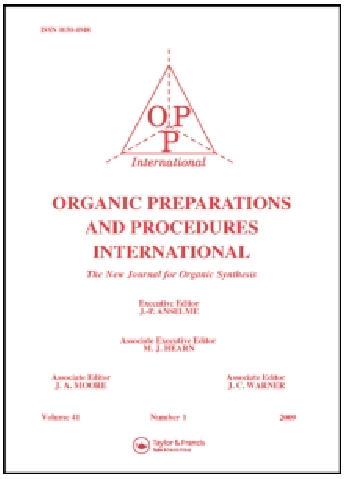

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A CONVENIENT SYNTHESIS OF 1-BENZYLINDOLES

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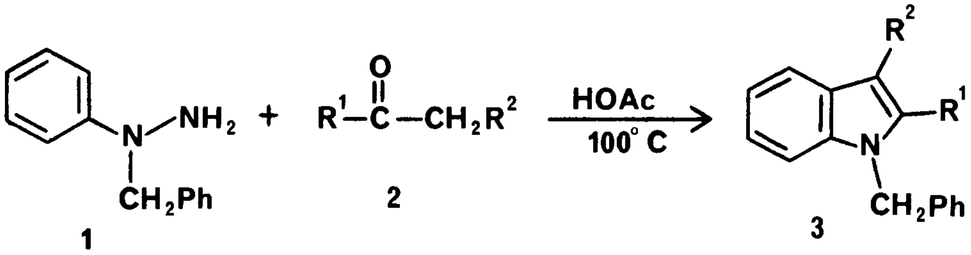
The benzyl group has been used not infrequently as an indole-nitrogen protecting group in indole alkaloid synthesis,[1] since it is both impervious to acidic and basic reagents and yet is easily removed under Birch conditions. Although 1-benzylindoles are normally prepared by N-alkylation of the appropriate indole under the influence of base,[2] we have found that in more complicated systems this N-benzylation does not always proceed smoothly, particularly in base-labile molecules. Therefore, we have investigated a direct, one-step synthesis of 1-benzylindoles using Fischer-indole methodology and report our results herein.

The requisite starting material, 1-benzyl-1-phenylhydrazine (1), was easily prepared by benzylation of phenylhydrazine or is commercially available as the hydrochloride salt (1•HCl). When either 1 or 1•HCl was allowed to react with an aldehyde or ketone 2 in hot (100°C) glacial acetic acid[3] for 1-2 hours the corresponding 1-benzylindole 3 was obtained in good to excellent yield, as summarized in the Table.



Table

Preparation of 1-Benzylindoles 3 from 1-Benzyl-1-phenylhydrazine (1) and Aldehydes or Ketones 2 in Acetic Acid

Aldehyde/Ketone[a] No.	R^1	R^2	Product[b]	Method[c]	Yield[d] (%)	mp (°C)
2a	$-(CH_2)_4-$		3a	A	91	41-43° (Ref.[4] 43-44°)
				B	85	
2b	$-(CH_2)_5-$		3b	A	69	69-70.5°[e]
2c	CH_3	CH_3	3c	A	62	61-64° (Ref.[5] 60-61°)
				B	89	
2d	H	C_2H_5	3d	A	62	30-32.5° (Ref.[4] 37.5-38.5°)
2e	CH_3	C_2H_5	3e	A	68	61-62.5° (Ref.[4] 64-65°)
2f	Ph	CH_3	3f	A	63	119-122° (Ref.[6] 112°)
2g	H	Ph	3g	A	80	64-66° (Ref.[7] 67-68°)

a) Commercial materials. b) All products exhibited satisfactory ^{1}H- and ^{13}C-N.M.R. spectra. c) Method A refers to the reaction with the free base of 1, and Method B refers to the reaction with the hydrochloride salt of 1; otherwise, the two methods are identical. d) Yields refer to column chromatographed product. e) This compound was previously described[8] but no physical properties were reported; Calcd. for $C_{20}H_{21}N$: C, 87.22; H, 7.69; N, 5.09; found: C, 87.16; H, 7.74; N, 5.08.

Although one can employ either 1 (Method A) or 1•HCl (Method B) in this Fischer synthesis of 3, one method may prove to be somewhat superior than the other in specific cases (cf. 3a, 3c). This synthesis of 3 works well in the preparation of 1,3-di- and 1,2,3-trisubstituted indoles but, thus far, has not been successful in the preparation of 1,2-disubstituted indoles. For example, acetone, acetophenone, butane-2,3-dione, and pinacolone all fail to give the corresponding indole under our conditions.

This method of synthesizing 1-benzylindoles 3 is an improvement over the conventional two-step methods (Fischer-indole/N-benzylation), and those two reported one-step methods which either require preformation of the phenylhydrazone[5] or afford lower yields of 3 (with a different catalyst).[4]

EXPERIMENTAL

1-Benzyl-1-phenylhydrazine (1).- To a magnetically stirred solution of 10.8 g (0.100 mol) of phenylhydrazine in 30 mL of distilled water were added 20 g of sodium bicarbonate and 11.9 mL (0.100 mol) of benzylbromide. The resultant mixture was refluxed for 3 h and then allowed to cool to 25°. The layers were separated and the yellow upper layer was diluted with 100 mL of ether, dried over sodium sulfate, and concentrated *in vacuo* to afford 19.6 g (99%) of 1 as a yellow oil. This material was identical with a sample prepared from the commercial hydrochloride salt, and was normally used without further purification. However, on standing several weeks at 0°C the oil darkens and can be distilled, bp 125-130°C/1.5 torr, lit.[9] 157-159°C/4 torr. ^{1}H-N.M.R. ($CDCl_3$): $\delta = 3.31$ (broad s, 2H), 4.49 (s, 2H), 7.10 (m, 10H) ppm.

General Procedure. 9-Benzyl-1,2,3,4-tetrahydrocarbazole (3a).- A magnetically stirred solution of 1.00 g (5.0 mmol) of 1-benzyl-1-phenylhydrazine (1) and 0.50 g (5.1 mmol) of cyclohexanone in 25 mL of glacial acetic acid was heated at 100°C under nitrogen for 2 h. The mixture was allowed to cool to 25°C, treated with 25 mL of distilled water, and stored overnight in the refrigerator. The supernatant liquid was decanted from a yellow oily residue and discarded. The oil was washed with 10 mL of saturated sodium bicarbonate solution and then dissolved in 20 mL of benzene. The benzene solution was dried over sodium sulfate and then chromatographed on a florisil column (benzene) to afford 1.20 g (91%) of 3a as a colorless oil which slowly crystallized on standing, mp 41-43°C, lit.[4] 43-44°C. ^{1}H-N.M.R. ($CDCl_3$): δ = 1.28 (m, 4H), 2.55 (m, 4H), 5.01 (s, 2H), 7.15 (m, 9H) ppm. ^{13}C-N.M.R. ($CDCl_3$): δ = 21.1, 22.1, 23.2 (two carbons), 46.1, 108.8, 109.8, 117.6, 118.7, 120.6, 126.0, 127.0, 127.4, 128.2, 128.5, 135.4, 136.6, 138.2 ppm.

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