## A New Synthesis of Pyrazolo[1,5-*a*]pyridine Derivatives[1]

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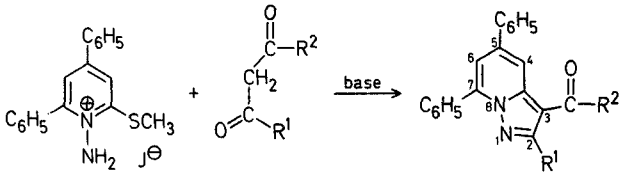
The wide variety of biological and pharmacological properties of pyrazolo[1,5-*a*]pyridine derivatives has led to the development of several methods for the synthesis of these compounds[2-10]. In the course of our investigations on the preparative utility of 1-amino-4,6-diphenyl-2-thioxo-1,2-dihydropyridine, we have reported two general methods for the synthesis of pyrazolo[1,5-*a*]pyridine derivatives. The first of these methods involves the reaction of 1-amino-2-methylthio-4,6-diphenylpyridinium iodide (**1**) with acetonitriles activated by another electron-delocalizing group[2] to give 3-substituted 2-amino-5,7-diphenylpyrazolo[1,5-*a*]pyridines; the second method involves the reaction of 1-amino-4,6-diphenyl-2-thioxo-1,2-dihydropyridine with phenacyl bromides followed by successive treatment with triethylamine and 3-chloroperbenzoic acid[11] to give 2-substituted 5,7-diphenylpyrazolo[1,5-*a*]pyridines. We report here the synthesis of 2,3-disubstituted pyrazolo[1,5-*a*]pyridines **3** by reaction of 1-amino-2-methylthio-4,6-diphenylpyridinium iodide (**1**) [readily available from 1-amino-4,6-diphenyl-2-thioxo-1,2-dihydropyridine and methyl iodide[12]] with 1,3-dicarbonyl compounds **2**.




**1** **2** **3**

The best results are obtained when the reaction is carried out in dimethylformamide in the presence of potassium *t*-butoxide (Method A) or sodium methoxide (Method B). Attempts with weaker bases such as triethylamine or pyrrolidine were unsuccessful. When treated with an excess of a 1,3-dicarbonyl compound **2** and potassium *t*-butoxide in dimethylformamide at 70°C, the *N*-aminoheterocycle **1** is directly converted into the pyrazolo[1,5-*a*]pyridine **3** in good yield (Table 1). Completion of the reaction was checked by T.L.C. We believe that the formation of **3** involves nucleophilic attack of the enolate anion on the 2-position of the pyridinium cation followed by elimination of methanethiol and cyclocondensation.

It is worthy of note that the two *phenyl* groups in compound **1** are essential for the convenient preparation of 1-amino-2-methylthiopyridinium salts from 2-thioxo-2*H*-pyrans via 1-amino-2-thioxo-1,2-dihydropyridines. Thus, for example, 4,6-dimethyl-2-thioxo-2*H*-pyran reacts with hydrazine to give a complex mixture in which 1-amino-4,6-dimethyl-2-thioxo-1,2-dihydropyridine (the precursor of the 1-amino-2-methylthiopyridinium salt) cannot be detected. An alternative route to alkyl-substituted 1-amino-2-methylthiopyridinium salts involving amination of the corresponding 2-methylthiopyridines gives unsatisfactory results because *N*-amination is accompanied by *S*-amination.

Determination of the structure of compounds **3** was accomplished on the basis of spectral data and microanalyses. Thus, the stretching vibrations of the C=O group were found, characteristically, at $\nu \approx 1650$ cm$^{-1}$ for the ketone **3a** and at $\nu \approx 1750$ cm$^{-1}$ for the esters **3b-f**. In addition, compound **3f** shows bands due to the amide group. Salient features of the $^1$H-N.M.R. spectra are given in Table 2.

The method appears to be quite general, it proceeds satisfactorily for 1,3-diketones, aliphatic and aromatic $\beta$-ketoesters, and malonic esters. It has hitherto only been briefly mentioned[13,14] that *N*-aminopyridinium cations react with ethyl acetoacetate in the presence of base to give the corresponding pyrazolo[1,5-*a*]pyridine.

**2,3-Disubstituted 5,7-Diphenylpyrazolo[1,5-*a*]pyridines 3; General Procedures:**

Method A: To a stirred solution of the 1,3-dicarbonyl compound (**2**; 5 mmol) in dry dimethylformamide (3 ml), potassium *t*-butoxide (0.56 g, 5 mmol) is added and stirring is continued for 1 h at room temperature. Then, a solution of 1-amino-2-methylthio-4,6-diphenylpyridinium iodide (**1**; 0.42 g, 1 mmol) in dry dimethylformamide (15 ml) is added. The mixture is stirred at 70°C for 12–15 h. After cooling to room temperature, the solution is poured into cold water (60 ml) and the precipitated solid is separated by filtration and recrystallized from ethanol.

Method B: To a stirred solution of the 1,3-dicarbonyl compound (**2**; 1 mmol) in dry dimethylformamide (5 ml), sodium methoxide (0.054 g, 1 mmol) is added and stirring is continued for 3 h at room tempera-

**Table 1.** Preparation of 2,3-Disubstituted 5,7-Diphenylpyrazolo[1,5-*a*]pyridines **3**

| 3 | $R^1$ | $R^2$ | Reaction Conditions | Yield[a] [%] | m.p.[b] [°C] | Molecular formula[c] |
|---|---|---|---|---|---|---|
| **a** | $CH_3$ | $CH_3$ | *t*-$C_4H_9$—OK, 12 h | 70 | 206–208° (needles) | $C_{22}H_{18}N_2O$ (326.4) |
| **b** | $CH_3$ | $OCH_3$ | *t*-$C_4H_9$—OK, 12 h | 75 | 152° (needles) | $C_{22}H_{18}N_2O_2$ (342.4) |
| **c** | *n*-$C_3H_7$ | $OC_2H_5$ | *t*-$C_4H_9$—OK, 15 h | 63 | 108° (prisms) | $C_{25}H_{24}N_2O_2$ (384.5) |
| **d** | $C_6H_5$ | $OC_2H_5$ | $NaOCH_3$, 18 h | 60 | 158° (needles) | $C_{28}H_{22}N_2O_2$ (418.5) |
| **e** | $CH_3$ | $OC_2H_5$ | $NaOCH_3$, 12 h | 72 | 147° (needles) | $C_{23}H_{20}N_2O_2$ (356.4) |
| **f** | OH | $OC_2H_5$ | $NaOCH_3$, 15 h | 50 | 141° (needles) | $C_{22}H_{18}N_2O_3$ (358.4) |

[a] Yield of isolated pure product.
[b] Uncorrected.
[c] The microanalyses (except for **3a** and **3e**) were in good agreement with the calculated values: C, ±0.18; H, ±0.09; N, ±0.11 [**3a**: H, −0.48; **3e**: C, −0.46; H, −0.50].

**Table 2.** Spectral Data of Compounds **3**

| 3 | M.S.[a] *m/e* (%) | I.R. (Nujol)[b] $\nu$ [$cm^{-1}$] | $^1$H-N.M.R. (DMSO-$d_6$/$TMS_{int}$)[c] $\delta$ [ppm] |
|---|---|---|---|
| **a** | 326 ($M^+$, 57), 311 (100), 283 (12), 230 (17), 203 (15), 202 (19), 155 (22), 77 (33) | 3060, 1650, 1625, 1540, 1515, 1495, 1380, 1360, 1205, 1150, 1080, 950, 870, 780, 770, 705, 680 | 2.97 (s, 3H, 2-$CH_3$); 3.72 (s, 3H, CO—$CH_3$); 7.2–8.41 (m, 12$H_{arom}$) |
| **b** | 342 ($M^+$, 100), 327 (5), 311 (90), 283 (20), 277 (43), 257 (11), 230 (8), 202 (8), 77 (5) | 3060, 1700, 1640, 1540, 1500, 1450, 1380, 1230, 1150, 1100, 860, 770, 700 | 3.1 (s, 3H, 2-$CH_3$); 3.9 (s, 3H, O—CO—$CH_3$); 7.3–8.3 (m, 12$H_{arom}$) |
| **c** | 384 ($M^+$, 100), 355 (80), 339 (25), 283 (80), 271 (30), 230 (8), 219 (7), 202 (11), 77 (10) | 3060, 1690, 1640, 1550, 1500, 1460, 1380, 1300, 1280, 1225, 1160, 1110, 1085, 770, 700 | 0.95 (t, 3H, $CH_2$—$CH_2$—$CH_3$); 1.35 (t, 3H, O—CO—$CH_2$—$CH_3$); 1.6 (m, 2H, $CH_2$—$CH_2$—$CH_3$); 3.0 (t, 2H, $CH_2$—$CH_2$—$CH_3$); 4.3 (q, 2H, O—CO—$CH_2$—$CH_3$); 7.2–8.4 (m, 12$H_{arom}$) |
| **d** | 418 ($M^+$, 43), 417 (55), 389 (27), 373 (31), 345 (100), 313 (9), 268 (13), 203 (9), 202 (11), 115 (8), 77 (17) | 3070, 1700, 1635, 1550, 1500, 1270, 1240, 1220, 1150, 1060, 870, 765, 700 | 1.60 (t, 3H, O—$CH_2$—$CH_3$); 4.34 (q, 2H, O—$CH_2$—$CH_3$); 7.05–8.4 (m, 17$H_{arom}$) |
| **e** | 356 ($M^+$, 100), 327 (41), 311 (58), 283 (72), 230 (23), 203 (17), 202 (25), 102 (15), 77 (31) | 3060, 1690, 1640, 1550, 1500, 1470, 1455, 1230, 1170, 1160, 1110, 890, 860, 790, 770, 705 | 1.38 (t, 3H, O—$CH_2$—$CH_3$); 3.1 (s, 3H, 2-$CH_3$); 4.31 (q, 2H, O—$CH_2$—$CH_3$); 7.1–8.4 (m, 12$H_{arom}$) |
| **f** | 358 ($M^+$, 16), 357 (21), 341 (21), 328 (7), 312 (42), 268 (100), 230 (65), 203 (22), 202 (15), 115 (17), 102 (19), 77 (31) | 3270, 3060, 1745, 1695, 1635, 1550, 1505, 1495, 1215, 1150, 1090, 775, 760, 750, 700 | 1.58 (t, 3H, O—$CH_2$—$CH_3$); 4.43 (q, 2H, O—$CH_2$—$CH_3$); 7.1–8.6 (m, 12$H_{arom}$) |

[a] Recorded at 70 eV on a Hewlett-Packard 5980A instrument.
[b] Recorded on a Nicolet 5DX spectrometer.
[c] Recorded at 80 MHz on a Varian FT-80 spectrometer.

ture. Then, a solution of 1-amino-2-methylthio-4,6-diphenylpyridinium iodide (**1**; 0.28 g, 0.66 mmol) in dry dimethylformamide (10 ml) is added. The mixture is stirred at 70°C for 12–18 h. After cooling to room temperature, the mixture is poured into cold water (40 ml) and the precipitated solid is separated by filtration and recrystallized from ethanol.

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