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A tandem carbonylation/cyclization radical process of 1-(2-iodoethyl)indoles and pyrrole

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Abstract

The AIBN-induced radical reaction of 1-(2-iodoethyl)indoles and pyrroles with Bu_3SnH under 80 atm of CO was examined. Carbon monoxide was efficiently trapped by an alkyl radical to form an acyl radical which underwent intramolecular addition to the aromatic system to produce bicyclic aromatic ketones after in situ oxidation.

Keywords: acylation; acyl radical; carbonylation; heteroaromatic systems.

Intramolecular acylation represents a useful methodology for construction of bicyclic aromatic ketones used as important synthetic intermediates or as ultimate targets. The Friedel–Crafts acylation and Vilsmeier–Haack reactions are among the most commonly used methods to obtain aromatic ketones. It is well known that the Vilsmeier–Haack acylation works well for electron-rich aromatic systems, but gives low yields or fails entirely, on aromatic systems which are not so activated.[1] The radical acylation of aromatic systems has rarely been studied.[2] The alkylation of such systems, especially those bearing electron attracting substituents, under free radical conditions is, however, well known.[3] On the basis of these precedents, we decided to examine the intramolecular acylation of non-electron-rich systems under radical conditions.

Several methods to generate acyl radicals are known, although most of them suffer from decarbonylation problems or from difficulties in preparing the starting materials.[4] Ryu et al.[5] described the efficient trapping of CO by a variety of alkyl radicals. In such transformations, an acyl radical is formed when CO is trapped by an alkyl radical, which, in turn, is generated from an alkyl iodide or bromide via abstraction of a halogen atom by a tin radical. Later, Ryu et al.[5] also demonstrated that an acyl radical could be added

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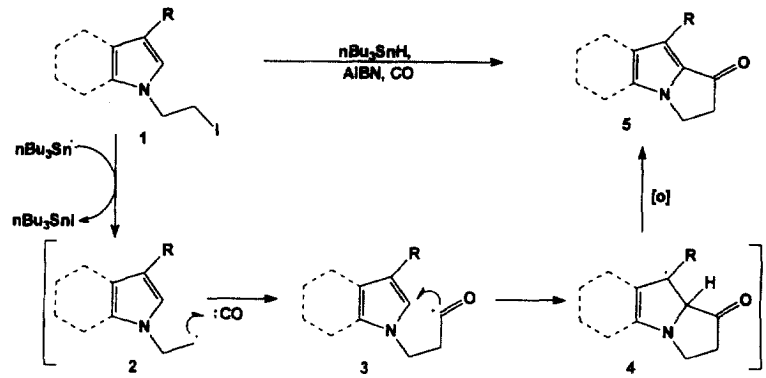
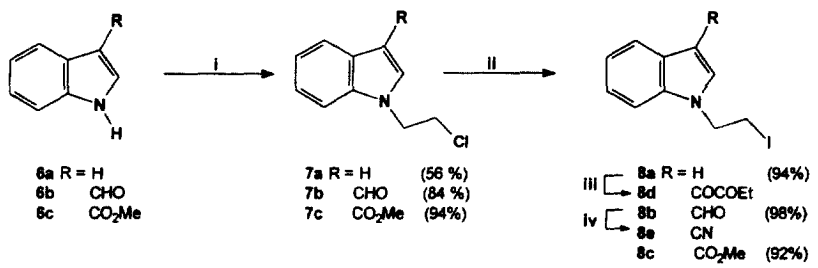
to the double bond of an alkene when present.[6] The formation of an acyl radical from an alkyl radical and its subsequent intramolecular addition to an aromatic system represents an attractive way to obtain bicyclic aromatic ketones since the starting iodides are usually readily available.

We describe here preliminary results of a tandem carbonylation/cyclization radical process in heteroaromatic systems bearing electron-attracting substituents. The AIBN-induced radical reaction of 1-(2-iodoethyl)indoles and pyrroles **1** (Scheme 1) with Bu_3SnH under pressure of CO was examined with the expectation that the acyl radical **3**, derived from **2** and CO, would undergo intramolecular addition to C-2 of the heteroaromatic system, and the benzylic radical **4** so obtained, upon in situ oxidation would produce the bycyclicketone **5**. The rearomatization (oxidation) of species such as **4** in Bu_3SnH-mediated reactions is well known, although the mechanism is not fully understood.[3a–c,7]



Scheme 1.

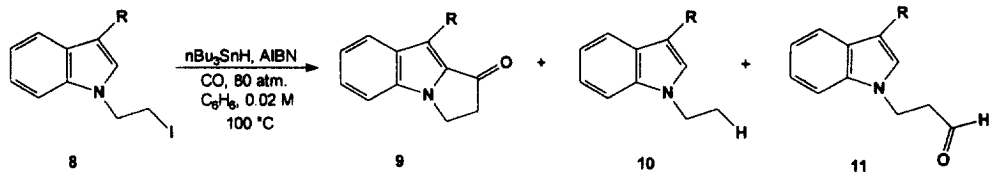
The 3-substituted 1-(2-iodoethyl)indoles **8a–c** were synthesized by a halogen exchange reaction from the corresponding chlorides, which were prepared in good yields from the appropriate 3-substituted indoles by alkylation with 1,2-dichloroethane under phase transfer conditions (Scheme 2).[8] The alkali sensitive ethyl oxalyl derivative **8d** was prepared in moderate yield by the direct acylation of **8a** with ethyl oxalyl chloride. The cyano compound **8e** was easily prepared from formyl derivative **8b** by known methodology.[9]



Scheme 2. Conditions: (i) 1,2-dichloroethane, NaOH 50%, nBu_4NI; (ii) NaI, CH_3CN reflux, 24 h; (iii) ethyl oxalyl chloride, Py, CH_2Cl_2, (61%); (iv) $NH_2OH \cdot HCl$, $MgSO_4$, TsOH, toluene, reflux (68%)

When a benzene solution 0.02 M of 3-formyl-1-(2-iodoethyl)indole (**8b**) was heated at 80°C[10] with 1.2 equiv. of *n*-Bu_3SnH and 0.2 equiv. of AIBN under 80 atm of CO for 3 h, most of the starting material was recovered and low yields of cyclization and reduction products were isolated (Scheme 3). In order to minimize the reduction product and to force consumption of the starting material, we decided to add the tin hydride in three small portions (0.4 equiv. each time) at 1 h intervals.[11] At the end of this time, TLC analysis showed that the starting material had almost completely disappeared and that ketone **9** was the major product. It was also found that 1.2 equiv. of AIBN[12] was better than 0.2 equiv. to ensure

completion of the reaction. Substrates **8a–e** were tested (Table 1) under these conditions and cyclization products were obtained in moderate yields when the indole system had an electron withdrawing group at C-3 (entries 2–5). Surprisingly, even the parent indole **8a**, which is known not to react efficiently with alkyl radicals,[3] gave substantial amounts of the cyclization product **9a**, accompanied by the expected reduction products **10a** and **11a**.



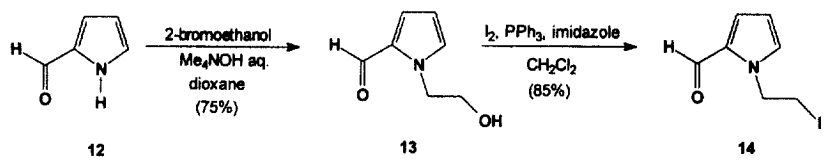
Scheme 3.

Table 1
Tandem carbonylation/cyclization reaction

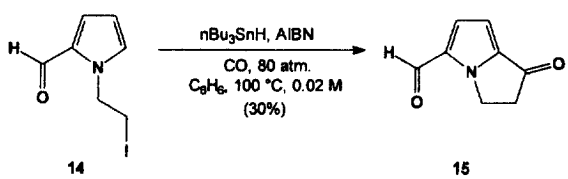
Entry	Substrate	R	Cyclization product Yield (%)	Reduction product Yield (%)	Aldehyde Yield (%)
1	**8a**	H	**9a** (39)	**10a** (22)	**11a** (30)
2	**8b**	CHO	**9b** (62)	**10b** (32)	—
3	**8c**	CO_2Me	**9c** (48)	**10c** (24)	**11c** (12)
4	**8d**	COCOEt	**9d** (43)	**10d** (30)	—
5	**8e**	CN	**9e** (61)	**10e** (34)	traces

All compounds were identified by mass spectrometry and ^1H NMR and IR spectroscopy.[11]

In order to extend the reaction to the pyrrole system, 2-formyl-1-(2-iodoethyl)pyrrole **14** was required. This compound was initially obtained by the halogen exchange process, but it was contaminated with significant amounts of the chloride, which could not be easily removed. It was found, however, that alkylation of 2-pyrrolecarboxaldehyde **12** (Scheme 4) with 2-bromoethanol, using Me_4NOH as a phase transfer catalyst, gave good yields[13] of alcohol **13**, which was efficiently converted into the iodide **14**, using Lange's procedure.[14] When **14** was subjected to the optimum conditions described above, pyrrolopyrrole **15** was isolated in a 30% yield (Scheme 5).



Scheme 4.



Scheme 5.

1. Conclusions

The reaction sequence reported herein is particularly interesting since two C–C bonds are formed in the process, and acylation takes place at a site different from that which would occur under electrophilic conditions. It opens up an alternative means of effecting intramolecular acylation of heteroaromatic systems to give products which are potentially useful synthetic intermediates for pyrrolizidine alkaloid synthesis.

Acknowledgements

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11. Typical Procedure: A benzene solution 0.02 M of 1-(2-iodoethyl)indole or pyrrole (1 equiv.), nBu$_3$SnH (0.4 equiv.) and AIBN (0.4 equiv.) under 80 atm of CO was heated at 100°C for 1 h. After this time the autoclave was cooled to room temperature and another 0.4 equiv. of nBu$_3$SnH and 0.4 equiv. of AIBN were added, and the mixture was heated at 100°C for 1 h under 80 atm of CO. This process is repeated once more. The autoclave 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). After the solvent was evaporated the crude product was purified by flash column chromatography (Hex-EtOAc). Selected spectral data of final products: **8a** IR ($CHCl_3$): ν_{max} 1710 cm^{-1}; MS (EI) *m/z*: M$^+$=171 (100%); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.77–7.73 (m, 1H), 7.40–7.05 (m, 3H), 6.87–6.80 (m, 1H), 4.41 (t, 2H, *J*=6.5 Hz), 3.22(t, 2H, *J*=6.38 Hz). **8b** IR ($CHCl_3$): ν_{max} 1659 cm^{-1}, 1718 cm^{-1}; MS *m/z*: M$^+$=199 (100%); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 10.49 (s, 1H), 8.47–8.43 (m, 1H), 7.49–7.37 (m, 3H), 4.56 (t, 2H, *J*=6.32 Hz), 3.32 (t, 2H, *J*=5.78 Hz). **8c** IR ($CHCl_3$): ν_{max} 1700 cm^{-1}, 1732 cm^{-1}; MS *m/z*: M$^+$=229 (100%); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.35–8.30 (m, 1H), 7.44–7.25 (m, 3H), 4.44 (t, 2H, *J*=6.2 Hz), 3.97 (s, 3H), 3.25 (t, 2H, *J*=5.86 Hz). **8d** IR ($CHCl_3$): ν_{max} 1648 cm^{-1}, 1727 cm^{-1}; MS *m/z*:

M^+=271, 198 (100%); ^1H NMR ($CDCl_3$, 200 MHz): δ 8.49–8.45 (m, 1H), 7.49–7.40 (m, 3H), 4.52 (t, 2H, *J*=7.08 Hz), 4.45 (q, 2H, *J*=7.08 Hz), 3.28 (t, 2H, *J*=5.58 Hz), 1.41 (t, 3H, *J*=7.18 Hz). **8e** IR ($CHCl_3$): ν_{max} 2223 cm^{-1}, 1724 cm^{-1}; MS *m/z*: M^+=196 (100%); ^1H NMR ($CDCl_3$, 200 MHz): δ 7.90–7.86 (m, 1H), 7.56–7.35 (m, 3H), 4.54 (t, 2H, *J*=6.2 Hz), 3.31 (t, 2H, *J*=5.88 Hz). **14** IR ($CHCl_3$): ν_{max} 1720, 1669 cm^{-1}; MS *m/z*: M^+=149 (100%); ^1H NMR ($CDCl_3$, 200 MHz): δ 9.75 (s, 1H), 7.12 (d, 1H, *J*=4.16 Hz), 6.72 (d, 1H, *J*=4.20 Hz), 4.62 (t, 2H, *J*=6.29 Hz), 3.11 (t, 3H, *J*=6.06 Hz).

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13. Me_4NOH (20% in water) was added to a stirred solution of pyrrole-2-carboxaldehyde (0.5 g, 5.25 mmol) and 2-bromoethanol (2 ml, 28.2 mmol) in dioxane (25 ml). The mixture was stirred for 12 h at 50°C, then 10 ml of water was added and the crude product was extracted with EtOAc. The organic layer was dried, and the solvent was removed in vacuo to gave an oily residue which was purified by silica gel chromatography to afford **11** as a red oil (75%).
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