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CONCURRENT ENAMINE RECYCLIZATION

V. I. Terenin and A. S. Ivanov

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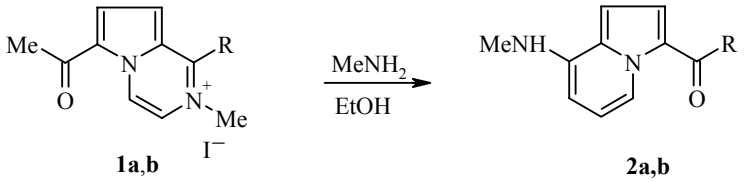
Trifluoroacetylpyrrolo[1,2-*a*]pyrazines are capable of undergoing nucleophilic cyclotransformations involving the carbonyl atom of the trifluoroacetyl group in the formation of a new ring [1]. In the present work the recyclization of pyrrolo[1,2-*a*]pyrazine salts containing an acyl group with an α-methyl and α-methylene fragment instead of a trifluoroacetyl group was studied.

It was found that the 3-benzoyl- and 3-isobutyryl-8-methylaminoindolizines (**2a)** and (**2b)**, i.e., the products from cyclization involving the acetyl group, are formed as a result of the reaction of 6-acetyl- and 6-acetyl-1-isopropylpyrrolo[1,2-*a*]pyrazinium methiodides **1a** and **1b** with an alcohol solution of methylamine.



1a,**b** **2a,b**

1 a R = Ph, **b** R = *i*-Pr

The reaction of the 6-acetyl-1-ethylpyrrolo[1,2-*a*]pyrazine (**1c**) and 1-methyl-6-propionylpyrrolo[1,2-*a*]-pyrazinium (**1d**) salts with an alcohol solution of methylamine leads to a mixture of isomeric 3-acyl-8-methylaminoindolizines **3** and **4**.

Opening of the pyrazine ring in compounds **1c**,**d** leads to the formation of one and the same acyclic intermediate **A**, which contains two enamine components capable of participating in further cyclization. The ratio of the products of the discovered rearrangement is determined by the ratio of the rates of reaction of the Schiff base fragment with one (a) or other (b) enamine part of the intermediate **A**.

Irrespective of which initial salt takes part in the reaction and also of the time and temperature of the process (from 1 h 30 min at 140°C to one month at 25°C), the ratio of the reaction products (total yield 31%) remains constant at 2.5:1 (**3**:**4**). The larger proportion of compound **3** (path a) is obviously explained by the higher reactivity of the substituted enamine fragment of intermediate **A** compared with the unsubstituted fragment.

M. V. Lomonosov Moscow State University, Moscow 119992, Russia; e-mail: vter@org.chem.msu.ru.
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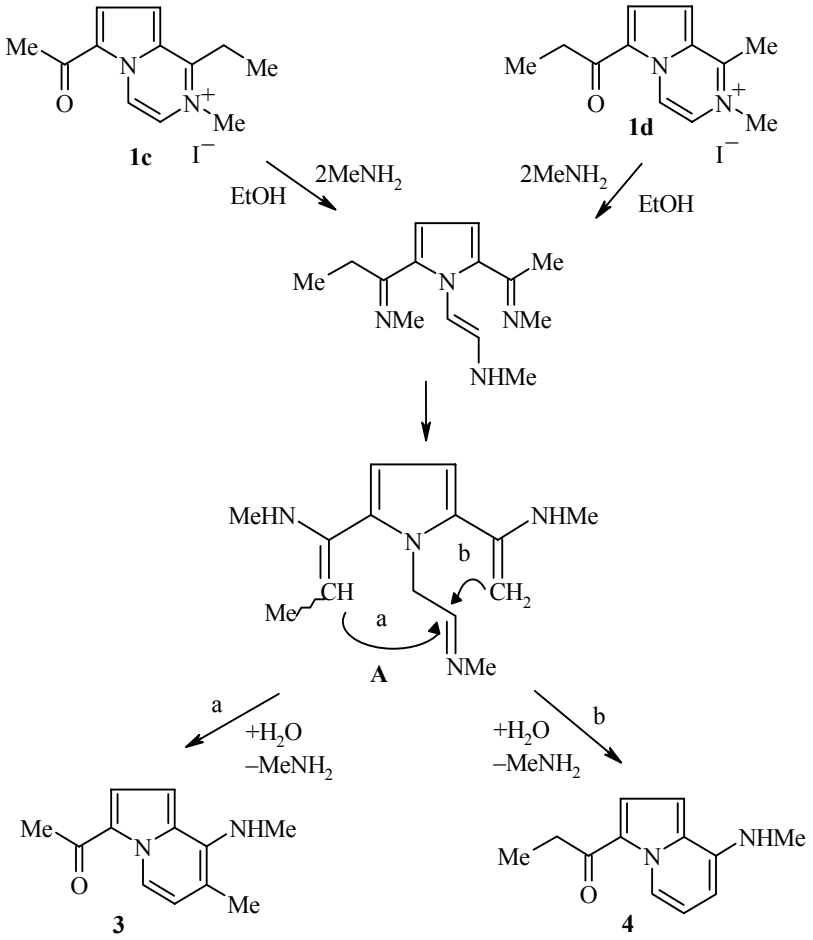
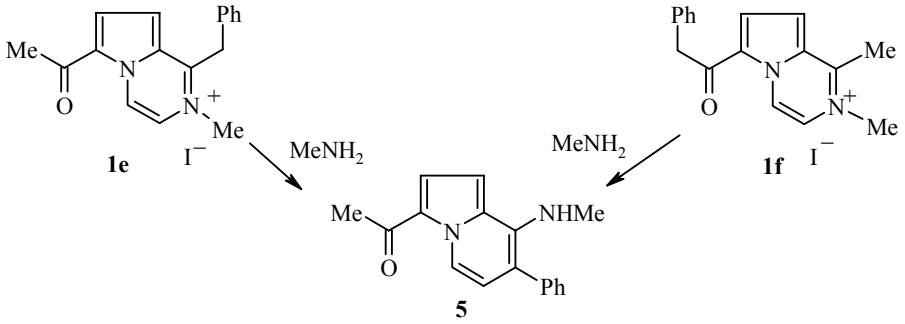


In the case of the recyclization of the salts **1e**,**f** only the formation of 3-acetyl-8-methylamino-7-phenylindolizine (**5)** was detected.



The result can be explained by the fact that cyclization in the intermediate only takes place at the benzyl group since the reactivity of the methylene group in the benzyl substituent is significantly higher than that of the methyl.

The ^{1}H NMR spectra were recorded on a Bruker Avance-400 spectrometer (400 MHz) in deuterochloroform at 28°C with TMS as internal standard. The mass spectra were recorded on a Kratos MS-30 instrument with electron impact ionization energy 70 eV. The reactions and the purity of the obtained compounds were monitored by TLC on Silufol plates in the benzene and 1:1 benzene–ethyl acetate systems with development in iodine vapor.

3-Acyl-8-methylaminoindolizines 2a,b, 3, 4, and 5 (General Procedure). A mixture of the quaternary salt **1a-f** (1 mmol) and a 40% alcohol solution of methylamine (5-6 ml) was heated in a sealed tube at 70-80°C for 2 h. A few drops of water were added to the reaction mixture, the mixture was evaporated to dryness, and water (50 ml) was added to the residue. The mixture was boiled for 2-3 h and extracted with ethyl acetate. The extract was dried with 3 Å sieves, evaporated, and separated on a chromatographic column with silica gel 35/60 in benzene.

3-Benzoyl-8-methylaminoindolizine (2a). Yield 15%; mp 80-82°C (hexane). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.01 (3H, s, NH$\underline{CH_3}$); 4.00 (1H, br. s, NH); 6.34 (1H, d, $J_{7,6}$ = 7.2, H-7); 6.44 (1H, d, $J_{1,2}$ = 4.5, H-1); 6.90 (1H, t, *J* = 7.2, H-6); 7.23 (1H, d, $J_{2,1}$ = 4.5, H-2); 7.50 (3H, m, *p*,*m*-C_6H_5); 7.84 (2H, m, *o*-C_6H_5); 9.30 (1H, d, $J_{5,6}$ = 7.2, H-5). Mass spectrum, *m*/*z* (I_{rel}): 250 $[M]^+$ (43), 167 (57), 149 (100). Found, %: C 76.74; H 5.55; N 11.12. $C_{16}H_{14}N_2O$. Calculated, %: C 76.80; H 5.60; N 11.20.

3-Isobutyryl-8-methylaminoindolizine (2b). Yield 12%; mp 136-138°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.28 [6H, d, *J* = 6.8, CH($\underline{CH_3}$)$_2$]; 3.01 (3H, s, NH$\underline{CH_3}$); 3.45 [m, C$\underline{H}$(CH$_3$)$_2$]; 3.89 (1H, br. s, NH); 6.23 (1H, d, $J_{7,6}$ = 7.5, H-7); 6.41 (1H, d, $J_{1,2}$ = 4.5, H-1); 6.82 (1H, t, *J* = 7.5, H-6); 7.48 (1H, d, $J_{2,1}$ = 4.5, H-2); 9.45 (1H, d, $J_{5,6}$ = 7.5, H-5). Mass spectrum, *m*/*z* (I_{rel}): 216 $[M]^+$ (78), 173 (100), 145 (36). Found, %: C 71.98; H 7.25; N 12.88. $C_{13}H_{16}N_2O$. Calculated, %: C 72.22; H 7.40; N 12.96.

3-Acetyl-7-methyl-8-methylaminoindolizine (3). Mp 124-125°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.31 (3H, s, 7-CH$_3$); 2.55 [3H, s, C(O)$\underline{CH_3}$]; 3.10 (3H, s, NH$\underline{CH_3}$); 3.98 (1H, br. s, NH); 6.58 (1H, d, $J_{1,2}$ = 4.6, H-1); 6.68 (1H, d, $J_{6,5}$ = 7.1, H-6); 7.45 (1H, d, $J_{2,1}$ = 4.6, H-2); 9.49 (1H, d, $J_{5,6}$ = 7.1, H-5). Mass spectrum, δ, ppm (I_{rel}): 202 $[M]^+$ (100), 187 (75), 159 (70). Found, %: C 71.39; H 7.09; N 13.99. $C_{12}H_{14}N_2O$. Calculated, %: C 71.28; H 6.93; N 13.86.

8-Methylamino-3-propionylindolizine (4). Mp 141-142°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.28 (3H, t, *J* = 7.2, CH$_2\underline{CH_3}$); 2.95 (2H, q, *J* = 7.2, $\underline{CH_2}$CH$_3$); 2.99 (3H, s, NH$\underline{CH_3}$); 4.00 (1H, br. s, NH); 6.20 (1H, d, $J_{7,6}$ = 7.6, H-7); 6.39 (1H, d, $J_{1,2}$ = 4.6, H-1); 6.79 (1H, t, *J* = 7.6, H-6); 7.44 (1H, d, $J_{2,1}$ = 4.6, H-2); 9.38 (1H, d, $J_{5,6}$ = 7.5, H-5). Mass spectrum, δ, ppm (I_{rel}, %): 202 $[M]^+$ (83), 173 (100), 145 (55). Found, %: C 71.35; H 7.09; N 13.65. $C_{12}H_{14}N_2O$. Calculated, %: C 71.28; H 6.93; N 13.86.

3-Acetyl-8-methylamino-7-phenylindolizine (5). Yield 45-47%; the product was an oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz) 2.59 (3H, s, C(O)$\underline{CH_3}$); 2.95 (3H, s, NH$\underline{CH_3}$); 3.95 (1H, br. s, NH); 6.71 (1H, d, $J_{1,2}$ = 4.5, H-1); 6.77 (1H, d, $J_{6,5}$ = 7.0, H-6); 7.44-7.50 (6H, m, C_6H_5, H-2); 9.53 (1H, d, $J_{5,6}$ = 1.0, H-5). Mass spectrum, (I_{rel}, %): 264 $[M]^+$ (100), 249 (14), 221 (24), 206 (15). Found, %: C 77.36; H 6.00; N 10.43. $C_{17}H_{16}N_2O$. Calculated, %: C 77.27; H 6.06; N 10.60.

REFERENCES

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