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A Novel Method of Indole Ring System Construction: One-Pot Synthesis of 4- and 6-Nitroindole Derivatives *via* Base Promoted Reaction Between 3-Nitroaniline and Ketones

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Abstract: Base promoted condensation of ketones $RCOCH_2R'$ with 3-nitroaniline results in formation of the corresponding 4- and 6-nitro-2-R-3-R'-indoles. This multistep process apparently includes oxidative nucleophilic substitution of hydrogen in the aromatic ring of the aniline by the enolate anion and subsequent cyclization of the so formed *ortho*-aminoketone intermediate to indoles *via* a Baeyer type reaction. © 1999 Elsevier Science Ltd. All rights reserved.

Key words: Indoles, nitroarenes, enolates.

The indole ring system is present in numerous natural products, pharmaceuticals, plant protection agents, dyes etc., and so there is a continuous interest in methods of indole synthesis.[2] Because of the importance of indole derivatives there are many methods for the synthesis of the indole ring system. Nevertheless, new, simple and efficient ways for constructing indole rings are still in great demand. Of particular interest are methods for the synthesis of indoles substituted in both the carbocyclic and heterocyclic rings, including nitroindoles. Since the nitro group is perhaps the most versatile substituent, which can easily be converted into a variety of other groups, nitroindoles are attractive starting materials in the synthesis of more elaborate molecules.[3] There are few reported methods for the synthesis of nitroindoles.[4] Direct nitration of indole and its derivatives is applicable mostly to the synthesis of 5- and 7-nitroindoles [5a] and 3-acetyl-6-nitroindole.[5b] A convenient synthesis of nitroindoles exists in the Fischer cyclization of nitrophenylhydrazones of ketones to give 5-nitroindoles or mixtures of 4- and 6-nitroindoles, depending on the position of the nitro group in the starting hydrazone.[6] A useful procedure for the synthesis of 4- and 6-nitroindoles from 2-methyl-3- or 5-nitroanilines was reported by Bergman.[7] We have reported a method for the synthesis of 4- and 6-nitroindoles based on the conversion of the amino group of 3-nitroaniline to an isonitrile and subsequent vicarious nucleophilic substitution of hydrogen (VNS) in the reaction with α-halocarbanions.[8] The *ortho*- and *para*- nitrobenzylic carbanions produced in the VNS reaction undergo cyclization *via* addition to the isocyano group to form the indole. However, this method requires prior preparation of nitrobenzoisonitriles and the indoles so obtained always contain hydrogen at the 2-position.

Here we report a new very simple method for the direct conversion of 3-nitroaniline **1** into substituted nitroindoles *via* condensation with ketones under strongly basic conditions.[9] For example, when a solution of **1** and acetophenone **2a** in DMSO was treated with *t*-BuOK a moderately exothermic reaction took

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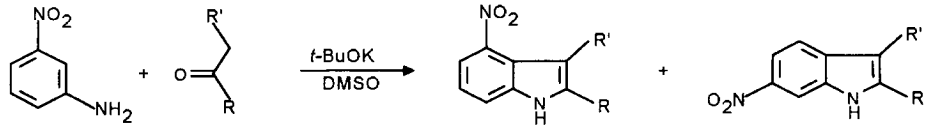
place. Standard work-up and chromatographic isolation gave 2-phenyl-4-nitroindole **3a** in 62 % yield. It should be stressed that the isomeric 2-phenyl-6-nitroindole **4a** was found only in a minute quantity (below 1 %). Many other ketones **2b-g** react with **1** in a similar way to give mixtures of the corresponding 4- and 6-nitroindoles depending on R and R' (eq 1). Some examples of this reaction are collected in Table 1.



(eq 1)

1 **2a-g** **3a-g** **4a-g**

R,R' = Ph, H, **a**; 2-pyridyl, H, **b**; Me, H, **c**; *t*-Bu, H, **d**; Me, Me, **e**; Et, Me, **f**; $(CH_2)_4$, **g**.

Table 1. Reaction of 3-nitroaniline with various ketones

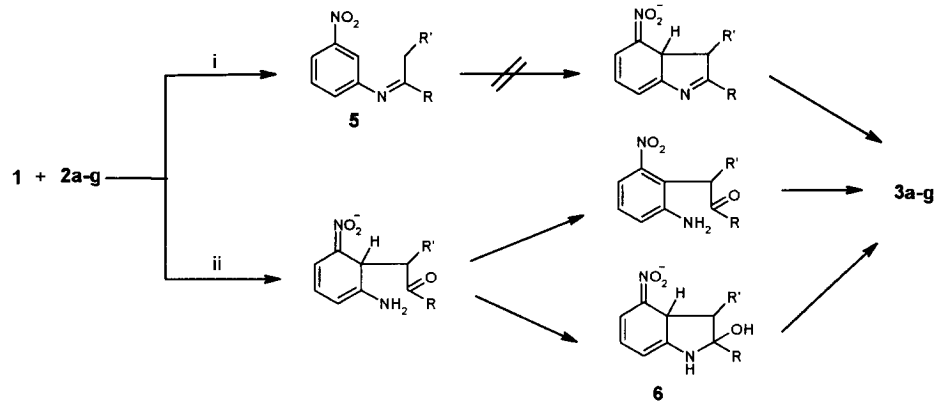
Substrate	R	R'	Time (h)	Products	Yield (%)[a]	mp (°C) [b]
2a	Ph	H	2	**3a**	62	205 (206) [4a]
2b	2-Pyridyl	H	5	**3b** [10]	53	167
2c	Me	H	4	**3c**	67	202 (198) [4a]
2d	*t*-Bu	H	3	**3d** [11]	42	173
2e	Me	Me	4	**3e**	32	173 (175) [3b]
				4e	26	142 (142) [3b]
2f	Et	Me	3	**3f**	33	175 (175) [3d]
				4f	30	165 (164) [3d]
2g	$(CH_2)_4$		3	**3g**	34	152 (153) [3c]
				4g	13	169 (172) [3c]

[a]Isolated yields based on **1**. *[b]Melting points are uncorrected, literature mp for known compounds are given in brackets.*

The formation of indoles according to eq 1 is obviously a multistep process where one of the steps should be an oxidative nucleophilic substitution of hydrogen (ONSH) with an enolate anion.[12] Two principal pathways appear to be feasible for this transformation: (i) initial addition of the amino group of **1** to the carbonyl group of **2** resulting in the formation of an imine **5** which, upon deprotonation, undergoes subsequent intramolecular ONSH to give indoles; (ii) addition of the enolate anion to the nitroaromatic ring resulting in ONSH followed by intramolecular condensation of the ketone so obtained with the *ortho*-amino group *via* a Baeyer type reaction (Scheme 1).[13] Pathway (i) can be excluded because the imine **5a**, separately prepared from acetophenone **2a** and **1**, under the typical reaction conditions gave a complex mixture of products in which indoles **3a** or **4a** were not detected by TLC. The reaction proceeding *via* path (ii) requires that addition of the enolate anion to the nitroaniline ring takes place mainly in vicinity of the amino group. It appears that the produced σ^H adducts are stabilized by way of interaction between the amino and carbonyl group.

Moreover, one can assume that such interaction can result in C-N bond formation giving hypothetical σ^H adduct **6** containing an aminal moiety, dissociation of which to **1** and **2**, associated with the departure of a nonstabilized carbanion should be very unfavourable.

Scheme 1



Oxidation followed by elimination of water gives the final indoles **3a-g**. Since the reaction proceeds without any external oxidant, one can suppose that the σ^H adducts are oxidized by atmospheric oxygen. Interestingly, the reaction of **1** with methyl ketones **2a**, **2b**, **2c** and **2d** gave almost exclusively 4-nitroindoles **3a-d**, with only traces of the 6-nitro isomers **4a - 4d** being detected. Obviously, addition of the enolate occurs mainly in position 2- of **1**. This orientation corresponds with many previous observations that VNS in 3-nitroanisole, 3-nitrohalobenzenes and 3-nitro-N,N-dimethylaniline proceeds preferentially at position 2-.[14] On the other hand, more sterically demanding enolates of **2e**, **2f** and **2g** add in both positions 2- and 6- of **1** so that mixtures of 4- and 6-nitroindoles **3e-g** and **4e-g** are produced. Another important feature of this process is the strong preference for the reaction of enolates of methyl alkyl ketones *via* the secondary carbon. Indeed, in the reaction of ethyl methyl ketone **2e** only the 2,3-dimethyl derivatives **3e** and **4e** are obtained and possible isomeric 2-ethylindole derivatives were not isolated. We expect that future studies of this new reaction will provide an efficient general methodology for indole synthesis, which could be of significant practical value due to the availability of the starting materials and simplicity of the procedure .[15]

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(10) **4-Nitro-2-(2-pyridyl)indole (3b).** ^{1}H NMR ($CDCl_3$) δ 10.38 (br s, 1H), 8.64 - 8.60 (m, 1H), 8.14 (d, 1H, J_1 = 8.02 Hz, J_2 = 0.83 Hz), 7.97 (d, 1H, J_1 = 8.00 Hz, J_2 = 1.09 Hz), 7.83 (d, 1H, J_1 = 7.48 Hz, J_2 = 1.76 Hz), 7.79 - 7.76 (m, 1H), 7.67 (d, 1H, J_1 = 8.05 Hz, J_2 = 0.85 Hz), 7.33 - 7.25 (m, 2H). MS m/z 239, 209, 193. Anal. Calcd for $C_{13}H_9N_3O_2$: C, 65. 30; H, 3.76; N, 17.57. Found: C, 65.00; H, 3.67; N, 17.21.

(11) **2-*t*-Butyl-4-nitroindole (3d).** ^{1}H NMR ($CDCl_3$) δ 8.50 (br s, 1H), 8.10 (d, 1H, J_1 = 8.09 Hz, J_2 = 0.84 Hz), 7.64 (d, 1H, J_1 = 7.93 Hz, J_2 = 0.85 Hz), 7.22 - 7.14 (d, 1H, J = 8.02 Hz), 7.07 - 7.04 (d, 1H, J_1 = 2.42 Hz, J_2 = 0.87 Hz), 1.45 (s, 9H). MS m/z 218, 203, 186, 157. Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.05; H, 6.42; N, 12.84. Found: C, 65.78; H, 6.35; N, 12.61.

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(15) **General Experimental Procedure**. To a stirred solution of **1** (5 mmol) and ketone **2** (10 mmol) in DMSO (10 mL), 1.12 g (10 mmol) *t*-BuOK was added in one portion. After stirring for 2 - 5 h at room temperature the red coloured reaction mixture was poured into cold water, slightly acidified (pH 4 - 5), the products were extracted with EtOAc, dried with $MgSO_4$ and then isolated with use of column chromatography (SiO_2, toluene/hexane, 1:1).