



A Publication  
of Reliable Methods  
for the Preparation  
of Organic Compounds

## Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at [http://www.nap.edu/catalog.php?record\\_id=12654](http://www.nap.edu/catalog.php?record_id=12654)). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

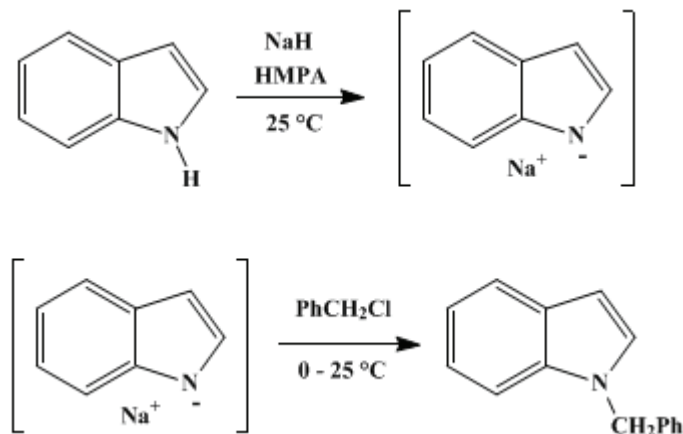
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*These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.*

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## **N-ALKYLINDOLES FROM THE ALKYLATION OF SODIUM INDOLIDE IN HEXAMETHYLPHOSPHORIC TRIAMIDE: 1- BENZYLINDOLE**

**[1*H*-Indole, 1-(phenylmethyl)-]**



Submitted by George M. Rubottom<sup>1</sup> and John C. Chabala<sup>2</sup>.  
Checked by R. E. Ireland and James E. Kleckner.

### 1. Procedure

*Caution! Hexamethylphosphoric triamide (HMPA) vapors have been reported to cause cancer in rats.<sup>3</sup> All operations with hexamethylphosphoric triamide should be performed in a good hood, and care should be taken to keep the liquid off the skin.*

A 100-ml., three-necked flask fitted with a reflux condenser, a magnetic stirring bar, and a gas-inlet tube is charged with 2.34 g. (0.0200 mole) of [indole](#) (Note 1) and 15 ml. of [hexamethylphosphoric triamide](#) (Note 2) under a static atmosphere of [argon](#). The flask is cooled to 0° with an ice bath, and 0.53 g. (0.022 mole) of [sodium hydride](#) is added to the stirred solution over a period of 10 minutes (Note 3). The resulting slurry is stirred for 5 hours at room temperature (Note 4) then cooled to 0° (ice bath) before 2.53 g. (2.30 ml., 0.0200 mole) of [benzyl chloride](#) (Note 5) is added as rapidly as possible to the stirred mixture. The mixture is stirred for 8–15 hours (overnight), during which time the ice in the ice bath melts, and the temperature of the reaction flask gradually rises to room temperature. The mixture is then diluted with 15 ml. of water and extracted with three 25-ml. portions of [diethyl ether](#). The combined ethereal extracts are washed with two 40-ml. portions of water and dried with anhydrous [magnesium sulfate](#). After filtration the solvent is removed at reduced pressure, and 4.4 g. of crude [1-benzylindole](#) is obtained as a liquid. After bulb-to-bulb distillation of this material in a Kügelrohr oven [120–130° (0.0025 mm.)], crystallization of the distillate from 15 ml. of hot [ethanol](#) affords 3.46–3.61 g. (83–87%) of [1-benzylindole](#). A second crop of 0.17–0.26 g. (4–6%) is obtained on concentration of the mother liquors to 6 ml. The total yield of [1-benzylindole](#), m.p. 43–44°, is 3.72–3.78 g. (90–91%) (Note 6) and (Note 7).

### 2. Notes

1. Commercial [indole](#) (Matheson, Coleman and Bell) was used with no further purification.
2. Commercial HMPA (Aldrich) was stored over Linde 4 A Molecular Sieves and used without further purification.
3. A batch of 0.93 g. of a 57% [sodium hydride](#) dispersion in mineral oil is washed with [hexane](#) to

remove the mineral oil immediately prior to use. The slow addition in the cold minimizes the small amount of foaming caused by hydrogen evolution.

4. This stirring time insures complete formation of sodium indolide.

5. Commercial benzyl chloride (Matheson, Coleman and Bell) was used without further purification.

6. The recrystallized product has  $^1\text{H}$  NMR absorptions ( $\text{CDCl}_3$ ) at  $\delta$  5.21 (s, 2H), 6.52 (d,  $J = 3.4$  Hz., 1H), 7.0–7.4 (m, 9H), and 7.5–7.7 (m, 1H).

7. 1-Benzylindole colors significantly in contact with air at room temperature (ca. 1 week), but keeps indefinitely under argon.

### 3. Discussion

Generally, the alkylation of sodium indolide, generated from indole and sodium amide in liquid ammonia, has been used for the preparation of *N*-alkylindoles.<sup>4,5,6,7,8,9,10,11,12</sup> The drawback to this method is the use of liquid ammonia. The procedure outlined here<sup>13</sup> overcomes this problem and affords pure *N*-alkylindoles in excellent yields. Further, the use of the hexamethylphosphoric triamide–sodium hydride system affords conditions leading to the formation of the *N*-alkylindoles with little or no side reaction leading to *C*-alkylated products.<sup>13,14</sup> Table I illustrates the generality of the method.

TABLE I  
ALKYLATION OF INDOLE SODIUM WITH R-X IN HMPA SOLVENT

R-X	Yield of <i>N</i> -Alkylindole, %	b.p. or m.p.
$\text{CH}_3\text{I}$	94	b.p. 73–75°/2.4 mm. (Ref. <sup>15</sup> , b.p. 70–75/2 mm.)
$\text{C}_2\text{H}_5\text{I}$	92	b.p. 83–86°/0.6 mm. (Ref. <sup>16</sup> , b.p. 82–85°/0.7 mm.)
$\text{CH}_2=\text{CHCH}_2\text{Br}$	84	b.p. 72–73°/0.12 mm. (Ref. <sup>7</sup> , b.p. 114–116°/6 mm.)
$\text{C}_6\text{H}_5\text{CH}_2\text{Cl}$	90–91	m.p. 43–44° (Ref. <sup>6</sup> , m.p. 44°)

### References and Notes

1. Department of Chemistry, University of Puerto Rico, Rio Piedras, Puerto Rico 00931. [Present address: Department of Chemistry, University of Idaho, Moscow, Idaho 83843.]
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### Appendix

#### Chemical Abstracts Nomenclature (Collective Index Number);

**(Registry Number)**

ethanol (64-17-5)

ammonia (7664-41-7)

diethyl ether (60-29-7)

hydrogen (1333-74-0)

benzyl chloride (100-44-7)

magnesium sulfate (7487-88-9)

sodium amide (7782-92-5)

sodium hydride (7646-69-7)

Indole (120-72-9)

hexane (110-54-3)

argon (7440-37-1)

hexamethylphosphoric triamide (680-31-9)

1-Benzylindole,  
1H-Indole, 1-(phenylmethyl)- (3377-71-7)

SODIUM INDOLIDE