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Generation and Intermolecular Reactions of 2-Indolylacyl Radicals

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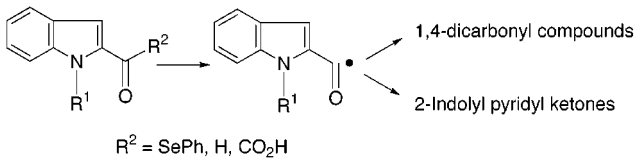
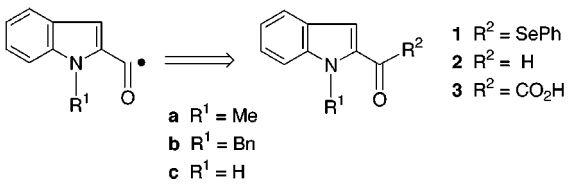
ABSTRACT



The generation of 2-indolylacyl radicals from the corresponding phenyl selenoesters, aldehydes, and α-keto carboxylic acids and the scope of their participation in intermolecular addition reactions to carbon−carbon double bonds have been studied. Whereas the phenyl selenoester method has provided easy access to a variety of 1,4-dicarbonyl compounds bearing the 2-acylindole moiety, the glyoxylic acid route has been employed for the preparation of 2-indolyl pyridyl ketones.

Over the past years, radical reactions have become increasingly important in organic synthesis[1] and now they are commonly used as key steps in the construction of complex natural products.[2] In particular, addition of nucleophilic acyl radicals[3] to alkenes provides a useful and practical method for the formation of carbon−carbon bonds leading to unsymmetrical ketones. In the context of our studies on the synthesis of 2-acylindole alkaloids,[4] we are currently investigating the possibility that a variety of 2-acylindole compounds can be prepared through reactions of 2-indolylacyl radicals with appropriate acceptors. In this Letter we describe the generation of this type of radical from different precursors (phenyl selenoesters **1**, aldehydes **2**, and glyoxylic acids **3**, Scheme 1) and their role in intermolecular reactions with alkenes and pyridines. To our knowledge, there are no precedents for the generation and use of 2-indolylacyl radicals in synthesis.

Scheme 1



Selenoesters react readily with stannyl and tris(trimethylsilyl)silyl radicals to give acyl radicals.[3] In this field, Boger[5] has reported a ketone synthesis based on the acyl transfer reaction of phenyl selenoesters to alkenes using *n*-Bu_3SnH as the radical mediator. With this work in mind, we set out to explore the addition of 2-indolylacyl radicals derived from phenyl selenoesters **1a**,**b**[6] (Scheme 2) to the alkene acceptors depicted in Table 1. As expected, the reaction worked reasonably well (60−66% yield) with simple electron-deficient alkenes and styrene (entries 1−3) using Method A (*n*-Bu_3SnH, AIBN, C_6H_6, 80 °C, slow addition),[7] with little or no competitive reduction (0−5%) and no evidence of competitive decarbonylation. Whereas substitution at the

Scheme 2

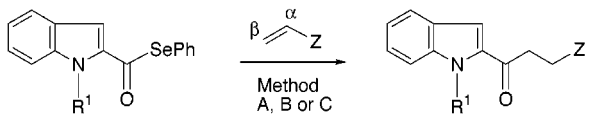


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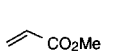
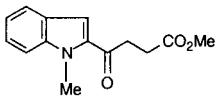
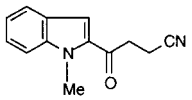
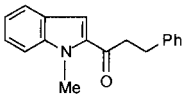
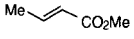
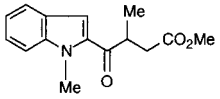
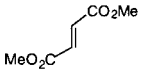
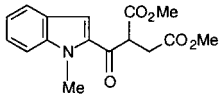
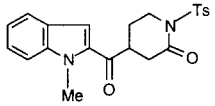
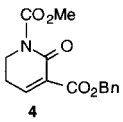
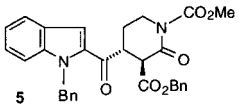
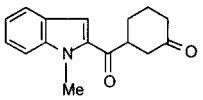
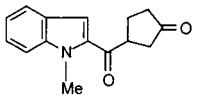
Table 1. Intermolecular Addition Reactions of 2-Indolylacyl Radicals Derived from Phenyl Selenoesters **1**

entry	indole derivative	alkene acceptor	products[a]	method[b]	yield (%)[c]
1	**1a**			A	62
2	**1a**			A	66
3	**1a**			A	60
4	**1a**			A	54
5	**1a**			A	24[d]
6	**1a**			A B	0 15[d]
7	**1b**			B	58
8	**1a**			A C	15[d] 52
9	**1a**			C	55

[a] All compounds were fully characterized by spectroscopic analysis (NMR) and gave satisfactory HRMS and/or combustion data. [b] All reactions were carried out on a 0.6 mmol scale, using a four (or five)-fold excess of the alkene acceptor. **Method A**: *n*-Bu_3SnH (1.2 equiv,), AIBN (0.15 equiv), C_6H_6, reflux, slow addition. **Method B**: TTMSS (2 equiv), AIBN (2 equiv), C_6H_6, reflux, slow addition. **Method C**: *n*-Bu_6Sn_2 (2 equiv), *hν*, C_6H_6, reflux. [c] Isolated yields of chromatographically pure material. [d] Recovering of 2-indolecarbaldehyde **2a** in 60−65%.

β-carbon of the alkene component by a methyl group (i.e., methyl crotonate, entry 4) did not affect significantly the effectiveness of the addition, the substitution by an electron-withdrawing substituent (i.e., dimethyl fumarate, entry 5) gave a lower yield of the corresponding addition product together with substantial amounts of 2-indolecarbaldehyde **2a**.

Clearly the amide carbonyl group does not have enough electron-withdrawing capacity to guarantee the intermolecular alkene addition reaction: from **1a** and *N*-tosyl-5,6-dihydro-2(1*H*)pyridone[8] (entry 6), addition was observed only when the poorer hydrogen-atom donor tris(trimethylsilyl)silane[9] (TTMSS, AIBN, C_6H_6, 80 °C, slow addition, Method B)[10] was used as the radical mediator, although the yield was low. More satisfactorily, 2-indolylacyl radical derived from **1b** reacted productively with α,*β*-unsaturated lactam ester **4**[8] under the above Method B conditions (entry 7). Taking into account that the *N*-benzyl protecting group can be easily removed in 2-acylindoles,[11] the resulting 2-indolyl 4-piperidyl ketone **5** can be envisaged as potentially useful for the synthesis of 2-acylindole alkaloids (e.g., apparicine, dasycarpidone).[12]

When 2-cycloalkenones were used as alkene acceptors (entries 8 and 9), the use of standard *n*-Bu_3SnH conditions (Method A) provided a modest yield of the corresponding adducts. Knowing the ability of TTMSS to reduce ketones,[9] the use of nonreductive conditions (*n*-Bu_6Sn_2, *hν*, C_6H_6, 80 °C, Method C)[13] was the most satisfactory solution in these cases to avoid the competitive reduction of the intermediate acyl radical. Under these conditions, the corresponding diketone adducts were isolated in acceptable yield. This result can be rationalized by considering that the initially formed α-keto radical **A**, coming from the addition of the indolylacyl radical to the enone, reacts with excess *n*-Bu_6Sn_2 to give a tin enolate, which would undergo hydrolysis during the workup (Scheme 3). The results shown in Table 1 clearly

(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.

(2) (a) Jasperse, C. P. Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237−1286. For representative examples, see: (b) Koert, U. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 405−407.

(3) For a review on the chemistry of acyl radicals, see: Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev.* **1999**, *99*, 1991−2069.

(4) (a) Bennasar, M.-L.; Vidal, B.; Bosch, J. *J. Org. Chem.* **1997**, *62*, 3597−3609. (b) Bennasar, M.-L.; Vidal, B.; Kumar, R.; Lázaro, A.; Bosch, J. *Eur. J. Org. Chem.* **2000**, 3919−3925.

(5) (a) Boger, D. L.; Mathvink, R. J. *J. Org. Chem.* **1989**, *54*, 1777−1779. (b) Boger, D. L.; Mathvink, R. J. *J. Org. Chem.* **1992**, *57*, 1429−1443.

(6) Selenoesters **1a** and **1b** were prepared in 60% and 96% yield, respectively, by reaction of the corresponding carboxylic acid triethylammonium salt with PhSeCl and Bu_3P in THF at room temperature, following the procedure reported by the following: Batty, D.; Crich, D. *Synthesis* **1990**, 273−275.

(7) **General Procedure (Method A)**: *n*-Bu_3SnH (0.8 mmol) in C_6H_6 (3 mL) was added over a period of 1 h (syringe pump) to a heated (reflux) solution of **1a** (0.64 mmol), the alkene acceptor (3.2 mmol), and AIBN (0.1 mmol) in C_6H_6 (6 mL). After an additional 2−3 h at reflux, the solution was concentrated under reduced pressure, and the resulting residue was chromatographed (flash, hexanes−AcOEt).

(8) Casamitjana, N.; López, V.; Jorge, A.; Bosch, J.; Molins, E.; Roig, A. *Tetrahedron* **2000**, *56*, 4027−4042.

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

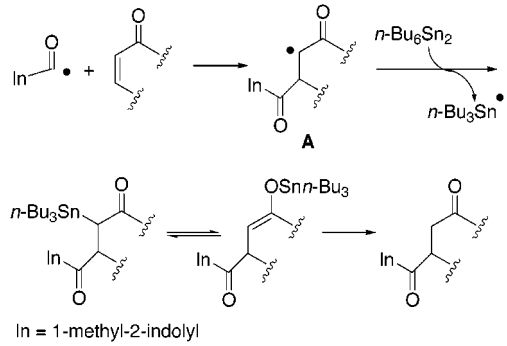
(10) **General Procedure (Method B):** TTMSS (1.28 mmol) and AIBN (1.28 mmol) in C_6H_6 (4 mL) were added over a period of 2 h (syringe pump) to a heated (reflux) solution of **1a**,**b** (0.64 mmol) and the alkene acceptor (3.2 mmol) in C_6H_6 (12 mL). After an additional 2−3 h at reflux, the reaction was worked up as in the above Method A.

(11) Watanabe, T.; Kobayashi, A.; Nishiura, M.; Takahashi, H.; Usui, T.; Kamiyama, I.; Mochizuki, N.; Noritake, K.; Yokoyama, Y.; Murakami, Y. *Chem. Pharm. Bull.* **1991**, *39*, 1152−1156. For synthetic applications, see ref 4.

(12) (a) Joule, J. A. In Indoles, The Monoterpenoid Indole Alkaloids; Saxton, J. E., Ed. In *The Chemistry of Heterocyclic Compounds*; Weissberger, A., Taylor, E. C., Eds.; Wiley: New York, 1983; Vol. 25, Part 4; Chapter VI. (b) Alvarez, M.; Joule, J. In *Monoterpenoid Indole Alkaloids*; Saxton, J. E., Ed. In *The Chemistry of Heterocyclic Compounds*; Taylor, E. C., Ed.; Wiley: Chichester, 1994; Vol. 25, Supplement to Part 4; Chapter 6.

(13) **General Procedure (Method C)**: A solution of **1a** (0.65 mmol), cycloalkenone (2.60 mmol) and *n*-Bu_6Sn_2 (1.30 mmol) in C_6H_6 (30 mL) was refluxed under sun-lamp irradiation (300 W) for 24 h. The reaction was worked up as in the above Method A.

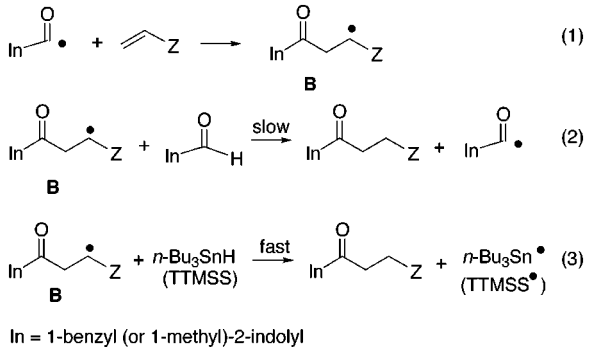
Scheme 3



illustrate that the phenyl selenoester route provides easy access to 1,4-dicarbonyl compounds bearing a 2-acylindole moiety.

Taking into account that acyl radicals can also be generated by homolytic scission of the aldehyde C(O)−H bond in the presence of *tert*-butoxyl radicals,[3] we decided to study this process from 2-indolecarbaldehyde **2b**.[14] However, we were not able to induce any radical addition from **2b** and several acceptors such as methyl acrylate or methyl crotonate. Only the starting products were recovered when the reactions were thermally initiated by di-*tert*-butyl hyponitrite[15] or photochemically initiated by *tert*-butyl *p*-benzoylperbenzoate.[16] This result probably reflects the slow hydrogen abstraction by the electrophilic adduct radical **B** from the aromatic aldehyde (Scheme 4, eq 2), which would generate a relatively

Scheme 4

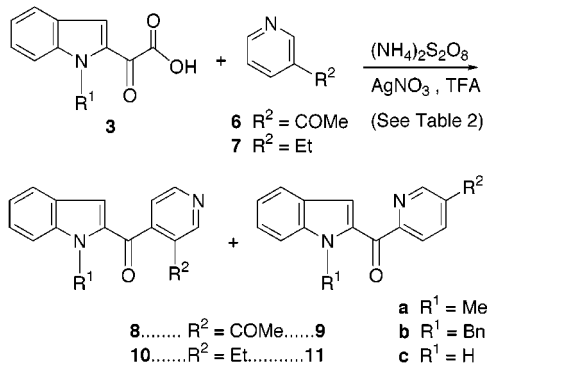


poor nucleophilic indolylacyl radical, as compared with the more nucleophilic [tributylstannyl or tris(trimethylsilyl)silyl] radical, generated in the productive propagation step using *n*-Bu_3SnH or TTMSS in the selenoester method (eq 3).[15]

Finally, we considered the generation of 2-indolylacyl radicals under oxidative conditions. We focused our attention on the Minisci transformation,[3,17] a classical reaction that was recognized as being preparatively useful well before the reemergence of radical reactions in synthesis. Minisci and co-workers[18] have developed the Ag(I)-catalyzed oxidative decarboxylation of α-keto acids using the peroxydisulfate anion as the oxidant as a source of acyl radicals able to undergo addition to protonated heteroaromatic bases (e.g., pyridines). These oxidative conditions determine the return to aromatic derivatives, the net result being the substitution at the α- and/or γ-position of the ring.[19]

For our study we selected indoleglyoxylic acids **3a**−**c**,[20] and their oxidative decarboxylation was tested toward pyridines **6** and **7** under the above conditions (Scheme 5).[21]

Scheme 5



As can be observed in Table 2, mixtures of C-4 (**8**, **10**) and C-6 (**9**, **11**) acylation products were generally obtained. The best yields (90%) were observed when the reaction was performed with 3-acetylpyridine (**6**) and *N*-methylindole derivative **3a** (entry 1, compare with entries 4 and 5) in a 1:1 mixture of H_2O−CH_2Cl_2 at 40 °C. In accordance with the literature,[22] the solvent influences the regioselectivity of the addition since the use of 4:1 CH_3CN−H_2O (entry 2) significantly changes the ratio of products obtained. As expected, due to polar effects the use of 3-ethylpyridine (**7**) as the acceptor was less efficient (entry 3).

Table 2. Minisci-Type Reactions of Indoleglyoxylic Acids **3a**−**c** with Pyridines **6** and **7**

entry	indole derivative	pyridine	products[a,b] (ratio)[c]	yield (%)[d]
1	**3a**	**6**	**8a** + **9a** (1:1)	90
2	**3a**	**6**	**8a** + **9a** (7:1)[e]	40
3	**3a**	**7**	**10a** + **11a** (0:1)	20
4	**3b**	**6**	**8b** + **9b** (1:1)	30
5	**3c**	**6**	**8c** + **9c** (1:1)	20

[a] Experimental conditions: indole **3** (2 equiv), pyridine **6** or **7** (1 equiv), $(NH_4)_2S_2O_8$ (2 equiv), $AgNO_3$ (0.2 equiv), TFA (3 equiv), 1:1 H_2O−CH_2Cl_2, 40 °C. [b] All compounds were fully characterized by spectroscopic analysis (NMR) and gave satisfactory HRMS and/or combustion data. [c] The regioisomeric ratio was determined by the ^1H NMR integration of the reaction mixtures. [d] Isolated yields of chromatographically pure material. [e] In 4:1 CH_3CN−H_2O as the solvent system.

(14) Suzuki, H.; Iwata, C.; Sakurai, K.; Tokumoto, K.; Takahashi, H.; Hanada, M.; Yokoyama, I.; Murakami, Y. *Tetrahedron* **1997**, *53*, 1593−1606.

(15) Dang, H.-S.; Roberts, B. P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 67−75.

(16) Gottschalk, P.; Neckers, D. C. *J. Org. Chem.* **1985**, *50*, 3498−3502.

In conclusion, 2-indolylacyl radicals, generated for the first time from phenyl selenoesters **1a**,**b** and α-keto acids **3a**−**c**, open new synthetic possibilities for the preparation of 2-indolyl ketones, including a variety of 1,4-dicarbonyl compounds (keto esters, keto lactams, diketones) and indolyl pyridyl ketones. This radical approach provides an alternative synthetic route to 2-indolyl ketones, which are usually formed by electrophilic acylation of the indole ring.

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(17) Minisci, F. *Synthesis* **1973**, 1−24.

(18) Fontana, F.; Minisci, F.; Barbosa, M. C. N.; Vismara, E. *J. Org. Chem*. **1991**, *56*, 2866−2869.

(19) For a recent application of the Minisci reaction, see: Doll, M. K.-H. *J. Org. Chem*. **1999**, *64*, 1372−1374.

(20) Indoles **3a**[20a] and **3c**[20b] were prepared following previously reported procedures: (a) Ziegler, F. E.; Spitzner, E. B. *J. Am. Chem. Soc*. **1973**, *95*, 7146−7149. (b) Hasan, I.; Marinelli, E. R.; Lin, L.-C. C.; Fowler, F. W.; Levy, A. B. *J. Org. Chem*. **1981**, *46*, 157−164. Indole **3b** was prepared in 74% yield by *N*-benzylation of **3c** with benzyl bromide (1.1 equiv) and NaH (2.2 equiv) in 5:1 DMF−THF.

(21) **General Procedure**: Indole **3** (0.8 mmol) and $(NH_4)_2S_2O_8$ (0.8 mmol) were added in four portions over a period of 1 h to a preheated (40 °C), vigorously stirred mixture of pyridine **6** or **7** (0, 4 mmol), $AgNO_3$ (0.08 mmol), and TFA (1.2 mmol) in 1:1 H_2O−CH_2Cl_2 (30 mL). The reaction mixture was basified with 10% aqueous NaOH and extracted with CH_2Cl_2. Both regioisomers were easily separated by flash chromatography (SiO_2, AcOEt−hexanes).

(22) Minisci, F.; Vismara, E.; Fontana, F. *Heterocycles* **1989**, *28*, 489−519.