)** as a yellow solid: 33.4 g (65%). Crystallization from acetonitrile afforded 30 g (59%) of yellow crystals, mp136-137°C; ^{1}H NMR ($CDCl_3$) δ 4.53(s, 2H), 7.22-7.35(m, 3H), 7.47-7.49(m, 3H); ^{13}C NMR ($CDCl_3$): δ 36.57, 107.91, 127.81, 128.71, 129.29, 136.54, 137.80, 147.32, 154.76, 170.43; MS *m/z* 312 (M^++1), 310 (M^+-1). Anal. Cacld for $C_{12}H_8N_4Cl_2S$: C, 46.45; H, 2.6; N, 18.07. Found: C, 46.22; H, 2.58; N, 18.01.

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