Methylthio Activating Groups in the Synthesis of Isoquinolines

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Methylthio activating groups have been found to improve the yields in six different isoquinoline syntheses: in four cases the improvement was from zero, in the unactivated system, to between 54 and 94%.

Most of the widely used syntheses of isoquinolines proceed by acid-catalysed attack of a suitable functionalised *N*-substituted phenethylamine or benzylamine on the benzene ring of the amine. They are thus representative of a wider range of reactions proceeding by electrophilic attack on an aromatic system, many of which are dependent on the presence of suitably placed electron-donating substituents. In the absence of activating groups, reactions of the last kind either fail completely, at temperatures below the decomposition point of the starting material, or give relatively poor yields under forcing conditions.

The most widely used activating group in the synthesis of isoquinolines has been the methoxy group, which is difficult to remove after cyclisation and is therefore not desirable where the unsubstituted ring is required. Methylthio appeared to be a suitable alternative, which would lend itself to removal by reductive desulphurisation. The activating potential of methylthio in this kind of reaction has been established in the benzylaminonitrile rearrangement.[1]

It was an important preliminary to this work that we should find a convenient synthesis of 3-methylthiobenzaldehyde,[2] from which all the phenethylamines and benzylamines used as intermediates are derived. All the starting materials were prepared from this aldehyde by variations of the literature methods used for the methoxy analogues.[3,4]

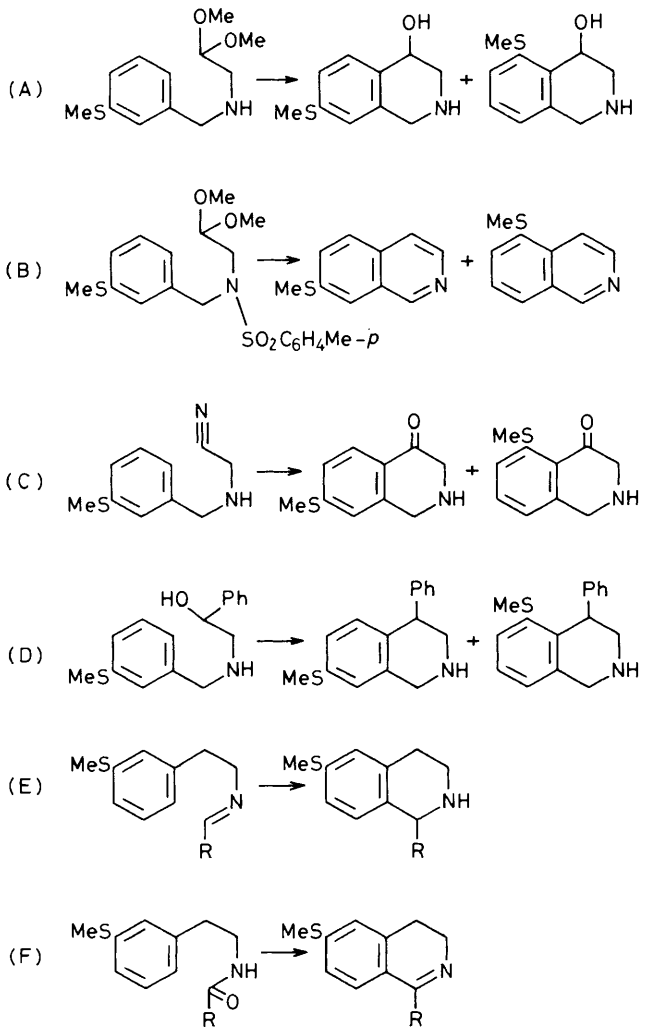
The types of cyclisation chosen for investigation were those which we have found to be reliable with the methoxy analogues: they are detailed in Scheme 1 as reactions (A)—(F). Where possible reaction conditions were as described in the original literature for the methoxy analogues; any variations or innovations are detailed in footnotes to Table 1. The use of anhydrous hydrogen fluoride in place of concentrated sulphuric acid for the benzylaminonitrile [reaction (C)] was particularly beneficial and is also useful for the methoxy analogue.[5]

It may be noted that, compared to the results in Table 1, reactions (A)—(C) and (E) do not give any cyclisation products[6—10] in the absence of an activating group. The

Table 1. The results and conditions for reactions (A)—(F).

			Isomer composition[g] (isolated yield)[h]/%			
Cyclisation[a]	Cyclising agent	Crude yield/%	*ortho*	M.p. (°C)	*para*	M.p. (°C)
(A)	HCl	91[b]	37 (7)	138—140	49 (32)	102
(B)	HCl	54	7 (4)	oil	47 (33)	46—47
(C)	H_2SO_4	13	7.5 (2[j])		5.5[i]	
	HF[c]	76	69 (51[j])	182—185[j]	7[i]	
(D)	PPA[d]	88	42 (6[j])	169—174[j]	46 (24[j])	203—208[j]
	TFA[e]	79	37		42	
	HF[f]	78	38		40	
(E) R = 1-Ph	TFA	94	—		94 (75)	79—80
R = 1-H	HCl	58	—		58 (51[j])	230—235[j]
(F) R = 1-Ph	$POCl_3$	89	—		89 (64[k])	166—169[k]
R = 1-H	$POCl_3$	21	—		21 (15[k])	147—151[k]

[a] For the methoxy analogues of (A), see refs. 6, 7; (B), ref. 8; (C), refs. 9, 10; (D), ref. 13; (E), ref. 14 (Ph), 15 (H); (F), ref. 16 (Ph), 17 (H). [b] 4-Hydroxytetrahydroisoquinolines (ref. 6). [c] Room temp., 20 days. [d] PPA = polyphosphoric acid, 75—80 °C for 1 h. [e] TFA = trifluoro acetic acid, reflux, 7 h. [f] Room temp., 18 h. [g] Determined by gas chromatography or ^{1}H n.m.r. spectroscopy. [h] For identification purposes only: no attempt was made to optimise isolation procedures. [i] Identified by reduction and comparison with the product from reaction (A). [j] Hydrochloride. [k] Hemioxalate.



Scheme 1

Pictet–Spengler reaction [(E), R = Ph] was recently reported to succeed without activation,[11] but in our hands only starting materials were obtained.

We have desulphurised several of our cyclic products by treatment with nickel boride in yields of between 84 and 93%. The method, which is basically that of Truce and co-workers,[12] also reduces ketones to alcohols. In the present series of compounds the crude product from reaction (D), *i.e.* the mixture of methylthio-4-phenyltetrahydroisoquinolines, gave clean 4-phenyl-1,2,3,4-tetrahydroisoquinoline in 84% yield, using a molar ratio of organosulphur compound : nickel chloride : sodium borohydride of 1 : 10 : 30. Provided that sufficient nickel boride was formed the ratios were not critical. In some cases a basic product was adsorbed on the catalyst and was best liberated by dissolution in dilute hydrochloric acid followed by basification with ammonia to form the nickel complex before extraction with chloroform. With this modification applied when required, no desulphurisation has as yet failed. Some of the other compounds which have been desulphurised are as follows (product and percentage yield in brackets): 4-methylthiobenzaldehyde (benzyl alcohol, 94%), *N*-methyl-4-methylthiobenzylamine (*N*-methylbenzylamine, 91%), 3-(4-ethylthiobenzoyl)-3-methyl-1,2,3,4-tetrahydroisoquinoline[1] [3-(α-hydroxybenzyl)-3-methyl-1,2,3,4-tetrahydroisoquinoline, 91%], 4-(4-methylthiophenyl)-3-imidazoline-5-spirocyclohexane[1] (5-phenylimidazoline-4-spirocyclohexane, 92%), 4-(4-methylthiophenyl)-1,5,5-trimethyl-3-imidazoline[1] (5-phenyl-3,4,4-trimethylimidazoline, 93%). The imidazolines underwent a double-bond shift which will be discussed elsewhere.

Since the activating group is removed later it does not matter whether cyclisation proceeds *ortho* or *para*, but it is interesting to note the variation in the proportions of the two isomers. The benzylamines gave proportionately more material from cyclisation *ortho* to the activating group than the phenethylamines: in one case the *ortho* product [reaction (C) with hydrogen fluoride] predominated.

We thank the S.E.R.C. for an award (to M. R. E.).

Received, 7th October 1983; Com. 1329

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