Tandem radical addition/cyclization of 1-(2-iodoethyl)indoles and pyrroles with methyl acrylate under Fenton-type conditions

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Dedicated to Professor Joseph M. Muchowski on the occasion of his 65th birthday, and in recognition of his valuable contribution to chemistry in Mexico
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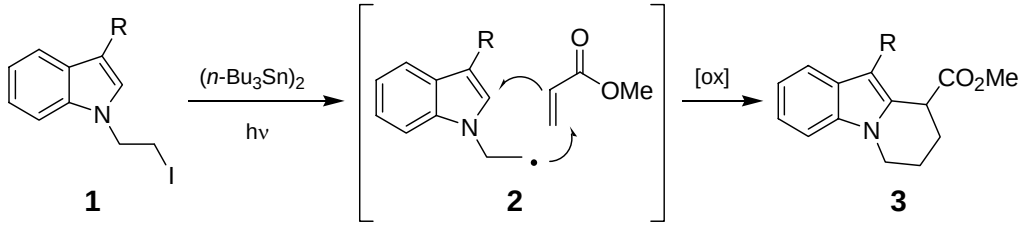
Abstract
Benzindolizidine and indolizidine systems were generated in moderate yields by a consecutive radical addition/cyclization/oxidation process from substituted 1-(2-iodoethyl)indoles and 1-(2-iodoethyl)pyrroles, respectively, with methyl acrylate under Fenton-type conditions.

Keywords: Free radicals, radical addition, Fenton-type oxidation, benzindolizidine, indolizidine

Introduction

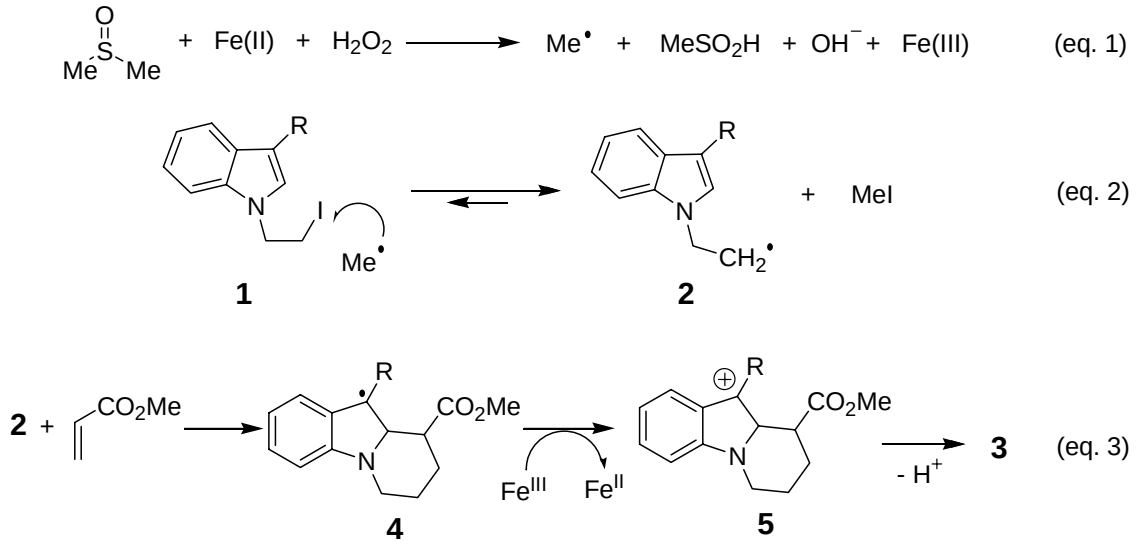
Over the last several years, addition of radicals to an aromatic nucleus followed by oxidation to restore the aromatic system have received considerable synthetic attention.[1] In this context, in a recent communication we have described a straightforward access to the benzindolizidine **3,** featuring a tandem radical addition-cyclization process of 1-(2-iodoethyl)indoles and methyl acrylate (Scheme 1).[2] In this reaction, the primary radical **2** adds to the double bond of methyl acrylate and the so formed electrophilic radical undergoes cyclization onto the aromatic system yielding the desired product in the course of a not well understood oxidation mechanism.[1–3]



Scheme 1

In this process, two new carbon-carbon bonds are created in one step from readily accessible starting materials. Indeed, more recently, Bennasar and coworkers[3] have constructed the cyclopenta[*b*]indole ring system in the course of a similar radical cascade process comprising an intermolecular 2- and 3-indolylacyl radical addition-oxidative cyclization, also under reaction conditions mediated by *n*-Bu_6Sn_2.

In our experiments some inconveniences using hexa(*n*-butyl)ditin have been encountered: In certain cases, the reaction is inhibited without any apparent reason, and there is also the problem of the toxicity of tin compounds and their disposal. In order to overcome the later problems we decided to examine alternative conditions to accomplish the same process. In this context, the application of Fenton-type conditions to acchieve an oxidative radical cyclization onto pyrrole and indole systems as reported by Muchowski et al.[4] a few years ago was of special importance for our purpose. This Fenton-type technology not only works in a tin-free environment, but also solves the well known problem of the oxidative re-aroamatization step in the reaction mechanism, which arises in tin-mediated reactions.[1–3] This process is supported by the pioneering work of Torsell and co-workers,[5] who demonstrated that methyl radicals could be efficiently generated from DMSO under Fenton conditions (Scheme 2, eq. 1) and also in the successful work of Minisci et al.[6] and Bacciochi et al.[7] by adding virtually any alkyl radical under similar conditions to heteroaromatic compounds when the reaction was carried out in the presence of appropriate alkyl iodides.



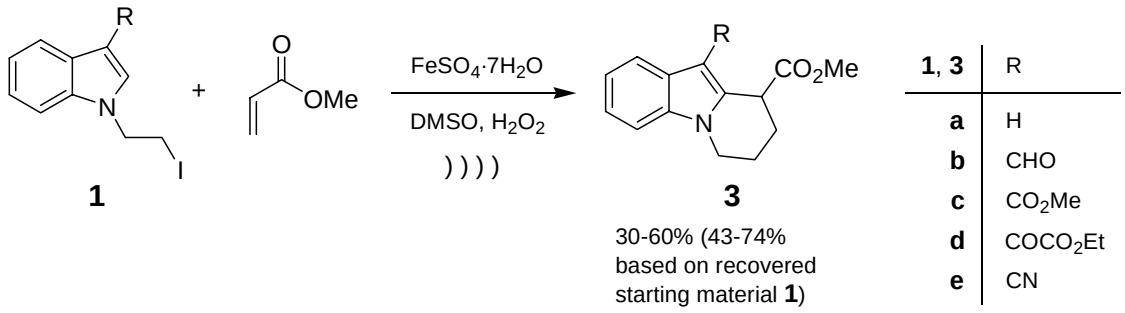
Scheme 2

On the basis of the favorable equilibrium of eq. 2 (Scheme 2) we reasoned that radical **2** could be produced from iodide **1** under these Fenton-type conditions. Consequently, the benzylic radical **4**, formed in the course of the addition/cyclization cascade process, would be oxidized by

the action of Fe(III) and afford the carbocation intermediate **5**, which would provide the desired product **3** by losing a proton (Scheme 2, eq. 3).[4]

Results and Discussion

Ferrous sulfate heptahydrate (1 equiv.) was suspended in a solution of 3-formyl-1-(2-iodoethyl)-indole **1b**[8] and methyl acrylate (2 equiv.) in dimethylsulfoxide (Scheme 3). A 30% solution of hydrogen peroxide (10 equiv.) was added dropwise to the solution, within a 15 min period with sonication.[9] In preliminary attempts to effect the desired reaction sequence, we observed that the reaction ceased after the addition of hydrogen peroxide. Indeed, the desired product was isolated in low yield along with a considerable amount of recovered starting material **1b**. In order to improve the conversion of the starting material further quantities of hydrogen peroxide were added but failed to reinitiate the reaction. Finally, it was found that the reaction can be reinitiated upon addition of Fe(II) salt (1 equiv.) together with hydrogen peroxide (10 equiv) within a period of fifteen minutes. This second addition of reagents improved the conversion, however it was not enough to consume all starting material. After four consecutive additions the reaction stopped, and addition of further quantities of reagents failed to reinitiate it. Besides, it was observed that the addition of more methyl acrylate (2 equiv) after the second addition of reagents enhanced the product yields.

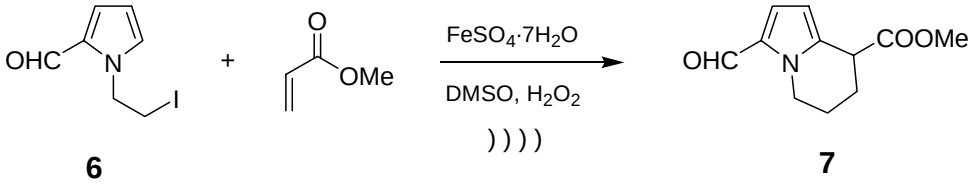


Scheme 3

During the addition of hydrogen peroxide the reaction temperature rose to 40 ºC; hence, the reaction mixture should be allowed to cool to room temperature before further addition. With these experimental modifications moderate yields of the benzindolizidine derivatives **3** were obtained together with small but in some cases considerable quantities of recovered starting material. In general, overall yields were better than those obtained using reaction conditions mediated by *n*-Bu_6Sn_2.[2]

In the light of the above results, we extended this method to 1-(2-iodoethyl)-1*H*-pyrrole-2-carbaldehyde (**6**) (Scheme 4). This compound was subjected to oxidative conditions as described above, and the expected indolizidine derivative **7** was isolated in moderate yield as the major

product. Moreover, this process provides a rather short access to the functionalized indolizidine ring system. Consequently, this process represents a very attractive entry to this alkaloid family, many members of which exhibit interesting biological activity.[10]

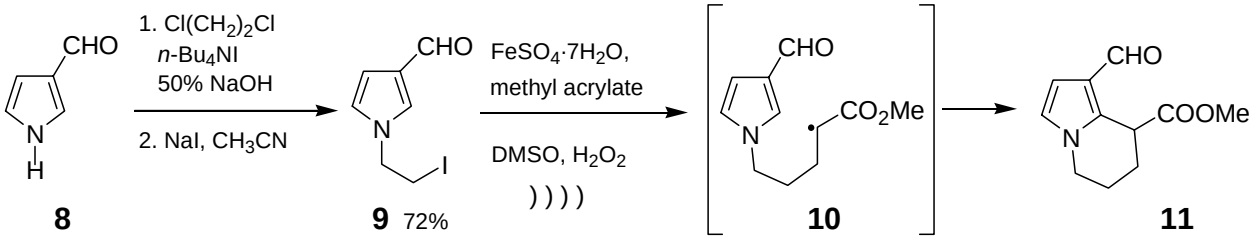


6 **7**

48% (78% based on recovered **6**)

Scheme 4

Muchowski et al.[4] have shown that nucleophilic radical addition at 2-C is particularly favorable on 3-acylated pyrroles due to a large LUMO coefficient at this site.[11] However, it was also shown that the system has significant and approximately equal HOMO coefficients at 2-C and 5-C. In view of that, it was interesting to study the regiochemistry of the addition reaction of the electrophilic radical **10** to 3-formylpyrrole. On the basis of a favorable SOMO/HOMO interaction attack at both sites to equal extends was expected. Thus, 1-(2-iodoethyl)-*1H*-pyrrole-3-carbaldehyde **9** was synthesized by alkylation of 3-formylpyrrole **8**[12] followed by halogen exchange (Scheme 5).[8, 13] Surprisingly, the main cyclization product was **11**, reflecting the attack of the electrophilic radical at position C-2, and no trace of a product resulting from attack at 5-C was detected.

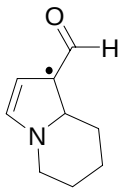


8 **9** 72% **10** **11**

50% (68% based on recovered **9**)

Scheme 5

The proton NMR spectrum of compound **11** shows two doublet signals at δ 6.5 and δ 6.6 ($J_{4,5}$ = 3.0 Hz, characteristic of a 2,3-disubstituted pyrrole. For reasons which we do not understand, it seems this specific cyclization reaction is not entirely governed by Frontier



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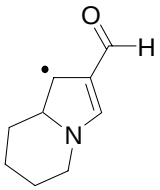

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Molecular Orbitals. Apparently, this result might be better explained on the basis that the radical generated by addition at 2-C of **12** is more stabilized (it is stabilized by both the carbonyl group and C=C bond) than that generated by addition at 5-C of **13** (no delocalization into the acyl moiety).[14]

Conclusions

A radical addition/oxidative cyclization cascade reaction is described, which provides straight forward access to benzindolizidine and indolizidine derivatives from readily accessible starting materials and under tin-free conditions. To the best of our knowledge these experiments represent the first example of a cascade reaction conducted under Fenton-type conditions.

Experimental Section

General Procedures. ^{1}H NMR spectra of $CDCl_3$ solutions were recorded with a Varian Unity instrument at 200 and 300 MHz (internal tetramethylsilane as reference). IR spectra were obtained with a Nicolet FT-IR Magna 750 spectrometer. Chromatography was carried out using silica gel. Mass spectra were recorded with a JEOL JEM-AX505HA instrument at a voltage of 70 eV.

1-(2-Iodoethyl)-1*H*-pyrrole-3-carbaldehyde (9). Aqueous sodium hydroxide (50%, 5 mL) was added at 0 ºC to a stirred solution of pyrrole-3-carbaldehyde (**8**,[13] 0.50 g, 5.26 mmol) and tetra(*n*-butyl)ammonium iodide (1.89 g, 5.26 mmol) in 1,2-dichloroethane (10 mL). The mixture was vigorously stirred and heated at reflux for 1.5 h. The cooled mixture was diluted with water and extracted with dichloromethane. The organic phase was washed successively with 2 N hydrochloric acid and water, dried over sodium sulfate, and evaporated *in vacuo*. The residue was percolated through a short column of silica gel using hexane/ethyl acetate (8:2) as eluent. 1-(2-Chloroethyl)-1*H*-pyrrole-3-carbaldehyde was obtained as colorless oil (0.66 g, 80%). IR ($CHCl_3$): $\tilde{\nu}$ 1665, 1535 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ: 3.78 (2H, t, *J* = 7.0 Hz), 4.25 (2H, t, *J* = 7.0 Hz), 6.66 (1H, dd, *J* = 1.7, 3.0 Hz), 6.72 (1H, t, *J* = 2.7 Hz), 7.35 (1H, t, *J* = 1.9 Hz), 9.76 (1H, s); EI-MS: *m/z* (%) 157 (100, M^+).

To a stirred solution of 1-(2-chloroethyl)-1*H*-pyrrole-3-carbaldehyde (0.5 g, 3.18 mmol) in acetonitrile (10 mL) was added dry NaI (0.95 g, 6.3 mmol). The vigorously stirred suspension was heated at reflux for 18 h. The cold mixture was diluted with water and extracted with ether. The organic phase was washed with $Na_2S_2O_3$ solution (10%), dried over sodium sulfate and evaporated in vacuo. The residue was percolated through a short column of silica gel using hexane/ethyl acetate (8:2) as eluent. 1-(2-Iodoethyl)-1*H*-pyrrole-3-carboxaldehyde (**9**) was obtained as colorless oil (0.71 g, 90%). IR ($CHCl_3$): $\tilde{\nu}$ 1672, 1528 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 3.42 (2H, t, *J* = 7.0 Hz), 4.29 (2H, t, *J* = 7.0 Hz), 6.66 (1H, dd, *J* = 1.9, 3.76 Hz), 6.70 (1H, t, *J* = 2.7 Hz), 7.35 (1H, t, *J* = 1.9 Hz), 9.76 (1H, s); EI-MS: *m/z* (%) 249 (100, M^+).

Oxidative radical cyclization of the iodides 1, 6, 9. General procedure

To an ultrasonically irradiated solution of 3-substituted 1-(2-iodoethyl)indoles **1a-e,**[8] of 1-(2-iodoethyl)-1*H*-pyrrole-2-carbaldehyde (**6**)[8] or 1-(2-iodoethyl)-1*H*-pyrrole-3-carbaldehyde (**9**) in DMSO (15 mL/mmol of starting material **1**, **6**, or **9**), containing methyl acrylate (2 equiv.) and $FeSO_4 \cdot 7H_2O$ (1 equiv.) was added dropwise with a pipette a solution of hydrogen peroxide (30%, 10 equiv.) in such a way that the reaction temperature did not exceed 40 ºC (usually within a 15 min period). The reaction mixture was allowed to cool to room temperature, and $FeSO_4 \cdot 7H_2O$ (10 equiv.) was added followed by dropwise addition of H_2O_2 (30%, 10 equiv.). Again, the reaction mixture was allowed to cool to room temperature, and more methyl acrylate (2 equiv.), DMSO (7.5 mL/mmol) and $FeSO_4 \cdot 7H_2O$ (1 equiv.) were added followed by dropwise addition of H_2O_2 (30%). A final addition of $FeSO_4 \cdot 7H_2O$ (1 equiv.) and H_2O_2 (30%, 10 equiv.) was made as described before. .When the fourth addition was completed, the reaction mixture was poured into water and extracted with dichloromethane, and the extract was washed with aqueous sodium sulfite solution (10%), dried over sodium sulfate and evaporated in vacuo. The residue was then purified by column chromatography on silica gel (hexane/EtOAc). Spectral data of the indole derivatives **3a-e** and the 3-formyl-5,6,7,8-tetrahydroindolizine derivative **7** were identical with those reported previously.[2]

Methyl 6,7,8,9-tetrahydropyrido[1,2-*a*]indole-9-carboxylate (3a).[2] Yellow oil (30%), along with recovered starting material **1a** (45%). IR ($CHCl_3$): $\tilde{\nu}$ 1625, 1643 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.52–7.58 (1H, m), 7.05–7.30 (3H, m), 6.39 (1H, s), 405–409 (3H, m), 3.77 (3H, s), 2.0-2.32 (4H, m); EI-MS: *m/z* 229 (%) (55, M^+).

Methyl 10-formyl-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-9-carboxylate (3b).[2] Colorless oil (37%), along with recovered starting material **1b** (50%); IR ($CHCl_3$): $\tilde{\nu}$ 2449, 1734, 1647, 1437, 1203, 1172, 754 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 10.21 (1H, s), 8.14–8.17 (1H, m), 7.29–7.34 (3H, m), 435–4.58 (1H, m), 4.26–4.33 (1H, m), 3.94–4.03 (1H, m), 3.74 (3H, s, OCH_3), 2.10–2.46 (4H m); EI-MS: *m/z* 257 (%) (90, M^+); HRMS (FAB+): Calcd for $C_{15}H_{15}O_3N$: 257.1052; found: 257.1052.

Dimethyl 6,7,8,9-tetrahydropyrido[1,2-*a*]indole-9,10-dicarboxylate (3c).[2] White solid (60%), mp 134–136 ºC, along with recovered starting material **1c** (24%); IR ($CHCl_3$): $\tilde{\nu}$ 3246, 2947, 2922, 1668, 1528, 774 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 8.09–8.19 (1H, m), 7.23–7.32

(3H, m), 461–4.65 (1H, m), 4.23–4.33 (1H, m), 3.90–4.00 (1H, m), 3.88 (3H, s), 3.73 (3H, s), 2.11–2.36 (4H, m); EI-MS: *m/z* 287 (%) (20, M^+); HRMS (FAB+): Calcd for $C_{16}H_{17}O_4N$: 287.1158; found: 287.1153.

Methyl 10-[ethoxy(oxo)acetyl]-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-9-carboxylate (3d).[2] Yellow oil (35%) along with recovered starting material **1d** (20%); IR ($CHCl_3$): $\tilde{\nu}$ 3419, 2925, 2854, 1736, 1442, 1200, 1165, 771 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.74–7.82 (1H, m, H-9), 7.26-7.36 (3H, m), 4.57–4.64 (1H, m), 4.46 (2H, c, *J* = 7.1), 4.22–4.36 (2H, m), 3.74 (3H, s), 2.20–2.47 (4H m,), 1.47 (3H, t, *J* = 7.1); EI-MS: *m/z* 329 (%) (43, M^+); HRMS (FAB+): Calcd for $C_{18}H_{19}O_5N$: 329.1263; found: 329.1255.

Methyl 10-cyano-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-9-carboxylate (3e).[2] Colorless oil (51%) along with recovered starting material **1e** (20%). IR ($CHCl_3$): $\tilde{\nu}$ 2958, 2210, 1647, 1742, 1453, 1203, 1174, 757 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.69–7.81 (1H, m,), 7.27–7.39 (3H, m), 418–4.29 (2H, m,), 3.93–4.06 (1H, m), 3.80 (3H, s,), 2.04–2.47 (4H m,); EI-MS: *m/z* (%) 254 (40, M^+); HRMS (FAB+): Calcd for $C_{15}H_{14}O_2N_2$: 254.1055; found: 254.1062.

Methyl 3-formyl-5,6,7,8-tetrahydroindolizine-8-carboxylate (7).[2] Yellow oil (48%; 78% based on recovered starting material **6**). The instability of **7** did not permit full characterization. IR ($CHCl_3$): $\tilde{\nu}$ 1734 (CO), 1655 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.87–2.20 (4H, m,), 3.76 (3H, s, CH_3O), 3.91 (1H, m, 8-H), 4.39 (2H, m), 6.17 (1H, d, *J* = 4.2 Hz), 6.90 (1H, d, *J* = 4.2 Hz, 2-H), 9.47 (1H, s, CHO); EI-MS: *m/z* (%) 207 (30, M^+), 148 (100).

Methyl 1-formyl-5,6,7,8-tetrahydroindolizine-8-carboxylate (11). Yellow oil (50%; 68% based on recovered starting material **9**). The instability of **11** did not permit full characterization. IR ($CHCl_3$): $\tilde{\nu}$ 1735 (CO), 1662 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.93–2.25 (4H, m, 6-H, 7-H), 3.72 (3H, s, CH_3O), 3.83–4.11 (2H, m, 5-H), 4.28 (1H, m, 8-H), 6.56 (1H, d, *J* = 3.06 Hz, 2-H), 6.6 (1H, d, *J* = 3.04 Hz, 3-H), 9.77 (1H, s, CHO); EI-MS: *m/z* (%) 207 (40, M^+), 148 (100); HRMS (FAB+): Calcd for $C_{11}H_{13}NO_3$ (M^++1): 208.0974; found: 208.0967.

Acknowledgments

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