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Intramolecular Reactions of 2-Indolylacyl Radicals: Access to 1,2-Fused Ring Indole Derivatives

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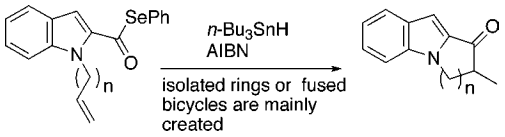
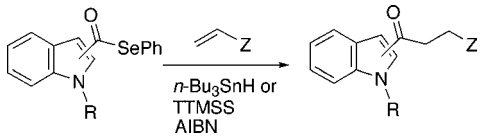
ABSTRACT



The generation of 2-indolylacyl radicals from the corresponding phenyl selenoesters under reductive conditions and their behavior in intramolecular addition reactions to carbon–carbon double bonds located at the indole nitrogen have been studied.

Radical reactions have long been recognized as important tools in organic synthesis,[1] often being used as key steps in the construction of complex natural products.[2] In particular, the addition of *functionalized* acyl radicals[3] to multiple C−C bonds constitutes a useful method for the synthesis of acyclic and cyclic ketones. The reaction of selenoesters with stannyl and tris(trimethylsilyl)silyl radicals is one of the most practical ways to generate these radical intermediates,[3] although other protocols and precursors can be used.[4] Our interest in the chemistry of functionalized indoles as common substructures of many natural and medicinal compounds[5] led us to explore the reactivity and synthetic possibilities of indolylacyl radicals. Thus, with Boger's work on benzoyl radicals in mind,[6] 2- and 3-indolylacyl radicals were generated from the corresponding phenyl selenoesters under reductive conditions and allowed to intermolecularly react with alkene acceptors, providing easy access to 2-[7] and 3-acylindoles[8] (Scheme 1). Our efforts were then focused on the *intramolecular* version of the above radical reactions, as a general approach to a great variety of polycyclic indolyl ketones.[9] We herein report our preliminary results concerning this new indole annulation procedure, using 2-indolylacyl

Scheme 1



(1) (a) Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4, pp 715−777 and 779−831. (b) Giese, B.; Kopping, B.; Göbel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. *Org. React*. **1996**, *48*, 301−856. (c) Renaud, P., Sibi, M. P., Eds. *Radicals in Organic Synthesis*; Wiley-VCH: Weinheim, 2001.

(2) (a) Koert, U. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 405−407. (b) McCarroll, A. J.; Walton, J. C. *Angew. Chem., Int. Ed.* **2001**, *40*, 2224−2248.

(3) For reviews on acyl radical chemistry, see: (a) Ryu, I.; Sonoda, N.; Curran D. P. *Chem. Rev*. **1996**, *96*, 177−194. (b) Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev*. **1999**, *99*, 1991−2069.

(4) For recent examples of the generation of acyl radicals from thiolesters, see: (a) Crich, D.; Yao, Q. *J. Org. Chem*. **1996**, *61*, 3566−3570. (b) Ozaki, S.; Adachi, M.; Sekiya, S.; Kamikawa, R. *J. Org. Chem*. **2003**, *68*, 4586−4589. (c) Benati, L.; Calestani, G.; Leardini, R.; Minozzi, M.; Nanni, D.; Spagnolo, P.; Strazzari, S. *Org. Lett*. **2003**, *5*, 1313−1316. From acyl hydrazides, see: (d) Braslau, R.; Anderson, M. O.; Rivera, F.; Jiménez, A.; Haddad, T.; Axon, J. R. *Tetrahedron* **2002**, *58*, 5513−5523. (e) Bath, S.; Laso, N. M.; López-Ruiz, H.; Quiclet-Sire, B.; Zard, S. Z. *Chem. Commun*. **2003**, 204−205.

(5) Sundberg, R. J. *Indoles*; Academic Press: New York, 1996; pp 105−134.

(6) Boger, D. L.; Mathvink, R. J. *J. Org. Chem*. **1992**, *57*, 1429−1443.

(7) Bennasar, M.-L.; Roca, T.; Griera, R.; Bosch, J. *Org. Lett*. **2001**, *3*, 1697−1700.

(8) Bennasar, M.-L.; Roca, T.; Griera, R.; Bassa, M.; Bosch, J. *J. Org. Chem*. **2002**, *67*, 6268−6271.

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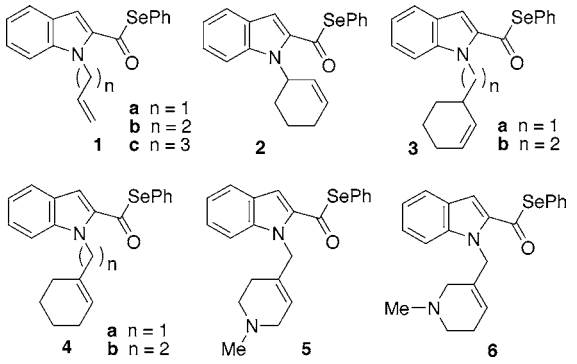


Figure 1.

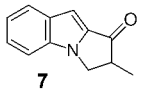
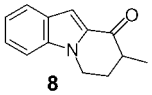
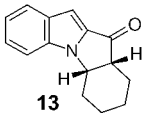
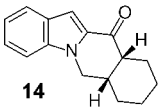
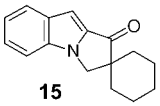
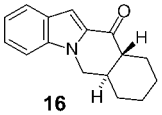
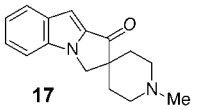
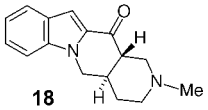
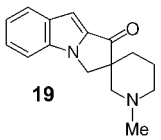
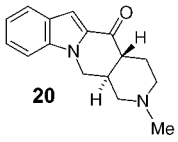
radicals in cyclization reactions upon alkene acceptors located at the indole nitrogen.[10]

With the aim of studying the scope of this cyclization process for the construction of isolated or fused rings, indole selenoesters **1**−**6** (Figure 1), which carry different alkenyl, cyclohexenyl, or tetrahydropyridyl moieties at the nitrogen, were selected as radical precursors. These compounds were prepared from the respective carboxylic acids,[11] following the procedure reported by Batty and Crich.[12] The results of the radical reactions, performed in all cases under standard reductive conditions (*n*-Bu_3SnH, AIBN, benzene, reflux, slow addition), are depicted in Table 1.

Consistent with empirical rules for alkyl radical cyclizations,[1b] as well as previous results with benzoyl radicals,[6] the 5-hexenoyl radical derived from **1a** showed a strong preference for the formation of the five-membered ring through the exo mode to give **7** as the only isolable product in 84% yield (entry 1).[13] Compound **7** has the pyrrolo[1,2-*a*]indole skeleton characteristic of mytomycins,[14] a group of metabolites from *Streptomyces* that have attracted much attention due to their antitumoral and antibacterial activity. Significantly, cyclization of the 6-heptenoyl radical[15] derived from **1b** was also totally exo regioselective, leading to pyrido[1,2-*a*]indole **8** in 70% yield (entry 2). No evidence of radical reduction (i.e., formation of an aldehyde) coming from direct hydrogen abstraction from the hydride or an eventual [1,5]-hydrogen atom transfer was observed. In contrast to the benzoyl series, the formation of a seven-membered ring did not occur from **1c**, only aldehyde **9** (Figure 2) being isolated in 70% yield. Reduction to **9** was also observed when the poorer hydrogen-atom donor tris(trimethylsilyl)silane[16] was used as the radical mediator.

We were also interested in the possibility of promoting a cascade reaction from selenoester **1a**, involving a cyclization process followed by an intermolecular addition of the intermediate cyclopentylmethyl radical **A** to an external electron-deficient alkene (Scheme 2).[17] To this end, **1a** was treated with *n*-Bu_3SnH-AIBN in the presence of different

Table 1. Radical Cyclization of Indoles **1**−**6**[a]

entry	indole	products	cyclization mode	yield[b]
1	**1a**	 **7**	5-exo	84
2	**1b**	 **8**	6-exo	70
3	**2**	 **13**	5-exo	70
4	**3a**	 **14**	6-exo	70
5	**4a**	 **15**	5-exo	10
		 **16**	6-endo	75
6	**5**	 **17**	5-exo	27
		 **18**	6-endo	25
7	**6**	 **19**	5-exo	30
		 **20**	6-endo	35

[a] *n*-Bu_3SnH (1.1 mol), AIBN (10 mol %), C_6H_6, 0.06 M, reflux, syringe pump. [b] Isolated yield of chromatographically pure material.

(9) For recent examples of intramolecular reactions of acyl radicals generated from *alkyl* phenyl selenoesters, see: (a) Double, P.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2005−2007. (b) Evans, P. A.; Raina, S.; Ahsan, K. *Chem. Commun.* **2001**, 2504−2505 and references therein. (c) Allin, S. M.; Barton, W. R. S.; Bowman, W. R.; McInally, T. *Tetrahedron Lett.* **2001**, *42*, 7887−7890.

(10) For related cyclizations involving 2-indolyl radicals, see: Dobbs, A. P.; Jones, K.; Veal, K. T. *Tetrahedron* **1998**, *54*, 2149−2160.

(11) See the Supporting Information for complete details.

(12) Batty, D.; Crich, D. *Synthesis* **1990**, 273−275.

(13) Tetracycle **7** has been prepared by cyclization of a 2-indolylacyl radical generated from an alkynylthiol ester. See ref 4c.

(14) Remers, W. A.; Dorr, R. T. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1988; Vol. 6, pp 1−74.

(15) For a recent study on cyclization of 6-heptenyl radicals, see: Bailey, W.; Longstaff, S. C. *Org. Lett.* **2001**, *3*, 2217−2219.

(16) Chatgilialoglu, C. *Acc. Chem. Res.* **1992**, *25*, 188−194.

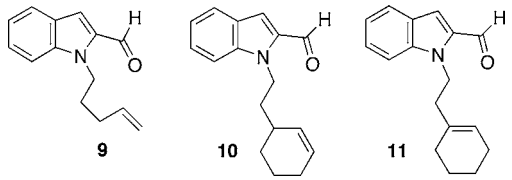
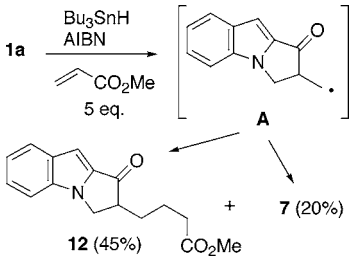


Figure 2.

amounts of methyl acrylate. The best yields (45%) of the desired 2-substituted pyrrolo[1,2-*a*]indole **12** were obtained when the reaction was performed in the presence of 5 equivalents of alkene. However, minor amounts (20%) of **7**, coming from the direct reduction of the radical **A**, were also formed. Confirming the fast 5-exo cyclization, the simple alkene-addition product was not detected in any assay.

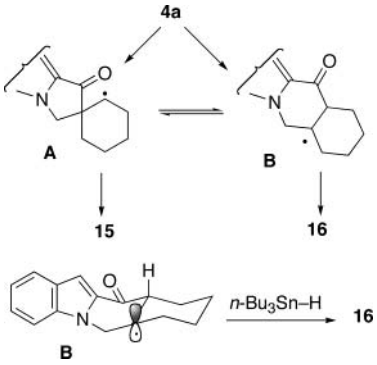
Scheme 2. Radical Cyclization−Intermolecular Addition Cascade Reaction



The formation of fused rings via an exo cyclization mode was investigated from selenoesters **2** and **3a**,**b**, bearing a 2-cyclohexenyl moiety directly attached to the indole nitrogen or separated by one or two methylene groups. In these series, we expected the cyclization of the 2-acyl radical to the cyclic alkene to occur in a cis manner owing to steric constraints imposed by the ring system.[18] Subsequent reduction of the cyclic radical adduct at the α-position of the ring junction would account for the formation of the final products. Indeed, clean 5- and 6-exo cyclizations took place from **2** and **3a** to give stereoselectively the cis-fused tetracycles **13** and **14** (entries 3 and 4, 70%). Tetracycle **14** could be quantitatively transformed into the thermodynamically more stable trans-fused tetracycle **16** (see below) by treatment with MeONa in MeOH. In contrast, 7-exo cyclization did not occur from **3b**, and only aldehyde **10** (Figure 2) was isolated from the reaction mixtures.

The higher alkene substitution present in the 2-indolylacyl radical derived from **4a** retarded the usually favored 5-exo cyclization mode in benefit of the 6-endo mode. Thus, the trans-fused tetracycle **16** was isolated as the major product in 75% yield along with minor amounts (10%) of the spiro compound **15** (entry 5). As the exo-endo product ratio was not significantly affected by the hydride concentration, we assumed that it reflected the kinetic composition of the initially formed radical adducts **A** and **B** rather than the equilibration between these intermediates through an intramolecular rearrangement (Scheme 3).[19] On the other hand, the trans configuration of **16** is the result of the stereoselective axial hydrogen abstraction of the bridgehead radical **B** from the hydride.[18,20]

Scheme 3



Disappointingly, the 2-indolylacyl radical derived from **4b**, with an additional carbon atom in the connecting chain, underwent reduction to aldehyde **11** (Figure 2) under the reaction conditions, thus indicating that both 6-exo and 7-endo ring closure were too slow for the radical chain to be productive.

With the aim of extending the above regioselective 6-endo cyclizations to the construction of fused azacyclic systems, we next turned our attention to selenoesters **5** and **6**, in which a double bond of the same substitution pattern as **4a** is included in a 4- or 3-substituted 1,2,5,6-tetrahydropyridine moiety.[21]

Rather surprisingly, in both cases the crude cyclization product was shown by ^{1}H NMR to be a nearly equimolecular mixture of the corresponding spiro (**17** and **19**) and fused piperidine compounds (**18** and **20**), from which pure regioisomers were isolated in yields depicted in Table 1 (entries 6 and 7). As in the above carbocyclic series, the 6-endo cyclization products **18** and **20** were exclusively obtained

(17) For similar 5-exo cyclizations−intermolecular additions, see: (a) Boger, D. L.; Mathvink, R. J. *J. Am. Chem. Soc*. **1990**, *112*, 4003−4008. (b) Tsunoi, S.; Ryu, I.; Fukushima, H.; Tanaka, M.; Komatsu, M.; Sonoda, N. *Synlett* **1995**, 1249−1251.

(18) Curran, D. P.; Porter, N. A. Giese, B. *Stereochemistry of Radical Reactions*; WCH: Weinheim, 1996.

(19) For a discussion, see: Chatgilialoglu, C.; Ferreri, C.; Lucarini, M.; Venturini, A.; Zavitsas, A. A. *Chem. Eur. J.* **1997**, *3*, 376−387. See also ref 6.

(20) Beckwith, A. L. J.; Gream, G. E.; Struble, D. L. *Aust. J. Chem*. **1972**, *25*, 1081−1105.

(21) In the literature, there are several reports of alkyl and aryl radical cyclizations upon azacyclic systems, most of them 1,4,5,6-tetrahydropyridines, to give heterocycles bearing the nitrogen atom in the new ring formed. See inter alia: (a) Mangeney, P.; Hamon, L.; Raussou, S.; Urbain, N.; Alexakis, A. *Tetrahedron* **1998**, *54*, 10349−10362. (b) Zhang, W. *Tetrahedron* **2001**, *57*, 7237−7262. (c) Zhang, W.; Pugh, G. *Tetrahedron* **2003**, *59*, 3009−3018. For radical cyclizations upon 1,4,5,6-tetrahidropyridines where a carbocycle is created, see: (d) Ripa, L.; Hallberg, A. *J. Org. Chem*. **1998**, *63*, 84−91. (e) Clive, D. L. J.; Yeh, V. S. C. *Tetrahedron Lett.* **1999**, *40*, 8503−8507.

as trans-fused stereoisomers due to the stereoselective reduction of the intermediate radical adducts. The different exo-endo regioselectivity exhibited by 2-indolylacyl radicals derived from **5** and **6** with respect to **4a** deserves comment. It seems reasonable to assume that, as a consequence of the inclusion of a nitrogen atom in the preexisting ring, the 6-endo pathway is kinetically decelerated.

In summary, a new indole annulation procedure based on intramolecular reactions of 2-indolylacyl radicals has been developed. When appropriate carbon−carbon double bonds connected to the indole nitrogen are used as acceptors, the procedure provides straightforward access to cyclic ketones fused to the 1,2-position of the indole nucleus, which should be of interest for the synthesis of natural products and medicinal compounds.

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Supporting Information Available: Experimental procedures and characterization data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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