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A tandem radical addition/cyclization process of 1-(2-iodoethyl)indoles and methyl acrylate

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Abstract

Benzindolizidine systems are generated in moderate yields by a hexabutylditin mediated consecutive radical addition, cyclization, oxidation process from 1-(2-iodoethyl)indoles and methyl acrylate. © 2000 Published by Elsevier Science Ltd.

Keywords: radical cycloaddition; radical addition; hexabutylditin; indole systems.

The alkyl radical addition to double bonds activated by one or more electron attracting groups is a synthetic process, which has considerable utility.[1] The intramolecular oxidative radical addition to the indole system[2a–f] and some others heteroaromatic systems has also recently been shown to have preparative importance,[2] and has been used for natural product synthesis.[2a,c] The one pot coupling of these two processes has, however, rarely been studied.[2b,e,f] We envisage such a process as one in which the stabilized radical **3** (Scheme 1), derived by the intermolecular addition of the indolylethyl radical **2** to methyl acrylate, would add intramolecularly to C-2 of the indole nucleus to generate benzindolizidine derivatives **5**, after rearomatization of the tricyclic radical **4**. This article describes some of our preliminary results in this area.

In a few preliminary attempts to effect the desired sequence of reactions, tributyltin hydride and AIBN were added slowly to a benzene solution of **1** and methyl acrylate but in most cases the major new compound produced was the 3-substituted-1-ethylindole **6** resulting from the reductive deiodination of the starting material. In contrast, sun-lamp irradiation of a solution (0.02 M) of the 1-(2-iodoethyl)indoles[3] **1** in degassed refluxing benzene, containing methyl acrylate (4 equiv.), and hexabutylditin[4] (2 equiv.) gave the tricyclic indolizidine derivatives **5**[5] as the major products (Table 1), presumably by a mechanism of the type shown in Scheme 1.

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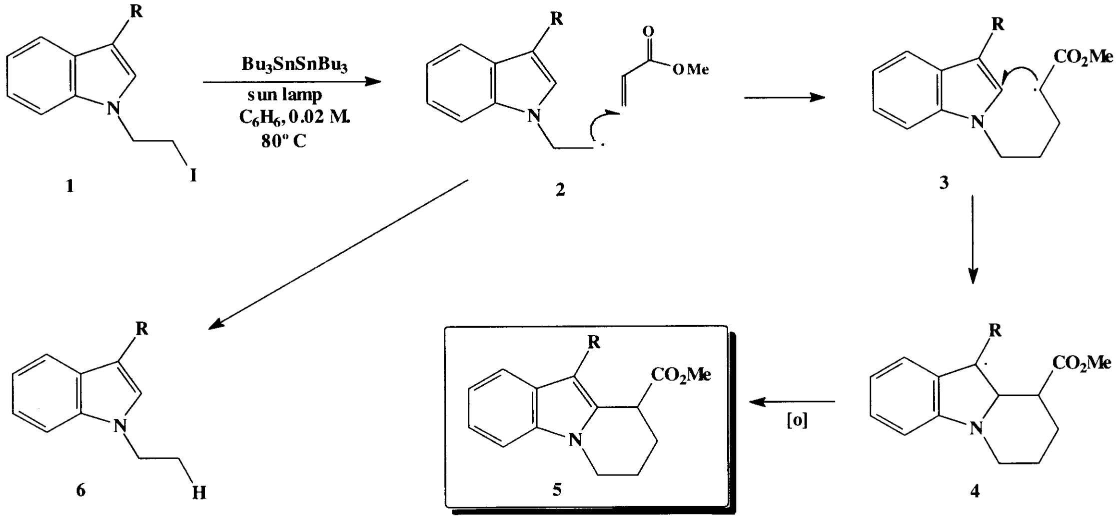


Scheme 1.

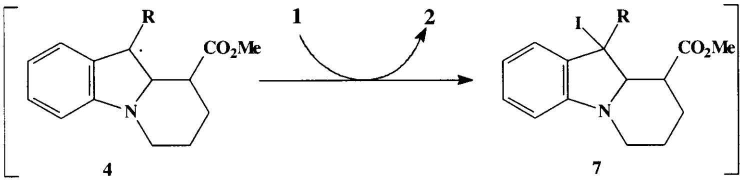
Table 1
Tandem addition/cyclization radical process[a]

Entry	Substrate	R	Cyclization product yield (%)	Reduction product yield (%)	Starting material recovered (%)
1	**1a**	H	**5a** (15)	–	–
2	**1b**	CHO	**5b** (45)	**6b** (31)	–
3	**1c**	CO_2Me	**5c** (60)	Traces	(11)
4	**1d**	$COCO_2Et$	**5d** (32)	–	–
5	**1e**	CN	**5e** (54)	–	(10)

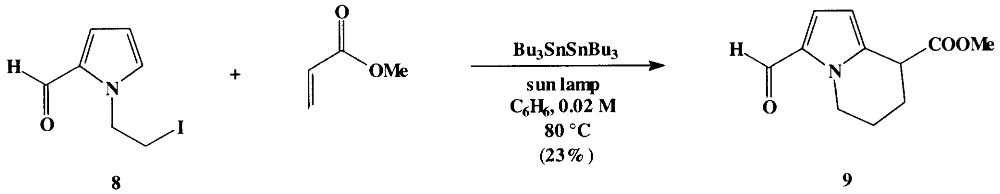
[a] All compounds were identified by mass spectrometry and ^{1}H NMR and IR spectroscopy.[5]

The aromatization of **4** may occur by the loss of HI from the iodide **7** (Scheme 2), formed by an atom transfer mechanism[4] which is different to that proposed by Bowman in Bu$_3$SnH/AIBN mediated reactions.[2g] Such a process is expected to be catalytic in hexabutylditin, which is obviously not so in the cases described herein, probably for thermodynamic reasons since, a primary alkyl radical **2** would be produced from a stabilized benzylic radical **4**.

In the light of above results, 2-formyl-1-(2-iodoethyl)pyrrol[3] **8** (Scheme 3) was also subjected to the tandem radical addition/cyclization process, and the indolizidine derivative **9** was isolated in modest yield as the major product together with a small amount of starting material (Scheme 3).



Scheme 2.



Scheme 3.

In closing, a tandem radical coupling/oxidative cyclization sequence is described which provides benzindolizidine derivatives, in one step, from easily accessible starting materials. In this interesting process, two new carbon–carbon bonds are created in a manner reminiscent of a Diels–Alder reaction.

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References

1. (a) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*; Pergamon: Oxford, 1986. (b) Curran, D. P. *Synthesis* **1988**, 417. (c) Mothewell, W. B.; Crich, D. *Free Radical Chain Reactions in Organic Synthesis*; Academic: New York, 1992.
2. (a) Muchowski, J. M.; Cho, I. S.; Jaime-Figueroa, S.; Artis, R. D. *J. Org. Chem.* **1994**, *59*, 2456. (b) Osaki, S.; Mitoh, H.; Ohmori, H. *Chem. Pharm. Bull.* **1996**, *44*, 2020. (c) Ziegler, F. E.; Belema, M. *J. Org. Chem.* **1997**, *62*, 1083. (d) Moody, C. J.; Norton, C. L. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2639. (e) Liard, A.; Quiclet-Sire, B.; Saicic, R. N.; Zard, S. Z. *Tetrahedron Lett.* **1997**, *38*, 1759. (f) Kaoudi, T.; Quiclet-Sire, B.; Seguin, S.; Zard, S. Z. *Angew. Chem., Int. Ed.* **2000**, *39*, 732. (g) Bowman, W. R.; Mann, E.; Parr, J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2991 and references cited therein.
3. Starting materials were prepared as reported before: Miranda, L. D.; Cruz-Almanza, R.; Pavón, M.; Alva, E.; Muchowski, J. M. *Tetrahedron Lett.* **1999**, *40*, 7153–7157.
4. Curran, D. P.; Tamine, J. *J. Org. Chem.* **1991**, *56*, 2746. (b) Curran, D. P.; Chen, M.-H. *J. Am. Chem. Soc.* **1987**, *109*, 6558. (c) Curran, D. P.; Kim, D. *Tetrahedron Lett.* **1986**, *27*, 5821. (d) Keck, E. G.; Byers, J. H. *J. Org. Chem.* **1985**, *50*, 5442.
5. **Typical Procedure**: A solution (0.02 M) of 1-(2-iodoethyl)indoles **1** in degassed benzene, containing methyl acrylate (4 equiv.), and hexabutylditin (2 equiv.) was refluxed with sun-lamp irradiation. The reaction was monitored by TLC analysis, and was terminated when no starting material was present (6–12 h). After this time, the reaction was cooled, the solvent was removed under reduced pressure and the residue was partitioned between hexane and acetonitrile. The polar layer was washed with hexane (five times). The solvent was then evaporated and the crude product was purified by flash column chromatography (hexane–EtOAc). *Selected spectral data of final products*: **5a** IR ($CHCl_3$): ν_{max} (cm^{-1}) 2652, 1643, 1100; MS (EI) *m*/*z*: $M^+=229$ (55%); ^1H NMR ($CDCl_3$, 200 MHz): $\delta=7.52$–7.58 (m, 1H, H-9), 7.05–7.30 (m, 3H, H-6,7,8), 6.39 (s, 1H, H-10), 405–4.09 (m, 3H, 1-CH and 4-CH_2), 3.77 (s, 3H, OCH_3), 2.0–2.32 (m, 4H, 2-CH_2 and 3-CH_2); **5b** IR ($CHCl_3$): ν_{max} (cm^{-1}) 2449, 1734, 1647, 1437; MS (EI) *m*/*z*: $M^+=257$ (90%); ^1H NMR ($CDCl_3$, 300 MHz): $\delta=10.21$ (s, 1H), 8.14–8.17 (m, 1H, H-9), 7.29–7.34 (m, 3H, H-6,7,8), 435–4.58 (m, 1H, 1-CH), 4.26–4.33 (m, 1H, 4-CH_2), 3.94–4.03 (m, 1H, 4-CH_2), 3.74 (s, 3H, OCH_3), 2.10–2.46 (m, 4H, 2-CH_2 and 3-CH_2); **5c** IR ($CHCl_3$): ν_{max} (cm^{-1}) 3246, 2947, 1668; MS (EI) *m*/*z*: $M^+=287$ (20%); ^1H NMR ($CDCl_3$, 200 MHz): $\delta=8.09$–8.19 (m, 1H, H-9), 7.23–7.32 (m, 3H, H-6,7,8), 461–4.65 (m, 1H, 1-CH),

4.23–4.33 (m, 1H, 4-CH_2), 3.90–4.00 (m, 1H, 4-CH_2), 3.88 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 2.11–2.36 (m, 4H, 2-CH_2 and 3-CH_2); **5d** IR ($CHCl_3$): ν_{max} (cm^{-1}) 3419, 2925, 2854, 1736, 1442; MS (EI) m/z: $M^+ = 329$ (43%); ^1H NMR ($CDCl_3$, 200 MHz): $\delta = 7.74$–7.82 (m, 1H, H-9), 7.26–7.36 (m, 3H, H-6,7,8), 4.57–4.64 (m, 1H), 4.46 (c, 2H, $J = 7.1$), 4.22–4.36 (m, 2H), 3.74 (s, 3H, OCH_3), 2.20–2.47 (m, 4H), 1.47 (t, 3H, $J = 7.1$); **5e** IR ($CHCl_3$): ν_{max} (cm^{-1}) 2958, 2210, 1647, 1742, 1453; MS (EI) m/z: $M^+ = 254$ (40%); ^1H NMR ($CDCl_3$, 200 MHz): $\delta = 7.69$–7.81 (m, 1H, H-9), 7.27–7.39 (m, 3H, H-6,7,8), 418–4.29 (m, 2H, 1-CH and 4-CH_2), 3.93–4.06 (m, 1H, 4-CH_2), 3.80 (s, 3H, OCH_3), 2.04–2.47 (m, 4H, 2-CH_2 and 3-CH_2), **9** IR ($CHCl_3$): ν_{max} (cm^{-1}) 1734, 1655; MS (EI) m/z: $M^+ = 207$ (40%); ^1H NMR ($CDCl_3$, 200 MHz): $\delta = 9.47$ (s, 1H, CHO), 6.90 (d, 1H, $J = 4.2$ Hz), 6.17 (d, 1H, $J = 4.2$ Hz), 4.4 (m, 2H), 3.4 (m, 1H), 3.76 (s, 3H, OCH_3), 1.87 (s, 4H, -CH_2-CH_2-).