

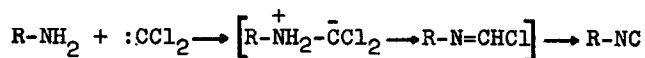
AN IMPROVED PROCEDURE FOR THE HOFMANN CARBYLAMINE
SYNTHESIS OF ISONITRILES

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Isonitriles are the only known stable compounds of formally divalent carbon. They have attracted considerable attention in the last fifteen years.^{1,2} There are basically three synthetically useful methods for the preparation of isonitriles. The two oldest of these have been known for over a century.^{3,4} One involves the alkylation of silver cyanide with alkyl iodides to yield silver-isonitrile complexes from which the isonitrile can be obtained by treatment with KCN. The other involves treatment of primary amines with chloroform and strong base (the so-called Hofmann Carbylamine Reaction). Nef⁵ was the first to recognize dichlorocarbene as an intermediate in this reaction.



The most recent method is the dehydration of monosubstituted formamides. This approach was discovered almost simultaneously by Hagedorn,⁶ Corey,⁷ and Ugi.⁸ Ugi has shown the phosgene-triethylamine system to be most effective.⁹

This dehydration procedure involves two steps: the formation of the formamide by treatment of the primary amine either with 98% formic acid¹⁰ or ethyl (methyl) formate¹¹ followed by dehydration of the substituted formamide. Yields for each step are in the vicinity of 70 - 90%, giving overall yields of 50 - 80%.

This constituted a significant improvement over the Hofmann Carbylamine

reaction which generally yield 20% with chloroform and ethanolic KOH and up to 45% using modifications like powdered KOH or KOt-Bu in pentane.⁹ Higher yields have been reported¹² but have been found to be non-reproducible.¹³ The pyrolytic decomposition of sodium trichloroacetate in the presence of primary aryl amines is a procedural modification which is limited by the high temperatures required.¹⁴

We should like to report a significant improvement in the Hofmann Carbyl-amine reaction, the simplicity, convenience and overall yield of which make it a competitive alternative to the dehydration procedure.

Makosza and Wawrzyniewicz¹⁵ have shown that dichlorocarbene may be generated efficiently from chloroform and 50% aqueous NaOH in a heterogeneous system by use of the phase transfer catalyst benzyltriethylammonium chloride (I). I is soluble in both the aqueous and the organic phase. Solution of I in the basic aqueous phase followed by anion exchange generates the benzyltriethylammonium hydroxide ion pair which is soluble in the organic phase. Reaction of hydroxide ion with chloroform gives dichlorocarbene and regenerates I. High yields of 1,1-dichlorocyclopropanes are obtained by performing the reaction in the presence of olefins. Similar results have been reported by Starks¹⁶ utilizing tetraalkylammonium salts as phase transfer catalysts.

We have used phase transfer catalysis to generate dichlorocarbene in the presence of primary amines and have obtained a variety of isonitriles in yields of 40 - 60% after purification by fractional distillation. A typical preparation follows:

(All isonitrile preparations should be carried out in an efficient fume hood because of the pungent odor and toxicity of some isonitriles.) A 500 ml round bottom flask equipped with a magnetic stirring bar and reflux condenser is charged with aniline (0.2 mole, 18.6 g), alcohol free chloroform (0.2 mole, 24 g), benzyltriethylammonium chloride (0.5 g) and dichloromethane (60 ml). 50% Aqueous NaOH solution (60 ml) is added in one portion. After an induction period of about ten minutes, the dichloromethane refluxes spontaneously, keeping the reaction mixture at a temperature of ca. 40°C. After about one hour the refluxing ceases and the mixture is stirred for one additional hour. The reaction mixture is di-

luted with water (200 ml) and the isonitrile is extracted with dichloromethane, washed with water, brine and dried over MgSO_4 or K_2CO_3 . Distillation affords the pure phenyl isocyanide (12 g, 57%, bp 50 - 52°C/11 torr). Typical yields are summarized in the table below.

TABLE
Synthesis of Isonitriles by the Hofmann Carbylamine Reaction^a

<u>Isonitrile</u>	<u>Yield^b</u> <u>(percent)</u>	<u>Boiling Point</u> <u>(°C/torr)</u>
n-butyl	60	40-42/11
benzyl	55	92-93/11
n-dodecyl (lauryl)	41	115-118/0.1
cyclohexyl	48	67-72/13
phenyl	57	50-52/11

- a. All examples are known compounds; physical properties agree with literature (see ref. 9).
b. For amine-free distilled material.

The yields above compare favorably with the best yields ever obtained for the carbylamine reaction and are competitive with the overall yields obtained by the two step formylation-dehydration technique. Further applications of phase transfer catalysis in carbene chemistry is the subject of active investigation.

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