

## New 'One-pot' Synthesis of Indoles under Non-acidic Conditions ( $S_{RN}1$ reaction)

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**Summary** Indoles can be obtained directly in high yields under non-acidic conditions by application of the  $S_{RN}1$  reaction to *o*-iodoaniline.

THE development of new synthetic methods for the construction of the indole nucleus, particularly under non acidic conditions, is an area of current interest. Various types of reaction have been described<sup>1</sup> including the intramolecular yne reaction.<sup>2</sup> We now report a simple high-yield method based on nucleophilic aromatic substitution *via* a radical intermediate ( $S_{RN}1$  reaction)<sup>3</sup> derived from *o*-iodoaniline.

In a typical experiment, a solution of the appropriate potassium enolate (7 mmol) was prepared under nitrogen in 50 ml of liquid ammonia at  $-33^\circ\text{C}$  using  $\text{R}^1\text{CH}_2\text{COR}^2$  (7 mmol) and freshly sublimed potassium *t*-butoxide (7 mmol). *o*-Iodoaniline was then introduced. After irradiation for a short time (*ca.* 15 min) the mixture was quenched with  $\text{NH}_4\text{Cl}$  and worked up. The results are reported in the Table.

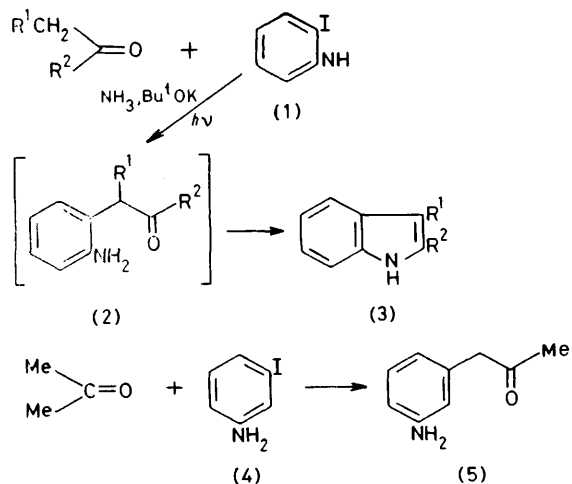
TABLE. Reaction of *o*-iodoaniline (**1**) with potassium enolates to give the cyclized products (**3**).<sup>a</sup>

Irradiation time/min <sup>b</sup>	Product	R <sup>1</sup>	R <sup>2</sup>	% Yield <sup>c</sup>
13	( <b>3a</b> )	H	H	75 (49) <sup>d</sup>
15	( <b>3b</b> )	H	Me	100 (83)
10	( <b>3c</b> )	H	Pr <sup>1</sup>	100 (78)
18	( <b>3d</b> )		$-\text{[CH}_2\text{]}_4-$	40 (36) <sup>e</sup>

<sup>a</sup> Reaction of *m*-iodoaniline (**4**) with acetone gave the product (**5**) (66% isolated yield) and recovered (**4**) (20–25%); neither the cyclized product (**3b**) nor aniline were detected. <sup>b</sup> Hanau 100 W high-pressure mercury lamp. <sup>c</sup> Yield of product relative to starting iodoaniline, determined by g.l.c. Yields in parentheses are for pure products isolated by column chromatography, identical (i.r., n.m.r., and mass spectroscopy) with authentic samples. For (**3c**): m.p.  $74^\circ\text{C}$  [lit., M. H. Palmer and P. S. McIntyre, *J. Chem. Soc. (B)*, 1969, 446, m.p.  $74^\circ\text{C}$ ] and (**5**) (from *m*-iodoaniline) spectral data were in agreement with the structures assigned. *o*-Iodoaniline was not recovered in the reactions to give (**3a–d**), nor was aniline detected, except in the cases indicated. <sup>d</sup> Aniline (25%) also formed. <sup>e</sup> Aniline (59%) also formed.

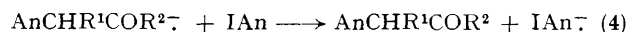
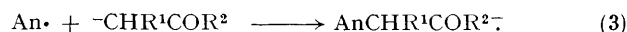
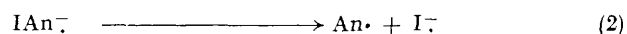
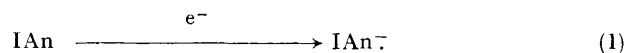
The initial product of the reaction is the *ortho* substituted aniline (**2**), which, on work-up, undergoes cyclisation to give the indoles and the tetrahydrocarbazole (**3a-c**) (**3d**).

The following criteria serve to establish that the reaction is indeed an  $S_{RN}1$  reaction (Scheme). (i) No reaction occurs without u.v. irradiation. (ii) The reaction is almost completely quenched by oxygen even with u.v. light. (iii) The substitution reaction is regioselective. The alternative mechanism involving an aryne intermediate would have led to a mixture of *ortho* [ultimately (**3**)] and *meta* substitution product (**5**), and would not have required any photostimulation. We have verified that under similar experimental conditions *m*-iodoaniline (**4**) yields



only the *meta* substitution product (**5**) with no trace of (**3b**).<sup>4</sup>

Therefore, the general reaction scheme [equations (1)–(4)] proposed by Bunnett<sup>3</sup> for the  $S_{RN}1$  mechanism is also operative in the case of the iodoanilines (IAN = iodoaniline) (**1**) and (**4**).



Formation of aniline was observed in reactions leading to indole (**3a**) and carbazole (**3d**) but not in the case of (**3b**) and (**3c**); its origin is probably from  $\text{An}^\bullet$  (step 2). It is generally known that aromatic  $S_{RN}1$  reactions occur for phenyl halides bearing alkyl, alkoxy, phenyl, carboxylate, and benzoyl substituents, whereas dimethylamino-, hydroxy-, and nitro-groups are known to interfere.<sup>5</sup> Here we have shown that with the free primary amino function of iodoaniline the aromatic  $S_{RN}1$  reaction can also occur. Thus, we have notably enlarged the scope of the reaction.

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<sup>1</sup> M. Mori, K. Chiba, and Y. Ban, *Tetrahedron Letters*, 1977, 1037; M. Mori and Y. Ban, *ibid.*, 1979, 1133; Y. Ito, K. Kobayashi, and T. Saegusa, *ibid.*, p. 1039; A. G. Schultz, and W. K. Hagman, *J. Org. Chem.*, 1978, **43**, 3391; P. J. Gassman, T. J. Van Bergen, D. P. Gilbert, and B. W. Cue, Jr., *J. Amer. Chem. Soc.*, 1974, **96**, 5495; P. J. Gassman and T. J. Van Bergen, *ibid.*, p. 5508; P. J. Gassman, D. P. Gilbert, and T. J. Van Bergen, *J.C.S. Chem. Comm.*, 1974, 201.

<sup>2</sup> R. Huisgen and H. Konig, *Chem. Ber.*, 1959, **92**, 203; R. Huisgen, H. Konig, and N. Bleeker, *ibid.*, p. 424; J. F. Bunnett and B. F. Hrutford, *J. Amer. Chem. Soc.*, 1961, **83**, 1691, and references therein; I. Fleming and M. Woolias, *J.C.S. Perkin I*, 1979, 827; 829.

<sup>3</sup> For recent reviews see: J. F. Bunnett, *Accounts Chem. Res.*, 1978, **11**, 413; J. F. Wolfe and D. R. Carver, 'Organic Preparations and Procedures International,' 1978, p. 227.

<sup>4</sup> This experiment was carried out by M. T. Le Goff. A full account of the work will be published elsewhere.

<sup>5</sup> J. F. Bunnett and J. E. Sundberg, *Chem. Pharm. Bull. (Japan)*, 1975, **23**, 2620; R. A. Rossi, R. H. de Rossi, and A. F. Lopez, *J. Org. Chem.*, 1976, **41**, 3371.