

THE FORMATION OF ACYLIMINO-DERIVATIVES OF INDOLES AND PYRROLES
BY REACTIONS WITH NITRILIUM SALTS

Stephen C. Eyley,^a Robert G. Giles,^b and Harry Heaney^{b*}

(a) Research and Development Laboratories, Fisons plc, Pharmaceutical Division,
Loughborough, Leicestershire, LE11 0RH

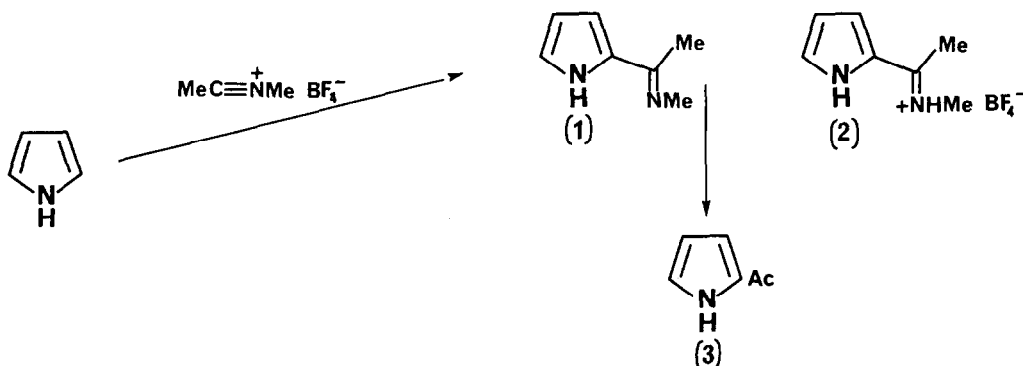
(b) Department of Chemistry, The University of Technology,
Loughborough, Leicestershire, LE11 3TU

Summary: N-Methylnitrilium fluoroborates are prepared rapidly by warming trimethyloxonium fluoroborate with a slight excess of the nitrile, subsequent addition of indoles and pyrroles at low temperatures (-50° to -20°) gives iminium salts (and hence ketones) in high yields.

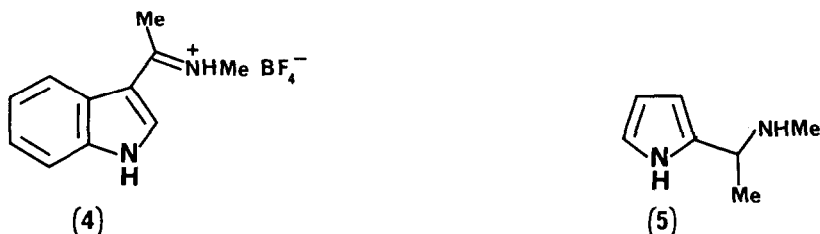
Although 2-acetylpyrrole¹ and 1,3-diacetyl-² or 3-acetyl-³ indole can be prepared by the reaction of acetic anhydride with pyrrole and indole respectively, high yields of C-acylated products can only be obtained by indirect methods.⁴ Thus, the well known reactions of pyrrol-⁵ and indolyl-⁶ magnesium chlorides with acyl halides have been improved by recent methodology in which 2-pyridylthiol esters have been shown to give 2-acylpyrroles in yields of 80 to 95%.⁷ The reactions of nitriles with both pyrroles and indoles in the presence of hydrogen chloride also result, after hydrolytic work-up, in the formation of acceptable yields of C-acylated products.^{8,9} We now report some of our results of reactions of nitrilium salts with pyrrole and indole and some of their derivatives.

Nitrilium salts have been prepared by a number of methods, including most recently by the interaction of alkyl chloroformates with Lewis acid complexes of nitriles.¹⁰ However, we have observed that N-methylacetoneitrilium fluoroborate is conveniently prepared in almost quantitative yield by allowing an excess of acetonitrile to react with trimethyloxonium fluoroborate at room temperature for about 15h. Other N-methylnitrilium fluoroborates were prepared rapidly and in reasonable yields (ca. 75%) by warming trimethyloxonium fluoroborate with a slight excess of the nitrile until the evolution of dimethyl ether ceased. In this way we were able to obtain salts from propionitrile, butyronitrile, and benzonitrile. Although commercially available, we prefer to make fresh batches of trimethyloxonium fluoroborate by passing dimethyl ether into a solution of dimethoxycarbenium fluoroborate in dichloromethane.¹¹

The addition of a solution of pyrrole in dichloromethane to *N*-methylacetoneitrilium fluoroborate suspended in dichloromethane at room temperature, was accompanied by a pronounced exotherm and the *N*-methyl-imine (1)¹² was isolated in 23% yield after treatment with water and basification of the aqueous solution. When the addition was carried out at -30° and the solution was stored at -20° for 16h the imine (1) and the fluoroborate salt (2) were isolated in 16% and 78% yield respectively. The salt (2) was converted into the imine (1) in almost quantitative yield using cold aqueous (2M) sodium hydroxide and when the imine (1) was heated under reflux with aqueous sodium acetate, 2-acetylpyrrole (3) was isolated in 92% yield.



The reaction of indole with *N*-methylacetoneitrilium fluoroborate in dichloromethane, initially at -50°, then at -20° for 24h, resulted in the formation of the red salt (4) [λ_{max} 249 ($\log_{10} \epsilon$ 4.24), 264 (4.24), and 328 (4.45) nm] in 95% yield. Whereas a red colour developed in the above reaction immediately on mixing, no colour was seen when mixing was carried out at -70°.



It is clear, therefore, that although no attempt has been made to optimise the yields in the reactions studied the best temperatures to use will be near to those now reported. The generality of these reactions is indicated by the fact that good yields of iminium salts have been obtained from reactions with a number of derivatives of pyrrole and indole as well as from reactions with *N*-methylnitrilium salts derived from benzonitrile, propionitrile, and butyronitrile. The details of the yields obtained are given in the TABLE. We were surprised to find that no reaction was observed between indole and *N*-2,6-dimethylphenylacetoneitrilium fluoroborate (prepared by the thermolysis of 2,6-dimethylbenzenediazonium fluoroborate in acetonitrile) and 2,6-dimethylacetanilide was isolated after treatment of the reaction mixture with water.

In some of the entries in the TABLE we indicate that the imine is isolated in addition to the iminium salt. The amount of each compound obtained depends on the solubility of the iminium salt in dichloromethane: in two reactions of pyrrole with N-methylacetoneitrilium fluoroborate we isolated the imine (1) and the iminium salt (2) in 16 and 78% and 5 and 89% yields respectively. In the reaction of pyrrole with N-methylpropionitrilium fluoroborate the iminium salt was completely soluble in the amount of dichloromethane used but the expected imine was isolated in 97% yield and gave after Kugelrohr distillation pure crystalline imine in 86% yield. These results indicate that the imine can be isolated in excellent yields if it is the required product.

TABLE

Heterocycle	Nitrilium Salt	Iminium Salt (%) [§]	Imine (%) [§]	Ketone (%) ^{§*} (after hydrolysis)
	[R-CN-Me] ⁺ [BF ₄] ⁻			
1. Pyrrole	R = Me	78	16	92
2. Pyrrole	R = Me	89	5	
3. Pyrrole	R = Et	-	97	66
4. Pyrrole	R = Pr	-	83	84
5. Pyrrole	R = Ph	78	8	58
6. 2,5-Me ₂ -pyrrole	R = Me	90	-	68
7. Indole	R = Me	95	-	56
8. Indole	R = Et	63	35	63 [¶]
9. Indole	R = Pr	77	-	72
10. Indole	R = Ph	90	-	99
11. 1-Me-indole	R = Me	70	-	71
12. 2-Me-indole	R = Me	82	8	86
13. 3-Me-indole	R = Me	33	34	41
14. 2-Ph-indole	R = Me	72	-	67
15. 1-PhCH ₂ -indole	R = Me	81	-	67
16. 1,2-Me ₂ -indole	R = Me	70	-	84

[§] No attempt has been made to optimise the yields in these reactions. The orientation of the substituent is as expected, that is with the exception of 2,5-dimethylpyrrole and 3-methylindole the imino-group is located at the 2-position in the pyrrole and at the 3-position in the indole.

* The yields of ketones reported are for products recrystallised to high purity.

[¶] Yield based on a "one pot reaction" starting from trimethyloxonium fluoroborate without the isolation of any other intermediate.

In a "one pot reaction" without isolation of the iminium salt, the interaction of pyrrole with N-methylacetoneitrilium fluoroborate was followed by heating under reflux with aqueous sodium acetate, giving 2-acetylpyrrole in 80% yield after recrystallisation to constant melting point.

Our results show that a wide range of acyl-pyrroles and -indoles can be prepared in excellent yields and it is clear that the imines and iminium salts are themselves suitable substrates for conversion into a variety of other products. Thus, the iminium salt (2) was reduced by means of sodium borohydride in methanol and gave the amine (5) in 65% yield.

We are currently extending this work by using other derivatives of indole and pyrrole as well as by the use of other nitrilium salts in order to obtain desirable target molecules.

We thank Fisons plc (Pharmaceuticals Division) and the SERC for a research training award under the CASE scheme (to R.G.G.).

References and footnote

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12. Satisfactory microanalytical and spectral data are available for all of the new compounds described. Some of the imines and their salts exist as mixtures of diastereoisomers and they have not been separated, at this time.

(Received in UK 1 July 1985)