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Chemical Research and Development Laboratories
Technical Report**

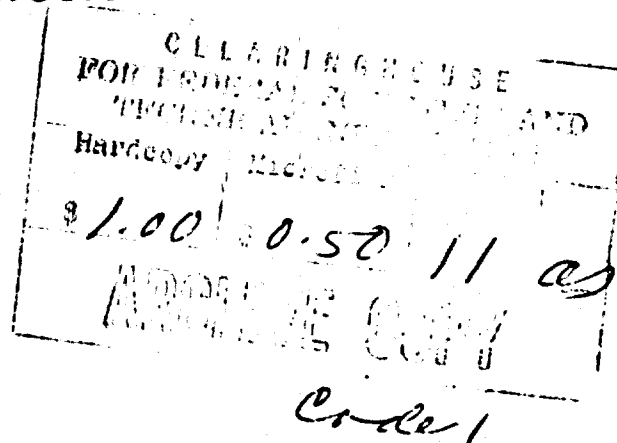
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Isocyanide Synthesis

by

Daniel J. Hoy
Edward J. Poziomek

December 1965



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ISOCYANIDE SYNTHESIS

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Directorate of Defensive Systems**

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FOREWORD

This work was conducted under Task 1C622401A10204, Detection and Warning Investigations. The experimental data are contained in notebook 7174, pp 70-85. The work was performed during October and November 1964.

Acknowledgments

Elemental analyses were performed by the Analytical Research Branch, Chemical Research and Development Laboratories, Edgewood Arsenal, Md.

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When this report has served its purpose, DESTROY it.

DIGEST

Methyl, n-butyl, sec-butyl, and tert-butyl isocyanides were prepared by reacting p-toluenesulfonyl chloride, quinoline, and the corresponding N-alkyl formamide in a rotary evaporator at 1.5-mm. Hg pressure. The isocyanides distill upon formation and were collected in a dry ice trap. One distillation without a fractionating column gave a 50% to 75% yield of chromatographically (GLC) pure product. The simplicity of the procedure and facility of obtaining large quantities of high purity aliphatic isocyanides is a distinct improvement over published procedures.

This procedure is recommended for the synthesis of all isocyanides having a boiling point of 150-175°C/760 mm or less. Optimum yields will be obtained when a reaction flask size of no less than 2 liters, a formamide charge of no more than 25 gm, and a pressure of no greater than 2.0 mm are used.

ISOCYANIDE SYNTHESIS

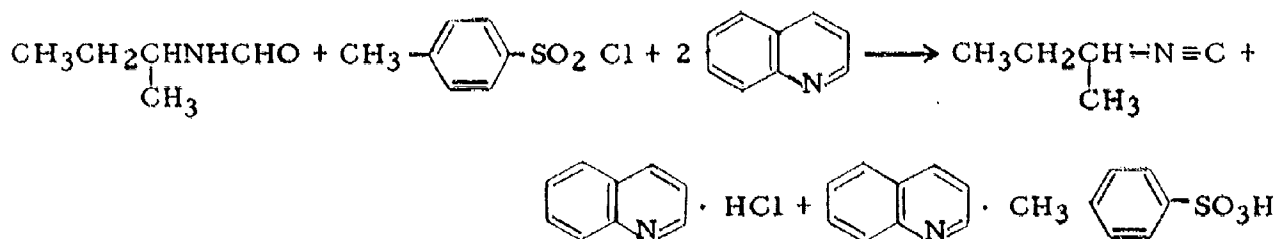
I. INTRODUCTION.

Aliphatic isocyanides have been prepared by reacting an alkyl halide with silver cyanide, by reacting a primary amine with dichlorocarbene, and by dehydrating an alkyl formamide with a strong electrophile in the presence of a tertiary base. The formamide dehydration is the method of choice, requiring inexpensive reagents and giving uniformly good to excellent yields (40% to 95%).¹ In spite of the good chemical methods reported for isocyanide synthesis, the isolation of large quantities (10 gm) of high purity material (99% to 100%) is very difficult.

This publication describes a convenient procedure for the synthesis of all isocyanides having a boiling point of 150-175°C/760 mm or less.

II. PROCEDURE.

sec-Butyl Isocyanide



Caution! Isocyanides are extremely toxic and vile smelling. The reaction must be carried out in a hood and the vacuum pump is best vented to a hood. Ethyl isocyanide has been reported to explode.²

The apparatus consists of a rotary evaporator equipped with a rotating ice-cooled condenser flask and a 2-liter reaction flask immersed in a water bath that can be heated to 50°C. The evaporator is connected to a dry ice acetone trap (Note 1) with clean rubber tubing and then to an oil pump protected with a Drierite® filled gas-absorption tube (Note 2). The apparatus is assembled and tested for ability to achieve a 1.5- to 2.0-mm vacuum prior to mixing the reagents.

sec-Butylformamide, 26.0 gm (0.257 moles) (Note 3), is added to a mixture of 50.0 gm (0.262 moles) of p-toluenesulfonyl chloride (Note 4) and 120 ml (1.0 moles) of quinoline (Note 5) in a 2-liter flask. The flask is attached to the rotary evaporator and immersed in the water bath at room temperature. The evaporator is turned on and the system evacuated to about 1.5 mm. sec-Butyl isocyanide immediately begins distilling into the dry ice-acetone cold trap. After the reaction proceeds for 15 min, the temperature of the water bath is slowly raised during 30 min to 50°C. When the isocyanide no longer bubbles from the reaction solution, the apparatus is opened to air and the product is warmed to room temperature. The isocyanide is transferred to a distillation apparatus (Note 6) and distilled at atmospheric pressure. A forerun of 0.5 to 1.0 ml, which may be slightly cloudy (Note 7), is collected; the remainder, bp 109-110°C/760 mm, is pure sec-butyl isocyanide (Note 8), a colorless vile smelling liquid (Note 9). Weight of pure material is 13.4 gm (61% to 63%), n_D^{23} 1.3860 (Note 10).

Notes

1. An ordinary vacuum trap with a F 45/50 joint is convenient.
2. A 2.8×50 cm U tube was used. The Drierite[®] helps reduce the small quantities of isocyanide that reach the pump; however, an oil change was necessary to completely remove the odor.
3. sec-Butylformamide was synthesized by refluxing sec-butylamine with a 50% excess of ethyl formate for 16 hr. Complete removal of all low boiling compounds is necessary or they will contaminate the isocyanide.
4. Eastman Kodak "white label" or a similar high quality commercial reagent is satisfactory.
5. Fisher Scientific Company reagent quinoline, bp 235-237°C, was used without purification. The large excess serves as solvent and increases the yield of isocyanide. When 5% excess quinoline was used, the crude yield dropped to 50%.
6. Crude yield is about 70%. No fractionating column was used.
7. The most likely contaminant is a trace of water. Care should be taken to prevent condensation of water from the atmosphere by cooling the vacuum trap immediately prior to evacuation and rapid warming to room temperature when the vacuum is broken.

8. No impurities were found by gas-liquid chromatography using a 3/8 in. x 10 ft column of 20% 1-hydroxyethyl 2-heptadecenyl gly-oxalidine on 60/80 mesh KOH washed Chromosorb W®.
9. The equipment can be decontaminated by washing with 5% methanolic H₂SO₄.
10. A larger quantity of isocyanide can be obtained by increasing the amount of initial reactant charge; however, the percent yield will be reduced. The yield of isocyanide is somewhat dependent on distillation rate since secondary reactions occur in the reaction mixture. Repetitive runs are recommended if larger quantities are needed. Only pure isocyanides stored in a refrigerator (triple packaging necessary to prevent odor contamination) are stable indefinitely.

A. Methods of Preparation.

sec-Butyl isocyanide has been prepared by the dehydration of sec-butylformamide with quinoline and p-toluenesulfonyl chloride.³

B. Merits of the Preparation.

This procedure is applicable to the synthesis of all aliphatic isocyanides of approximate bp 160°C or less and tends to improve upon all methods previously reported in "Organic Syntheses"^{4, 5} and the chemical literature.^{3, 6, 7, 8} The synthesis is simple, rapid, requires minimum handling of the toxic isocyanides, and affords good yields of high purity product without distilling through a fractionating column. A similar simple procedure appears in the literature but suffers from small scale and low yields.³ The reaction scale and yield have been substantially increased by utilizing the rotary evaporator. Methyl (41% yield), n-butyl (46% yield) and tert-butyl (71% yield) isocyanides have been prepared by this method and gave chromatographically pure products after one distillation without using a column. The indicated yields of methyl and n-butyl isocyanides were obtained under less than optimum conditions.

III. RESULTS.

Several isocyanides were synthesized to illustrate the scope of the reaction procedure:

	<u>bp</u> <u>°C/mm</u>	<u>amount</u> <u>gm</u>	<u>yield</u> <u>%</u>
Methyl isocyanide	59-61/766	16.4	41*
n-Butyl isocyanide	124-125/766	28.2	46**
s-Butyl isocyanide	109-110/766	22.5	57
t-Butyl isocyanide	90-91/765	29.2	71

IV. CONCLUSIONS.

This procedure is recommended for the synthesis of all isocyanides having a boiling point of 150-175°C/760 mm or less. Optimum yields will be obtained when a reaction flask size of no less than 2 liters, a formamide charge of no more than 25 gm, and a pressure of no greater than 2.0 mm are used.

* Yield appreciably decreased because pressure was 20 mm instead of recommended 1 to 2 mm.

** Yield lowered by using 50 gm of formamide instead of recommended 25 gm.

LITERATURE CITED

1. Ugi, I., and Meyr, R. Ger. 1,084,715, July 7, 1960.
2. Lemoult. Compt. rend. 143, 902 (1906).
3. Casanova, J., Jr., Schuster, R. E., and Jerner, N. D. J. Chem. Soc. 4280 (1963).
4. Jackson, H. L., and McKusick, B. C. Org. Syntheses, Coll. Vol. 4, 438 (1963).
5. Ugi, I., Meyr, R., Lipinski, M., Bodesheim, F., and Rosendahl, F. Org. Syntheses, 41, 13 (1961).
6. Hofmann, A. W. Ann., 146, 107 (1868).
7. Gautier, A. Ann. 146, 119 (1868).
8. Ugi, I., and Meyr, R. Chem. Ber. 93, 239 (1960).

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13. ABSTRACT Good yields of (41' to 71') analytically pure aliphatic isocyanides have been prepared by dehydrating the corresponding N-alkyl formamide with p-toluene-sulfonyl chloride and quinoline in a rotary evaporator at 2-mm pressure. The procedure is simple, rapid, convenient and applicable to any isocyanide that boils below 160 degrees C/760 mm.		
14. KEYWORDS Formamide Dehydration Rotary evaporator Quinoline Isocyanide p-Toluenesulfonyl chloride Synthesis Toxicity sec-Butylformamide Aliphatic Methyl isocyanide n-Butylisocyanide Isonitrile tert-Butyl isocyanide		