A New General Approach for the Synthesis of 2-Substituted-3*H*-indol-3-one *N*-Oxide Derivatives

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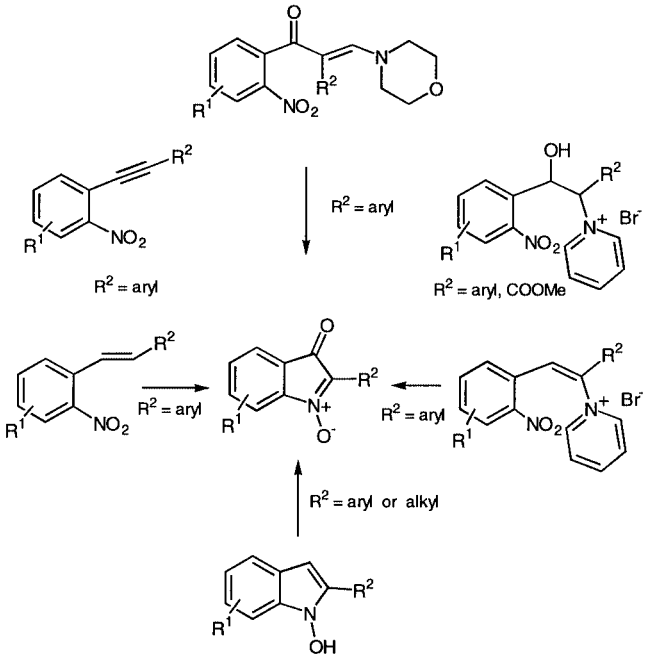
Abstract: 2-aryl (phenyl, 1,3-benzodioxolyl) and 2-alkyl (ethyl, *sec*-butyl)-3*H*-indol-3-one *N*-oxides were synthesized by a new general method involving a reductive intramolecular cyclization reaction of *ortho*-diketo nitrobenzene derivatives.

Key words: isatogens, nitrone, α-diketone, intramolecular cyclization, oxidation

Introduction

2-Substituted-3*H*-indol-3-one *N*-oxides, more frequently named isatogens, are brightly colored solids that do not occur naturally. Some of them show a variety of biological properties such as significant activity against a range of bacteria,[1] mycobacteria[2] and fungi[3] and are also able to antagonize the relaxant response to adenosine-5-triphosphate in mammals.[4] In addition, they are also able to trap oxygen and carbon-centered radicals as reported in different works.[5]

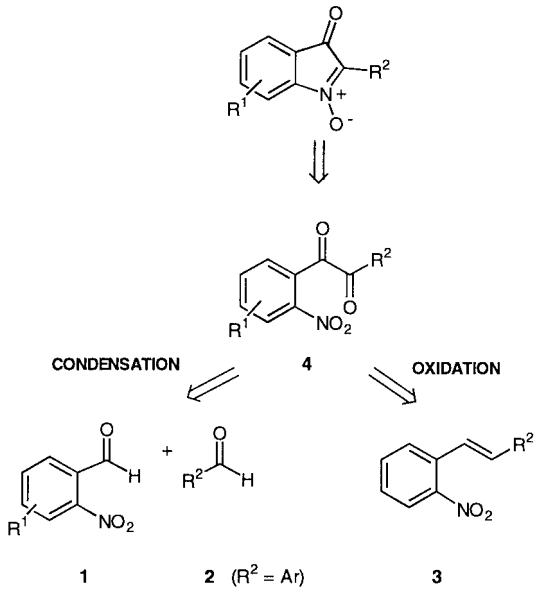
To date, this type of molecule has been synthesized via two main methods involving either the oxidation of a 1-hydroxy-2-substituted indole[6] or the intramolecular cyclization of an *ortho*-substituted nitrobenzene precursor[7] (Scheme 1). However, the first strategy, applicable to both alkyl and aryl substituted isatogens, requires a multi-step preparation of the indole intermediate and the second synthetic approach is limited to 2-aryl 3*H*-indol-3-one *N*-oxides. Besides, in most cases, the cyclization reactions afford the desired nitrone in poor yields or require several days to reach completion. Thus, synthetic routes towards isatogens having a wide scope and efficiency are still rare. We thus report here a simple and general approach to the synthesis of 2-substituted-3*H*-indol-3-one *N*-oxides.



Scheme 1

A retrosynthetic analysis of isatogens led us to propose the preparation of the cyclic nitrone by a cyclization reaction between a hydroxylamine and a carbonyl group. Therefore, α-diketone **4** appears as a pivotal intermediate to this approach (Scheme 2).

In order to test the feasibility of this strategy, we firstly tried to obtain 2-nitro benzil intermediates by condensation of two aromatic aldehydes **1** and **2** (Scheme 2). For this purpose, we have synthesized the 1,3-dithiane of piperonal aldehyde. However, under basic conditions (BuLi) this acyl anion equivalent failed to react with 6-nitropiperonal to give the protected form of the desired diketone

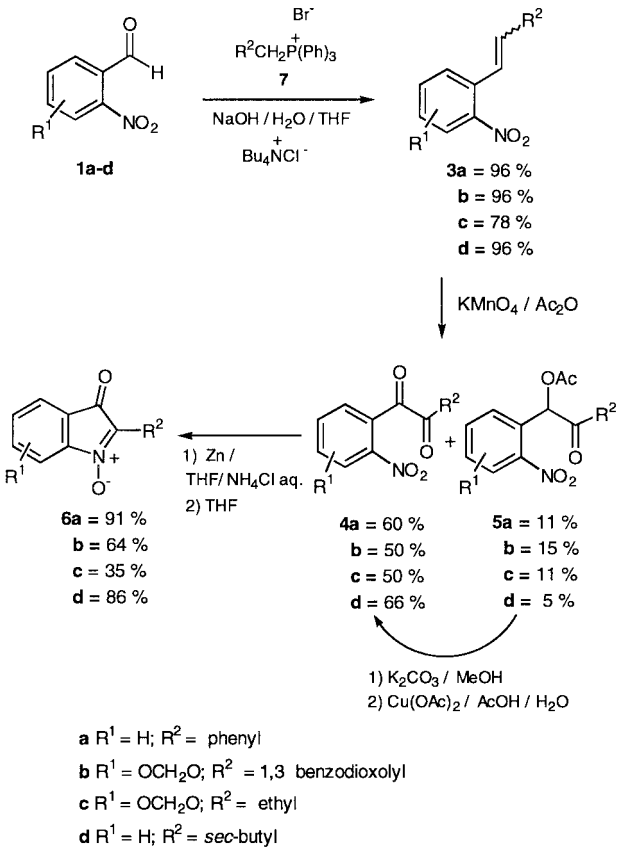


Scheme 2

4b. Attempts to employ piperonal as electrophilic partner and 6-nitropiperonal as acyl anion equivalent were also unsuccessful. We also tried to obtain dione **4** by direct oxidation of the corresponding alkene **3** (Scheme 2) which was in turn prepared in excellent yield by an olefination reaction[8] between *ortho*-nitrobenzaldehyde derivatives **1** and Wittig phosphonium bromides **7** (Scheme 3). Recently, Filimonov et al.[9] have described a method to transform carbon-carbon multiple bonds into 1,2-diketones by action of HBr/DMSO or I_2/DMSO. All our attempts to obtain α-diketone from stilbene **3** under these conditions failed. In contrast, oxidation of a mixture of *Z/E*-stilbene **3a** with potassium permanganate in acetic anhydride,[10] afforded **4a** in 60% yield and ketoacetate **5a** in 11% yield. These compounds were easily separated by column chromatography on silica gel (eluent: cyclohexane /ethyl acetate 80:20). The position of the acetate group in **5a** could be unequivocally determined by EI/MS since the bond between the two central benzylic carbon atoms is easily cleaved under electron impact conditions. Indeed, the EI/MS spectrum of **5a** showed two peaks at *m/z* 105 and 135 relative to fragment ions C_7H_5O and $C_8H_7O_2$, respectively. Finally, reduction of **4a** with Zn(0)/NH_4Cl for 20 min and then heating of the hydroxylamine intermediate in THF for 3 hours, cleanly afforded **6a**[11] (91%) whose spectral data are comparable with the literature. Even though a competitive process resulting from attack of the oxygen atom at another carbonyl group might be expected,[12] it did not interfere in this case. The hydroxylamine intermediate was not isolated since cyclization to isatogen takes place spontaneously under workup conditions.

A similar result was also obtained with a substituted aryl derivative. Piperonal intermediate **4b** gave isatogen **6b**[13] in 64% yield. The structure of **6b** was confirmed by an unambiguous synthesis via the pyridinium ethanol intermediate (Scheme 1) from which **6b** could only be obtained in a poor yield (~10%).

In the first part of this study, the carbon atom attached to the 2-position of the isatogen molecule is sp^2 hybridized. In order to extend this route to the preparation of 2-substituted isatogen molecules with an sp^3 carbon atom attached to the 2-position, we investigated the preparation of alkyl isatogens where R is ethyl or *sec*-butyl. The corresponding diketone intermediates **4c** and **4d** were prepared as reported above in 50% and 66% yield, respectively. In fact, oxidation of **3c** and **3d** by the action of $KMnO_4$ is accompanied by the formation of ketoacetate **5**. It is interesting to note that the competitive acetylation reaction is regioselective in all cases and that the ketoacetate derivative **5** can be easily recycled to give the corresponding diketone.[14] For instance, using methanolic potassium carbonate, the ketoacetate **5c** was saponified to the corresponding α-hydroxy ketone which was in turn oxidized by cupric acetate to dione **4c** with an overall yield of 68%. Under the same cyclization conditions as above, diketones **4c** and **4d** led to the formation of the desired isatogen derivatives **6c**[15] and **6d**,[16] respectively.



Scheme 3

Conclusion

The strategy developed in this work, based on the reductive intramolecular cyclization of *ortho*-nitrobenzene precursors, provides a simple and versatile route to isatogens bearing both aryl and alkyl substituents in the 2-position.

Acknowledgement

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References and Notes

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(11) **General experimental procedure for isatogen preparation. Synthesis of 2-phenyl-3*H*-indol-3-one *N*-oxides:** To a solution of **4a** (0.150 g, 0.59 mmol) in THF (10 mL) was added a 10% aq solution of NH_4Cl (11 mL) and Zn (0.150 g). After 20 min of stirring at r.t., the mixture was filtered and the two liquid phases separated. The organic phase was dried (Na_2SO_4) and concentrated in vacuum. The residue was dissolved in THF (10 mL) and heated under reflux for 4 h. Evaporation of the solvent and purification of the crude product by column chromatography (SiO_2, cyclohexane/ethyl acetate 80:20) gave 0.120 g (91%) of **6a** as a red solid. Rf: 0.58 (cyclohexane/ethyl acetate 80:20). M.p. = 180 °C, m.p. lit. = 186 °C. IR (KBr) cm^{-1}: 3064.3; 1719.3 (ν C = O); 1700.4 (ν C = O); 1596.4; 1520.8 (ν C = N); 1470.3; 1382.1; 1311.3; 1179.2 (ν N-O); 1070.8; 872.6; 754.7. ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm): 8.67-8.62 (m, 2H); 7.74 - 7.45 (m, 7H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 114.8 (CH), 121.9 (CH), 122.8 (C), 125.9 (C), 127.8 (2 × CH), 128.5 (2 × CH), 130.6 (CH), 131.1 (CH), 133.0 (C), 134.7 (CH), 147.8 (C), 186.7 (C). EI/MS *m/z* : 223 (M^+); 206 (M^+ - 17); 105.

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(13) Isatogen **6b** in solution (CH_2Cl_2) presents a violet color. Rf: 0.38 (cyclohexane/ethyl acetate 80:20). M.p. = 202-204 °C (decomposition). IR (KBr) cm^{-1}: 2915.1; 1702.8 (ν C = O); 1471.7; 1301.9; 1259.4 (ν C-O-C); 1188.7; 1103.8; 1033.0; 806.6. ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm): 5.99 (s, 2H); 6.10 (s, 2H); 6.88 (d, *J* = 8.5 Hz, 1H); 6.96 (s, 1H); 7.10 (s, 1H); 8.20 (d, *J* = 1.4 Hz, 1H); 8.28 (dd, *J* = 8.5 Hz and 1.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 97.5 (CH), 101.7 (CH_2), 102.5 (CH), 103.3 (CH_2), 107.5 (CH), 108.8 (CH), 116.6 (C), 120.4 (C), 123.5 (CH), 131.3 (C), 145.0 (C), 147.8 (C), 149.5 (C), 149.6 (C), 153.1 (C), 186.2 (C). FAB/MS *m/z*: 312 (M^++1); 295 (M^+ - 16); 149.

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(15) Compound **6c**: dark red solid. Rf: 0.41 (cyclohexane/ethyl acetate 80:20). M.p. = 136 °C. IR (KBr) cm^{-1}: 3084.9; 2896.5; 1698.1 (ν C = O); 1542.5 (ν C = N); 1471.7; 1462.3; 1358.5; 1306.6; 1287.7 (ν C-O-C); 1217.0; 1122.6; 1075.5; 1037.7; 957.5. ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm,): 1.18 (t, *J* = 7.6 Hz, 3H); 2.61 (q, *J* = 7.6 Hz, 2H); 6.11 (s, 2H); 6.95 (s, 1H); 7.08 (s, 1H). NMR ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 9.9 (CH_3), 15.2 (CH_2), 97.5 (CH), 102.5 (CH), 103.2 (CH_2), 117.0 (C), 139.1 (C), 144.4 (C), 149.6 (C), 152.5 (C), 185.9 (C). EI/MS *m/z* : 219 (M^+); 202 (M^+ - 17); 174; 120; 62.

(16) Compound **6d** : yellow solid. Rf : 0.59 (cyclohexane / ethyl acetate 80:20). M.p. = 101-102 °C. IR (KBr) cm^{-1}: 3102.1; 3083.2; 2960.3; 1700.4 (ν C = O); 1601.1 (ν C = C); 1530.3 (ν C = N); 1459.4; 1431.0; 1374.3; 1161.6; 1076.6; 906.4; 764.7; 533.1. ^1H NMR ($CDCl_3$, 200 MHz) : δ (ppm) : 0.95 (d, *J* = 6.6 Hz, 6H); 2.17 (m, 1H); 2.55 (d, 2H); 7,54 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 22.8 (2 × CH_3), 26.8 (CH), 30.2 (CH_2), 113.9 (CH), 121.4 (CH), 123.1 (C), 131.0 (CH), 134.4 (CH), 139.0 (C), 147.4 (C), 187.1 (C). EI/MS *m/z* : 203 (M^+), 186 (M^+ - 17), 161, 144, 116, 89, 76, 50, 43.

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