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Formation of *N*-Alkylamides from Nitriles, Alcohols and Boron Trifluoride

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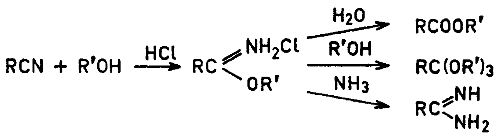
The addition of alcohols to nitriles in presence of Lewis acids was studied. *N*-Alkylamides, *e.g.* *N*-*tert*-butylphenylglyoxylamide, were formed in good yields using a secondary or tertiary alcohol and boron trifluoride. No detectable amounts of secondary or tertiary alkyl esters could be isolated.

Alcohols are known to react with nitriles in acidic medium. Imidates, ortho esters, esters, unsubstituted amides, and *N*-substituted amides are formed. Primary, secondary, and tertiary alcohols react differently and moreover the choice of acid is also a product determining factor.

Primary alcohols and nitriles, when treated with hydrogen chloride,[1] give imidates, which are useful intermediates in the preparation of esters,[2] ortho esters,[2] and amidines.[3] Tertiary alcohols do not form imidates with nitriles and hydrogen chloride, but are dehydrated to unsaturated compounds.[4] Primary alcohols and nitriles do not react in the presence of sulfuric acid, but both secondary and tertiary alcohols react to yield *N*-alkylamides.[5,6] Using a Lewis acid such as boron trifluoride primary alcohols and nitriles yield esters *via* ortho esters.[7]



$$\mathrm{RCN} + \mathrm{R'OH} \xrightarrow{\mathrm{HCl}} \mathrm{RC}\begin{smallmatrix}\nearrow \mathrm{NH_2Cl} \\ \searrow \mathrm{OR'}\end{smallmatrix} \begin{matrix}\xrightarrow{\mathrm{H_2O}} \mathrm{RCOOR'} \\ \xrightarrow{\mathrm{R'OH}} \mathrm{RC(OR')_3} \\ \xrightarrow{\mathrm{NH_3}} \mathrm{RC}\begin{smallmatrix}\nearrow \mathrm{NH} \\ \searrow \mathrm{NH_2}\end{smallmatrix}\end{matrix} \qquad (1)$$

This report deals with the reaction of nitriles and secondary or tertiary alcohols in the presence of Lewis acids, a reaction not described in literature. Different nitriles were treated with tertiary butyl alcohol and Lewis acids, *viz.* boron trifluoride, aluminium chloride, or zinc chloride. No formation of esters or imidates was noted, but with boron trifluoride the corresponding *N*-*tert*-butylamides were isolated, often in very good yields, 80–90 %, *cf.* Table 1. Aluminium chloride and zinc chloride proved to be less effective

Table 1.

	N-Alkylamide	M.p. or b.p.	M.p. or b.p. lit.	Yield %
I	$CH_3CONHC(CH_3)_3$	m.p. 97–98°	m.p. 98°[a]	85
II	$CH_2{=}CHCONHC(CH_3)_3$	m.p. 126–129°	m.p. 126–128°[b]	88
III	$C_6H_5CONHC(CH_3)_3$	m.p. 134–135°	m.p. 133.5–134°[c]	92
IV	$C_6H_5COCONHC(CH_3)_3$	m.p. 80–81°	[d]	72
V	$CH_3CONHCH(CH_3)C_2H_5$	b.p. 115–116°/ 16 mm	b.p. 119°/18 mm[e]	65

[a] Ritter, J.J. *U.S. Pat.* 2,573,673. [b] Plaut, H. and Ritter J.J. *J. Am. Chem. Soc.* **73** (1951) 4067. [c] Prajsnar, B. and Troszkiewiez, C. ***Roszniki** Chem.* **36** (1962) 853; *Chem. Abstr.* **59** (1963) 504. [d] Not earlier prepared. [e] White, E.R. *J. Am. Chem. Soc.* **77** (1955) 6008.

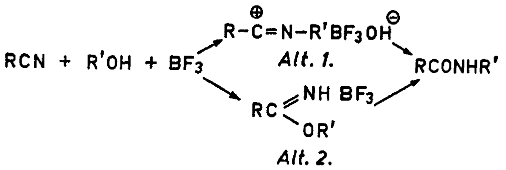
Melting points were determined on a Kofler hot stage microscope. The IR spectra of the compounds I–V were recorded on a Perkin Elmer 421 spectrophotometer, and the NMR spectra were run on a Varian A-60 spectrometer at 60 Mc/s. Elemental analysis of compound IV: Found C 70.49; H 7.37. Calc. for $C_{12}H_{15}NO_2$ (205.25): C 70.22; H 7.37. The analysis was carried out by Alab, Uppsala Sweden. The purity of compound V was confirmed by VPC using a F&M Research Chromatograph 810 fitted with a 15 ft. 10 % Carbowax 20M on 60–80S column.

acids in this case. The method provides a mild and efficient route to *N*-alkylamides, which can be readily hydrolyzed to give tertiary amines.

Boron trifluoride, boron trifluoride etherate, and the nitrile:boron trifluoride (1:1) complex[8,9] all proved to be useful in the reaction. Generally the methods using gaseous boron trifluoride or the nitrile:boron trifluoride complex gave better yields. If tertiary butyl alcohol was replaced by secondary butyl alcohol, the reaction proceeded in a lower yield, about 65 %. Using a primary alcohol in excess — 3 moles per mole of nitrile — the corresponding ester was isolated.[7] When only one equivalent of primary alcohol was used, no reaction was noted.

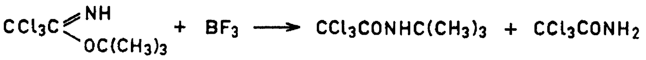
Two mechanisms for the reaction are possible. One proceeding *via* an initial attack of a carbonium ion on the nitrile nitrogen, the other *via* an intermediary imidate rearranging into the *N*-alkylamide.

There is support for both routes. *N*-Alkyl nitrilium ions, as formed according to the first mechanism, are also proposed intermediates in the Ritter reaction[5,6] using nitrile, tertiary alcohol and sulfuric acid. Moreover, alkylation of nitriles by trialkyl oxonium fluoborates give *N*-alkyl nitrilium salts.[10]



(2)

The mechanism *via* intermediary imidates suggested as an alternative route includes an acid catalyzed nucleophilic attack on the nitrile carbon. A similar attack is known from the Houben-Hoesch synthesis, where the nucleophile is an aromatic ring. An example of the assumed rearrangement of *O-tert*-alkyl imidates into *N-tert*-alkylamides is described in literature.[11] The only *O-tert*-alkylimidate listed, *viz.* that of trichloroacetonitrile gives the corresponding amide, when treated with boron trifluoride.[11]



$$CCl_3C\begin{matrix}\nearrow NH\\ \searrow OC(CH_3)_3\end{matrix} + BF_3 \longrightarrow CCl_3CONHC(CH_3)_3 + CCl_3CONH_2 \qquad (3)$$

The possibility that a conversion of the intermediary nitrilium salts or imidates into amides occurs during the isolation of products has been considered. However, it was rejected since *N*-alkylamides were also the product when the reaction mixture was treated with liquid ammonia. Nitrilium salts or imidates should have given *N*-alkylamidines [11] or unsubstituted amidines,[3] respectively. The infrared spectrum of the reaction mixture, taken after evaporation of solvent, was in accordance with that of an amide as boron trifluoride complex.[12]

EXPERIMENTAL

A two-necked flask (100 ml) equipped with a gas inlet tube, a magnetic stirrer, and a drying tube was charged with the nitrile (0.10 mole) and the alcohol (0.30 mole). At 0° boron trifluoride (0.12 mole) was slowly bubbled into the solution with stirring. The colourless, viscous mixture formed was stirred for another 12 h at 20°. Methylene chloride or ether (100 ml) was added and the mixture was neutralized by sodium hydroxide (5 M) or triethylamine followed by the addition of water. After separation of the two layers, extraction with an additional 20 ml of methylene chloride was made. The combined organic layers were washed three times with water saturated with sodium chloride. After drying over sodium sulfate, and removal of solvent, a crystalline residue was collected. The product was purified by recrystallization or sublimation.

As an alternative to gaseous boron trifluoride, its diethyl etherate was used. In this case the mixture had to be refluxed for 10 h for a complete conversion of nitrile to amide.

As a third alternative the 1:1 complex of acetonitrile and boron trifluoride [10] (0.10 mole) was added to *tert*-butyl alcohol (0.30 mole) under inert athmosphere. After stirring for 10 h at 20° the product was isolated as described above.

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