Tetrahedron Letters,Vol.28,No.27,pp 3145-3146,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

SYNTHESIS OF INDOLIZINES STARTING FROM PYRYLIUM SALTS [1]

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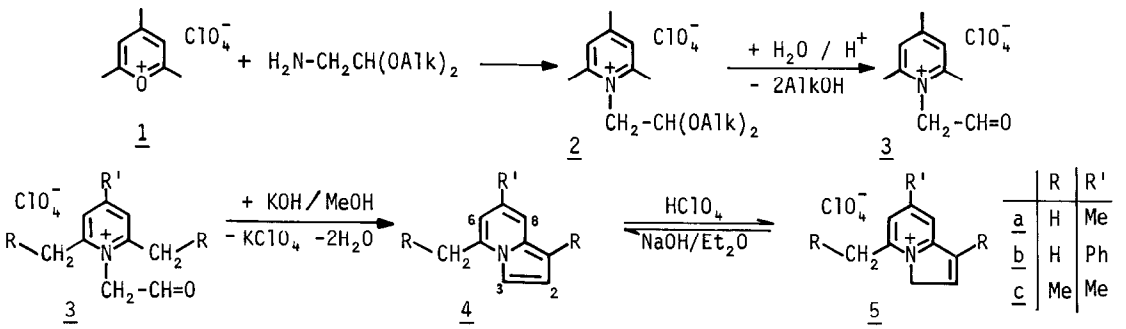
Abstract. *β-N-Pyridinium acetaldehydes with alkyl substituents in the 2 and 6 positions of the pyridinium ring, obtained from the corresponding pyrylium salts, cyclise in alkaline medium to new indolizines. This high-yield reaction sequence is optimal for indolizines unsubstituted in the five-membered ring which are difficultly accessible by other methods.*

From the reaction of pyrylium salts 1 with commercially available aminoacetaldehyde dialkylacetals, followed by acid hydrolysis of the crystalline pyridinium acetals 2, we obtained the new, crystalline pyridinium aldehydes 3. When these aldehydes have 2- and 6- alkyl substituents, a smooth conversion into the novel indolizines 4 can be effected by treatment with alkali hydroxides. Indolizines 4a-c[2] were isolated as 3*H*-indolizinium perchlorates 5a-c[3] :

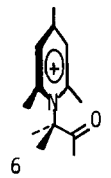


The initial pyrylium salts are readily accessible from inexpensive starting materials.[4] Experimental procedures[5] are straightforward ; the pyridinium salts 2 and 3 are obtained in nearly quantitative yields (90-99%) while the indolizinium perchlorates 5 are isolated in very good (>95% for 5a and 5b) or moderate yields (60% for 5c). Taking into account previous syntheses,[6] the present route appears to be optimal for indolizines unsubstituted in the five-membered ring. These compounds can not be obtained by the usual Chichibabin synthesis based upon quaternisation of pyridines with α-halo-carbonyl derivatives.

All new compounds gave satisfactory microanalyses; their UV, IR and ^{1}H-NMR spectra are in agreement with the structures given above. A striking feature of the ^{1}H-NMR spectra of all aldehydes 3 is the absence of coupling between the aldehydic and the vicinal methylenic protons. Previous ^{1}H-NMR studies[7] indicate that this coupling should be approximately 0.1 Hz if the substituted acetaldehyde is exclusively in the *s-cis (gauche)* conformation 6. One notes

the similar absence of coupling between the methylenic protons and the 2-proton of the 3*H*--indolizinium perchlorates 5a-c.[3,8]

Whenever a 2- or a 6-phenyl group is present in the pyrylium salt 1, the acetals 2 cyclise during the acid hydrolysis yielding quinolizinium salts 7 ; this reaction was described by Katritzky and coworkers[9] for 2,4,6-triphenyl-substituted analogs of 2 :



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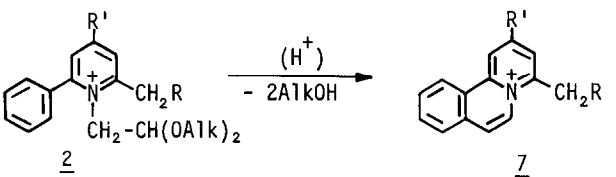

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References and Notes

1. Presented in part at the 6th IUPAC Conference on Organic Synthesis, Moscow, 1986.

2. ^{1}H-NMR data for indolizines 4 in CCl_4, δ(ppm), 4a : 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,1-H), 6.83 (1H,d,J=3 Hz,2-H), 7.07 (2H,broad s, 3- and 8-H) ; 4b : 2.56 (3H,s,5-Me), 6.73 (1H,s,6-H), 6.90 (1H,m,2-H), 7.20-7.70 (8H,m) ; 4c : 1.36 (3H,t,J=7.5 Hz,CH_2-Me), 2.27 (3H,s,7-Me), 2.32 (3H,s,1-Me), 2.69 (2H,q,J=7.5 Hz, CH_2-Me), 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).

3. Melting points (°C) and ^{1}H-NMR data for 3*H*-indolizinium perchlorates 5 in CF_3COOH, δ(ppm), 5a : 219-21° ; 2.69 (3H,s,7-Me), 2.83 (3H,s,5-Me), 5.28 (2H,s,3-H_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) ; 5b : 215-17° ; 2.83 (3H, s,5-Me), 5.25 (2H,s,3-H_2), 7.23 (1H,d,J=6.5 Hz,2-H), 7.3-7.7 (7H,m), 8.03 (1H,s,8-H); the 1*H*-tautomer is present in this case (25%) as shown by a peak at 4.16 ppm (1-CH_2) ; 5c : 118-20° ; 1.58 (3H,t,J=7.5 Hz,CH_2-Me), 2.36 (3H,d,1-Me), 2.78 (3H,s,7-Me), 3.13 (2H,q, J=7.5 Hz,CH_2-Me), 5.08 (2H,broad s,3-H_2), 7.12 (1H, broad s,2-H), 7.58 (1H,s,6-H), 7.70 (1H,s,8-H), an allylic coupling (1.5 Hz) exists between 1-Me and 2-H.

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5. Pyridinium salts 2 were prepared by adding dropwise aminoacetaldehyde dialkylacetals (0.1 mol) to a suspension of the pyrylium salt (0.1 mol) in dichloromethane. After the exothermal reaction subsided, the clear, deep red solution was stirred (5 hrs.) at room temperature, then the acetals 2 were precipitated with diethyl ether in 90-95% yield.
   Aldehydes 3 were obtained by treatment of acetals 2 with equimolar quantities of perchloric acid in acetic acid and refluxing the solution for 4 hrs. Precipitation with diethyl ether gave in 98-99% yield the pyridinium aldehydes.
   Cyclisation of aldehydes 3 was effected by treatment of their methanolic solution with an equimolar quantity of potassium hydroxide dissolved in methanol and heating at 30-60° for 5 or 10 hrs, depending on the 2- and 6- alkyl substituents (methyl or ethyl). Addition of charcoal and filtration of the inorganic potassium salt affords a clear solution from which 3*H*-indolizinium salts are precipitated by addition of perchloric acid and then diethyl ether. From perchlorates the free bases are liberated with aqueous sodium hydroxide.

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(Received in UK 13 April 1987)