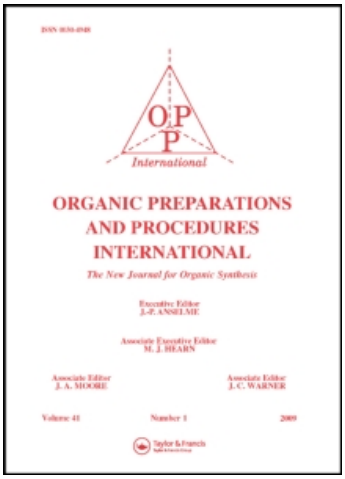

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SYNTHESIS OF ALKYL INDOLIZINES FROM PYRYLIUM SALTS

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SYNTHESIS OF ALKYL INDOLIZINES FROM PYRYLIUM SALTS

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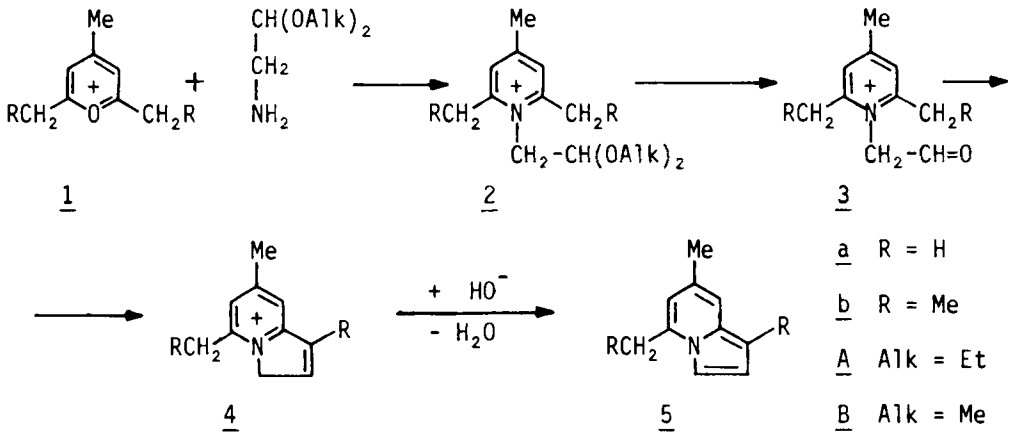
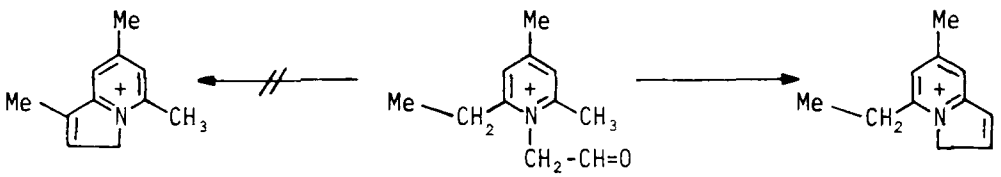
We have recently shown that 3*H*-indolizinium perchlorates 4 can be prepared in good yields starting from pyrylium salts (1) with methyl (R = H) or ethyl (R = Me) groups in the 2- and 6- positions, by the following reaction sequence.[1]



In view of the interest in indolizine chemistry,[2] and the availability of pyrylium salts,[3] we report here the experimental details associated with the above reaction sequence. This route to substituted indolizinium salts 4 and corresponding indolizines 5 is also applicable in those cases when the classical Chichibabin quaternisation of pyridines with α-halogenated carbonyl compounds fails, i.e. for indolizines unsubstituted in the five-membered ring. This fact explains why the indolizinium salts 4 and indolizines 5

derived therefrom were unsynthesized till now, in spite of the fact that numerous other, constitutionally isomeric, indolizine derivatives are known. Furthermore, we show now that the cyclisation of *N*-pyridinium acetaldehydes 3 proceeds with a high regioselectivity when an α-ethyl group competes with an α-methyl group. Thus, from 2-(2-ethyl-4,6-dimethylpyridinium-1)-acetaldehyde 3c, only one crystalline indolizinium perchlorate was obtained, namely 4c. This fact agrees with the observation[1] that cyclisations involving methyl groups proceed faster and in higher yields than cyclisations involving ethyl CH_2 groups.



3c 4c

EXPERIMENTAL SECTION

Melting points were determined on a hot-stage apparatus and are uncorrected. Infrared spectra were obtained in KBr pellets on a Jena UR-20 spectrometer. ^{1}H-NMR spectra were run either in $CDCl_3$ or in CF_3COOH solutions with tetramethylsilane as internal standard, on a Varian A-60A instrument.

2-(2,4,6-Trimethylpyridinium-1)-acetaldehyde diethylacetal Tetrafluoroborate (2aA). General Procedure.- In a three-necked 250 ml round-bottom flask equipped with a magnetical stirrer, dropping funnel and reflux condenser, 2,4,6-trimethylpyrylium tetrafluoroborate[4] (1a, 38 g, 0.18 mol) was suspended in 100 ml dichloromethane. Aminoacetaldehyde diethylacetal (24 g, 24.8 ml, 0.18 mol, commercial product) was added dropwise so that a gentle reflux was maintained. The deeply red solution was stirred overnight at room temperature and ether (100 ml) was added to precipitate the product. It was collected, washed with ether and dried to yield 53 g (90 %) of 2aA.

^{1}H-NMR ($CDCl_3$), δ (ppm) : 1.21 (6H, t, J = 7.5 Hz, $OCH_2\underline{Me}$), 2.60 (3H, s,

4-Me), 2.93 (6H, s, 2- and 6-Me), 3.70 and 3.80 (4H, m, nonequivalent OCH_2), 4.70 (2H, distorted d, $\overset{+}{N}$-CH_2), 4.80 (1H, distorted t, CH_2-CH=, J = 4.5 Hz), 7.61 (2H, s, 3- and 5-H) ; mp. 143-145°.

Anal. Calcd. for $C_{14}H_{24}BF_4NO_2$: N, 4.31

Found : N, 4.16

The corresponding perchlorate, mp. 121-122°, has an identical ^{1}H-NMR spectrum ; IR (cm^{-1}) : 625, 1100, 1585, 1650.

Similarly, by using aminoacetaldehyde dimethylacetal (Aldrich) and 2,4,6-trimethylpyrylium perchlorate,[5] the corresponding pyridinium dimethylketal perchlorate (2aB), mp. 130-131° was obtained in 94 % yield ; ^{1}H-NMR ($CDCl_3$), δ (ppm) : 2.53 (3H, s, 4-Me), 2.85 (6H, s, 2- and 6-Me), 3.47 (6H, s, OMe), 4.72 (3H, broad s, $\overset{+}{N}$-CH_2-CH=), 7.52 (2H, s, 3- and 5-H).

2-(2,6-Diethyl-4-methylpyridinium-1)-acetaldehyde dimethylacetal Perchlorate (2bB).- Similarly, 1b (15 g, 60 mmol) and aminoacetaldehyde dimethylacetal (6.3 g, 60 mmol) reacted in 50 ml dichloromethane to afford 17 g (84 %) of 2bB, mp. 65-67°. ^{1}H-NMR ($CDCl_3$), δ (ppm) : 1.45 (6H, t, J = 7.5 Hz, CH_2Me), 2.63 (3H, s, 4-Me), 3.22 (4H, q, J = 7.5 Hz, CH_2Me), 3.47 (6H, s, OMe), 4.77 (3H, m, CH_2-CH=), 7.63 (2H, s, 3- and 5-H).

Anal. Calcd. for $C_{14}H_{24}ClNO_6$: N, 4.15 ; Cl, 10.50

Found : N, 4.00 ; Cl, 10.75

2-(2-Ethyl-4,6-dimethylpyridinium-1)-acetaldehyde dimethylacetal Perchlorate (2cB).- Analogously, 2.9 g (76 %) of 2cB were obtained from 1c (2.8 g, 12 mmol) and aminoacetaldehyde dimethylacetal (1.25 g, 12 mmol), mp. 95-96°. ^{1}H-NMR ($CDCl_3$), δ (ppm) : 1.42 (3H, t, J = 7.5 Hz, 2-CH_2Me), 2.56 (3H, s, 4-Me), 2.86 (3H, s, 6-Me), 3.18 (2H, q, J = 7.5 Hz, 2-CH_2Me), 3.46 (6H, s, OMe), 4.72 (3H, m, CH_2-CH=), 7.50 (2H, s, 3- and 5-H).

Anal. Calcd. for $C_{13}H_{22}ClNO_6$: N, 4.33 ; Cl, 10.95

Found : N, 4.60 ; Cl, 10.71

2-(2,4,6-Trimethylpyridinium-1)-acetaldehyde Tetrafluoroborate (3a). General Procedure.- In a round-bottom flask equipped with a reflux condenser the diethylacetal 2aA (11 g, 34 mmol) was dissolved in 33 ml acetic acid and 10 ml 48% tetrafluoroboric acid. The mixture was refluxed for 4 hrs, then ether was added to precipitate the product. Filtration and air drying gave 8.4 g (99 %) of crude 3a, mp. 155-156°. ^{1}H-NMR (CF_3COOH), δ (ppm) : 2.64 (3H, s, 4-Me), 2.70 (6H, s, 2- and 6-Me), 5.80 (2H, s, $\underline{CH_2}$-CHO), 7.60 (2H, s, 3- and 5-H), 10.00 (1H, s, CH_2-$\underline{CHO}$). It is noteworthy that the absence of coupling between the aldehydic and the methylenic vicinal protons persists also in other solvents (CD_3SOCD_3, H_2SO_4, pyridine-d_5, CD_3COCD_3). In pyridine-d_5 an upfield shift occured for the 4-methyl signal while the 2- and 6-methyl signal was shifted downfield, increasing thus the chemical shift difference between the α- and γ-methyl groups from 0.08 ppm (in other solvents) to 0.33 ppm in C_5D_5N. In C_5D_5N and acetone-d_6 about 10% of 3a is present as the enolic tautomer.

Anal. Calcd. for $C_{10}H_{14}BF_4NO$: N, 5.58

Found : N, 5.33

The corresponding perchlorate was obtained similarly by acid hydrolysis (70% $HClO_4$) of acetals 2aA or 2aB, mp. 173-175° ; IR (cm^{-1}) : 625, 1100, 1588, 1650, 1735 ; identical ^{1}H-NMR spectrum with the BF_4^- salt ; ^{13}C-NMR (CF_3COOH + CD_2Cl_2), δ (ppm) : 21.98 (2- and 6-Me), 22.13 (4-Me), 62.60 (CH_2) 130.27 (3- and 5-C), 157.02 (4-C), 162.88 (2- and 6-C), 196.49 (CHO).

Anal. Calcd. for $C_{10}H_{14}ClNO_5$: N, 5.31 ; Cl, 13.45

Found : N, 5.33 ; Cl, 13.60

2-(2,6-Diethyl-4-methylpyridinium-1)-acetaldehyde Perchlorate (3b).- The acetal 2bB (6.7 g, 20 mmol) was hydrolysed as above with 15 ml acetic acid and 1 ml 70% perchloric acid, giving 5.7 g (98 %) of 3b, mp. 204-206°. ^{1}H-NMR (CF_3COOH), δ (ppm) : 1.45 (6H, t, J = 7.5 Hz, $CH_2\underline{Me}$), 2.70 (3H, s, 4-Me), 2.98 (4H, q, J = 7.5 Hz, $\underline{CH_2}Me$), 6.00 (2H, s, $\overset{+}{N}$-CH_2), 7.68 (2H, s,

3- and 5-H) 10.00 (1H, s, CH=O).

Anal. Calcd. for $C_{12}H_{18}ClNO_5$: N, 4.80 ; Cl, 12.16

Found : N, 5.00 ; Cl, 12.40

2-(2-Ethyl-4,6-dimethylpyridinium-1)-acetaldehyde Perchlorate (3c).- Hydrolysis of 2.6 g (8 mmol) of 2cB in 10 ml acetic acid and 0.5 ml 70% $HClO_4$ gave 1.8 g (81 %) of 3c, mp. 138-139°. ^{1}H-NMR (CF_3COOH), δ (ppm) : 1.42 (3H, t, J = 7.5 Hz, 2-CH_2Me), 2.65 (6H, broad s, 4- and 6-Me), 2.95 (2H, q, J = 7.5 Hz, 2-CH_2Me), 5.75 (2H, s, $\overset{+}{N}$-CH_2), 7.65 (2H, s, 3- and 5-H), 10.00 (1H, s, CH=O).

Anal. Calcd. for $C_{11}H_{16}ClNO_5$: N, 5.05 ; Cl, 12.77

Found : N, 5.30 ; Cl, 13.18

5,7-Dimethyl-3*H*-indolizinium Perchlorate (4a). General Procedure.- In a 100 ml flask provided with a magnetic stirrer, the aldehyde 3a (10 g, 40 mmol) was dissolved in 25 ml of boiling methanol and treated with KOH (2.5 g, 45 mmol) dissolved in 50 ml of boiling methanol. The flask was then stoppered and left for two days at room temperature with occasional stirring. After filtration of the precipitated KBF_4 (5 g, 36 mmol), 70% $HClO_4$ was added dropwise to the clear solution which was stirred subsequently for 3 hrs. The precipitated 4a was then filtered off and dried to afford 9.3 g (95 %) of crude product. Recrystallization from boiling methanol containing charcoal gave a pure sample with mp. 219-221° (dec.). IR (cm^{-1}) : 625, 707, 766, 878, 1100, 1560, 1637, 2955, 3075, 3100. ^{1}H-NMR (CF_3COOH), δ (ppm) : 2.69 (3H, s, 7-Me), 2.83 (3H, s, 5-Me), 5.28 (2H, s, 3-CH_2), 7.16 (1H, d, J = 6.5 Hz, 1-H), 7.48 (1H, d, J = 6.5 Hz, 2-H), 7.51 (1H, s, 6-H), 7.77 (1H, s, 8-H).

Anal. Calcd. for $C_{10}H_{12}ClNO_4$: N, 5.70

Found : N, 5.85

1,7-Dimethyl-5-ethyl-3*H*-indolizinium Perchlorate (4b).- Similarly, 3b (11.8 g, 45 mmol) and 2.5 g KOH were stirred in methanol for four days after which 4.0 ml 70% $HClO_4$ precipitated the product (7.4 g, 60 %), mp. 119-120°. IR (cm^{-1}) : 625, 800, 875, 1100, 1562, 1630, 2960, 3070, 3090. ^{1}H-NMR (CF_3COOH), δ (ppm) : 1.58 (3H, t, J = 7.5 Hz, CH_2Me), 2.36 (3H, d, J = 1.5 Hz, 1-Me), 2.78 (3H, s, 7-Me), 3.13 (2H, q, J = 7.5 Hz, CH_2Me), 5.08 (2H, broad s, 3-CH_2), 7.12 (1H, broad s, 2-H), 7.58 (1H, s, 6-H), 7.70 (1H, s, 8-H).

Anal. Calcd. for $C_{12}H_{16}ClNO_4$: N, 5.12

Found : N, 5.04

5-Ethyl-7-methyl-3*H*-indolizinium Perchlorate (4c).- Aldehyde 3c (5.0 g, 18 mmol) was stirred in methanol with 1.1 g KOH and then 2.0 ml 70% $HClO_4$ gave 2.9 g (62 %) of 4c, mp. 188-189°. IR (cm^{-1}) : 625, 705, 880, 1100, 1555, 1600, 2965, 3070, 3095. ^{1}H-NMR (CF_3COOH), δ (ppm) : 1.56 (3H, t, J = = 7.5 Hz, 5-CH_2Me), 2.73 (3H, s, 7-Me), 3.13 (2H, q, J = 7.5 Hz, 5-CH_2Me), 5.30 (2H, s, 3-CH_2), 7.19 (1H, d, J = 6.5 Hz, 1-H), 7.53 (1H, d, J = 6.5 Hz, 2-H), 7.58 (1H, s, 6-H), 7.79 (1H, s, 8-H).

Anal. Calcd. for $C_{11}H_{14}ClNO_4$: N, 5.40

Found : N, 5.68

5,7-Dimethylindolizine (5a). General Procedure.- ^{1}H-NMR Spectra of free bases could be conveniently recorded by dissolving the corresponding indolizinium perchlorate in pyridine-d_5 and filtering directly into the NMR vial. Alternatively, for preparative purposes, the purified indolizinium perchlorates were treated either with (i) aqueous sodium hydroxide, the indolizine was then extracted into CCl_4 or Et_2O which were dried and subsequently evaporated, or (ii) sodium methoxide in methanol followed by addition of CCl_4, azeotropic distillation of methanol, filtration of the precipitated $NaClO_4$ and final evaporation of CCl_4. Remarkable aromatic solvent-induced shifts were observed in the ^{1}H-NMR spectra in pyridine-d_5 and in CCl_4 containing

benzene-d_6. ^{1}H-NMR (CCl_4), δ (ppm) : 2.21 (3H, s, 7-Me), 2.41 (3H, s, 5-Me), 6.20 (1H, s, 6-H), 6.33 (1H, d, J = 3 Hz, 2-H), 7.07 (2H, broad s, 3- and 8-H).

1,7-Dimethyl-5-ethylindolizine (5b).- ^{1}H-NMR (CCl_4), δ (ppm) : 1.36 (3H, t, J = 7.5 Hz, CH_2Me), 2.27 (3H, s, 7-Me), 2.32 (3H, s, 1-Me), 2.69 (2H, q, J = 7.5 Hz, CH_2Me), 6.04 (1H, s, 6-H), 6.49 (1H, d, J = 3 Hz, 2-H), 6.93 (1H, d, J = 3 Hz, 3-H, and 1H, s, 8-H).

5-Ethyl-7-methylindolizine (5c).- ^{1}H-NMR (CCl_4), δ (ppm) : 1.33 (3H, t, J = 7.5 Hz, 5-CH_2Me), 2.23 (3H, s, 7-Me), 2.68 (2H, q, J = 7.5 Hz, 5-CH_2Me), 6.06 (1H, s, 6-H), 6.20 (1H, d, J = 3.5 Hz, 1-H), 6.65 (1H, t, J = 3.5 Hz, 2-H), 6.97 (2H, broad s, 3- and 8-H).

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