



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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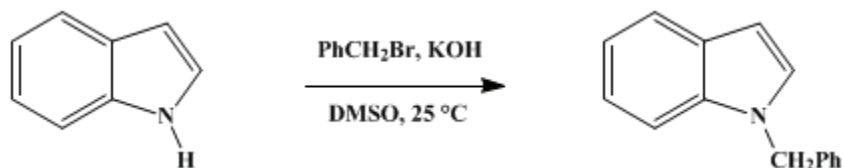
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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1-BENZYLINDOLE

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



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1. Procedure

A 500-ml. Erlenmeyer flask equipped with a magnetic stirring bar is charged with 200 ml. of dimethyl sulfoxide (Note 1) and 26.0 g. (0.399 mole) of potassium hydroxide (Note 2). The mixture is stirred at room temperature for 5 minutes before 11.7 g. (0.100 mole) of indole (Note 3) is added. Stirring is continued for 45 minutes before 34.2 g. (0.200 mole) of benzyl bromide (Note 4) is added (Note 5). After being stirred for an additional 45 minutes the mixture is diluted with 200 ml. of water. The mixture is extracted with three 100-ml. portions of diethyl ether, and each ether layer is washed with three 50-ml. portions of water. The combined ether layers are dried over calcium chloride, and the solvent is removed at slightly reduced pressure (Note 6). The excess benzyl bromide is removed by distillation at approximately 15 mm., and the residue is distilled, yielding 17.5–18.4 g. (85–89%) of 1-benzylindole, b.p. 133–138° (0.3 mm.). The distillate crystallizes upon cooling and scratching; recrystallization from ethanol gives material melting at 42–43° (Note 7) and (Note 8).

2. Notes

1. The dimethyl sulfoxide used was not rigorously dried but should not contain an appreciable amount of water.
2. Freshly crushed 86% potassium hydroxide pellets were used.
3. A commercial grade of indole is satisfactory.
4. Reagent grade benzyl bromide was used without further purification.
5. Cooling with an ice–water bath moderates the exothermic reaction.
6. The submitters used a Büchi rotary evaporator (water aspirator).
7. The submitters have obtained yields as high as 20 g. (97%).
8. ¹H NMR (CDCl₃): 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).

3. Discussion

Although the *N*-alkylation of pyrrole² and indole³ has been reported on many occasions, a generally applicable, simple, high yield procedure was not available. Many simple procedures give mixtures of products because of the ambident nature of the anions; however, alkylation at nitrogen is usually predominant in strongly ionizing solvents. Recent methods include alkylations of indole in liquid ammonia,⁴ *N,N*-dimethylformamide,⁵ and hexamethylphosphoric triamide.⁶

The use of dimethyl sulfoxide as a dipolar aprotic solvent is well known;⁷ the present method can be regarded as a model procedure and has been applied to the preparation of a number of *N*-*n*-alkyl pyrroles and *N*-*n*-alkyl indoles.⁸ The yield of *N*-benzylindole is considerably higher than in previously reported preparations and is as good as that reported for the preparations of *N*-methylindole in liquid ammonia.⁴ The present method is, however, less laborious and quicker. Very high yields are obtained using *n*-alkyl halides and moderately good yields with secondary alkyl halides. The reactions may be compared with those recently reported for pyrrolythallium⁹

The procedure has been much used for the alkylation of a variety of indoles,¹⁰ including a modification using sodium methoxide in the methylation of tetrahydroalstonine.¹¹ The wide applicability of the method is indicated by the methylation of diarylamines such as 10,11-dihydro-5H-dibenzo[b,f]azepine.¹² An extension to the acylation of indoles has been reported using, for example, acetic anhydride-KOH in dimethyl sulfoxide.¹³

References and Notes

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Appendix

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

pyrrylthallium

tetrahydroalstonine

acetic anhydride-KOH

ethanol (64-17-5)

calcium chloride (10043-52-4)

ammonia (7664-41-7)

ether,
diethyl ether (60-29-7)

nitrogen (7727-37-9)

sodium methoxide (124-41-4)

potassium hydroxide (1310-58-3)

Pyrrole (109-97-7)

benzyl bromide (100-39-0)

N,N-dimethylformamide (68-12-2)

Indole,
1H-Indole (120-72-9)

dimethyl sulfoxide (67-68-5)

N-methylindole (603-76-9)

hexamethylphosphoric triamide (680-31-9)

1-Benzylindole,
N-benzylindole (3377-71-7)

10,11-dihydro-5H-dibenzo[b,f]azepine (494-19-9)