A SIMPLE ROUTE TO INDOLIZINE-2-CARBOXYLATES. CYCLOADDITION REACTIONS OF PYRIDINIUM ARYLSULPHONYLMETHYLIDES.

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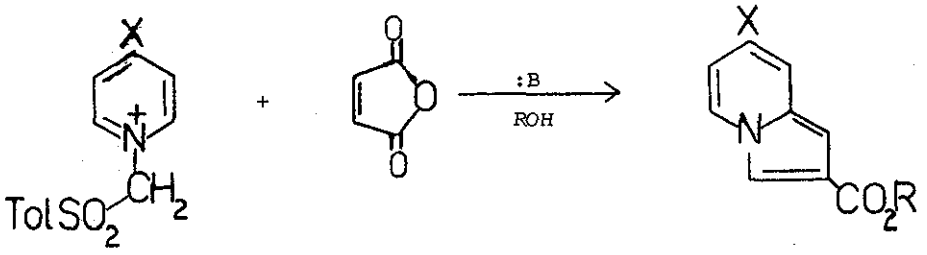
Pyridinium-p-toluenesulphonylmethylides react with maleic anhydride in the presence of alcohols to give indolizine-2-carboxylates in a process involving selective decarboxylation and aromatization, and with phenylcyanoacetylene to give 1-cyano-2-phenylindolizines.

The 1,3-dipolar cycloaddition of pyridinium arylsulphonylmethylides with dimethyl acetylenedicarboxylate has been described recently[1] and led to the formation of 1,2-dimethoxycarbonylindolizines. Reaction with methyl propiolate gave the 1-methoxycarbonylindolizine. We now report the synthesis of indolizine-2-carboxylates via a novel route.

Reaction of 4-benzoyl-1-p-toluenesulphonylpyridinium trifluoromethanesulphonate (1; X=COPh) with maleic anhydride in the presence of triethylamine

or DBU in chloroform containing ethanol gave 7-benzoyl-2-ethoxycarbonyl-indolizine (2; X=COPh, R=Et)(34.4%), m.p. 145-147°.[2] A similar reaction carried out in methylene chloride containing methanol gave 2 (X=COPh, R=Me) (60%), m.p. 205°. The orientation of the carboxyl function was established by the hydrolysis of dimethyl 7-benzoylindolizine-1,2-dicarboxylate[1] with alcoholic KOH to give 7-benzoylindolizine-2-carboxylic acid, m.p. 262° (decomp.), identical with the acid obtained from 2 (X=COPh, R=Et), and was esterified to 2 (X=COPh, R=Me or Et). It is known[3] that carboxyl groups in the 1- and 3-positions of indolizine are labile. The methyl ester was different from the 1-carboxylate obtained previously.[1] 4-Cyano-1-p-toluene-



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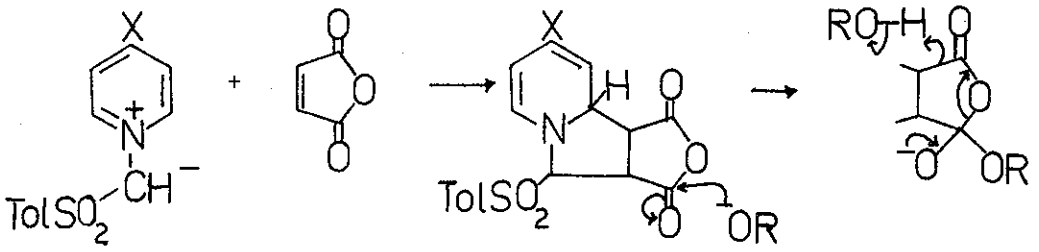
sulphonylpyridinium triflate (1; X=CN) similarly gave 2 (X=CN, R=Me), m.p. 205° (26%), but the yield of 2 (X=H, R=Et) from 1 (X=H) was very low. It seems as though an electron-withdrawing substituent in the pyridine ring is required to give respectable yields of 2. The nature of the products formed in the absence of an electron-withdrawing substituent is under investigation.

A possible mechanism for the formation of 2 would involve a cycloaddition of maleic anhydride to the ylide (3) to give a tetrahydroindolizine, followed

by attack by the alcohol at the C_2 carbonyl, decarboxylation of the C_1 carboxyl, elimination of toluenesulfinic acid and aromatization.[4] Alternatively, Michael addition of 3 to the anhydride would give 5 which would



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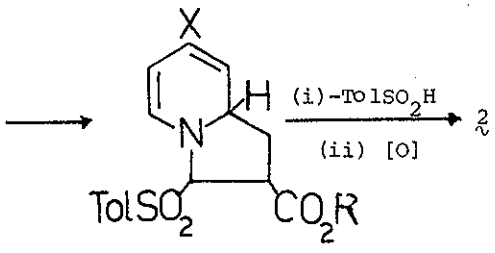

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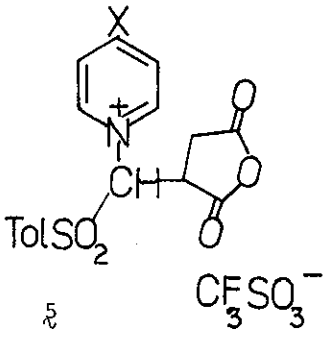

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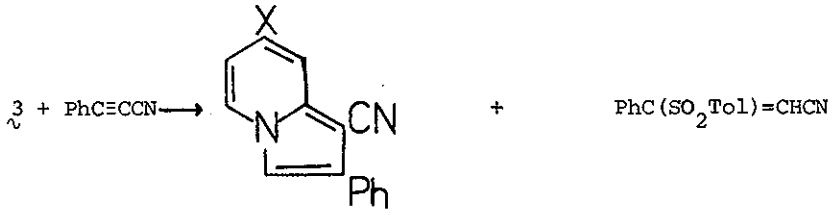
then react with alcohol at the more hindered carbonyl group of the maleic anhydride.[5] Decarboxylation and cyclization would then give 4. This stepwise addition and cyclization could account for the observed need for an electron-withdrawing substituent in the pyridine ring.

The ylides (3; X=COPh, Me, CN, H and 3,5-Me_2) and phenylcyanoacetylene give 1-cyano-2-phenylindolizines (6)[2] in moderate yields and β-p-toluenesulphonylcinnamonitrile (7), m.p. 114°.



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