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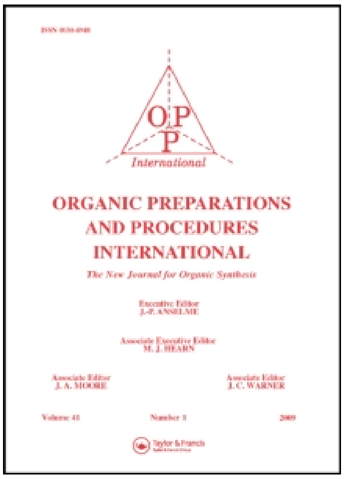

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CONVENIENT PREPARATION OF 2,3-DIALKYLINDOLES

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CONVENIENT PREPARATION OF 2,3-DIALKYLINDOLES

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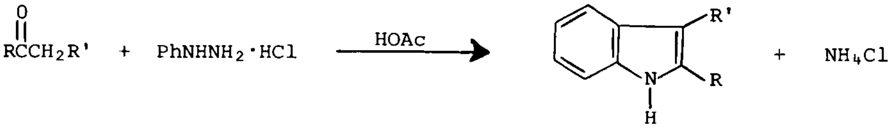
The Fischer indole synthesis is the most commonly used method for the preparation of indoles. Since the initial work of Fischer,[1] the synthesis of indoles usually has been carried out in two steps, first the preparation of the aldehyde or ketone phenylhydrazone followed in a separate step, by treatment of phenylhydrazone with a catalyst at a suitable temperature or with heat alone.[2] Various catalysts used for the second step are well-documented in review articles.[3] In the course of our work on reactions of 2,3-dialkylindoles, we have developed a simple one step procedure for synthesis of several 2,3-dialkylindoles,[4] by heating a mixture of the appropriate ketone, phenylhydrazine hydrochloride and glacial acetic acid under reflux for 3 hrs. Work-up followed by purification provides the pure indoles. In addition to its obvious simplicity ("one-pot"), the present method avoids use of toxic phenylhydrazine. The pure indoles have been obtained in over 60% yield, compared to 35-50% yield obtained in the two-step reaction.[3]



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The generality of this method is demonstrated by preparation of several 2,3-dialkylindoles as shown in the Table.

Table 1. 2,3-Dialkylindoles

R	R'	yield of I (%)	bp(mm) or mp	lit. bp(mm) or mp
CH_3	CH_3	63	106-107°	106°[a]
CH_3	C_2H_5	63	115.5-116° (0.8mm)	120° (1mm)[b]
C_2H_5	CH_3	68	62-65°	64-66°[c]
CH_3	n-C_3H_7	50	123.5-124° (0.8mm)	131-135° (1.1mm)[d]
CH_3	i-C_3H_7	64	120-121° (0.7mm)	120° (0.8mm)[b]
CH_3	n-C_4H_9	81	130-131° (0.8mm)	124-127° (1mm)[e]
CH_3	n-C_5H_{11}	72	144.5-145° (0.9mm)	205-206° (23mm)[f]
CH_3	$CH_2C_6H_5$	80	117-119°	116°[g]

(a) Ref.1. (b) A. H. Jackson and P. Smith, Tetrahedron, 24, 2227 (1964). (c) S. McLean and G. Dmitrienko, Can. J. Chem., 49, 3642 (1971). (d) A. R. Bader, R. J. Bridgwater and P. R. Freeman, J. Am. Chem. Soc., 83, 3319 (1961). (e) V. F. Martynov and I. A. Kastron, J. Gen. Chem. USSR (Engl. transl.), 28, 2119 (1958). (f) N. P. Buu-Hoi and R. Royer, Rec. Trav. Chem. Pays-Bas, 66, 305 (1947). (g) S. Kuroda, J. Pharm. Soc. Jap., 493, 1313 (1923); CA, 17, 3031 (1923).

EXPERIMENTAL

Caution! 2,3-Dimethylindole has an intense and persistent odor. All operations described below might well be carried out in a well-ventilated fume hood.

2,3-Dimethylindole.-A Typical Procedure.-A 1-ℓ, three necked round bottom flask fitted with two efficient condensers and containing 36.0 g. (0.5 mole) of methyl ethyl ketone, 200 ml. of glacial acetic acid and 57.6 g. (0.4 mole) of phenylhydrazine hydrochloride was heated with an oil bath at 90°. After about 25 minutes, the mixture reached 90° and the liquid started to bubble. At this stage the flask was removed from the hot bath and within a few minutes, a rapid reaction began followed by vigorous reflux of acetic acid.[5] After about 10 minutes the exothermic reaction had subsided and the flask was lowered into the hot bath and heated at 90° for an additional 2.5 hrs. The reaction mixture was cooled to room temperature and poured into 600 g. of ice. After 0.5 hour the precipitated solid was collected and washed with 1-ℓ of water. The wet solid was dissolved into 600 ml. of diethyl ether and washed with 150 ml. of 10% aqueous HCl. The organic layer was then washed with two 150 ml. portions of 5% aqueous NaOH and two 150 ml. portions of water. The ethereal layer was finally extracted with brine and dried over magnesium sulfate. After filtration, the solvent was evaporated under vacuum on the rotary evaporator leaving 50.3 g. (91%) of crude solid 2,3-dimethylindole, mp. 101-104°. Recrystallization of the finely powdered material from 500 ml. of petroleum ether (60-80°)[6] yielded 46.0 g. (80%) of an off-white solid, mp. 102-106°. If further purification is desirable, this solid is dissolved in 250 ml. of boiling diethyl ether, treated with charcoal and filtered. The filtrate is concentrated on a steam bath while adding about 300 ml. of petroleum ether (30-60°) in 25 ml. portions until recrystallization begins. The mixture is cooled, filtered using suction and dried in air for a few minutes, giving 34.8 g. (63%) of 2,3-dimethylindole as glistening leaflets, mp. 106-107°, lit.[1] mp. 106°; ν_{max} (Nujol) 3360 cm^{-1} (N-H); δ($CDCl_3$, 13 mg/0.25 ml.) 2.20 (s, 3-Me) and 2.28 (s, 2-Me); λ_{max} (MeOH) 225 (37,000), 280 (8000) and 290 nm (6500).

2-Methyl-3-methyl-d_3-indole was prepared by the same method from methyl ethyl ketone 4,4,4-d_3, δ($CDCl_3$, 13 mg/0.25 ml.) 2.28 (s, 2-Me).[4a]

<u>Other 2,3-Dialkylindoles</u>

On a smaller scale, a mixture of 0.05 mole ketone, 30 ml. of glacial acetic acid and 0.04 mole of phenylhydrazine hydrochloride was refluxed for 3 hrs. and worked-up as described above. The solids were recrystallized from ether-petroleum ether (30-60°) and liquids were purified by fractional distillation. 2,3-Dialkylindoles oxidise readily in air (see note 6^{4b}). Yields and melting or boiling points of indoles prepared by this method are given in the Table. The purity of indoles was checked spectroscopically and by thin layer chromatography (SiO_2, benzene: petroleum ether-1:1).

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4. (a) V. Dave and E. W. Warnhoff, Can. J. Chem., 49, 1911 (1971);
   (b) Idem. ibid. in press.
5. On the present scale with two efficient condensers, external cooling during the vigorous reflux of acetic acid is not necessary. However, on a larger scale, cooling may be necessary and ice-bath should be on hand for immediate cooling of the flask during exothermic reaction.
6. Purification of 2,3-dialkylindole using benzene or chloroform should be avoided since the compound undergoes more rapid aerial oxidation in these solvents giving hydroxylindolenine dimer.[4] Unnecessary exposure to air in any organic solvent should be avoided.

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