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An Expeditious One-Pot Synthesis of *N*-Substituted 6-Nitroindoles from Indolines

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Summary. This paper reports an one-pot method for the concomitant alkylation – oxidation (aromatization) of indolines, particularly effective to get easy access to *N*-alkyl-6-nitroindoles, which are useful platforms in medicinal chemistry. *N*-alkyl-6-nitroindoles are obtained in good yield (64–91%) by reaction at room temperature in non-degassed *DMF* of 6-nitroindoline, an alkyl halide, and NaH as base. The presence of NaH appears to be essential for a high yield conversion.

Keywords. Heterocycles; Indole; Indoline; Oxydation; Aromatization.

Introduction

Indole represents a privileged structural element in medicinal chemistry with a considerable number of applications in drug discovery [1]. Indole templates constitute a major family of targets with a broad array of pharmacological activities, which have made them medicinally important and synthetically challenging. In this connection, we recently developed tetracyclic structures with a central *N*-substituted indole moiety in order to design products with anti-proliferative activity against cancer cells (Scheme 1, structure **B**, structure **D** [2]). The central indole system, because of its inherent poor chemical stability, had to be generated at the end of the scheme from an indoline precursor.

Various methods can effectively be employed to synthesize indoles from indolines such as oxidation by MnO_2 [3], $CuCl_2$ [4], *DDQ* [5], trichloroisocyanuric acid (*TCCA*) [6], phenylseleninic anhydride [7], or catalytic dehydrogenation using a metal catalyst such as Pd/C [8] or *Raney* nickel [9]. Taken together, these results suggest that a feasible approach to *N*-substituted indolic derivatives may consist in the concomitant alkylation – oxidation (aromatisation) of indolines [10].

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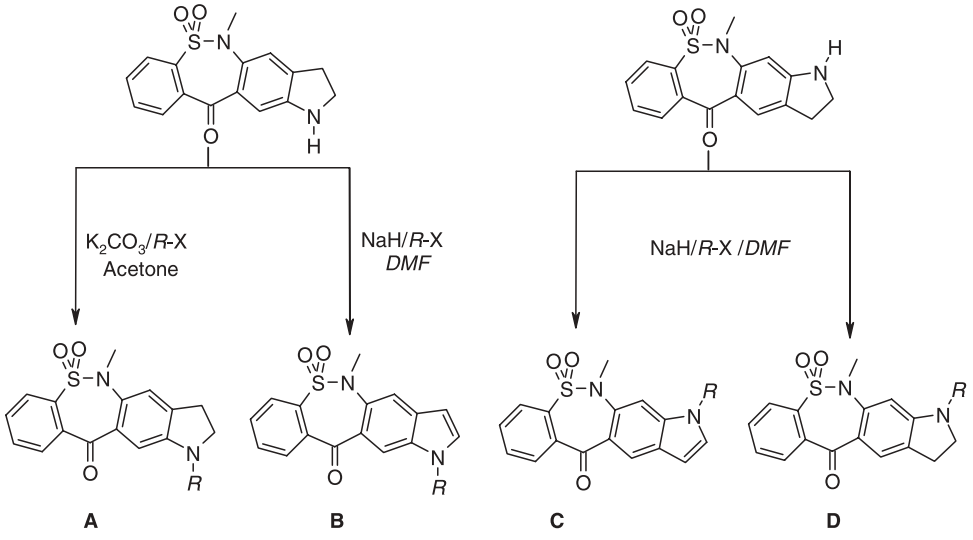
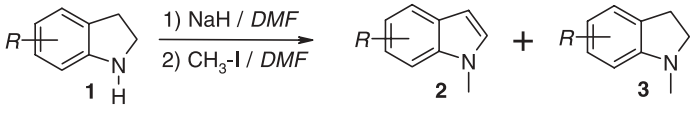


Scheme 1

Results and Discussion

In this approach applied to structure **A**, among the various methods to alkylate indoline [11], we first used K_2CO_3 in acetone and, after a long reaction time (4 days), we obtained the corresponding *N*-substituted indolines. In order to reduce the reaction time, we decided to use NaH as base in *DMF* which, surprisingly enough, was found to promote access to *N*-substituted indoles (structure **B**) in an extremely efficient one-pot *N*-substitution – oxidation process (80–90%, Scheme 1). However, upon application of the same procedure to compounds of structure **C** (which are closely related to **B**), use of NaH in *DMF* did not lead to the desired the *N*-substituted indoles but rather the *N*-substituted indolines (structure **D**). It was consequently anticipated that the electronic demand of the substituents was of major importance for the success of this concomitant *N*-substitution – oxidation process.

In an effort to ascertain the synthetic value of this procedure, a study involving simple indoline model compounds (Table 1) was undertaken to investigate the application of this substitution – oxydation. From commercially available indolines, the corresponding *N*-methyl indoles (**2a**–**2d**) and/or *N*-methyl indolines (**3a**–**3d**) were obtained in the presence of NaH (1.5 equiv.) and methyl iodide (1.5 equiv.) in *DMF* [12]. As indicated in Table 1, indoline **1a** gave a ∼50:50% (^{1}H NMR) ratio of the *N*-substituted indole **2a** [13] and *N*-substituted indoline **3a** [14]. In contrast, the electron-withdrawing nitro group in position 5 (**1c**) and electron-donating methoxy



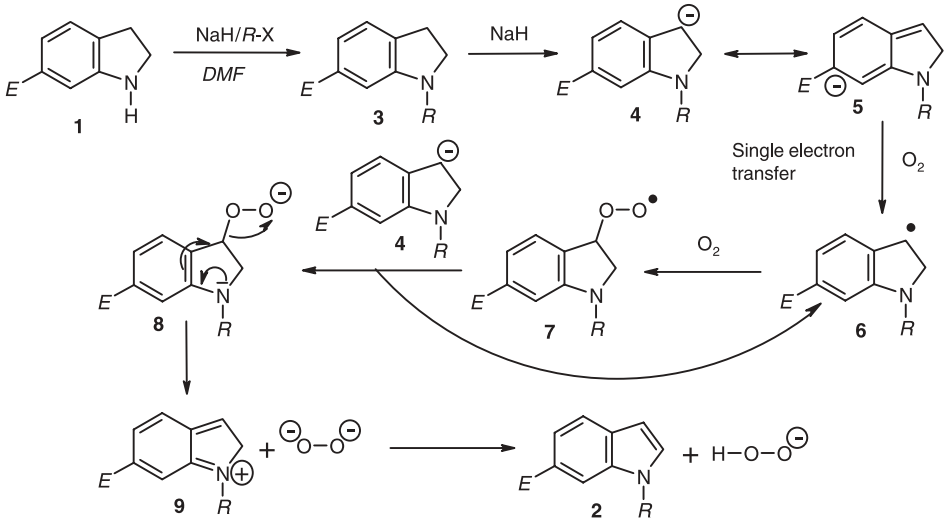
Scheme 2

Table 1. NaH-mediated alkylation – oxydation of indolines (**1a**–**1d**)

Indoline	*R*	Substituted indole, yield %	Substituted indoline, yield %
1a	H	**2a**: 50	**3a**: 50
1b	5-OMe	**2b**: 0	**3b**: 75
1c	5-NO_2	**2c**: 0	**3c**: 90
1d	6-NO_2	**2d**: 83	**3d**: 0

group in position 5 (**1b**) gave exclusively *N*-substituted indolines **3b** [15] and **3c** [16, 17] in 75 and 90% yield. In accordance with this observation, a previous observation [12] indicated that 5-bromoindoline with alkyl halides in the presence of NaH gave exclusively *N*-alkyl-5-bromoindolines. Indoline substituted with a strong electron-withdrawing substituent such as the nitro group in position 6 (**1d**) clearly promoted this concomitant substitution – oxidation process giving **2d** with 83% yield. All these facts underscore the importance of the positioning of the electron-withdrawing substituent for the success of the aromatisation.

It is noteworthy that **1c** and **1d** show opposite behavior (Table 1) and this provides further insight into the mechanistic aspect of these transformations. The more acidic **1c** is selectively *N*-methylated while **1d**, with the 6-NO_2 group activating the benzylic methylene in position 3, undergoes both methylation and oxidation. Moreover, **1a** is selectively *N*-methylated (and not oxidized) when treated with methyl iodide in the presence of potassium carbonate in acetone or *DMF*. It should be kept in mind also that oxidized compounds are always isolated in their *N*-alkylated form. Consequently, it can be advanced that *N*-alkylation is a primary event in the overall process. Effectively, *N*-methyl-6-nitroindoline was oxidized into *N*-methyl-6-nitroindole in the presence of NaH. On the basis of all the aforementioned arguments, we can therefore propose a tentative mechanism (Scheme 3)

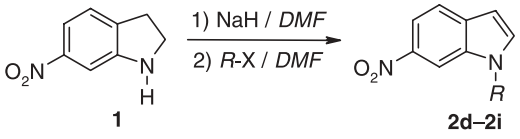


Scheme 3. Mechanism of the one-pot oxidation – *N*-substitution process

involving air oxygen. It is known, indeed, that *DMF* is a good solvent of oxygen. This mechanism proposed here appears in clear agreement with *Cannon*'s previous observation that indolines are air oxidized in strongly basic media [18].

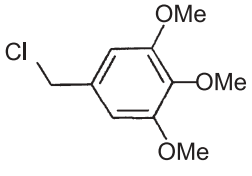
In this mechanism, the first reaction is the nucleophilic substitution of the indole. In the second step, NaH initiates the oxidation by withdrawing a proton in the benzylic position 3 of the *N*-substituted indoline **3** to give the corresponding anion **4**. Structure **4** (in resonance with **5**) combines with molecular oxygen *via* a single electron transfer to produce the radical species **6**. This radical **6** then interacts with another oxygen molecule, which leads to the peroxyradical **7**. Subsequent recombination of **7** with **4** generates the peroxyanion **8** simultaneously with the production of **6**. Elimination of the peroxydianion from **8** affords the iminium **9**, which is then converted to indole **2** by the abstraction of a proton by the peroxydianion, giving rise to a hydroperoxide anion.

A key feature in this mechanism is the proposal of a benzylic radical. Quantum-mechanical calculations at AM1 and PM3 level show that the 6-NO_2 substitution favors the radical species **6** while the 5-NO_2 substitution destabilizes the same radical species. Semi-empirical quantum-mechanical calculations were performed with MOPAC 6.0 using the AM1 and PM3 Hamiltonians for **1c** and **1d**. Atom-centered partial charges and molecular electrostatic potentials (ESP) were calculated by the method of *Mulliken* as implemented in MOPAC 6.0. A conformational search was performed for each compound. The capto-dative stabilisation of the benzylic radical could be appreciated by calculating the partial charge difference (Δq) of the carbon neighboring the benzylic carbon [19]. Indeed, in 5-nitroindoline, Δq was equal to 0.014 while for the 6-nitro species this figure was 0.056, which represents a 4.1 fold increase.



Scheme 4

Table 2. *N*-Alkylindoles **2d–2i** synthesis from 6-nitroindoline (**1**) and alkyl halides

Products	*R*-X	Yield %
2d	CH_3–I	83
2e	C_2H_5–I	86
2f	C_3H_7–I	91
2g	C_4H_9–I	88
2h	C_6H_5–CH_2–Br	75
2i		64

The reaction was exemplified with several alkyl halides and the results are presented in Table 2. All *N*-alkyl-6-nitroindoles **2d**–**2i** were obtained in fair to good yields (64–91%). As 6-nitroindoline is effectively obtained by nitration of indoline in 90% yield [20] by a simple nitration in HNO_3–H_2SO_4 in the presence of a radical scavenger, the method reported here clearly offers a viable route to *N*-alkyl-6-nitroindoles and subsequent key applications in medicinal chemistry as illustrated by several recent disclosures [21, 22]. Our finding is in the line of a recent report by *Samet et al.* who described the aromatisation of the strongly electron-deficient 4,6-dinitro-1-(p-toluenesulfonyl)indoline by air oxidation at 70°C in pyridine.

Conclusion

In conclusion, we have developed a one-pot method for alkylation – oxydation of *N*-substituted indolines that is especially effective to get access to *N*-alkyl-6-nitroindoles in good yield by reacting at room temperature in *DMF* 6-nitroindoline, an alkyl halide, and NaH as base. The reaction was found to proceed smoothly and is likely to be extended to other indoline derivatives bearing electron-withdrawing groups in position 6. In view of the simplicity of the procedure and the high yields obtained, the procedure has some value for the production of indole compound ensembles using fast parallel synthesis techniques.

Experimental

Melting points were determined with a Büchi 535 capillary melting point apparatus and are uncorrected. ^{1}H NMR (300 MHz) spectra were obtained from solutions in $CDCl_3$ on a Bruker AC 300P apparatus. The NMR spectra were recorded at ambient temperature using *TMS* as internal reference. IR spectra were recorded using a dispersion of the product in KBr disks by means of a Perkin-Elmer Model 297 spectrometer. R_f values refer to thin layer chromatography plates (5.0×10 cm, 250 μm, silica gel 60 F_{254}), developed in the solvent system indicated. Mass spectra were recorded on a Mat SSQ710 mass spectrometer. All compounds reported had IR, ^{1}H and ^{13}C NMR, MS, and elemental analysis data consistent with their structures. The experimental elemental analysis figures were found to be within 0.4% of the calculated values. All reagents were purchased from Aldrich. **2a**, **3a**, **3b**, and **3c** mentioned in the text were identical with the compounds already described in Refs. [13–16].

Preparation of N-Substituted Indoles

A solution of 1.0 g of 6-nitroindoline (6 mmol) in 10 cm^3 of anhydrous *DMF* was added dropwise to a solution of 0.27 g of NaH (9 mmol) in 5 cm^3 of *DMF*. The solution was stirred at room temperature while a red color slowly developed. After 3 h, 0.56 cm^3 of CH_3I (9 mmol) diluted in 5 cm^3 of anhydrous *DMF* was added dropwise over 10 min and the mixture was stirred for 16 h at room temperature. The solution was evaporated *in vacuo* to dryness and 50 cm^3 of H_2O were added. The resulting precipitate was collected by filtration, washed with 100 cm^3 of H_2O, and recrystallized from ethanol.

N-Methyl-6-nitroindole (**2d**, $C_9H_8N_2O_2$)

Yield 0.9 g (83%), mp 73–74°C, TLC: R_f (CH_2Cl_2) = 0.75; ^{1}H NMR: $\delta = 3.90$ (s, 3H), 6.60 (d, $J = 2.72$ Hz, 1H), 7.36 (d, $J = 2.72$ Hz, 1H), 7.66 (d, $J = 8.72$ Hz, 1H), 8.02 (dd, $J = 2.18$, 8.72 Hz, 1H), 8.33 (d, $J = 2.18$ Hz, 1H) ppm; MS (70 eV): $m/z = 176$ (M^+).

N-Ethyl-6-nitroindole (**2e**, $C_{10}H_{10}N_2O_2$)

Yield 0.94 g (86%), mp 78–79°C, TLC: R_f (CH_2Cl_2) = 0.78; ^{1}H NMR: δ = 1.02 (m, 3H), 4.05 (m, 2H), 6.61 (d, J = 3.10 Hz, 1H), 7.41 (d, J = 3.10 Hz, 1H), 7.67 (d, J = 8.55 Hz, 1H), 8.03 (dd, J = 1.93, 8.55 Hz, 1H), 8.33 (d, J = 1.93 Hz, 1H); MS (70 eV): m/z = 190 (M^+).

N-Propyl-6-nitroindole (**2f**, $C_{11}H_{12}N_2O_2$)

Yield 0.95 g (91%), mp 65–66°C, TLC: R_f (CH_2Cl_2) = 0.8; ^{1}H NMR: δ = 0.99 (m, 3H), 1.92 (m, 2H), 4.19 (m, 2H), 6.60 (d, J = 3.37 Hz, 1H), 7.41 (d, J = 3.37 Hz, 1H), 7.67 (d, J = 8.65 Hz, 1H), 8.02 (dd, J = 1.93, 8.65 Hz, 1H), 8.33 (d, J = 1.93 Hz, 1H); MS (70 eV): m/z = 204 (M^+).

N-Butyl-6-nitroindole (**2g**, $C_{12}H_{14}N_2O_2$)

Yield 0.94 g (88%), mp 60–61°C, TLC: R_f (CH_2Cl_2) = 0.81; ^{1}H NMR: δ = 0.99 (m, 3H), 1.38 (m, 2H), 1.88 (m, 2H), 4.21 (m, 2H), 6.60 (d, J = 3.27 Hz, 1H), 7.40 (d, J = 3.27 Hz, 1H), 7.66 (d, J = 8.72 Hz, 1H), 8.02 (dd, J = 1.64, 8.72 Hz, 1H), 8.30 (d, J = 1.64 Hz, 1H); MS (70 eV): m/z = 218 (M^+).

N-Benzyl-6-nitroindole (**2h**, $C_{15}H_{12}N_2O_2$)

Yield 0.84 g (75%), mp 72–73°C, TLC: R_f (CH_2Cl_2) = 0.81; ^{1}H NMR: δ = 4.81 (s, 2H), 6.60 (d, J = 3.27 Hz, 1H), 7.40 (d, J = 3.27 Hz, 1H), 7.52 (m, 3H), 7.66 (d, J = 8.72 Hz, 1H), 7.88 (m, 2H), 8.02 (dd, J = 1.64, 8.72 Hz, 1H), 8.30 (d, J = 1.64 Hz, 1H); MS (70 eV): m/z = 252 (M^+).

N-(3,4,5-Trimethoxybenzyl)-6-nitroindole (**2i**, $C_{18}H_{18}N_2O_5$)

Yield 1.46 g (64%), mp 95–96°C, TLC: R_f (CH_2Cl_2) = 0.65; ^{1}H NMR: δ = 3.78 (s, 6H), 3.81 (s, 3H), 5.34 (s, 2H), 6.36 (s, 2H), 6.67 (d, J = 3.08 Hz, 1H), 7.42 (d, J = 3.08 Hz, 1H), 7.70 (d, J = 8.78 Hz, 1H), 8.04 (dd, J = 1.76, 8.78 Hz, 1H), 8.34 (d, J = 1.76 Hz, 1H); MS (70 eV): m/z = 342 (M^+).

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