Synthesis of 2,3-Disubstituted Indoles Under Mild Conditions

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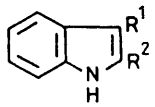
Summary The reaction, at room temperature, between ketone phenylhydrazones and phosphorus trichloride gives the corresponding 2,3-disubstituted indoles in high yields (70—90%).

FOR nearly a century the classical Fischer indolization[1] has been a mainstay in the synthesis of indole and its derivatives. In the course of our studies on phosphorus heterocycles, we have found[2] the unexpected formation of disubstituted indoles from the reaction between 2*H*-1,2,3-diazaphosphole derivatives[3] and alkyl halides. This result prompted us to try indolization using arylhydrazones and phosphorus trichloride. We report herein the result of this very simple reaction which permits the synthesis of 2,3-disubstituted indoles under mild conditions in contrast with the conditions of the classical Fischer method. Treatment of 0·01 mol of a ketone phenylhydrazone in 50 ml of benzene with an equimolar amount of phosphorus trichloride gave the corresponding 2,3-disubstituted indoles (**1**) in good yields (70—90%) after few minutes at room temperature.



(**1**)

The same indoles were obtained in good yields in a one-step reaction when a benzene solution of a ketone and phenylhydrazine was treated with PCl_3 without separation of the hydrazone. The 2,3-disubstituted indoles in the Table were prepared directly in this way, and the yields, based on the amount of ketone used, are for isolated pure indoles obtained by silica gel column chromatography and/or by crystallization. All the indoles were fully characterized by i.r., ^1H n.m.r., and mass spectroscopy and by comparison with authentic samples. Substituting PCl_5 for PCl_3 gave less satisfactory results, the yields of the indoles being lower. Moreover, at present, we have not been able to synthesize unsubstituted and mono-substituted indoles under these conditions. However our synthesis provides a simple, high-yield method for converting arylhydrazones into 2,3-disubstituted indoles that should be applicable to the synthesis of indoles which are also substituted in other positions and establishes that the indole nucleus can be constructed from arylhydrazones under very mild conditions.

TABLE. Reaction of phenylhydrazine with the ketones $R^1CH_2COR^2$ to give the indoles (**1**).

R^1	R^2	% Yield	M.p. (T/°C)
Ph	Ph	75	123—124[a]
Ph	$PhCH_2$	80	100—101[b]
Me	Et	70	64—65[c]
Me	Ph	75	90—92[d]
$Me_2C{=}CHCH_2$	Me	90	Oil[e]

[a] Lit. m.p. 123—124 °C (M. Z. Badr, M. M. Aly, and S. S. S. Salem, *Tetrahedron*, 1977, **33**, 3155). [b] Lit. m.p. 100—101 °C (B. Trenkler, *Justus Liebigs Ann. Chem.*, 1888, **248**, 113). [c] Lit. m.p. 65—66 °C (A. H. Jackson and P. Smith, *Tetrahedron*, 1968, **24**, 2227). [d] Lit. m.p. 91—93 °C (ref. as in footnote c). [e] Lit. b.p. 175—180 °C at 2·5 mmHg (Ng. Ph. Buu-Hoï and R. Royer, *Recl. Trav. Chim.*, 1947, **66**, 305).

We thank the Italian C.N.R. for financial support.

(*Received, 5th March* 1981; *Com.* 246.)

[1] For a review see: B. Robinson, *Chem. Rev.*, 1963, 373.
[2] G. Baccolini and P. E. Todesco, unpublished results.
[3] G. Baccolini and P. E. Todesco, *J. Org. Chem.*, 1975, **40**, 2318.