Synthesis of Heterocycles *via* Nitrilium Salts; XVI. Pyrazolo[3,4-*d*]pyrimidines

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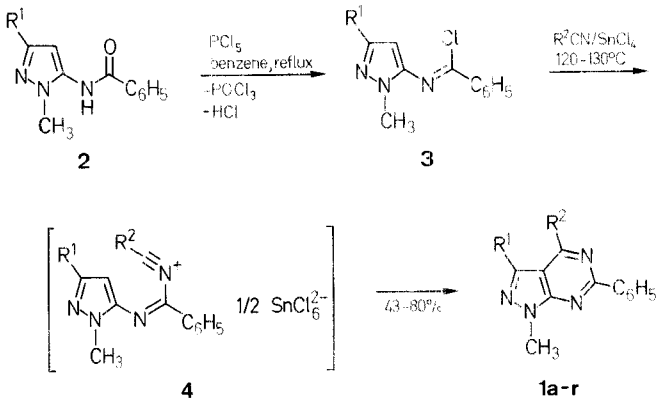
Based on the electrophilic properties of nitrilium salts formed by interaction of 5-aroylaminopyrazoles, nitriles, and Lewis acids, a new general method for the synthesis of pyrazolo[3,4-*d*]pyrimidines has been developed.

In the course of our investigations on nitrilium salts we were interested in the utilization of the reactivity of these salts to carry out different types of heterocyclizations. Based on the electrophilicity of the nitrilium salts towards certain types of C-atoms or electron-rich functional groups, we have developed new procedures for the synthesis of several heterocyclic systems, with the aim to find biologically active compounds of interest.[1,2]

We have now tried to obtain derivatives of pyrazolo[3,4-*d*]pyrimidine **(1)** by taking advantage of the particular reactivity of nitrilium salts as well as of the ready availability of the starting 5-aroylaminopyrazoles **(2)** and the commercial origin of the remaining reagents.

Most of the methods so far used[3] for the preparation of compounds of this type start with bifunctional pyrazole or pyrimidine derivatives, the rest of the bicyclic structure being formed by reactions known from analogous benzenic derivatives. The possibility of using nitrilium salts does not seem to have been considered.

We describe here a new method for the synthesis of the title compounds **(1)** which is easy to perform, highly efficient, and versatile with regard to substitution at positions 1, 3, 4, and 6 of the bicyclic ring system. It takes advantage of the susceptibility to electrophilic attack of the C-4 position of the pyrazole ring, and the ready formation of nitrilium salts **(4)** by interaction of imidoyl halides **(3)**, nitriles, and Lewis acids. Under the conditions employed, the nonisolated intermediate salts **4** undergo spontaneous cyclization to give the desired compounds 1 in satisfactory yields.



No attempt has been made to improve the yields by variation of the experimental conditions. The work was rather directed to the investigation of the influence of variation of substituents and reactants, in order to establish the scope and limitation of the method and to obtain a number of different derivatives **(1)** of pyrazolo[3,4-*d*]pyrimidine for pharmacological studies.

Table. Pyrazolo[3,4-d]pyrimidines **1** Prepared

Product	R^1	R^2	Yield (%)	m.p. (°C)	Molecular Formula[a]	^{1}H-NMR ($CDCl_3$/TMS)[b] δ (ppm)
1a	CH_3	CH_3	80	125–126	$C_{14}H_{14}N_4$ (238.3)	2.67 (s, 3H, 3-CH_3); 2.82 (s, 3H, 4-CH_3); 4.02 (s, 3H, 1-CH_3); 7.48 (m, 3H, 6-Ar); 8.50–8.62 (m, 2H, 6-Ar)
1b	CH_3	C_2H_5	78	98–100	$C_{15}H_{16}N_4$ (252.3)	1.40 (t, 3H, 4-CH_2CH_3); 2.60 (s, 3H, 3-CH_3); 3.10 (q, 2H, 3-CH_2CH_3); 3.98 (s, 3H, 1-CH_3); 7.40 (m, 3H, 6-Ar); 8.48–8.60 (m, 2H, 6-Ar)
1c	CH_3	*n*-C_3H_7	75	99–102	$C_{16}H_{18}N_4$ (266.3)	1.02 (t, 3H, 4-$CH_2CH_2CH_3$); 1.90 (m, 2H, 4-$CH_2CH_2CH_3$); 2.62 (s, 3H, 3-CH_3); 3.08 (t, 2H, $CH_2CH_2CH_3$); 4.0 (s, 3H, 1-CH_3); 7.35 (m, 3H, 6-Ar)
1d	CH_3	*i*-C_3H_7	70	70–72	$C_{16}H_{18}N_4$ (266.3)	1.45 [d, 6H, 4-$CH(CH_3)_2$]; 2.62 (s, 3H, 3-CH_3); 3.50 [m, 1H, $CH(CH_3)_2$]; 4.0 (s, 3H, 1-CH_3); 7.35–7.48 (m, 3H, 6-Ar); 8.50–8.60 (m, 2H, 6-Ar)
1e	CH_3	*n*-C_4H_9	75	66–68	$C_{17}H_{20}N_4$ (280.4)	0.98 [t, 3H, 4-$(CH_2)_3CH_3$]; 1.30–1.65 [m, 2H, 4-$(CH_2)_2CH_2CH_3$]; 1.65–2.10 (m, 2H-4-$CH_2CH_2CH_3$); 2.62 (s, 3H, 3-CH_3); 3.07 (t, 2H, 4-$CH_2(CH_2)_2CH_3$); 4.0 (s, 3H, 1-CH_3); 7.35–7.55 (m, 3H, 6-Ar); 8.5–8.7 (m, 2H, 6-Ar)
1f	CH_3	C_6H_5	70	145–146	$C_{19}H_{16}N_4$ (300.4)	2.40 (s, 3H, 3-CH_3); 4.07 (s, 3H, 1-CH_3); 7.40–7.65 (m, 6H, 4-Ar and 6-Ar); 7.77–7.90 (m, 2H, 4-Ar); 8.55–8.70 (m, 2H, 6-Ar)
1g	CH_3	*o*-$CH_3C_6H_4$	68	110–111	$C_{20}H_{18}N_4$ (314.4)	2.10 (s, 3H, 4-Ar CH_3); 2.30 (s, 3H, 3-CH_3); 4.10 (s, 3H, 1-CH_3); 7.25–7.50 (m, 7H, 4-Ar and 6-Ar); 8.55–8.65 (m, 2H, 6-Ar)
1h	CH_3	*m*-$CH_3C_6H_4$	70	131–133	$C_{20}H_{18}N_4$ (314.4)	2.35 (s, 3H, 4-Ar–CH_3); 2.40 (s, 3H, 3-CH_3); 4.0 (s, 3H, 1-CH_3); 7.25–7.60 (m, 7H, 4-Ar and 6-Ar); 8.60 (m, 2H, 6-Ar)
1i	CH_3	*o*-ClC_6H_4	58	138–140	$C_{19}H_{15}ClN_4$ (334.8)	2.20 (s, 3H, 3-CH_3); 4.12 (s, 3H, 1-CH_3); 7.35–7.55 (m, 7H, 4-Ar and 6-Ar); 8.60 (m, 2H, 6-Ar)
1j	CH_3	*p*-ClC_6H_4	60	158–160	$C_{19}H_{15}ClN_4$ (334.8)	2.22 (s, 3H, 3-CH_3); 4.0 (s, 3H, 1-CH_3); 7.35–7.75 (m, 7H, 4-Ar and 6-Ar); 8.45–8.65 (m, 2H, 6-Ar)
1k	CH_3	$C_6H_5CH_2$	72	95–97	$C_{20}H_{18}N_4$ (314.4)	2.52 (s, 3H, 3-CH_3); 4.0 (s, 3H, 1-CH_3); 4.40 (s, 2H, 4-$CH_2C_6H_5$); 7.15–7.30 (m, 5H, 4-$CH_2C_6H_5$); 7.40 (m, 3H, 6-Ar); 8.60 (m, 2H, 6-Ar)
1l	H	CH_3	65	102–104	$C_{13}H_{12}N_4$ (224.3)	2.60 (s, 3H, 4-CH_3); 4.01 (s, 3H, 1-CH_3); 7.38 (m, 3H, 6-Ar); 7.96 (s, 1H, 3-H); 8.45–8.60 (m, 2H, 6-Ar)
1m	H	C_2H_5	72	60–62	$C_{14}H_{14}N_4$ (238.3)	1.45 (t, 3H, 4-CH_2CH_3); 3.10 (c, 2H, 4-CH_2CH_3); 4.1 (s, 3H, 1-CH_3); 7.30–7.50 (m, 3H, 6-Ar); 8.0 (s, 1H, 3-H); 8.50–8.65 (m, 2H, 6-Ar)
1n	H	*n*-C_3H_7	77	76–78	$C_{15}H_{16}N_4$ (252.3)	1.0 (t, 3H, J = 7.5 Hz, 4-$CH_2CH_2CH_3$); 1.92 (m, 2H, 4-$CH_2CH_2CH_3$); 3.05 (t, 2H, J = 7.5 Hz, $CH_2CH_2CH_3$); 4.10 (s, 3H, 1-CH_3); 7.40 (m, 3H, 6-Ar); 8.05 (s, 1H, 3-H); 5.50–5.60 (m, 2H, 6-Ar)
1o	H	*i*-C_3H_7	75	60–61	$C_{15}H_{16}N_4$ (252.3)	1.48 [d, 6H, 4-$CH(CH_3)_2$]; 3.48 [m, 1H, $CH(CH_3)_2$]; 4.1 (s, 3H, 1-CH_3); 7.40 (m, 3H, 6-Ar); 8.05 (s, 1H, 3-H); 8.65 (m, 2H, 6-Ar)
1p	H	C_6H_5	80	132–134	$C_{18}H_{14}N_4$ (286.3)	4.1 (s, 3H, 1-CH_3); 7.40–7.65 (m, 6H, 4-Ar and 6-Ar); 8.20–8.35 (m, 3H, 3-H and 4-Ar); 8.60–8.75 (m, 2H, 6-Ar)
1q	H	*m*-$CH_3C_6H_4$	43	113–115	$C_{19}H_{16}N_4$ (300.4)	2.50 (s, 3H, 4-Ar–CH_3); 4.1 (s, 3H, 1-CH_3); 7.35–7.60 (m, 5H, 4-Ar and 6-Ar); 8.10 (m, 2H, 4-Ar); 8.30 (s, 1H, 3-H); 8.60–8.70 (m, 2H, 6-Ar)
1r	H	$C_6H_5CH_2$	78	114–115	$C_{19}H_{16}N_4$ (300.4)	4.05 (s, 3H, 1-CH_3); 4.43 (s, 2H, 4-$CH_2C_6H_5$); 7.20–7.50 (m, 8H, 6-Ar and 4-$CH_2C_6H_5$); 7.60 (s, 1H, 3-H); 8.50–8.65 (m, 2H, 6-Ar)

[a] Satisfactory microanalyses obtained: C ±0.27, H ±0.15, N ±0.31.
[b] All ^{1}H-NMR spectra were recorded with a Varian EM-390 spectrometer.

Pyrazolo[3,4-*d*]pyrimidines (1); General Procedure:
A mixture of the 5-aroylaminopyrazole[4,5] **2** (0.05 mol), dry benzene (20 ml), and phosphorus(V) chloride (10.42 g, 0.05 mol) is refluxed for 2 h. The solvent and the phosphoryl chloride formed in the reaction are evaporated *in vacuo* and the residue is treated with the nitrile (0.05 mol) and tin(IV) chloride (1.303 g, 0.05 mol). The mixture is heated for 2–3 h at 120–130°C. After cooling it is poured into aqueous 20% sodium hydroxide (300 ml) and extracted with ether (5 × 50 ml). The extracts are washed with water (50 ml) and treated with 2 normal hydrochloric acid (100 ml). The cooled acidic solution is made basic with aqueous 20% sodium hydroxide and again extracted with ether (5 × 25 ml). The combined extracts are dried with sodium sulfate and the solvent is removed in vacuo. The residue is recrystallized from ethanol.

When solid or high-boiling point nitriles are used, these can be added in the imidoyl halide formation step.

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