Hofmann Rearrangement of Primary, Substituted Acetamides to Nitriles with a Hypochlorite Liquid Triphasic System

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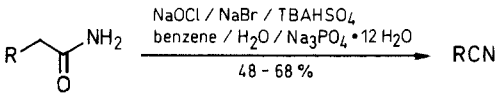
A hypochlorite liquid triphasic system prepared from aqueous sodium hypochlorite, sodium bromide, and tetrabutylammonium hydrogen sulfate was found to be effective in converting primary, substituted acetamides to nitriles with loss of one carbon via the Hofmann rearrangement in yields of 48–68%.

Several methods and reagents have been used to prepare nitriles by oxidation of the corresponding primary amines.[1] Good to moderate yields (60–75%) of nitriles can be obtained from simple procedures which react the amine with aqueous sodium hypochlorite in the presence of phase transfer catalysts or micelles.[2] However, even though nitriles are sometimes found as side products in the Hofmann rearrangement of primary acetamides because of oxidation of the desired amine product,[3] there appears to be no general procedure available for the direct rearrangement and oxidation of amides to nitriles in good yields.

Lee and Freedman, in their study of oxidation of amines with sodium hypochlorite in the presence of tetrabutylammonium hydrogen sulfate ($TBAHSO_4$), found that amides could be converted to nitriles in what was reported as generally low yields.[2a] However, specific yields were not given, products appear not to have been isolated, and aldehydes were observed as side products. No other reports of a general procedure for this process seem to exist, although a similar transformation of carboxylic acids (RCH_2CO_2H) to nitriles (RCN) with sodium nitrite and acetic anhydride has been observed.[4]

In a previous report, a new liquid triphasic system prepared from aqueous sodium hypochlorite, sodium bromide and $TBAHSO_4$ was described.[5] Tetrabutylammonium tribromide ($TBABr_3$) was formed in situ, and in the presence of solvents such as benzene, this formed an interfacial layer which was hydrophobic in character and had powerful brominating and oxidizing properties. For example, aromatic amides reacted to give amines which underwent further oxidation to yield a complex mixture of products.

Kajigaeshi has shown that $TBABr_3$ alone is an effective reagent for preparing amines from a variety of amides via the Hofmann degradation, although aliphatic amides require temperatures of 70°C.[6] It is now found that the sodium hypochlorite/$TBABr_3$ system reacts easily with primary substituted acetamides at room temperature to give nitriles in moderate to good yields.



The results for the degradation of a variety of amides are given in the Table. The reaction is run with only 25 mol% $TBAHSO_4$, suggesting that this salt has a catalytic function. Furthermore, unlike Lee and Freedman's results, no aldehydes seem to be formed as side products.[7] This is due, in part, to the use of an alkaline phosphate buffer which maintains the pH high enough to promote elimination over any possible hydrolysis. Another advantage of the triphasic reaction is the observation that there is no significant difference in yield when the alkyl R group is lengthened from C_4 to C_8. Normally, when amides are

Table. Rearrangement of RCH_2CONH_2 **1** to RCN **2**

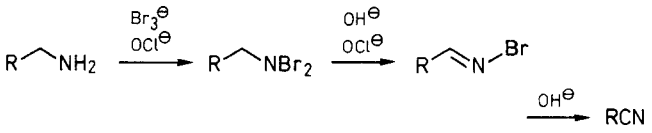
Product	R	Yield (%)		mp (°C) or bp (°C)/760 Torr (solvent)	
		GC	Isolated	found	reported
2a[a]	C_4H_9	62	55	138–141	142.3[9]
2b[b]	C_8H_{17}	66	60	221–223	224.4[10]
2c	*i*-C_4H_9	60	–[c]	–[c]	
2d[a]	Ph	70	68	188–189	191.1[9]
2e[d]	$PhOCH_2CH_2$	–	60	58.5–60.0 (hexane)	61–62[11]
2f[e]	1-naphthyl	–	55	35–36 (hexane)	37–38[12]
2g[f]	2-naphthyl	–	48	62.5–64.0 (isooctane)	66[14]

[a] IR and NMR data were identical with those of an authentic sample.
[b] IR (neat): $\nu = 2250\ cm^{-1}$. ^1H NMR ($CCl_4/CDCl_3$): $\delta = 0.90$ (t, 3H), 1.30 (m, 12H), 2.38 (t, 2H).
[c] Not isolated due to low boiling point. MS: *m/z* (%) = 82 ($M^+ - 1$, 4), 68 (11), 43 (100), 41 (70).
[d] IR (Nujol): $\nu = 2250\ cm^{-1}$. ^1H NMR (CCl_4/TMS): $\delta = 2.65$ (t, 2H), 4.03 (t, 2H) 6.70–7.38 (m, 5H).
[e] IR identical to that reported in the literature.[13] ^1H NMR (CCl_4/TMS): $\delta = 7.3–8.3$.
[f] IR (Nujol): $\nu = 2226\ cm^{-1}$. ^1H NMR (CCl_4/TMS): $\delta = 7.4–8.1$.

rearranged with bromine and alkali, poor yields of amines are obtained if R is larger than 6 carbons.[3,6] The higher yields oberved here are an indication that the key steps in the reaction take place in the hydrophobic interfacial layer.

The reaction most likely proceeds through a bromoimine intermediate similar to the chloroimine intermediate proposed by Lee and Freedman. When cyclohexyl amine is carried through the standard reaction conditions, an unstable compound is formed which is converted to cyclohexanone on further reaction with water. Its properties (see Experimental) are consistent with that of a bromoimine. In the case of primary amines, the bromoimine may undergo elimination faster than the chloroimine thus offering another explanation for the lack of formation of aldehydes as hydrolysis products.

A simple mechanism for amine oxidation which is consistent with all of the evidence is as follows:



Bromide ion is generated in the reaction upon elimination. It is reoxidized by OCl^- to Br_3^- thus enabling it to behave as a catalyst. Theoretically, only a small amount of $TBAHSO_4$ should be needed in the reaction, but the indicated amount is necessary to form an insoluble interfacial layer. Without this, significant reaction does not occur. Increase in the quantity of $TBAHSO_4$ accelerates the reaction rate but does not improve the yield of nitriles.

The aqueous NaOCl was Mallinckrodt AR with 11% available chlorine. It was stored in a refrigerator and the available Cl was checked periodically by iodimetric titration. All other materials were reagent grade and used as received. With the exception of 1-naphthylacetamide, which was purchased commercially, amides were prepared from the corresponding carboxylic acids by reaction with $SOCl_2$/DMF followed by treatment with NH_3.[8] They were purified by recrystallization from suitable solvents and had melting points matching literature values.

IR spectra were recorded on Perkin-Elmer IR 137 and FTIR 1600 spectrophotometers. NMR spectra were taken on a Varian EM 360L spectrometer, and GC was performed either on a Varian 1400 or a Shimadzu GC8A gas chromatograph using packed columns (1.5% OV-101, 1.5 m, 3 mm i.d. and 1.5% SP-2250/1.95% SP-2401, 2 m, 3 mm i.d.). GC/MS data were obtained from a Hewlett Packard 5890/5972 system. All melting points are corrected.

Conversion of Primary, Substituted Acetamides to Nitriles; General Procedure:

To a solution of NaBr (0.52 g, 5.0 mmol) in aq NaOCl (6.0 mL, 4.9 mmol) were added in succession $TBAHSO_4$ (0.12 g, 0.36 mmol) and benzene (5.0 mL) at r.t.. The mixture was stirred vigorously for a few min, then a solution of $Na_3PO_4 \cdot 12H_2O$ (1.25 g, 3.3 mmol) in H_2O (5.0 mL) was added. Immediately after, the amide substrate (1.5 mmol) was added and stirring continued. The initially formed interfacial layer disappeared upon addition of the phosphate. There was an induction period of approximately 5 min, at which point the mixture deepened in color, the interfacial layer reformed, and the temperature rose spontaneously to about 40 °C. Stirring was continued until all amide had disappeared and the mixture was near r.t. (30–45 min). After separating the three layers, the interfacial layer was washed simultaneously with sat. NaCl and additional benzene. The benzene solutions were combined, washed with 10% $NaHSO_3$ and 5% $NaHCO_3$, dried ($MgSO_4$), and either subjected to GC analysis or evaporated to dryness under reduced pressure.

For purposes of isolation of liquid products, the reaction was scaled up by a factor of 10 or 15 with no adverse effects. In these cases, once the mixture began to warm spontaneously, it was briefly cooled in ice to maintain its temperature at 40 °C and then stirring was continued without further cooling. The products were isolated by distillation through a microscale spinning band distillation column. Product identification was through spectral data or, in the case of pentanonitrile and benzonitrile, by comparison (GC, IR, NMR) with authentic samples (Table).

Reaction of NaOCl/$TBABr_3$ with Cyclohexyl Amine:

Cyclohexyl amine was reacted according to the general procedure except that no phosphate buffer was added. Reaction time was 30 min. The benzene solution was evaporated under reduced pressure at r.t. to give an unstable yellow oil. Its IR showed a small peak at $\nu = 1710\,cm^{-1}$ (indicative of cyclohexanone) and a C=N absorption at $\nu = 1620\,cm^{-1}$. No N–H peak was observed. A semiquantitative analysis indicated approximately 50% Br.[15] Calc. for $C_6N_{10}NBr$: Br, 45.39.

The oil was redissolved in benzene and stirred with H_2O overnight. The benzene solution was subjected to GC analysis which showed a single peak with retention time equal to that of cyclohexanone. Standard addition showed the yield to be about 65%.

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