A New Approach for the Synthesis of Fused Pyrroles. The Synthesis of Acyl Substituted Pyrrolo[1,2-*x*]azines

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N-Acetonyl- and *N*-phenacyl quaternary salts of α-methyl substituted heterocycles **16, 17, 21, 23** and **26** were converted with DMFDMA into the corresponding 3-acylpyrrolo[1,2-*a*]pyridine **18**, 7-benzoylpyrrolo-[1,2-*c*]pyrimidine **22**, and 6-benzoylpyrrolo[1,2-*a*]pyrazine derivatives **24** and **27**. A concurrent reaction produced methyl and phenyl substituted pyrrolo[1,2-*x*]azines **19, 20, 25** and **28**.

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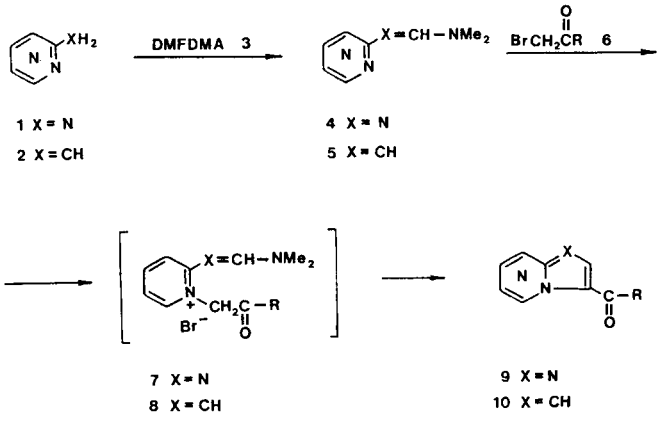
Derivatives of pyrrolo[1,2-*a*]pyridine (indolizine) have been first prepared from 2-methylpyridine and acetic anhydride [1]. The other methods include Diels-Alder reaction of pyridine and dimethyl acetylenedicarboxylate [2], the Tschitschibabin reaction [3] and transformations of pyrilium salts [4,5]. The syntheses and transformations of other azaindolizines, such as pyrrolo[1,2-*a*]pyridazines [6,7], pyrrolo[1,2-*c*]pyrimidines [8,9] and others [10] have been extensively studied recently.

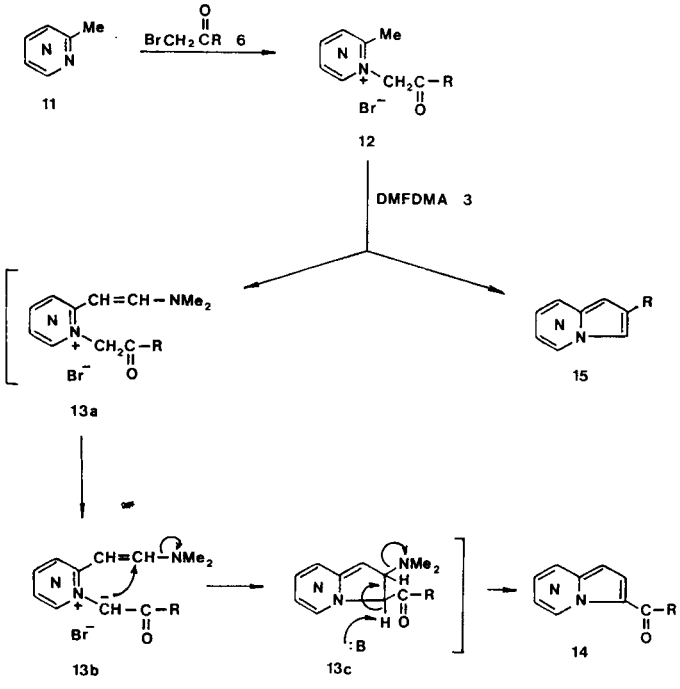
The 3-acyl substituted imidazo[1,2-*x*]azines (azaindolizines) have been prepared from the corresponding α-amino heterocycles **1** and DMFDMA **3** to form first *N,N*-dimethyl-*N'*-heteroarylformamidines **4**, as intermediates, followed by treatment with α-haloketones **6** to give the quaternary salts **7**, which have been, without isolation, transformed into bicyclic systems **9** [11] (Scheme 1).

Scheme 1



The application of an analogous reaction sequence **2** → **5** → **8** → **10** (Scheme 1) for the preparation of the corresponding pyrroloazines was not successful, since the α-methyl substituted azines do not react with DMFDMA **3** to give the corresponding enamines **5**. In order to overcome this problem, we selected an alternative reaction sequence. The α-methyl substituted azines **11** were treated first with an α-haloketone **6** to give the corresponding quaternary salt **12**. The quaternization increases the reactivity of the α-methyl group for reaction with DMFDMA **3** to give enamines **13**, which cyclize, without isolation, into acyl substituted pyrrolo[1,2-*x*]azines **14** (Scheme 2).

Scheme 2



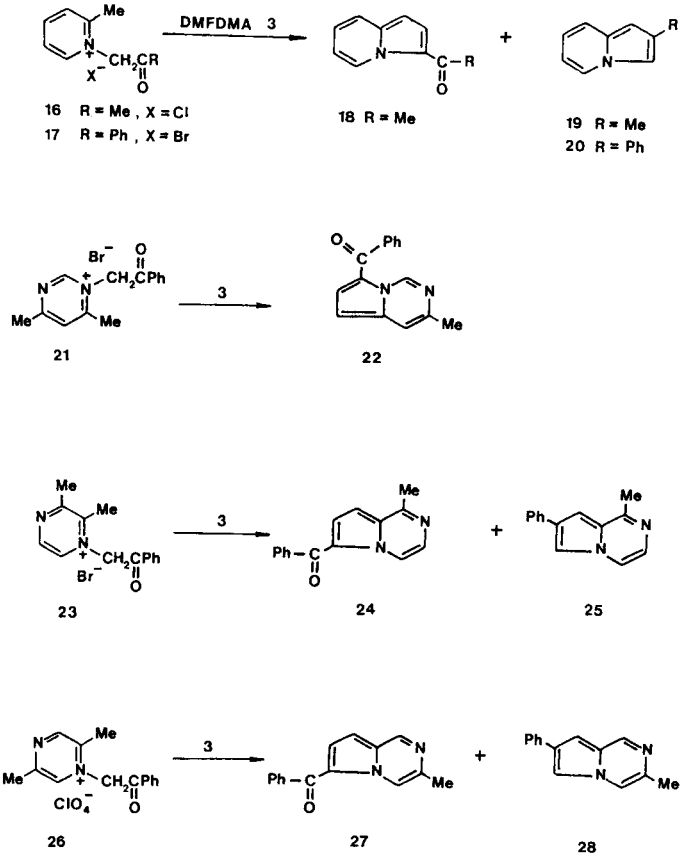
3-Acylindolizines are formed according to the following mechanism. First, the enamine **13a** is formed from quaternary salt **12** and DMFDMA **3**, followed by nucleophilic attack of the anion **13b**, generated from the active methylene group, attached to ring nitrogen atom, and elimination of the dimethylamino group to give the final indolizine **14**. However, a concurrent reaction, *i.e.* cyclodehydration of quaternary salt **12** in the presence of DMFDMA **3** as dehydrating agent, was observed to produce the corresponding 2-substituted indolizines **15**. In most cases, both types of products are formed.

In our studies the following methyl substituted heterocycles were selected: 2-methylpyridine, 4,6-dimethylpyrim-

idine, 2,3-dimethylpyrazine, and 2,5-dimethylpyrazine. They were transformed with chloroacetone or phenacyl bromide into the corresponding quaternary salts **16**, **17**, **21**, **23**, and **26**, respectively. Compound **23** was used without purification in further experiments, while **26** was isolated and purified in the form of perchlorate salt and used as such in further transformations.

Acetonylpyridinium salt **16** gave with DMFDMA a mixture of and 3-acetylpyrrolo[1,2-*a*]pyridine (**18**) and 2-methyl derivative **19** in 17% and 23% yield, respectively, while the phenacyl derivative **17** produced only 2-phenylpyrrolo-[1,2-*a*]pyridine in high yield. Pyrimidinium bromide **21** afforded 7-benzoyl-3-methylpyrrolo[1,2-*c*]pyrimidine **22**. In pyrazine series, mixtures of both products are produced. The pyrazinium salt **23** affords **24** and **25**, and **26** the corresponding **27** and **28**. The compound **25** can be obtained by Tschitschibabin method only in traces (Scheme 3).

Scheme 3



EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. The ^{1}H nmr spectra were recorded on a JEOL JNM C60 HL and microanalyses for C, H, and N on a Perkin Elmer Analyser 2400.

The following compounds were prepared according to the procedures described in the literature: 1-acetonyl-2-methylpyridinium chloride (**16**) [12], 2-methyl-1-phenacylpyridinium bromide (**17**) [12] and 4,6-dimethyl-1-phenacylpyrimidinium bromide (**21**) [13].

2,3-Dimethyl-1-phenacylpyrazinium Bromide (**23**).

A mixture of 2,3-dimethylpyrazine (1.08 g, 0.01 mole) and phenacyl bromide (3.0 g, 0.015 mole) in ethanol (8 ml) was heated under reflux for 3 hour. The solvent was evaporated *in vacuo* and the viscous residue was without purification used in further experiments.

2,5-Dimethyl-1-phenacylpyrazinium Perchlorate (**26**).

A mixture of 2,5-dimethylpyrazine (325 mg, 0.003 mole) and phenacyl bromide (650 mg, 0.00325 mole) in ethanol (6 ml) was heated under reflux for 90 minutes. The solvent was evaporated *in vacuo*. The residue was dissolved in diethyl ether (1 ml) and perchloric acid (2*M*, 3 ml) was added to the solution. The precipitate was collected by filtration and washed with ethanol to give **26**, yield 308 mg (31%), mp 187-203° (from ethanol); ^{1}H nmr (DMSO-d_6): δ 2.70 (s, 3H, Me), 6.47 (s, 2H, CH_2), 7.58-8.13 (m, 5H, Ph), 8.86 (s, 1H, H_3), 9.37 (s, 1H, H_6).

Anal. Calcd. for $C_{14}H_{15}ClN_2O_5$: C, 51.47; H, 4.63; N, 8.57. Found: C, 51.76; H, 4.86; N, 8.63.

3-Acetylpyrrolo[1,2-*a*]pyridine (**18**) and 2-Methylpirrolo[1,2-*a*]pyridine (**19**).

To a solution of 1-acetonyl-2-methylpyridinium chloride **16** [12], prepared from 2-methylpyridine (900 mg, 0.01 mole) and chloroacetone (900 mg, 0.01 mole) [12] in DMF (10 ml), DMFDMA (1.8 g, 0.015 mole) was added and the mixture was heated under reflux for 5 minutes. The solvent was evaporated *in vacuo* and the viscous material extracted with diethyl ether (3 times, 20 ml each time). The combinated extracts were dried with anhydrous magnesium sulfate. The solvent was evaporated *in vacuo* and the residue separated by column chromatography (silica gel 0.063-0.200 mm, and a mixture diethyl ether/petroleum ether 1:3) in two fractions: fraction 1 gave **19**, yield 284 mg (23%), mp 53-54°, lit mp 59° [14], 57-59° [12]; fraction 2 gave **18**, yield 260 mg (17%), mp 35-39°, lit mp 38-38.5° [15].

2-Phenylpyrrolo[1,2-*a*]pyridine (**20**).

A mixture of 2-methyl-1-phenacylpyridinium bromide (**17**, 936 mg, 0.0032 mole) and DMFDMA (720 mg, 0.006 mole) in DMF (10 ml) was heated under reflux for 10 minutes. The precipitate, after cooling in the refrigerator, was collected by filtration to give crude **20** (525 mg). The filtrate was evaporated *in vacuo* to give 85 mg of **20**, yield 610 mg (97%), mp 212-213° dec (from DMF), lit mp 215° [12].

7-Benzoyl-3-methylpyrrolo[1,2-*c*]pyrimidine (**22**).

A mixture of crude 4,6-dimethyl-1-phenacylpyrimidinium bromide (**21**) [16], prepared from 4,6-dimethylpyrimidine (432 mg, 0.004 mole) and phenacyl bromide (796 mg, 0.004 mole), DMFDMA (960 mg, 0.008 mole) in DMF (10 ml) was heated under reflux for 5 minutes. The solvent was evaporated *in vacuo* and the residue was extracted with diethyl ether. The combined extracts were dried with anhydrous sodium sulfate. The solvent was evaporated and the residue separated by column chromatography (silica gel, 0.063-0.200 mm, and diethyl ether/petroleum ether, 1:1, as eluent) to give **22**, yield 260 mg (28%), mp 143-144° (from cyclohexane); ^{1}H nmr (deuteriochloroform): δ 2.53 (s, 3H, 3-Me), 6.35 (d, 1H, H_5), 7.35 (d, 1H, H_6), 7.48 (s, 1H, H_4), 7.20-7.55

(m) and 7.65-7.85 (m) (Ph), 10.65 (s, 1H, H_1), J_{H_5,H_6} = 4.8 Hz.

Anal. Calcd. for $C_{15}H_{12}N_2O$: C, 76.26; H, 5.12; N, 11.86. Found: C, 75.87; H, 5.12; N, 11.90.

1-Methyl-7-phenylpyrrolo[1,2-*a*]pyrazine (**25**).

A mixture of the crude **23**, prepared from 2,3-dimethylpyrazine (1.08 g, 0.01 mole) and phenacyl bromide (3.0 g, 0.0 mole), water (6 ml), ethanol (1 ml) and saturated aqueous solution of potassium hydrogen carbonate (3 ml) was heated at 90° for 15 minutes. The solution was, after cooling to room temperature, extracted with diethyl ether (3 times, 20 ml each time). The combined extracts were dried with anhydrous magnesium sulfate, the solvent evaporated *in vacuo* and the residue purified by column chromatography (silica gel 0.063-0.200 mm, and diethyl ether as eluent) to give **25**, yield 75 mg (3.6%), mp 141-144° (from cyclohexane); ^{1}H nmr (deuteriochloroform): δ 2.69 (s, 3H, 1-Me), 6.99 (s, 1H, H_8), 7.22-7.70 (m, 8H, H_3, H_4, H_6, Ph).

Anal. Calcd. for $C_{14}H_{12}N_2$: C, 80.74; H, 5.80; N, 13.45. Found: C, 80.97; H, 5.87; N, 13.26.

6-Benzoyl-1-methylpyrrolo[1,2-*a*]pyrazine (**24**) and 1-Methyl-7-phenylpyrrolo[1,2-*a*]pyrazine (**25**).

A mixture of **23**, prepared from 2,3-dimethylpyrazine (0.54 g, 0.005 mole) and phenacyl bromide (1.5 g, 0.0075 mole), and DMFDMA (1.2 g, 0.010 mole) in DMF (5 ml) was heated under reflux for 5 minutes. The volatile components were evaporated *in vacuo*, water (10 ml) was added to the residue and the mixture was extracted with diethyl ether (3 times, 25 ml each time). The combined extracts were dried with anhydrous magnesium sulfate. The solvent was evaporated *in vacuo* and the residue separated by column chromatography (silica gel, 0.063-0.200 mm). The first fraction obtained by elution with a mixture of diethyl ether:-petroleum ether, 3:1, is ω-methoxyacetophenone, originating from the crude starting compound. The second fraction, after evaporation of the solvent, gave **24**, yield 215 mg (19%), mp 144-147° (from cyclohexane); ^{1}H nmr (deuteriochloroform): δ 2.75 (s, 3H, 1-Me), 6.70 (d, 1H, H_8), 7.15-7.50 (m) and 7.60-7.85 (m) (5H, Ph), 7.27 (d, 1H, H_7), 7.76 (d, 1H, H_3), 9.37 (d, 1H, H_4), J_{H_7,H_8} = 5.0 Hz, $J_{H_3H_4}$ = 4.3 Hz.

Anal. Calcd. for $C_{15}H_{12}N_2O$: C, 76.26; H, 5.12; N, 11.86. Found: C, 76.74; H, 5.19; N, 11.71.

The third fraction, obtained by elution with diethyl ether gave **25**, yield 115 mg (10%).

6-Benzoyl-3-methylpyrrolo[1,2-*a*]pyrazine (**27**) and 3-Methyl-7-phenylpyrrolo[1,2-*a*]pyrazine (**28**).

A mixture of **26** (980 mg, 0.003 mole) and DMFDMA (600 mg, 0.05 mole) in DMF (10 ml) was heated under reflux for 10 minutes. The volatile components were evaporated *in vacuo*, water (20 ml) was added to the residue, and the mixture was extracted with diethyl ether (3 times, 20 ml each time). The combined extracts were dried over anhydrous sodium sulfate, the solvent was then evaporated *in vacuo* and the residue was separated by column chromatography (silica gel 0.063-0.200 mm, and a mixture of diethyl ether/petroleum ether, 3:1, as eluent) into two fractions.

Fraction 1 is the compound **27**, yield 184 mg (26%), mp 117-119° (from cyclohexane); ^{1}H nmr (deuteriochloroform): δ 2.57 (s, 3H, 3-Me), 6.66 (d, 1H, H_8), 7.26 (d, 1H, H_7), 7.30-7.55 (m) and 7.65-7.90 (m) (5H, Ph), 8.93 (d, 1H, H_1), 9.43 (d, 1H, H_4), J_{H_7,H_8} = 7.2 Hz, J_{H_1,H_4} = 1.0 Hz.

Anal. Calcd. for $C_{15}H_{12}N_2O$: C, 76.26; H, 5.12; N, 11.86. Found: C, 76.49; H, 5.19; N, 11.85.

Fraction 2 is **28**, yield 143 mg (23%), mp 208° (from benzene); ^{1}H nmr (deuteriochloroform): δ 2.37 (s, 3H, 3-Me), 6.88 (s, 1H, H_8), 7.13-7.50 (m, 7H, H_1, H_6, Ph), 8.64 (s, 1H, H_4).

Anal. Calcd. for $C_{14}H_{12}N_2$: C, 80.74; H, 5.80; N, 13.45. Found: C, 81.03; H, 5.90; N, 13.18.

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