The Reaction of 1-Amino-4,6-diphenyl-2-methylthiopyridinium Iodide with Substituted Acetonitriles

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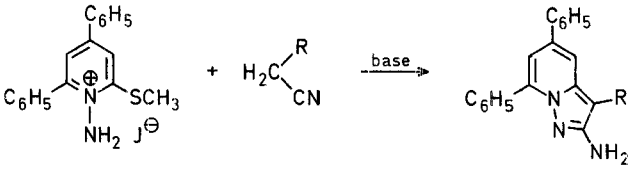
The biological and medicinal activities of several substituted pyrazolo[1,5-*a*]pyridines have initiated much recent research on the synthesis and chemistry of this class of compounds. Usually, previous syntheses involve reactions of *N*-aminopyridinium salts with 1,3-dicarbonyl compounds[1,2], acylating reagents[3-7], activated acetylenic bonds[8-13], thioacetals[14], dimethyl 1-chlorofumarate[15], 2-ethoxymethylenepentane-2,4-dione, or diethyl ethoxymethylenemalonate[16] and from alkylidenedihydropyridines[17,18,19]. Most of these reactions and, particularly those starting from unsubstituted pyridine *N*-imine, suffer from some difficulties and low yields.

We now describe the facile synthesis of 3-substituted 2-amino-5,7-diphenylpyrazolo[1,5-*a*]pyridines **3** by reaction of 1-amino-4,6-diphenyl-2-methylthiopyridinium iodide **(1)**, readily available from 1-amino-4,6-diphenylpyran-2-thione and methyl iodide[20], with acetonitriles **2**, activated by another electron-delocalizing group such as an ester, amide, hydrazide or a second nitrile group.



1 2 3

When treated with 1 equiv. of base and 1 equiv. of acetonitrile **2** in an appropriate solvent at reflux temperature, the aminopyridinium cation **1** underwent elimination of methanethiol and cyclization to give the corresponding pyrazolo[1,5-*a*]pyridine **3**. Of note are the good yields of pure, isolated products and furthermore the isolation of products is easily accomplished by removal of solvent in vacuo after which the crude pyrazolo[1,5-*a*]pyridines crystallize on standing.

The rate of the reaction was found to depend on the nature of the R substituent in the acetonitrile **2**. It was fast for R = cyano and slow for R = alkoxycarbonyl, carbamoyl, and carbazoyl. However, attempts to apply the reaction to cyanoacetic acid and chloroacetonitrile did not give satisfactory results. The completion of the reaction was checked by T.L.C. (Table).

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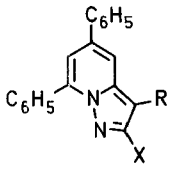
Table. *Compounds* **3**, **4**, *and* **5** *prepared*

Product No.	R	X	Reaction conditions base/solvent/time	Yield [%][a]	m.p. [°C][b]	Molecular formula[c]	I.R. (nujol) ν [cm^{-1}][d]	^{1}H-N.M.R. (DMSO-d_6)[e] δ [ppm]	M.S. *m/e* (M^+)
3a	—CN	—	$(C_2H_5)_3N$/ C_2H_5OH/5 h	82	208°	$C_{20}H_{14}N_4$ (310.4)	3440, 3280, 3200, 2210, 1630, 1560, 1500, 765, 705	6.4 (s, 2H); 7.2–7.95 (m, 12H)	310
3b	$COOC_2H_5$	—	pyrrolidine/ C_2H_5OH/20 h	63	196°	$C_{22}H_{19}N_3O_2$ (357.4)	3500, 3470, 3330, 3210, 1690, 1620, 1560, 1230, 1150, 740, 685	1.6 (t, 3H); 4.34 (q, 2H); 6.4 (s, 2H); 7.05–8.0 (m, 12H)	357
3c	$COOCH_3$	—	pyrrolidine/ C_2H_5OH/20 h	70	205°	$C_{21}H_{17}N_3O_2$ (343.4)	3470, 3310, 3210, 1690, 1670, 1150, 1090, 770, 690	3.9 (s, 3H); 6.35 (s, 2H); 7.05–7.95 (m, 12H)	343
3d	$CO—NH_2$	—	pyrrolidine/ C_2H_5OH/48 h	59	300°	$C_{20}H_{16}N_4O$ (328.4)	3420, 3370, 3260, 1630, 1600, 1215, 760, 690	6.2 (s, 2H); 7.0–8.0 (m, 14H)	328
3e	*CO—NH—NH$_2$*	—	*t-C$_4$H$_9$OK*/ *t*-C_4H_9OH/12 h	*61*	*235°*	*$C_{20}H_{17}N_5O$* (343.3)	*3470, 3380, 3340,* 3280, 1640, 1600, 1500, 765, 700	6.3 (s, 2H); 7.0–8.5 (m, 15H)	343
4a	—CN	N=CH—C_6H_5	—	75	220°	$C_{27}H_{18}N_4$ (398.5)	2210, 1640, 1620, 1580, 1540, 1505, 1225, 760, 690	7.5–8.1 (m, 17H); 9.05 (s, 1H)	398
4b	—CN	N(—CO—CH_3)$_2$	—	91	223°	$C_{24}H_{18}N_4O_2$ *(394.4)*	2220, 1730, 1720, *1640, 1580, 1500,* 890, 760, 700	2.3 (s, 6H); *7.33–7.83* (m, 12H)	394
4c	—CN	H	—	80	271°	$C_{20}H_{13}N_3$ (295.3)	2220, 1630, 1540, 1370, 1335, 1210, 860, 760, 690	7.38–8.07 (m, 13H)	295
4d	$COOC_2H_5$	N=CH—N$(CH_3)_2$	—	95	145°	$C_{25}H_{24}N_4O_2$ (412.5)	1690, 1630, 1545, 1230, 1150, 1100, 860, 760, 700	1.6 (t, 3H); 3.06 (s, 6H); 4.34 (q, 2H); *7.05–8.0* (m, 12H); 8.4 (s, 1H)	412
5a	CH_3	NH_2	—	90	>350°	$C_{22}H_{17}N_5$ (351.4)	3390, 3340, 3160, 1670, 1640, 1310, 1170, 760, 690	2.63 (s, 3H); 6.7 (s, 2H); 7.36–8.0 (m, 12H)	351
5b	C_6H_5	NH_2	—	57	>350°	$C_{27}H_{19}N_5$ *(413.5)*	3345, 3140, 1670, *1650, 1550, 1290,* 1150, 760, 695	*6.6 (s, 2H);* 7.38–8.2 (m, 17H)	413
5c	H	OH	—	87	327°	$C_{21}H_{14}N_4O$ (338.4)	3120, 1730, 1675, 1620, 1500, 1220, 1125, 770, 700	7.25–8.08 (m, 3H); 9.33 (s, 1H)	338

[a] Yield of isolated pure product.
[b] Uncorrected.
[c] The microanalyses were in good agreement with the calculated values (C ±0.28, H ±0.27, N ±0.25).
[d] Recorded on a Perkin-Elmer 457 spectrometer.
[e] Recorded at 80 MHz a Varian FT-80 spectrometer with TMS as an internal standard.

Structural elucidation of **3** was accomplished on the basis of spectral data, microanalysis, and chemical properties. The following evidence is in favour of the indicated structures: (a) the I.R. spectra of **3b–e** lack the band characteristic of —C≡N stretching frequency and show absorption in the region of amino group; (b) compound **3a** was easily converted to **3d** in good yield by treatment with 50% sulphuric acid; (c) the products **3** react with benzaldehyde, acetyl chloride, nitrous acid, and dimethylformamide dimethyl acetal to give the derivatives **4a–d**, the structure of which were substantiated by microanalytical data and spectral evidence; (d) the compound **3a** reacts with aliphatic and aromatic nitriles in the presence of dry hydrogen chloride gas to give the condensed pyrimidines **5a–b**; similarly, **3d** undergoes cyclization on reaction with dimethylformamide dimethyl acetal to give **5c** (Table).



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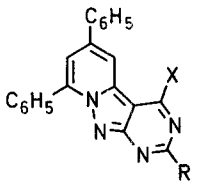

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3-Substituted 2-Amino-5,7-diphenylpyrazolo[1,5-*a*]pyridines 3; General Procedure:

To a solution of 1-amino-4,6-diphenyl-2-methylthiopyridinium iodide (**1**; 840 mg, 2 mmol) in the appropriate solvent (70 ml), activated acetonitrile (**2**; 2 mmol) and the base (2 mmol) are added. The reaction mixture is heated at reflux for 5–48 h (see Table), then cooled, and concentrated under reduced pressure to leave crude product **3** which is purified by recrystallization from ethanol.

3-Methyl(or phenyl)-1-amino-7,10-diphenylpyrido[1′,6′ : 2,3]pyrazolo-[5,4-*d*]pyrimidine (5a, b):

A stream of dry hydrogen chloride gas is passed through a mixture of the 2-amino-3-cyano-5,7-diphenylpyrazolo[1,5-*a*]pyridine (**3a**, 2 mmol) and acetonitrile or benzonitrile (2.5 mmol) in dioxan (100 ml) for 3 h. The resultant solution is heated at reflux temperature for 2 h. After cooling, the solution is concentrated under reduced pressure, the precipitate obtained is filtered off, and recrystallized from ethanol to give **5a** or **5b** (Table).

7,9-Diphenylpyrido[1′,6′ : 2,3]pyrazolo[5,4-*d*]-1(2*H*)-pyrimidone (5c):

To a solution of 2-amino-3-carbamoyl-5,7-diphenylpyrazolo[1,5-*a*]pyridine (**3d**; 656.8 mg, 2 mmol) in dry benzene (80 ml), dimethylformamide dimethyl acetal (238 mg, 2 mmol) is added. The reaction mixture is heated at reflux for 20 h, then cooled to room temperature and concentrated to dryness. The crude solid is crystallized from ethanol to give **5c** (Table).

5,7-Diphenylpyrazolo[1,5-*a*]pyridines 4a–d; General Procedure:

3-Substituted 2-amino-5,7-diphenylpyrazolo[1,5-*a*]pyridines **3** (2 mmol) are reacted with a slight excess of benzaldehyde (ethanol at reflux), sodium nitrite (acetic acid at 6 °C), acetyl chloride (benzene/potassium carbonate at reflux), and dimethylformamide dimethyl acetal (benzene at reflux) for 5–15 h. After cooling, the solvent is removed under reduced pressure and the crude solid is purified by crystallization from ethanol to give **4a–d** (Table).

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