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SYNTHESIS OF N-ALKYLATED DERIVATIVES OF PYRAZOLO[1,5-*a*]-PYRIMIDINE AND THEIR REACTION WITH METHYLAMINE

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With the object of studying the factors influencing the course of enamine rearrangements, we have carried out the N-alkylation of alkyl- and aryl-substituted pyrazolo[1,5-a]pyrimidines. Using the NOEDIF NMR spectroscopic method for the cases of 5,7-dimethyl-2-phenyl- and 2,5,7-triphenylpyrazolo[1,5-a]pyrimidines it was found that addition of the alkyl group occurs at the $N_{(4)}$ atom of the pyrimidine fragment in the pyrazolo[1,5-a]pyrimidine. It was shown that, when reacting with an alcoholic solution of methylamine, the 5,7-dimethyl-2-phenyl- and 2,5,7-triphenylpyrazolo[1,5-a]pyrimidine iodomethylates undergo decomposition to give 5-methylamino-3-phenylpyrazole and 5-(1,3-diphenyl-3-methylamino-2-propenylid-1-ene)amino-3-phenylpyrazole.

Keywords: iodoalkylates, methylamine, pyrazolo[1,5-*a*]pyrimidine, destruction, NOEDIF method, rearrangement, NMR.

It is known that carrying out enamine rearrangements in the pyrimidine series generally requires activation of the heterocycle towards nucleophilic attack. In the case of substituted 2-alkylpyrimidines this is achieved by alkylation, i.e. conversion of the recycled models to the pyrimidinium salts [1-5]. Attempts to rearrange several condensed pyrimidine systems containing a bridged nitrogen atom (e.g. pyrazolo[1,5-*a*]-pyrimidines) have needed activation of the molecule *via* introduction into the pyrimidine fragment of a powerful electron acceptor like the nitro group [6].

Our experiments have shown that pyrazolo[1,5-*a*]pyrimidines, containing alkyl or aryl groups in the pyrimidine nucleus do not rearrange under the action of various nucleophiles. Hence heating 5,7-dimethyl-, 5,7-dimethyl-2-phenyl, 2,5,7-triphenyl-, and 5-methyl-7-phenylpyrazolo[1,5-*a*]pyrimidines in alcoholic sodium ethylate solution or in alcoholic or aqueous-alcoholic solutions of potassium hydroxide, triethylamine, and methylamine do not yield the rearranged recyclization product and the starting materials are returned unchanged.

Continuing our study of the factors which influence the course of enamine rearrangements, we resolved to study the potential activation towards nucleophilic attack of alkyl- and aryl-substituted pyrazolo[1,5-*a*]-pyrimidines *via* N-alkylation of the biheterocycle. Hence we attempted to use the same system activation step as

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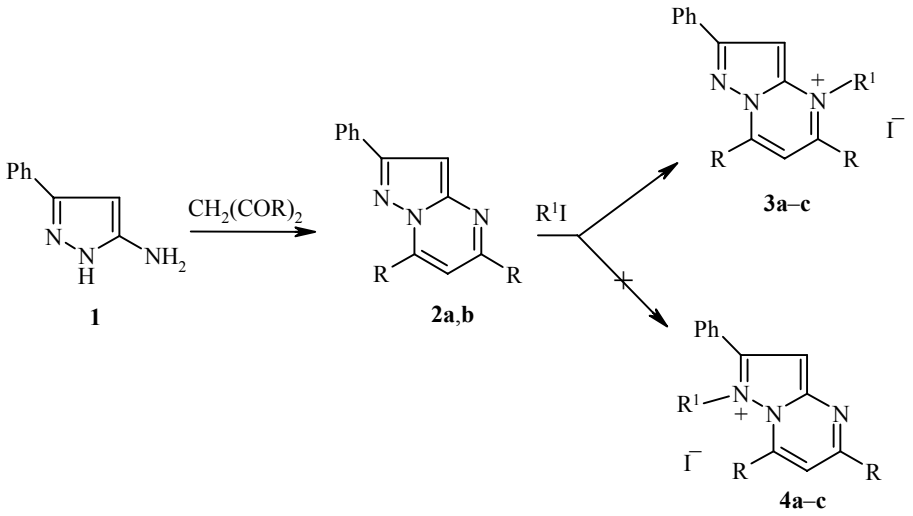
in the example of the non condensed pyrimidines. It was expected that quaternization of the nitrogen would lead to the formation of a strongly electron acceptor center and this might make easier the opening of the pyrimidine ring with the possibility of rearrangement.

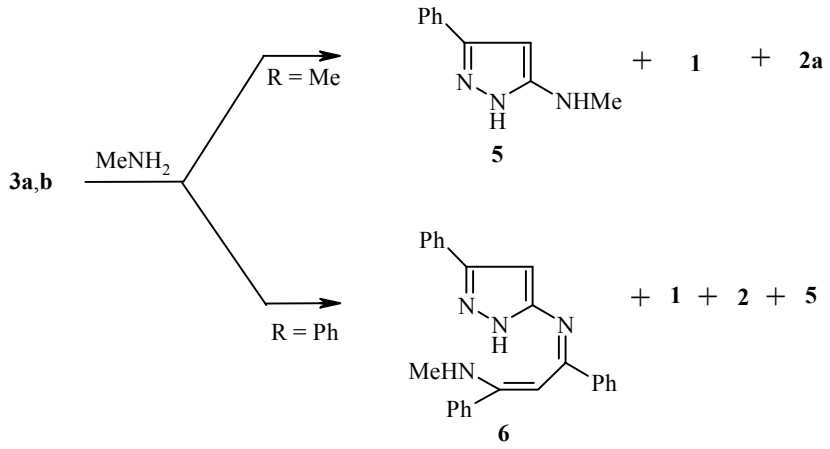
Treatment of 3-amino-5-phenylpyrazole with acetylacetone and with dibenzoylmethane gave the 5,7-dimethyl-2-phenyl- and 2,5,7-triphenylpyrazolo[1,5-*a*]pyrimidines **2a,b** which were converted to the corresponding N-alkyliodides by reaction with methyl- and ethyl iodides. Such an alkylation could occur ambiguously since there are several possible centers for attack. Information about the alkylation of pyrazolo[1,5-*a*]pyrimidines is absent in the literature. However, since the bridging nitrogen atom is evidently not favored towards reaction with nucleophiles (its free electron pair is involved in the conjugative formation of the aromaticity of the system), the targets for electrophilic attack by the alkyl group can be either of the other $N_{(1)}$ and $N_{(4)}$ atoms of the pyrazole or the pyrimidine rings and this could lead to the formation of compounds **3** or **4**. The structure of the synthesized materials, and hence the direction of attack of the alkyl group, was proved by ^{1}H and ^{13}C NMR spectroscopy and included the use of the double resonance methods NOEDIF and 2D-HETCOR (HMQC). It was found that the NOEDIF method unambiguously shows the position of the N-methyl group. Hence irradiation at the ^{+}N–Me frequency (δ 4.30 ppm) caused an NOE (nuclear Overhauser effect) on the 3-H and 5-methyl group protons and this uniquely shows that addition of the methyl group was at pyrimidine $N_{(4)}$ to give the salt **3a**.

A similar picture was also noted in a study of the methylation product of the 2,5,7-diphenyl derivative. NOEDIF experiments showed that irradiation of the N-methyl group gave a positive NOE at the singlet signal for proton 3-H and the doublet signal for the *ortho* protons of one of the phenyl groups. This is only possible when the reaction occurs at the pyrimidine ring nitrogen atom to give the salt **3b**.



2–4 a R = R^1 = Me; **b** R = Ph, R^1 = Me; **c** R = Me, R^1 = Et

We have also studied the behavior of the synthesized salts with an alcoholic solution of methylamine, i.e. under the conditions for the rearrangement of pyrimidinium salts [1, 2, 5]. It was found that the reaction of compound **3a** with methylamine gives 5-methylamino-3-phenylpyrazole **5** together with some of the product of demethylation of the salt **2a** and the aminopyrazole **1**. Reaction of the triphenyl derivative **3b** with the same solution gave the aminopyrazoles **1** and **5** together with the demethylation product and also the acyclic adduct **6** which is obtained upon opening of the pyrimidine ring. In both cases the recyclization products were not observed.



Hence quaternization of the nitrogen atom in the pyrimidine ring leads to opening of the ring but, evidently, the low nucleophilicity of the pyrazole ring hinders the recyclization. As a result, destruction of the pyrimidine fragment occurs to give the aminopyrazole derivative. A similar picture was noted previously with attempts to rearrange the unsubstituted pyrazolo[1,5-*a*]pyrimidine and also in the reaction of substituted 1,2,4-triazolo[4,3-*a*]pyrimidine with base where we isolated the destruction rather than the rearranged products [6, 7].

EXPERIMENTAL

NMR spectra were taken on a Varian Mercury 300 (300 MHz) spectrometer within the terms of the US CRDF RESC 17-5 program. TLC was performed on Silufol UV-254 plates in the system benzene–acetone (3:1) and visualized using iodine vapor. Preparative separation was carried out on L 5/40 silica gel.

5,7-Dimethyl-2-phenylpyrazolo[1,5-*a*]pyrimidine (2a). Acetylacetone (0.5 g, 0.005 mol) and glacial acetic acid (3-4 drops) were added to a solution of 5-amino-3-phenylpyrazole [8] (0.8 g, 0.005 mol) in absolute ethanol (20 ml). After 10 min a white crystalline precipitate was formed. The mixture was allowed to stand for a further 1 h. Yield 1 g (90%) of compound **2a**; mp 169-170°C (alcohol), R_f 0.57 (benzene–acetone, 4:1). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm, *J* (Hz): 2.5 (3H, s, CH_3); 2.76 (3H, s, CH_3); 6.68 (1H, s, 6-H); 6.81 (1H, s, 3-H); 7.35 (1H, m, 4'-H); 7.42 (2H, m, 3'- and 5'-H); 7.98 (2H, d, *J* = 7.2, 2'- and 6'-H). Found, %: C 75.50; H 5.99; N 18.53. $C_{14}H_{13}N_3$. Calculated, %: C 75.34; H 5.83; N 18.83.

2,5,7-Triphenylpyrazolo[1,5-*a*]pyrimidine (2b). A mixture of 5-amino-3-phenylpyrazole **1** (0.8 g, 0.005 mol), dibenzoylmethane (1.12 g, 0.005 mol), absolute ethanol (30 ml), and glacial acetic acid (1 ml) was refluxed for 12 h to give 1.2 g (70%) of the bright-yellow, powdery substance with mp 161-162°C (ethanol), R_f 0.85 (benzene–acetone, 3:1). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 7.1 (1H, s, 6-H); 7.38 (1H, s, 3-H); 7.4-7.65 and 8.1-8.25 (15H, m, C_6H_5). Found, %: C 82.73; H 4.70; N 11.79. $C_{24}H_{17}N_3$. Calculated, %: C 82.99; H 4.98; N 12.10.

5,7-Dimethyl-2-phenylpyrazolo[1,5-*a*]pyrimidine Iodomethylate (3a). A mixture of the pyrazolopyrimidine **2a** (0.56 g, 0.0025 mol) and methyl iodide (2 ml) was heated in a sealed ampule on a water bath for 12 h. The precipitated iodomethylate was filtered off and washed on the filter with ether to give 0.9 g (99%) of the light-yellow powdery substance with mp above 300°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm, *J* (Hz): 2.94 (3H, s, 5-CH_3); 3.05 (3H, s, 7-CH_3); 4.30 (3H, s, N–CH_3); 7.52 (3H, m, 3'-, 4'-, and 5'- H); 7.60 (1H, br. s, 6-H); 7.85 (1H, s, 3-H); 8.13 (2H, dd, J_1 = 7.8, J_2 = 1.9, 2'- and 6'-H). ^{13}C NMR spectrum (DMSO-d_6,

75.46 MHz), δ, ppm: 16.71 (7-CH_3); 19.60 (5-CH_3); 39.5 (N–CH_3); 90.46 (C-3); 109.24 (C-6); 126.12 (C^1-*ortho*); 128.33 (C^1-*meta*); 129.72 (C^1-*para*); 129.79 (C^1-*ipso*); 141.71, 153.89, 156.69, 159.43 (C-2, C-3a, C-7, C-5). Found, %: C 49.05; H 4.31; N 11.28. $C_{14}H_{13}N_3 \cdot CH_3I$. Calculated, %: C 49.33; H 4.42; N 11.51.

2,5,7-Triphenylpyrazolo[1,5-*a*]pyrimidine Iodomethylate (3b). A mixture of the pyrazolopyrimidine **2b** (0.7 g, 0.002 mol) and methyl iodide (3 ml) was heated in a sealed ampule for 20 h. The precipitated iodomethylate was filtered off and washed on the filter with ether to give 0.7 g (71%) of the dark-red colored crystals with mp 212°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 4.35 (3H, s, CH_3N); 7.29 (1H, s, 6-H); 7.53 (1H, s, 3-H); 7.5-8.37 (15H, m, Ph). Found, %: C 61.59; H 4.21; N 8.48. $C_{24}H_{17}N_3 \cdot CH_3I$. Calculated, %: C 61.36; H 4.12; N 8.59.

5,7-Dimethyl-2-phenylpyrazolo[1,5-*a*]pyrimidine Iodoethylate (3c). A mixture of the pyrazolopyrimidine **2a** (0.22 g, 0.001 mol) and ethyl iodide (4 ml) was heated at 90-100°C in a sealed ampule for 40 h. The precipitated iodoethylate was filtered off and washed on the filter with ether to give 0.35 g (92%) of the light-brown crystals not melting below 300°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm, *J* (Hz): 1.58 (3H, t, *J* = 7.2, $C\underline{H}_3CH_2N$); 2.98 (3H, s, 7-CH_3); 3.03 (3H, s, 5-CH_3); 4.78 (2H, q, *J* = 7.2, $CH_3C\underline{H}_2N$); 7.46-7.59 (3H, m, 3'-, 4'-, and 5'-H); 7.62 (1H, s, 6-H); 7.93 (1H, s, 3-H); 8.15 (2H, dd, J_1 = 7.9, J_2 = 1.6, 2'- and 6'-H). Found, %: C 50.43; H 4.51; N 10.98. $C_{14}H_{13}N_3 \cdot C_2H_5I$. Calculated, %: C 50.67; H 4.78; N 11.08.

Reaction of 5,7-Dimethyl-2-phenylpyrazolo[1,5-*a*]pyrimidine Iodomethylate (3a) with Methylamine. A mixture of the iodomethylate **3a** (0.37 g, 0.001 mol) and an ethanol solution of methylamine (15%, 12 ml) was heated in a sealed ampule on a water bath for 15 h. Solvent was removed at reduced pressure and the residue was washed with hot hexane (3×20 ml). Crystalline 5-methylamino-3-phenylpyrazole **5** precipitated from the hexane solution (0.08 g, 46%); mp 121-122°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.93 (3H, d, CH_3NH); 4.75-5.4 (2H, br. s, NH); 5.90 (1H, s, 4-H); 7.31-7.55 (5H, m, C_6H_5). Found, %: C 69.09; H 6.28; N 24.11. $C_{10}H_{11}N_3$. Calculated, %: C 69.34; H 6.40; N 24.26.

The hexane solution remaining after the separation of the pyrazole was placed on a column (hexane–ethyl acetate, 4:1) to give the pyrazolopyrimidine **2a** (0.05 g, 23%) with R_f 0.68 (benzene–acetone, 3:1) and 3-amino-5-phenylpyrazole **1** (0.02 g, 13%) with R_f 0.4 (benzene–acetone, 1:1). These two materials were identical to known samples in their melting point and chromatographic mobility.

Reaction of 2,5,7-Triphenylpyrazolo[1,5-*a*]pyrimidine Iodomethylate (3b) with Methylamine. A mixture of the iodomethylate **3b** (0.2 g, 0.0004 mol) and an alcohol solution of methylamine (15%, 6 ml) was heated in a sealed ampule on a water bath for 20 h. Solvent was removed at reduced pressure and the residue was washed with hot hexane and chromatographed on a column (benzene–acetone, 8:1) to give compound **2b** (0.07 g, 50%); mp 161°C and R_f 0.83 (benzene–acetone, 3:1), compound **6** (0.02 g, 13%) with R_f 0.74, the methylaminopyrazole **5** (0.1 g, 14%); mp 121°C and R_f 0.12, and the aminopyrazole **1** (0.01 g, 17%); R_f 0.4 (benzene–acetone, 1:1).

^{1}H NMR spectrum of compound **6** ($CDCl_3$), δ, ppm: 2.95 (3H, d, $C\underline{H}_3NH$); 4.18 (1H, q, $N\underline{H}CH_3$); 5.79 (1H, s, CH=); 7.39-7.91 (16H, m, 3- and 4-H, C_6H_5); 11.33 (1H, br. s, NH). Found, %: C 79.09; H 5.63; N 14.67. $C_{25}H_{22}N_4$. Calculated, %: C 79.34; H 5.86; N 14.80.

Compounds **1**, **2b**, and **5** were identical in chromatographic mobility and in melting point with known samples.

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