Novel Synthesis of Isoquinolin-3-ols

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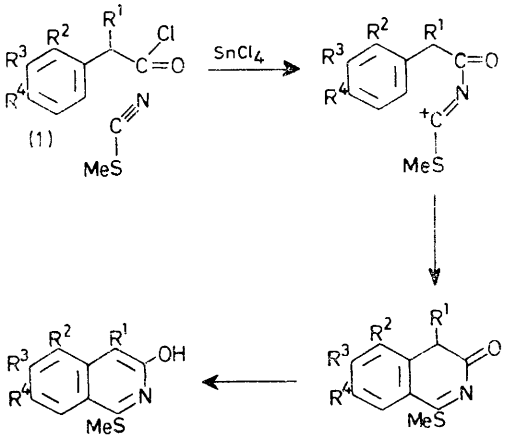
Summary Reaction of phenacetyl chlorides with alkyl or aryl thiocyanates in the presence of a Friedel–Crafts catalyst yields 1-substituted-isoquinolin-3-ols.

DERIVATIVES of isoquinolin-3-ol have previously been prepared by the cyclisation of *o*-acylphenylacetic acids with ammonia or amines,[1] the acid-catalysed cyclisation of *o*-cyanophenacyl halides,[2] and the diazotisation of 3-aminoisoquinoline obtained by the acid-catalysed cyclisation of *o*-cyanobenzyl cyanide.[3] These syntheses all involve the use of intermediates which are not easily accessible and so their scope is limited. We report a novel reaction which, although somewhat restricted in its versatility in that the isoquinolin-3-ol produced has a 1-alkylthio- or 1-arylthio-substituent, nevertheless provides a convenient route to many hitherto inaccessible compounds.



(1)

	R1	R2	R3	R4
a;	H	H	H	OMe
b;	H	H	OMe	H
c;	H	H	OMe	OMe
d;	H	H	H	Me
e;	H	H	Me	H
f;	H	Me	H	H
g;	Me	H	H	H

The reaction of phenethyl chloride with alkyl and aryl cyanides under Friedel–Crafts conditions to yield 1-substituted-3,4-dihydroisoquinolines is well documented[4] but we could find no reference to such a reaction with a phenacetyl chloride to yield an isoquinolin-3-ol, and in our hands no such reaction could be achieved between phenacetyl chloride and either acetonitrile or benzonitrile. In some experiments the amide corresponding to the nitrile was recovered but in the majority of experiments the product was an intractable tar. Either the phenacetylnitrilium ion does not form, or is so reactive that tars result. Reactions were achieved with methyl thiocyanate and phenyl thiocyanate and we rationalise this by suggesting that the powerful electron donating alkylthio- or arylthio-group stabilizes the phenacetylnitrilium ion to the extent that intramolecular ring closure can take place.

Phenacetyl chloride and its derivatives, (**1a**—**g**), and α- and β-naphthylacetyl chloride have all been cyclised to the corresponding 1-methylthioisoquinolin-3-ols. Indol-3-yl acetyl chloride likewise cyclised to 3-hydroxy-1-methylthiopyrido[3,4-*b*]indole. Nitrobenzene is the preferred solvent and anhydrous $SnCl_4$ the preferred catalyst. Yields vary from 10 to 65% but only in the case of phenacetyl chloride itself has any effort been made to maximise the yield (65%). The reaction failed with diphenylacetyl chloride, fluoren-2-ylacetyl chloride, and fluoren-9-ylacetyl chloride.

The reaction of cyanogen chloride with phenacetyl chloride was interesting in that the only isolable product was 3-amino-1-chloroisoquinoline (38% yield).

The MeS group in the above compounds is cleanly oxidised with monoperoxyphthalic acid to $MeSO_2$ and is then susceptible to nucleophilic replacement by primary and secondary amines, and cyanide, and azide ions.

All novel compounds reported have i.r., ^1H n.m.r., and mass spectra in accordance with the structures proposed.

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