Synthesis of Secondary Amides in Absence of Internal Catalysis

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A new modification of the Ritter reaction is reported wherein no internal catalysis is used to promote the reaction. A tertiary alkyl bromide (RBr) and a nitrile (R^1CN) are refluxed for 24 hr with the subsequent formation, in significant yield, of primary (R^1CONH_2) and secondary ($RNHCOR^1$) amides. When dry potassium cyanide is added to such a reaction mixture, RNHCHO is formed along with the other above-mentioned products.

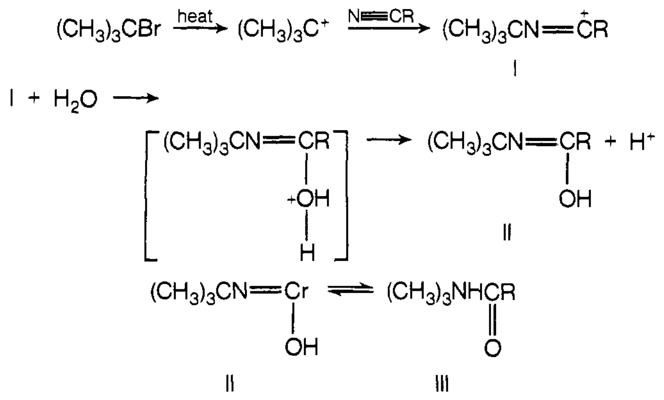
The formation of secondary amides via the addition of a carbonium ion to a nitrile was first described by Ritter and Minieri in 1948 (*7*). Since then, the Ritter reaction has been extended in scope to become one of the most versatile methods of amide synthesis (*4*).

Although the most common method of generating the carbonium ion has been by the addition of an acid to a reagent which easily forms a carbocation, many other methods of generating such a carbonium ion have also been published (*2, 4, 6*).

We wish to report another such modification of the Ritter reaction. Unlike other methods using alkyl halides (*5*), we have found that by refluxing a tertiary alkyl halide in a nitrile solvent, significant yields of secondary amides were obtained without employing internal catalysis (Table I).

At elevated temperatures, molecules with tertiary carbon–halogen bonds readily form carbonium ions which can then add to the nitrile moiety of the solvent molecule:

Scheme I



$$(CH_3)_3CBr \xrightarrow{heat} (CH_3)_3C^+ \xrightarrow{N\equiv CR} \underset{I}{(CH_3)_3CN{=}\overset{+}{C}R}$$

$$I + H_2O \longrightarrow \left[\begin{array}{c}(CH_3)_3CN{=}CR\\ |\\ {}^{+}OH\\ |\\ H\end{array}\right] \longrightarrow \underset{II}{(CH_3)_3CN{=}\underset{OH}{\underset{|}{C}}R} + H^+$$

$$\underset{II}{(CH_3)_3CN{=}\underset{OH}{\underset{|}{C}}r} \rightleftharpoons \underset{III}{(CH_3)_3NH\underset{O}{\underset{\|}{C}}R}$$

Any water present in the solvent (*1*) would add to this new carbonium ion, forming an initial imenol (II) which rapidly converts to the amide (III) tautomer. The formation of the primary amide can be visualized in the same manner, except that a hydrogen ion (from the formation of the imenol) rather than a carbonium ion adds to the nitrile.

The water content of reagent-grade nitrile solvents has been determined by Thompson and coworkers (*8*) to be approximately 6.8 × $10^{-3}M$. A water concentration of less than 2.0 × $10^{-3}M$ was observed for these same nitriles upon further purification (*3*). When these purified nitriles were used as solvents, no amide products were obtained. This shows that water is necessary for these reactions. Indeed, the addition of water to the solvent (2.5 × $10^{-2}M$) increased the product yield (Table I).

When dry, powdered potassium cyanide was allowed to reflux with the reaction mixtures, *N-tert*-butylformamide was also formed. In this case, we believe that the carbonium ion also adds to hydrogen cyanide which probably forms during the reflux reaction. The subsequent reaction would be the same as shown in Scheme I.

Experimental

The proton magnetic resonance (pmr) spectra were obtained on a Varian A60-A spectrometer with Silanor A (Merck Sharp & Dohme) as the solvent. The infrared (ir) spectra were obtained on a Hilger and Watts H1200 Infragraph. The products were isolated on a Varian Aerograph series 1700 vapor-phase chromatograph (vpc) using a 6-ft, ¼-in. o.d. column packed with 20% Carbowax 20 M on 60/80 mesh, acid washed, chromasorb P. The isolated products were spectrally compared with authentic samples unless otherwise noted. Yields were calculated using internal standards on the vpc.

Acetonitrile reaction (run 1). *Tert*-butyl bromide (5.0 grams, 0.03 mole) was added to 125 ml of reagent-grade acetonitrile (Mallinkrodt), and the reaction was refluxed for 24 hr. The reaction mixture was then evaporated under vacuum to about 5 ml. A 50-μl sample was injected into the vpc. The first fraction after the solvent peak was identified as *N-tert*-butylacetamide. The second fraction exhibited ir and pmr spectra identical to that for acetamide (Sadtler ir spectra #13207 and pmr spectra #4280).

Acetonitrile-water reaction (run 2). This reaction was run identically as run 1 except that acetonitrile containing 2.5 × $10^{-2}M$ water was used as the solvent. The product yields were different as indicated in Table I.

Acetonitrile-potassium cyanide reaction (run 3). This reaction was run identically as run 1 except that 3.9 grams (0.06 mole) of potassium cyanide were added to the reaction mixture. The first and third fractions were *N-tert*-butylacetamide and acetamide as in run 1. The second fraction exhibited an ir identical to that for *N-tert*-butylformamide (Sadtler ir #31854).

Propionitrile reaction (run 4). This reaction was run identically to run 1 except that reagent-grade propionitrile (Eastman-Kodak) was used as the solvent. The first fraction isolated from the vpc past the solvent peak was identified as *N-tert*-butylpropionamide. The second fraction exhibited ir and pmr spectra identical to that for propionamide (Sadtler ir #36430 and pmr #8231).

Propionitrile–water reaction (run 5). All reaction conditions were the same as run 4 except that propionitrile containing 2.5 × $10^{-2}M$ water was used as the solvent. The product yields were different as indicated in Table I.

Propionitrile–potassium cyanide reaction (run 6). All reaction conditions were the same as run 3 except that reagent-grade propionitrile was used as the solvent. The products were *N-tert*-butylpropionamide, *N-tert*-butylformamide, and propionamide.

Purified acetonitrile reaction (run 7). All reaction conditions were the same as run 1 except that the aceto-

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Table I. Reaction Parameters and Product Yields

Run	Halide	Nitrile solvent	Products	Yield, %
1	$(CH_3)_3CBr$	CH_3CN	$(CH_3)_3CNHCOCH_3$	35
			CH_3CONH_2	15
2	$(CH_3)_3CBr$	CH_3CN ($2.5 \times 10^{-2}M$ H_2O)	$(CH_3)_3CNHCOCH_3$	52
			CH_3CONH_2	18
3	$(CH_3)_3CBr$	CH_3CN (0.06*M* KCN)	$(CH_3)_3CNHCOCH_3$	27
			$(CH_3)_3CNHCOH$	18
			CH_3CONH_2	10
4	$(CH_3)_3CBr$	CH_3CH_2CN	$(CH_3)_3CNHCOCH_2CH_2$	15
			$CH_3CH_2COHN_2$	34
5	$(CH_3)_3CBr$	CH_3CH_2CN($2.5 \times 10^{-2}M$ H_2O)	$(CH_3)_3CNHCOCH_2CH_3$	56
			$CH_3CH_2COHN_2$	15
6	$(CH_3)_3CBr$	CH_3CH_2CN (0.06*M* KCN)	$(CH_3)_3CNHCOCH_2CH_3$	23
			$(CH_3)_3CNHCOH$	18
			$CH_3CH_2CONH_2$	9
7	$(CH_3)_3CBr$	CH_3CN[a]	No reaction	...
8	$(CH_3)_3CBr$	CH_3CH_2CN[a]	No reaction	...

[a] The solvent was purified before use (3).

nitrile solvent was purified before use (*3*), and a drying tube was attached to the reflux condenser. After 24 hr no product was observed.

Purified propionitrile reaction (run 8). All reaction conditions were the same as run 4 except that the propionitrile solvent was purified before use (*3*), and a drying tube was attached to the top of the condenser. After 24 hr no product was observed.

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