

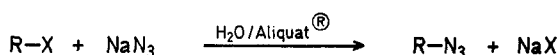
Phase-Transfer Catalysis; Preparation of Alkyl Azides

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The literature reports several methods for preparing alkyl azides¹. These methods all suffer from either low yield, complex workup procedures, or long reaction times. One of the main problems encountered when attempting the nucleophilic displacement of bromine from alkyl bromides by the azido group is separation of product from unreacted starting material. By using a phase-transfer catalyst² we have been able to achieve quantitative conversion of bromides into azides within modest reaction times. The product is then separated from the aqueous layer, dried, and distilled.

Several catalysts have been successfully employed. These include both quaternary ammonium salts, the usual catalysts for phase-transfer reactions, and amines³. While either the salts or the amines will serve efficiently as catalysts, shorter reaction times were possible with quaternary ammonium salts. Presumably, the amine reacts with the alkyl halide to generate an ammonium salt, which is the actual phase-transfer catalyst⁴.



The preparation of 1-azidobutane from 1-bromobutane using Aliquat 336⁵ as catalyst was 97% complete in 6 hours. With butylamine as catalyst, the reaction was 71% complete in 6 hours, while a 77% yield was obtained after 5 hours with tributylamine as catalyst.

The azide substitution on primary bromides was quite clean; however, in the case of bromo- or iodocyclohexane some cyclohexene was detected. This elimination product was readily separated from the product by distillation. Yields of isolated products are given in Table 1. All products were characterized by I.R., ¹H-N.M.R., and refractive index.

Table 1. Alkyl Azides (R—N₃) from Alkyl Bromides (R—Br)

| R | Yield [%] | b.p./torr | n _D ²⁰ | Literature Data ^{1, b} b.p./torr | n _D ²⁰ |
|-----------------------------------|-----------------|-----------|------------------------------|--|------------------------------|
| n-C ₄ H ₉ | 89 | 66°/157 | 1.4193 | 71°/225 | 1.4192 |
| n-C ₅ H ₁₁ | 89 | 68°/70 | 1.4267 | 63.5°/95 | 1.4266 |
| n-C ₆ H ₁₃ | 87 | 76°/45 | 1.4317 | 85°/63 | 1.4318 |
| n-C ₇ H ₁₅ | 92 | 84°/18 | 1.4371 | 70°/13 | 1.4343 |
| n-C ₈ H ₁₇ | 92 | 105°/22 | 1.4351 | 62°/3.3 | 1.4368 |
| n-C ₁₀ H ₂₁ | 93 | 76°/0.05 | 1.4442 | 67°/0.65 | 1.4425 |
| c-C ₆ H ₁₁ | 74 ^a | 74°/25 | 1.4700 | 72°/30 | 1.4693 |

^a G.L.C. analysis prior to distillation indicated a mixture of 85% azidocyclohexane and 15% cyclohexene.

A brief study indicates that the rate of the reaction is strongly influenced by the leaving group. Table 2 shows the results of a study with various alkyl halides.

Table 2. Influence of the Leaving Group X on the Reaction Rate of the Formation of Alkyl Azides (R—N₃) from Alkyl Halides (R—X)

| R—X | Reaction Time | Yield [%] |
|--------------------------------------|---------------|----------------------|
| n-C ₄ H ₉ —J | 2 h | 89 |
| n-C ₄ H ₉ —Br | 6 h | 97 |
| n-C ₄ H ₉ —Cl | 4.5 h | 48 |
| | 7.5 h | 65 |
| c-C ₆ H ₁₁ —J | 4.5 h | 77 (23% cyclohexene) |
| c-C ₆ H ₁₁ —Br | 7 h | 78 (12% cyclohexene) |

Thus, it is apparent that the iodide is the most reactive of the alkyl halides with the bromide exhibiting sufficient reactivity to be of preparative use.

In all cases, blank runs (no catalyst) produced low yields (<25%) in longer reaction times than the catalyzed reactions.

Alkyl Azides from Alkyl Halides; General Procedure:

The alkyl halide (0.08 mol) is added to a stirred 25% aqueous solution of sodium azide (10.25 g, 0.16 mol). Aliquat 336[®] 1.62 g, 0.004 mol) is added and the mixture is heated to 100° with vigorous stirring. The progress of the reaction is followed by G.L.C.⁶. When all the starting material is consumed, the mixture is cooled and the phases are separated. The organic layer is dried with a small amount of magnesium sulfate, the solvent evaporated, and the product distilled at reduced pressure.

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^{1a} P. A. S. Smith, *The Chemistry of Open-Chain Organic Nitrogen Compounds*, Vol. II, W. A. Benjamin, Inc., New York, 1966, p. 254.

^{1b} E. Lieber, T. S. Chao, C. N. R. Rao, *J. Org. Chem.* **22**, 238 (1957).

² J. Dockx, *Synthesis* **1973**, 441.

E. V. Dehmlow, *Angew. Chem.* **86**, 187 (1974); *Angew. Chem. Int. Ed. Engl.* **13**, 170 (1974).

Numerous examples of nucleophilic substitutions by phase-transfer catalyzed reactions are cited in these reviews.

³ W. P. Reeves, M. R. White, *Synth. Commun.* **6**, 193 (1976).

⁴ W. P. Reeves, R. G. Hilbrich, *Tetrahedron*, in press.

⁵ Aliquat 336[®] is mainly methyltriethylammonium chloride and was kindly furnished by General Mills Chemicals of Kankakee, Illinois.

⁶ G.L.C. analyses were conducted with a Perkin-Elmer model 990 gas chromatograph using a 20% Carbowax 6000 on 60/80 Chromosorb W, 20' × 1/8" stainless-steel column.