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PRELIMINARY NOTE

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Synthesis of Indolizines from N-(2,2,2-Trifluoroethyl)-  
pyridinium Triflate; Evidence for the Generation of  
Pyridinium (Trifluoromethyl)methylide

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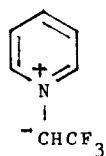
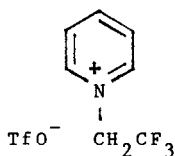
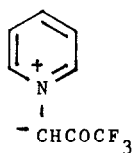
SUMMARY

Dimethyl 3-(trifluoromethyl)indolizine-1,2-dicarboxylate (4), 1,2,3-tris(trifluoromethyl)indolizine (5), and ethyl trans-2,3-bis(trifluoromethyl)-2,3-dihydroindolizine-1-carboxylate (7) have been obtained via treatment of N-(2,2,2-trifluoroethyl)pyridinium triflate (2) with a base (B) and dimethyl acetylenedicarboxylate [ $\longrightarrow$  4 (B = Et<sub>3</sub>N)] or perfluorobut-2-yne [ $\longrightarrow$  5 (B = K<sub>2</sub>CO<sub>3</sub>);  $\longrightarrow$  7 (B = Et<sub>3</sub>N)].

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\* To Whom enquiries should be addressed.

Published knowledge concerning the synthesis of indolizines carrying fluorinated substituents at the 3-position via reactions between fluorinated pyridinium methylides and dipolarophiles seems to be restricted to work with pyridinium (trifluoroacetyl)methylide (1) [1]. Noting that a bright yellow coloration indicative of methylide formation develops immediately when N-(2,2,2-trifluoroethyl)pyridinium triflate (2) dissolved



in dimethylformamide (DMF) or suspended in chloroform is treated with triethylamine, the procedure was repeated in the presence of dimethyl acetylenedicarboxylate (DMAD) as a dipolarophilic trap for the presumptive pyridinium (trifluoromethyl)methylide (3). Subsequent isolation of the new trifluoromethylated indolizine 4, albeit in low yield (11%), provided tangible evidence that  $\alpha$ -deprotonation of the pyridinium triflate (2) had occurred in classical fashion (see Scheme 1).\*

Potassium carbonate can also be used to trigger the involvement of N-(2,2,2-trifluoroethyl)pyridinium triflate

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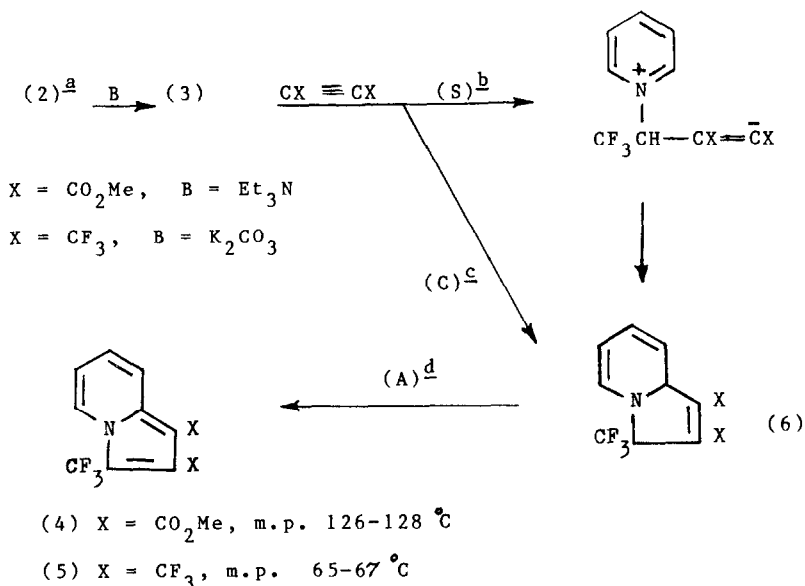
\* Exocyclic  $\alpha$ -deprotonation of quaternary pyridinium salts provides the commonest method for the production of pyridinium methylides [2].

(2) in 1,3-dipolar cycloadditions, as revealed by the isolation of 1,2,3-tris(trifluoromethyl)indolizine (5) (12% yield) from complex material obtained by shaking with perfluorobut-2-yne the yellow mixture produced by adding the triflate to a slurry of the anhydrous carbonate in DMF.

Attempts to isolate pyridinium (trifluoromethyl)methylide (3) have proved unsuccessful so far, and no light has yet been thrown on the actual mechanism [i.e. concerted vs stepwise (see Scheme 1)] of the 1,3-dipolar cycloaddition step involved in each of the reactions described above. Similarly, no information is available yet on the mode of oxidation of the presumptive dihydroindolizinic (6) precursors of 4 and 5 (Scheme 1).<sup>\*\*</sup> Progress in the last area hopefully may be possible through plans to pursue the discovery that treatment of N-(2,2,2-trifluoroethyl)pyridinium triflate (2) in chloroform with triethylamine followed by perfluorobut-2-yne (20 °C for 7 days then ca. 65 °C for 3 hours) gave a complex mixture from which only ethyl trans-2,3-bis(trifluoromethyl)-2,3-dihydroindolizine-1-carboxylate (7) could be isolated (16% yield). A plausible mechanism for the formation of 7 is shown in Scheme 2; the ethanol required was present as a stabilizer in the chloroform used as the reaction medium.

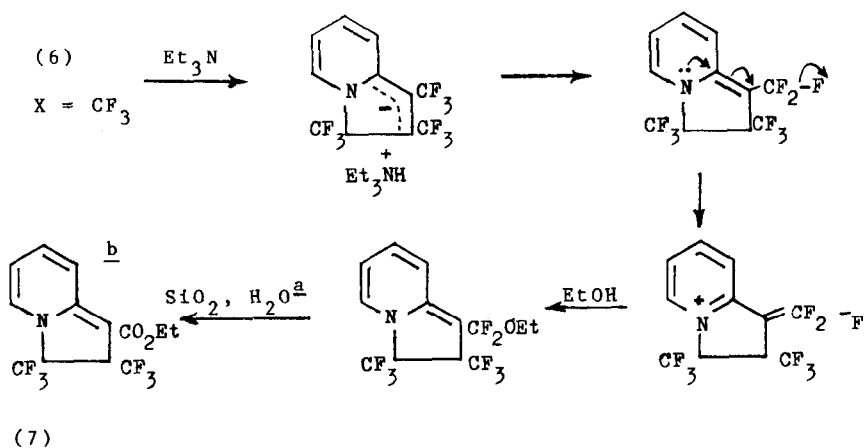
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<sup>\*\*</sup> See ref. 3 for relevant discussion of the mechanism of formation of indolizines via 1,3-dipolar cycloadditions of the type described here.



a From CF<sub>3</sub>SO<sub>2</sub>CH<sub>2</sub>CF<sub>3</sub> + Pyridine (90% yield); m.p. 50-52 °C.  
b Stepwise. c Concerted. d "Spontaneous" aromatization.

Scheme 1



a Dry-column flash chromatographic work up.  
b The CF<sub>3</sub> groups were shown to be trans disposed by X-ray crystallography.

Scheme 2

Correct elemental analyses [C,H,F and N except in the case of the triflate (2), where F was not determined] and spectroscopic data (i.r., n.m.r., mass) consistent with structures assigned were obtained for compounds 2, 4, 5 and 7.

The structure of the dihydroindolizine (7) was established absolutely by X-ray crystallography, the analysis being carried out by Dr. R. G. Pritchard (UMIST), to whom we are extremely grateful. We are also indebted to the Iraqi Ministry of Higher Education and Science for the award of a Scholarship (to S. N. M.).

- 1 R. E. Banks and S. N. Mohialdin, *J. Fluorine Chem.*, 34 (1986) 275.
- 2 I. Zugrăvescu and M. Petrovanu, 'N-Ylid Chemistry', McGraw-Hill: New York, 1976, p 156.
- 3 R. E. Banks, R. G. Pritchard, and J. Thomson, *J. Chem. Soc., Perkin Trans. I*, (1986) 1769.