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Regioselective Intramolecular Reactions of 2-Indolylacyl Radicals with Pyridines: A Direct Synthetic Entry to Ellipticine Quinones

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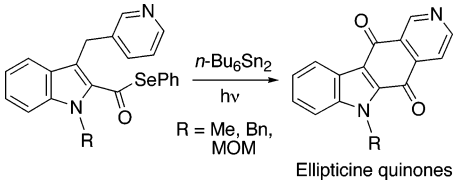
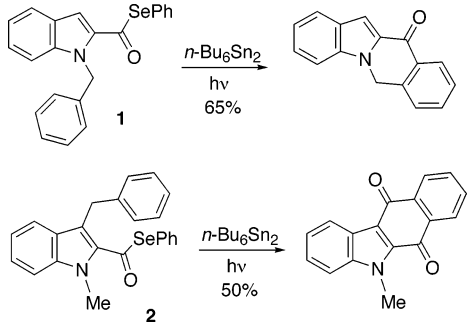


2-Indolylacyl radicals generated from the corresponding selenoesters under hexabutylditin−*hν* conditions undergo regioselective intramolecular reaction with unprotonated pyridines to give polycyclic indolylpyridyl ketones. For substrates bearing a (3-pyridyl)methyl moiety connected to the 3-position of the indole ring, the cyclization provides easy access to ellipticine quinones.

Intramolecular reactions of nucleophilic carbon-centered radicals with aromatic systems are often of synthetic value for the construction of polycyclic compounds incorporating aromatic rings.[1] Fully aromatic products are generally obtained after the oxidation of the initially formed cyclohexadienyl radical,[2] which takes place even under the most commonly used tributyltin hydride−AIBN *reductive* conditions.[3] In this context, cyclizations of aryl and alkyl radicals upon heteroaromatic substrates such as azoles,[4] indoles,[5,6] pyridines,[7] or quinolines[7a] have become increasingly important for the synthesis of otherwise quite inaccessible substituted heterocycles. However, similar processes involving acyl radicals, which have a high synthetic potential due to their intrinsic functionalization,[8] have scarcely been investigated.[9]

SCHEME 1



In the past few years, we have been studying the generation of 2- and 3-indolylacyl radicals from the corresponding phenyl selenoesters and their reactions with alkene acceptors under reductive conditions.[10] Our interest in this area led us to envisage intramolecular reactions of these radical intermediates with aromatic rings as a general approach to polycyclic aryl indolyl ketones, which are common substructures of many natural and medicinal compounds.[11] Thus, we have recently reported how 2-indolylacyl radicals, such as those derived from selenoesters **1** and **2** (Scheme 1), undergo cyclization upon phenyl rings under nonreductive (hexabutylditin, *hν*) conditions.[12] We believed that the extension of the above reactions to analogous pyridine substrates would be of interest, complementing the classical protocol of Minisci for the homolytic acylation of protonated pyridines under oxidative conditions,[13] mainly developed in its intermolecular version.[14] We herein report our work on this subject presenting as the

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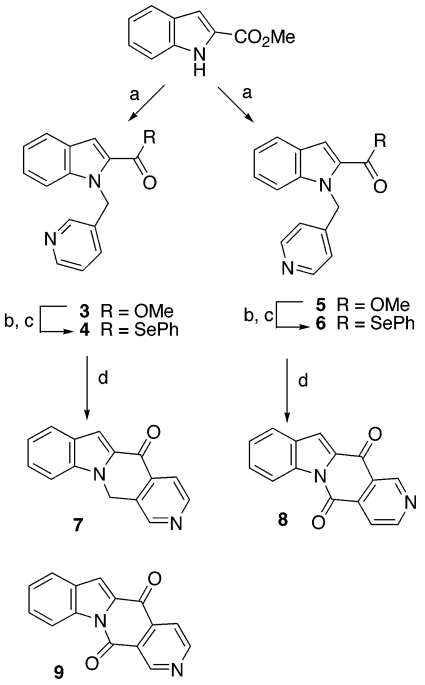
SCHEME 2[a]



[a] Reagents and conditions: (a) NaH, THF, 3- or 4-(chloromethyl)pyridine, HCl, rt, overnight, 70% (**3**), 65% (**5**); (b) 2 N KOH, MeOH-dioxane, reflux, 2 h, then 2 N HCl; (c) Et_3N, then PhSeCl, PBu_3, THF, rt, overnight, 82% (**4**), 83% (**6**); (d) *n*-Bu_6Sn_2, 300 W, C_6H_6, reflux, 24 h, 35% (**7**), 15% (**8**).

most significant result a straightforward synthetic entry to ellipticine quinones, which have an intrinsic interest as antitumor agents,[15] and are important intermediates in the synthesis of ellipticines.[16]

Selenoesters **4** and **6**, bearing 3- or 4-pyridylmethyl moieties connected to the indole nitrogen, were selected as substrates to study 2-indolylacyl radical cyclizations leading to indolo[1,2-*b*]naphthyridinones (Scheme 2), which constitute advanced intermediates in the earliest Gribble syntheses of ellipticine and analogues.[17,18] As expected, these radical precursors were easily accessible by N-alkylation of methyl indole-2-carboxylate with the appropriate (chloromethyl)pyridine, followed by hydrolysis of the resulting methyl esters **3** and **5**, and subsequent phenylselenation.

In analogy to our previous results for selenoester **1**,[12] we observed only premature reduction of the intermediate acyl radical to aldehyde **10** (Figure 1) when selenoesters **4** and **6** were submitted to standard reductive (*n*-Bu_3SnH o $(SiMe_3)_3SiH$−AIBN) conditions. However, the desired cyclization did take place upon treatment with *n*-Bu_6Sn_2 (2 mol, 300 W sun lamp), although the yields were lower than in the phenyl series. For selenoester **4**, the acylation took place exclusively at the 4-position of the pyridine ring to give tetracycle **7**, a deoxoderivative of the known ellipticine precursor **9**,[17] in 35% yield. No trace of the regioisomeric product coming from the alternative radical attack at the 2-position was detected. This regiochemical outcome is noteworthy, being in clear contrast with that observed in related reactions involving aryl radicals, which usually provide regioisomeric mixtures.[7] On the other hand, the 2-indolylacyl radical derived from selenoester **6** reacted at the 3-position of the pyridine ring in a less efficient way, ultimately leading to the overoxidized keto lactam **8**, a synthetic precursor of isoellipticine,[18] in 15% yield. In both cases, significant amounts (20−30%) of tin esters **11** (Figure 1) were also obtained.

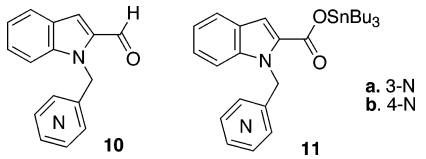
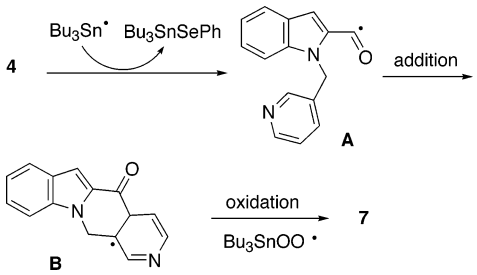


FIGURE 1. Other reaction products.

SCHEME 3



The cyclization process can be understood by studying the radical reactions depicted in Scheme 3 for selenoester **4**. After cleavage of *n*-Bu_6Sn_2 under the influence of heat and/or light, the resulting tributyltin radical generates the 2-indolylacyl radical **A**, which reacts at the 4-position of the pyridine ring to give the azacyclohexadienyl radical **B**. Subsequent oxidation would lead to **7**, probably by a simple hydrogen abstraction[19] by the peroxy radical *n*-$Bu_3SnOO^{\bullet}$ coming from the reaction of tin radicals with oxygen, which was not rigorously excluded from the reaction mixture. A similar addition−rearomatization mechanism followed by an additional oxidation at the interannular methylene group could account for the formation of keto lactam **8** from selenoester **6** (not shown).

The relative inefficiency of the above cyclizations with respect to the phenyl series (Scheme 1) was somewhat

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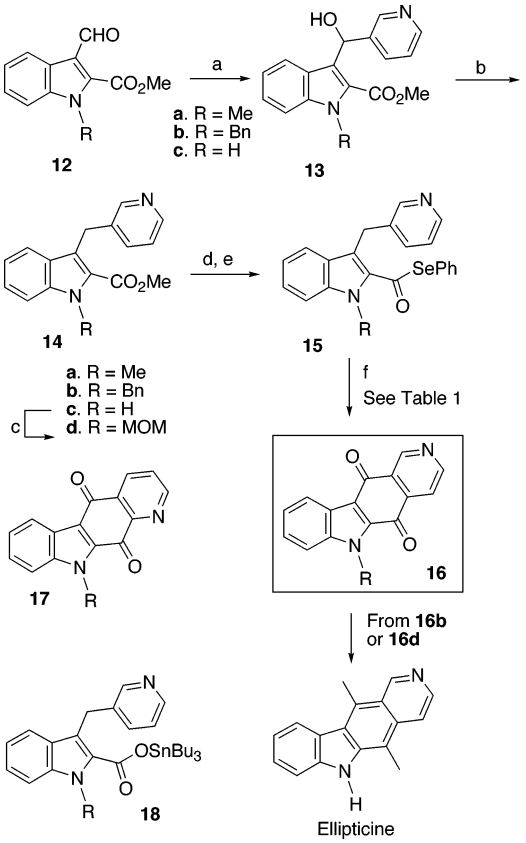
unexpected, as unprotonated pyridines have been reported to exhibit reactivity profiles toward most nucleophilic carbon-centered radicals that are similar to benzene derivatives.[13a] Nevertheless, these differences can be attributed to the presence of pendant electron-withdrawing 3- or, in particular, 4-pyridylmethyl moieties at the indole nitrogen, which would diminish the reactivity of the intermediate acyl radical. This would lead to a buildup of radical concentration, allowing undesired secondary reactions such as conversion into tin ester **11** to take place.[20]

We next turned to radical precursors in which the 3-pyridylmethyl moiety was attached at the indole 3-position. In this series, the hope was that the reaction would follow the same regiochemical course as described above for selenoester **4**, giving access to the pyrido[4,3-*b*]-carbazole skeleton characteristic of the indole alkaloid ellipticine. Considering that the substituent installed at the indole nitrogen could modulate the reactivity of the intermediate acyl radical and, consequently, determine the efficiency of the process, we decided to study the cyclization from a variety of N-substituted selenoesters **15a**−**d** (Scheme 4, Table 1).

Their preparation was a bit more laborious than in the above series, and required the use of 2,3-disubstituted indoles **12** as the starting products. Thus, reaction of **12a**−**c** with 3-pyridylmagnesium bromide, followed by triethylsilane reduction of the resulting carbinols **13a**−**c**, provided methyl esters **14a**−**c** in acceptable yields. *N*-(Methoxymethyl) ester **14d** was prepared by N-alkylation of the unsubstituted derivative **14c**, as triethylsilane reduction of carbinol **13** (R = MOM) resulted in the concomitant reduction of the N-substituent to give the *N*-methyl derivative **14a**. Subsequent hydrolysis of **14a**−**d**, followed by phenylselenation of the respective carboxylic acids, gave the target selenoesters **15a**−**d**.

To our delight, 2-indolylacyl radicals derived from *N*-methyl selenoesters **15a** and **15b** (entries 1 and 2) efficiently underwent regioselective cyclization upon the 4-position of the pyridine ring and, after the in situ oxidation at the interannular methylene group, gave the known ellipticine quinones **16a**[21] and **16b**[21,22] in 60 and 42% yield, respectively. Only minor amounts of regioisomers **17a** (5%) and **17b** (8%) were formed. However, the acyl radical derived from **15d** (entry 4) displayed diminished reactivity compared to that of those derived from **15a** and **15b**, probably due to the presence of the methoxymethyl group, which acts as an electron-withdrawing moiety. Thus, quinone **16d**[21] was isolated in a poor 10% yield along with trace amounts of the C-2 regioisomer **17d**. Attempts to improve this result using dicumyl peroxide[5f] were unsuccessful, as they led to the recovery of the starting selenoester.

SCHEME 4[a]



[a] Reagents and conditions: (a) 3-pyridylmagnesium bromide, −40°C to room temperature, 12 h; (b) Et_3SiH, TFA, rt, 7 h, **14a** (60%), **14b** (55%), **14c** (50%); (c) NaH, THF, MOMCl, 0 °C to room temperature, 12 h, 85%; (d) LiOH, 3:1 THF/H_2O, 65 °C, 5 h; (e) Et_3N, then PhSeCl, PBu_3, THF, rt, overnight, **15a** (80%), **15b** (76%), **15c** (70%), **15d** (80%); (f) *n*-Bu_6Sn_2, 300 W, C_6H_6, reflux, 24 h, see Table 1.

TABLE 1. *n*-Bu_6Sn_2-Mediated Radical Cyclization of Selenoesters 15

entry	selenoester	ellipticine quinone (yield, %)[a]	other products (yield, %)[a]
1	**15a**	**16a** (60)	**17a** (5), **18a** (10)
2	**15b**	**16b** (42)	**17b** (8)[b]
3	**15c**		**18c** (85)
4	**15d**	**16d** (10)	**17d** (2), **18d**[c]

[a] Isolated yields. [b] Minor amounts of the product coming from cyclization upon the benzene ring were also detected. [c] Not isolated. Major product in the reaction mixture (6:1 with respect to **16d** + **17d**).

Quite unexpectedly, cyclization did not occur for the unsubstituted selenoester **15c** (entry 3), indicating that the radical reaction was somehow inhibited by the presence of the indole NH group.[23] In the last two cases, it is somewhat significant that the undesired formation of tin esters **18c**,**d**, a minor process in the productive series, was the predominant pathway.[20]

As expected, ellipticine quinones **16a**, **16b**, and **16d** showed physical and spectroscopic data identical to those

(20) Formation of tin esters **11** and **18** can be explained by the reaction of the corresponding selenoesters with hexabutylditin oxide, which would be formed in the reaction mixture on exposure of hexabutylditin to light. Alternatively, they can be formed by reaction of the selenoesters with hexabutylditin, followed by oxidation of the resulting 2-indolylacyltin: Kosugi, M.; Naka, H.; Sano, H.; Migita, T. *Bull. Chem. Soc. Jpn*. **1987**, *60*, 3462−3464.

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previously described.[15,21,22] Because both **16b**[21,22,24] and **16d**[21] were transformed into ellipticine, the synthesis reported here constitutes a formal synthesis of this natural product.

In conclusion, we have shown that the cyclization of 2-indolylacyl radicals upon pyridines under *n*-Bu_6Sn_2–*hν* conditions takes place with notable regioselectivity to give tetracyclic indolyl 4-pyridyl ketones. The effectiveness of this radical protocol is illustrated by a fast synthetic entry to ellipticine quinones.

Experimental Section

General Procedure for the Radical Cyclization of Phenyl Selenoesters 4, 6, and 15. A solution of the appropriate selenoester (0.50 mmol) and *n*-Bu_6Sn_2 (0.51 mL, 1 mmol) in C_6H_6 (30 mL) was refluxed under Ar under sun lamp irradiation (300 W) for 24 h. The solution was concentrated under reduced pressure. The resulting residue was partitioned between hexanes (15 mL) and acetonitrile (15 mL), and the polar layer was washed with hexanes (3 × 15 mL). The solvent was removed, and the crude product was purified by flash chromatography (SiO_2). For **15b**, the crude product was treated with a 0.5 M solution of KOH in MeOH (10 mL) at room temperature for 2 h before the chromatography. Yields, methods of purification, and NMR data are given below.

12*H*-Indolo[1,2-*b*][2,7]naphthyridin-5-one (**7**): 35% yield; elution with 99:1 CH_2Cl_2/MeOH; mp 190−192 °C; ^{1}H NMR (500 MHz) δ 5.45 (s, 2H), 7.22 (ddd, J = 1.5, 7, 8.5 Hz, 1H), 7.46 (m, 2H), 7.52 (s, 1H), 7.77 (dt, J = 1, 1, 7 Hz, 1H), 8.08 (d, J = 5 Hz, 1H), 8.79 (d, J = 5 Hz, 1H), 8.89 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 42.2 (CH_2), 107.3 (CH), 110.2 (CH), 119.3 (CH), 122.0 (CH), 123.7 (CH), 126.5 (CH), 127.2 (C), 129.9 (C), 132.0 (C), 136.2 (C), 137.7 (C), 148.8 (CH), 149.6 (CH), 175.9 (C); HRMS calcd for $C_{15}H_{10}N_2O$ 234.0793, found 234.0798.

Indolo[1,2-*b*][2,6]naphthyridin-5,12-dione (**8**):[17] 15% yield; elution with 99:1 CH_2Cl_2/MeOH; ^{1}H NMR (200 MHz) δ 7.43 (t, J = 8 Hz, 1H), 7.64 (t, J = 8.4 Hz, 1H), 7.73 (s, 1H), 7.78 (d, J = 8 Hz, 1H), 8.25 (d, J = 5.2 Hz, 1H), 8.62 (d, J = 8.4 Hz, 1H), 9.13 (d, J = 5 Hz, 1H), 9.55 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 117.2 (CH), 117.4 (CH), 121.3 (CH), 124.1 (CH), 125.9 (CH), 126.5 (C), 128.6 (C), 130.4 (CH), 133.1 (C), 137.1 (C), 137.4 (C), 149.3 (CH), 155.5 (CH), 157.7 (C), 174.7 (C); HRMS calcd for $C_{15}H_8N_2O_2$ 248.0586, found 248.0596.

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6-Methyl-6*H*-pyrido[4,3-*b*]carbazole-5,11-dione (**16a**):[21] 60% yield; elution with 5:5 hexanes/AcOEt; mp 240−242 °C (lit.[21] 245 °C); ^{1}H NMR (500 MHz, assignment aided by HSQC and HMBC) δ 4.29 (s, 3H, NMe), 7.46 (ddd, J = 1, 6.5, 8 Hz, 1H, 9-H), 7.51 (d, J = 8.5 Hz, 1H, 7-H), 7.55 (ddd, J = 1, 6.5, 8 Hz, 1H, 8-H), 7.98 (d, J = 5 Hz, 1H, 4-H), 8.49 (d, J = 8.5 Hz, 1H, 10-H), 9.05 (d, J = 5 Hz, 1H, 3-H), 9.47 (s, 1H, 1-H); ^{13}C NMR (100.6 MHz, assignment aided by HSQC and HMBC) δ 32.2 (NMe), 111.1 (C-7), 118.7 (C-4), 119.4 (C-10b), 123.8 (C-10a), 124.3 (C-10), 125.3 (C-9), 126.6 (C-11a), 128.3 (C-8), 134.6 (C-5a), 139.2 (C-4a), 140.5 (C-6a), 148.5 (C-1), 155.1 (C-3), 178.3 (C-5), 180.7 (C-11).

6-Benzyl-6*H*-pyrido[4,3-*b*]carbazole-5,11-dione (**16b**):[21,22] 42% yield; elution with 7:3 hexanes/AcOEt; mp 256−258 °C (lit.[21] 268 °C); ^{1}H NMR (300 MHz) δ 6.00 (s, 2H), 7.18 (dd, J = 1.8, 8.1 Hz, 2H), 7.29 (m, 3H), 7.42−7.52 (m, 3H), 7.94 (dd, J = 0.6, 5.1 Hz, 1H), 8.52 (br d, J = 7.8 Hz, 1H), 9.03 (d, J = 5.1 Hz, 1H), 9.47 (s, 1H); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ 47.8 (CH_2), 112.6 (CH), 118.2 (C), 118.6 (CH), 122.8 (CH), 123.0 (C), 125.1 (CH), 126.1 (C), 126.8 (CH), 127.6 (CH), 128.0 (CH), 128.7 (CH), 134.5 (C), 136.7 (C), 139.0 (C), 139.5 (C), 147.2 (CH), 155.2 (CH), 177.4 (C), 180.3 (C). Anal. Calcd for $C_{22}H_{14}N_2O_2 \cdot 3/2H_2O$: C, 72.42; H, 4.69; N, 7.67. Found: C, 72.15; H, 4.33; N, 7.39.

6-(Methoxymethyl)-6*H*-pyrido[4,3-*b*]carbazole-5,11-dione (**16d**):[15,21] 10% yield; elution with 6:4 hexanes/AcOEt; mp 190−193 °C (lit.[21] 196−197 °C); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.40 (s, 3H), 6.16 (s, 2H), 7.25−7.60 (m, 2H), 7.68 (d, J = 8.6 Hz, 1H), 7.98 (d, J = 4.8 Hz, 1H), 8.50 (d, J = 8 Hz, 1H), 9.07 (d, J = 5.2 Hz, 1H), 9.47 (s, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 56.6 (CH_3), 75.4 (CH_2), 112.0 (CH), 118.6 (CH), 120.3 (C), 123.8 (C), 124.1 (CH), 125.4 (CH), 126.0 (C), 128.7 (CH), 134.5 (C), 139.0 (C), 140.2 (C), 148.4 (CH), 155.1 (CH), 177.8 (C), 181.0 (C).

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Supporting Information Available: General experimental protocols and detailed experimental procedures for the preparation of all synthetic intermediates. Characterization data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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