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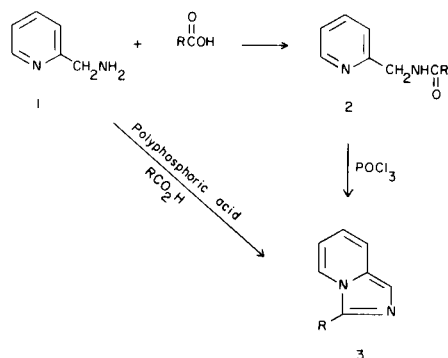
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Cyclization of amides of 2-aminomethylpyridine gave imidazo[1,5-*a*]pyridines. In several examples the literature preparation (phosphorus oxychloride) gave extensive tar formation. The use of phosphorus trichloride-triethylamine (-20°) gave the desired imidazo[1,5-*a*]pyridines.

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We recently had occasion to prepare some 3-substituted imidazo[1,5-*a*]pyridines (Table II). Two general procedures have been reported for the synthesis of imidazo[1,5-*a*]pyridines. Bower and Ramage (1) utilized phosphorus oxychloride for the ring closure of the amides



(2) derived from 2-aminomethylpyridine. Winterfeld and Franzke (2) utilized a one-step procedure in polyphosphoric acid.

This paper reports our use of phosphorus trichloride at low (-20°) temperatures in tetrahydrofuran/triethylamine to effect this ring closure. It was found that for several compounds (15,18,20; Table II) the use of phosphorus oxychloride gave extensive tar formation which was avoided by the use of phosphorus trichloride at low temperature (-15 to -20°). We feel this method is a useful alternative to the published procedures.

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. Ir spectra were determined in pressed potassium bromide disks. Nmr spectra were determined on a Varian spectrometer and shifts are reported in parts per million (δ) with TMS as an internal standard.

Amide Intermediate Preparation.

4-Chloro-*N*-(2-pyridinylmethyl)benzenepropanamide (4) (Method A).

A mixture of 2-aminomethylpyridine (10.8 g., 0.1 mole), *p*-chlorophenylpropionic acid (18.5 g., 0.1 mole) and toluene (1.2 l.) was heated at reflux temperature for 18 hours. The water evolved was collected by use of a Dean-Stark trap. The reaction mixture was washed with aqueous sodium bicarbonate and the organic layer was evaporated to dryness. The residue was recrystallized from cyclohexane/benzene to give 19 g. of white needles, m.p. 82-84°; ir (potassium bromide): 3325, 1640, 1600, 1580, 1540, 1500, 1440, 1100, 1020 and 775 cm^{-1} ; nmr (DMSO- d_6): δ 2.4-3.0 (m, 5H), 4.35 (d, $J = 6$, 2H), 7.0-7.9 (m, 7H), 8.46 (m, 1H).

2,4-Dichloro-*N*-(2-pyridinylmethyl)benzeneacetamide (5) (Method B).

To a solution of 2-aminomethylpyridine (10.8 g., 0.1 mole) and triethylamine (10 g., 0.1 mole) in chloroform (300 ml.) was added dropwise a solution of 2,4-dichlorobenzoylchloride (20.9 g., 0.1 mole) in chloroform (50 ml.). The mixture was heated at reflux temperature for 3 hours cooled and washed with aqueous sodium bicarbonate. The organic layer was dried (sodium sulfate) and evaporated. The residue was recrystallized from benzene/cyclohexane to give 20 g. of white solid, m.p. 113-114°; ir (potassium bromide): 3325, 1650, 1590, 1540, 1315, 1105, 840 and 750 cm^{-1} ; nmr (DMSO- d_6): δ 3.33 (s, 1H), 4.62 (d, $J = 6$, 2H), 7.1-8.0 (m, 5H), 8.46-8.66 (m, 1H), 8.9-9.3 (m, 1H).

Ring Closure.

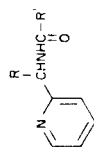
3-[3-(Trifluoromethyl)phenyl]imidazo[1,5-*a*]pyridine (15) (Method B).

Compound 7 (7.2 g., 0.02 mole) was dissolved in a mixture of THF (250 ml.) and triethylamine (15 ml.) and the solution was chilled to -20°. A solution of phosphorus trichloride (3.06 g., 0.022 mole) in THF (40 ml.) was added (nitrogen/atmosphere) at a rate which maintained a reaction temperature of -20 to -15°. After 20 minutes at -15 to -20°, tlc (silica gel) toluene/ethyl acetate 1/1 v/v indicated a complete reaction. The reaction mixture was poured into water (500 ml.) and the aqueous mixture was extracted with ethyl acetate (2 \times 400 ml.). The combined extracts were dried and evaporated to give 4.3 g. of residue which was purified on a silica gel column (toluene/ethylacetate 1/1 v/v). Recrystallization (hexane) of the product isolated from the column gave 3 g. of solid, m.p. 58-60°; ir (potassium bromide): 1600, 1350, 1320, 1300, 1245, 1160, 1115, 1065, 795, 745, 700 and 680 cm^{-1} ; nmr (deuteriochloroform): δ 6.4-6.9 (m, 2H), 7.3-7.75 (m, 4H) and 7.9-8.3 (m, 3H).

REFERENCES AND NOTES

- (1) J. D. Bower and G. R. Ramage, *J. Chem. Soc.*, 2834 (1955).
- (2) K. Winterfeld and H. Franzke, *Angew. Chem.*, **75**, 1101 (1963).

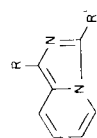
Table I
Amide Intermediates



Compound No.	R	R'	Yield %	Method (a)	M.p., °C	Analyses							
						C	H	N	Cl	C	H	N	Cl
4	H		76	A	82-84	65.57	5.50	10.20	12.90	65.12	5.45	10.28	12.84
5	H		71	B	113-114	55.53	3.58	9.97	25.22	55.33	3.58	10.10	25.25
6	H		60	A	108-109	79.44	6.00	9.26	—	79.50	5.90	9.24	—
7	H		30	A	174-175	46.55	3.35	7.76	—	46.44	3.41	8.00	—
8	H		30	A	168-169	58.65	3.94	9.12	23.08	59.07	3.95	9.26	23.40
9	H		66	A	104-105	54.03	3.89	9.00	22.79	54.22	3.90	9.13	22.58
10	H		69	A	134.5-135.5	56.97	4.10	—	24.02	56.96	4.19	—	24.35
11	C ₆ H ₅		50	B	110-112	63.88	3.95	7.84	19.85	63.55	3.99	7.65	19.83

(a) Method A: A toluene mixture of 2-aminomethylpyridine and the acid was heated at reflux under a Dean Stark trap until water evolution ceased. Method B: Reaction of 2-aminomethylpyridine with an acid chloride.

Table II
Imidazo[1,5-a]pyridines



Compound No.	R	R'	Yield %	Method (a)	M.p., °C	Analyses							
						C	H	N	Cl	C	H	N	Cl
12	H		60	A	92-93	70.17	5.10	10.91	13.81	70.03	5.23	10.89	13.86
13	H		30	A	92-93	59.34	3.06	10.65	26.95	59.14	3.18	10.56	26.83
14	H		30	A	138-140	84.47	5.67	9.85	—	84.63	6.02	10.12	—
15	H		58	B	58-60	64.12	3.46	10.68	—	64.35	3.58	10.75	—
16	H		30	A	185-186	62.30	3.49	9.69	24.52	62.02	3.60	9.45	24.43
17	H		73	A	120.5-121.5	60.67	3.64	10.01	—	60.49	3.73	10.13	—
18	C ₆ H ₅		50	B	215-217 (b)	54.31	3.12	6.67	—	54.07	3.23	6.85	—
19	H		40	A	145-146	59.34	3.06	10.65	26.95	59.39	2.92	11.04	26.73
20	H		20	B	150-151	57.36	3.44	9.56	24.19	56.98	3.37	9.71	23.51

(a) Method A: Phosphorus oxychloride in benzene according to the procedure of Bower and Ramage (1). Method B: Phosphorus trichloride (b) Hydrobromide salt.