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HETEROCYCLES FROM ISOCYANIDES, II [1]

A NEW INDOLE SYNTHESIS

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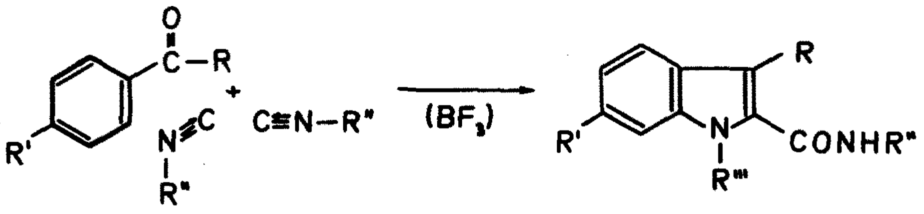
The reaction of a series of ketones with isocyanides in the presence of Lewis acids has been described in recent papers (1, 2). These investigations led to the synthesis of amides of alkenylglyoxylic acids (2) and indolenine-2-carboxanilides (1).

We now wish to report the formation of indole derivatives by treatment of aromatic ketones with t-butyl isocyanide. In this reaction, two molecules of the isocyanide always react with one molecule of the ketone. For example, when benzophenone is stirred with t-butyl isocyanide (3) in the presence of boron trifluoride for about thirty minutes at 0°C, 1-t-butyl-3-phenyl-indole-carboxylic acid-t-butyl amide (I) may be isolated by column chromatography. The ultraviolet spectrum of I shows the typical maxima of an indole system: λ_{max} (ε) = 225 (30, 000) and 283 nm (10, 000) in ethanol. The infrared spectrum of I in KBr shows characteristic bands at 3300 (NH), 1630 (amide I), 1550 (amide II) and 1450 cm^{-1}.

The mass spectrum (4) and the NMR spectrum (t-butyl groups at τ = 8.12 and 8.85, NH at τ = 4.52, and nine aromatic protons between τ = 2.2 and 2.9) are also in accord with the proposed structure I.

The use of benzoin as a reactant leads to the formation of the 3-benzoyl derivative (II) which shows an additional carbonyl band in the infrared at 1675 cm^{-1}.



I - V

R" = tert-butyl

	R	R'	R'''		m.p.[°C]
I	C_6H_5	H	$t\text{-}C_4H_9$	$C_{23}H_{28}N_2O$	178 - 179
II	COC_6H_5	H	$t\text{-}C_4H_9$	$C_{24}H_{28}N_2O_2$	159 - 160
III	CH_3	H	H	$C_{14}H_{18}N_2O$	199 - 200
IV	CH_3	C_6H_5	H	$C_{20}H_{22}N_2O$	237 - 238
V	CH_3	Cl	H	$C_{14}H_{17}N_2OCl$	192 - 193

We have also investigated this reaction with three acetophenones which would be expected to form products analogous to I and II but which gave products III - V (5) probably by BF_3-induced loss of isobutylene from the indole nitrogen in an additional step. In the acetophenone series, we have been unable to isolate a product with the t-butyl group still attached to the indole nitrogen.

This isocyanide reaction offers a simple synthesis of the indole skeleton under very mild conditions (0°C). The yields vary between 15 and 40% and are influenced by the ketone/isocyanide ratio and the nature of the ketone itself. It might be possible to introduce substituents into positions 4, 5, and 7 of the indole nucleus by using suitable aromatic ketones.

Applications of this indole synthesis are now being investigated in more detail in this laboratory.

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References

(1) Part I. B. Zeeh, Angew. Chem. **79**, 415 (1967).

(2) E. Müller and B. Zeeh, Tetrahedron Letters **1965**, 3951; Liebigs Ann. Chem. **696**, 72 (1966).

(3) I. Ugi and R. Meyr, Chem. Ber. **93**, 239 (1960).

(4) A detailed discussion of the mass spectra of all the indole derivatives will be part of a subsequent paper.

(5) All new compounds were fully characterized in terms of infrared, ultraviolet, NMR and mass spectra and gave correct elemental analyses.