A Novel One Step Synthesis of Pyrazolo[1,5-*a*]pyridine Derivatives

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A Novel one step synthesis of pyrazolo[1,5-*a*]pyridines has been developed by condensation of *N*-amino-3-cyano-4,6-dimethyl-2(1 *H*)-pyridone (**1**) with compounds containing acetyl or active methylene group in presence of anhydrous zinc chloride in refluxing dimethylformamide.

Pyrazolo[1,5-*a*]pyridine derivatives have been found to possess medicinal and biological activities[1] and have therefore created interest in the recent past in their synthesis.

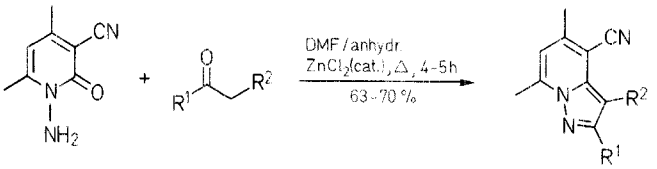
Syntheses of a variety of Pyrazolo[1,5-*a*]pyridines by different methods have been reported. For e.g. reactions of 1-*N*-amino-pyridinium salts with 1,3-dicarbonyl compounds,[2-3] acylating agents,[1,4-7] dimethyl 1-chlorofumarate,[8] 2-ethoxymethylene malonate,[9] acetylene derivatives[10-14] and thioacetals,[15] reactions of 1-*N*-amino-4,6-diphenyl-2-thiomethyl pyridinium iodide with activated acetonitrile derivatives,[16] and synthesis starting from alkylidene dihydropyridine derivatives.[17-19]

We have earlier communicated the synthesis of *s*-triazolo[1,5-*a*]pyridine derivatives involving condensation of *N*-amino-3-cyano-4,6-dimethyl-2(1 *H*)-pyridone (**1**) with carboxylicacid-amides in a novel single step.[20]

We report here a versatile novel simple one step synthesis of hitherto unknown 2,3-disubstituted-4-cyano-5,7-dimethylpyrazolo[1,5-*a*]pyridine derivatives.

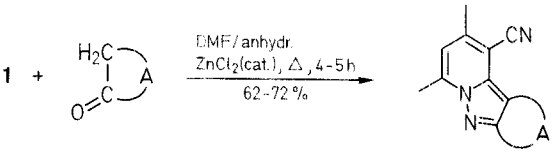
In the present study, *N*-amino-3-cyano-4,6-dimethyl-2(1 *H*)-pyridone (**1**) was condensed with a variety of compounds **2,4** containing acetyl or active methylene group by refluxing in dimethylformamide in presence of anhydrous zinc chloride.

The advantages of the present approach to pyrazolo[1,5-*a*]pyridines are that the preparation of the starting material **1** is very simple[21] compared to those used in the earlier reports. Further, the synthesis affords a variety of substitutions in 2- and 3-positions of the system and requires shorter reaction time.

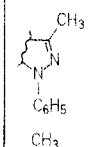
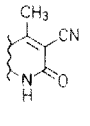
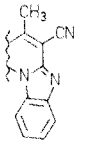


1 **2a-d** **3a-d**

2, 3	R^1	R^2
a	CH_3	$COCH_3$
b	C_6H_5	H
c	C_6H_5	$CO_2C_2H_5$
d	3-coumarinyl	H



4a-d **5a-d**

4/5	A	4/5	A
a		c	
b		d	

The key compound **1** used in the synthesis was prepared by the condensation of cyanoacetylhydrazide (preapared *in situ*) and acetylacetone in 88% yield on 50 g scale.

Some variations in the experimental conditions were tried:
- conducting the reaction in polyphosphoric acid;
- fusion of the reactants; and
- conducting the reaction at reflux temperature of an appropriate organic solvent in the presence of zinc chloride.

Table. Compounds **3** and **5** Prepared

Product	Yield[a] (%)	m.p. (°C)[b] (solvent)	Molecular Formula[c]	IR (Nujol) ν (cm^{-1})	^{1}H-NMR (Solvent) δ (ppm)	MS *m/e* (M^+)
3a	65	190 (acetic acid)	$C_{13}H_{13}N_3O$ (227.3)	2240, 1740, 1370, 975, 760	–	–
3b	70	168 (acetic acid)	$C_{16}H_{13}N_3$ (247.3)	2220, 1645, 1585, 1445, 1365, 1025, 845	DMSO-d_6/CF_3CO_2H (1:1): 2.85 (s, 3H); 2.95 (s, 3H); 6.3 (s, 1H); 7.3–8.0 (m, 5H)	247
3c	68	161 ($CHCl_3$)	$C_{19}H_{17}N_3O_2$ (319.4)	2240, 1710, 1630, 1425, 980	–	309
3d	63	284 (DMF)	$C_{19}H_{13}N_3O_2$ (315.3)	2240, 1720, 1650, 1430, 1035	–	–
5a	67	302 (acetic acid)	$C_{18}H_{15}N_2$ (259.3)	2220, 1715, 1620, 1450, 1360	Aceton-d_6: 2.3 (s, 3H); 2.8 (s, 6H); 6.2 (s, 1H); 7.2–8.0 (m, 5H)	–
5b	72	> 360 (DMF)	$C_{21}H_{14}N_6$ (350.4)	2220, 1665, 1575, 1450, 1370, 1070, 810	CF_3CO_2H: 2.2 (s, 3H); 3.1 (s, 3H); 5.8 (s, 1H); 7.0–7.5 (m, 3H); 8.4 (s, 1H)	–
5c	62	> 360 (DMF)	$C_{15}H_{11}N_5O$ (277.3)	2240, 1580, 1440, 1380, 1335, 1075	–	277
5d	69	208 (acetic acid)	$C_{20}H_{13}N_3$ (295.3)	2220, 1450, 1060, 850	–	–

[a] Yield of recrystallized pure product.
[b] Satisfactory microanalyses obtained: C ±0.27, H ±0.15, N ±0.25.

The best results were obtained when the reaction was carried out accordingly in dimethylformamide which gave pyrazolo[1,5-*a*]pyridine derivatives in one step and good yield (Table). The structures of the products **3a–d** and **5a–d** were confirmed by microanalyses and spectral data.

2,3-Disubstituted 4-Cyano-5,7-dimethylpyrazolo[1,5-*a*]pyridine Derivatives; General Procedure:

To a solution of *N*-amino-3-cyano-4,6-dimethyl-2(1*H*)-pyridone (**1**; 2.445 g, 15 mmol) and the appropriate compound containing acetyl or active methylene group **2** or **4**, (15 mmol) in dimethylformamide (8–10 ml) is added catalytic amount of anhydrous zinc chloride (0.5 g). The mixture is heated to reflux for 4–5 h (TLC monitoring, eluent: $CHCl_3$). The mixture is cooled to room temperature and added to ice-water mixture (150 ml) with continuous stirring when solid **3** or **5** separate. The product is filtered, washed with water, dried and recrystallized from appropriate solvents (Table).

One of the authors (RCP) is thankful to Council of Scientific and Industrial Research, New Delhi for the award of Junior and Senior Research Fellowships.

Received: 30 January 1986
(Revised form: 11 October 1986)

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