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Synthesis of Ellipticine: A Radical Cascade Protocol to Aryl- and Heteroaryl-Annulated[*b*]carbazoles

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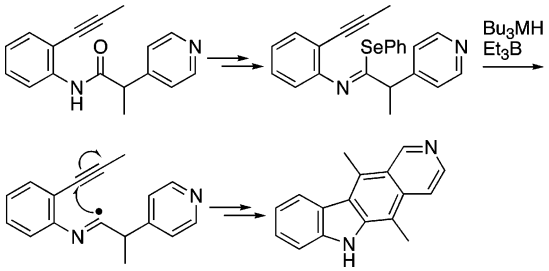
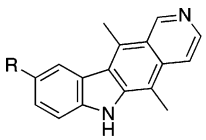


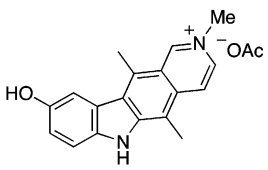
Imidoyl selanides, synthesized from amides, have been used as radical precursors of imidoyl radicals in cascade reactions. The novel radical cascade has been developed for the simple synthesis of the medicinally important aryl-annulated[*b*]-carbazoles. The protocol has been exemplified with the high-yielding total synthesis of the anticancer alkaloid ellipticine.

Aryl- and heteroaryl[*b*]carbazoles are an important class of biologically active compounds that include notable alkaloids of pharmaceutical interest.[1] Ellipticine **1** and its natural analogues **2** and **3**, first isolated in 1959,[2] have received a vast amount of attention because of their anticancer properties due to interaction with DNA. The synthetic analogue elliptinium **4** has been used clinically as an anticancer drug, including treatment of breast cancer, myeoblastic leukemia, and solid tumors.[1,3a] More recent studies have also indicated activity against HIV.[3b]

Ellipticine has proved a popular target for synthesis, and a wide variety of strategies have been reported.[1,4,5] Similarly, the structurally related aryl- and heteroaryl-annulated carbazoles have also received considerable synthetic attention.[1,4,6] However, few syntheses have been high-yielding and regioselective, and few syntheses have used mild conditions. Surprisingly, no radical methodologies have been reported, although biradicals have been used to synthesize benzo[*b*]carbazoles.[7] We report the results of our studies of a new radical protocol using imidoyl radical intermediates for the synthesis of aryl- and heteroaryl-[*b*]carbazoles and ellipticine **1** which meets the requirements of good yields, regioselectivity, and moderate conditions.



1: R = H
2: R = OH
3: R = OMe



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We recently published a novel methodology for the formation of imidoyl radicals **6** from amides via imidoyl selanides **5** (Scheme 1)[8] which has facilitated our new synthetic protocol. Cyclizations of imidoyl radicals onto alkynes have been previously used for radical cascade reactions. In these synthetic protocols, isocyanides[9] and isothiocyanates[10] were used as the imidoyl radical precursors. We envisaged that fused [*b*]carbazoles could be synthesized in just two steps at room temperature from easily available amides using our putative protocol (Scheme 2).

A range of amides **9** were synthesized in high yields using amide and Sonogashira couplings.[11] High yields could be obtained by carrying out either the amide

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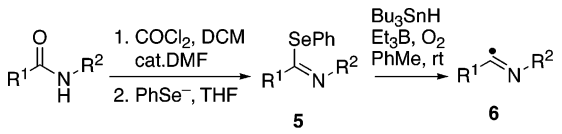
SCHEME 1. Formation of Imidoyl Radicals from Amides via Imidoyl Selanides



SCHEME 2. Retrosynthesis for Aryl- and Heteroaryl-Annulated[*b*]carbazoles

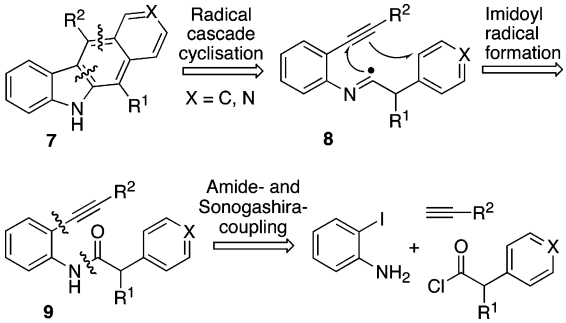
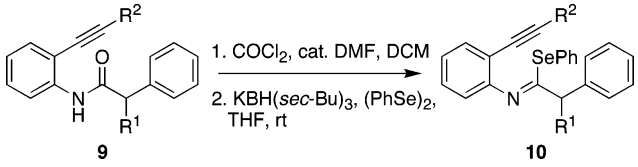


TABLE 1. Conversion of Amides to Imidoyl Selanides



entry		R^1	R^2		yield (%)[a]
1	**9a**	H	Ph	**10a**	22
2	**9b**	H	Me	**10b**	41
3	**9c**	Me	Ph	**10c**	67
4	**9d**	Me	Me	**10d**	61
5	**9e**	Me	CH_2OAc	**10e**	71
6	**9f**	Me	$SiMe_3$	**10f**	44
7	**9g**	Me	H	**10g**	46
8	**9h**	Me	CO_2Me	**10h**	57

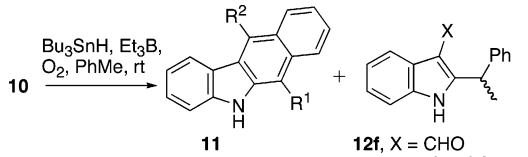
[a] Isolated yields.

coupling first, followed by the Sonogashira coupling, or vice versa, which is useful for building in diversity if required. The amides were converted to imidoyl selanides in moderate to good unoptimized yields (Table 1).

Initial cyclization reactions were performed using Bu_3SnH with AIBN as the initiator in refluxing toluene, but poor yields were obtained. The best results were obtained using Et_3B and O_2 for radical initiation at room temperature. After some optimization, the best conditions were found to be the addition of Et_3B (10 equiv) to deoxygenated solutions of the imidoyl selanides and Bu_3SnH, introduction of an O_2 bleed, stirring normally for 24 h, deoxygenation again, further addition of Et_3B (10 equiv), and stirring until the selanide **10** was consumed. The second deoxygenation was required to lower the concentration of O_2 so that the second portion of Et_3B was not consumed too rapidly. The somewhat unorthodox procedure successfully yielded the required cyclized products in up to 55% yields (Table 2).

Some of the reactions also gave monocyclized products. For example, for **10f** (entry 6) none of the desired carbazole **11f** was detected and the desilylated carbazole **11g** and the 3-formylindole **12f** were isolated (Scheme 3). Similarly, **10h** (entry 8) also yielded the indole **12h**

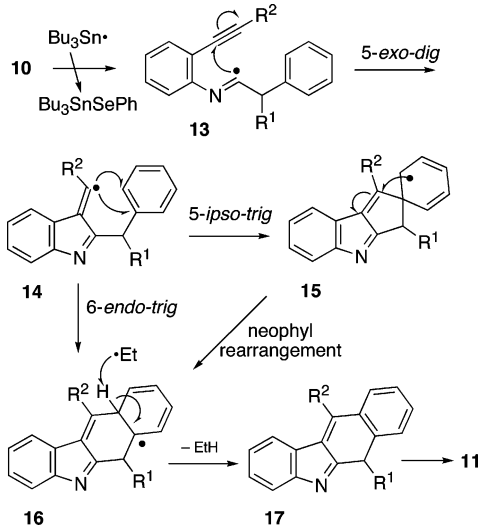
TABLE 2. Radical Cascade Reactions To Form Benzo[*b*]carbazoles



entry		R^1	R^2	t (h)	product, yield (%)[a]
1	**10a**	H	Ph	7[b]	**11a**, 33
2	**10b**	H	Me	24	**11b**, 15
3	**10c**	Me	Ph	48	**11c**, 55
4	**10d**	Me	Me	48	**11d**, 54
5	**10e**	Me	CH_2OAc	72	**11e**, 40
6	**10f**	Me	$SiMe_3$	48	**11f**, 0 **11g**, 18 **12f**, 33
7	**10g**	Me	H	6	**11g**, 18
8	**10h**	Me	CO_2Me	72	**11h**, 19 **12h**, 29

[a] Isolated yields. [b] Using AIBN/Δ.

SCHEME 3. Proposed Mechanism for the Radical Cascade Reaction



as well as the expected carbazole **11h**. (Scheme 3). We suggest that interception of the electrophilic vinyl radical intermediate (**14**, $R^2 = CO_2Me$) by the nucleophilic Bu_3SnH competes with further cyclization. For the terminal alkyne **10g** (entry 7), the cyclization competes with the addition of tributyltin radicals ($Bu_3Sn^•$) to the alkyne, and only an 18% yield of the carbazole **11g** was obtained. HPLC analysis of the product mixtures indicated a large number of very minor impurities but no other significant products other than those indicated.

We propose the mechanism as shown in Scheme 3 for the formation of the carbazoles. Although the (*Z*)-imidoyl selanides should yield the *trans*-imidoyl radicals **13**, theoretical and EPR spectroscopic analysis also shows that the *trans*-radicals are more stable.[12] The imidoyl radicals **13** undergo selective 5-*exo*-cyclization onto the alkynes. Evidence[9,10,13] suggests that the vinyl radical **14** undergoes a 5-*exo*-cyclization to **15** followed by a neophyl rearrangement to **16**, but a 6-*endo*-cyclization cannot be

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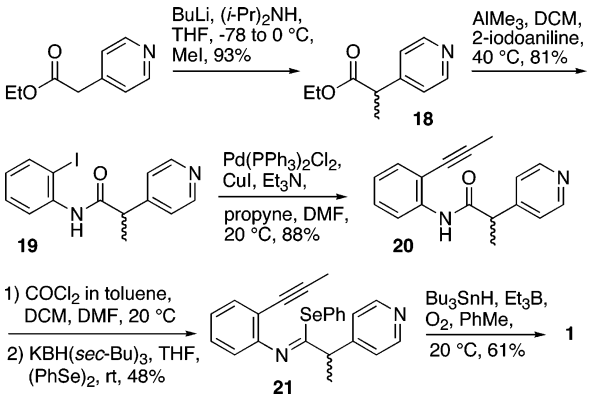
SCHEME 4. Total Synthesis of Ellipticine



ruled out. Studies indicate that the mechanism of rearomatization of π-radical intermediates (e.g., **16**) in Bu_3-SnH-mediated reactions is by H-abstraction by the initiator or a breakdown fragment therefrom.[14] In these reactions, we propose that the hydrogen is abstracted by ethyl radicals generated from the Et_3B initiator. Rapid tautomerism of the bicyclic products **17** yields the benzocarbazoles **11**.

The new protocol was applied to a total synthesis of ellipticine **1** from ethyl 2-(4-pyridyl)acetate in five steps with an overall yield of 19% (Scheme 4). Trimethylaluminum was used to synthesize amide **19**. While the last two steps have good rather than excellent yields, the overall yield is higher and the number of steps is smaller than almost all reported syntheses. Our synthesis avoids high-temperature reactions and indole protection/deprotection problems of previous syntheses and also facilitates the easy application of diversity. The pharmaceutical industry is reluctant to use Bu_3SnH because of its toxicity. Therefore, we repeated the radical cascade using the nontoxic tributylgermanium hydride (Bu_3GeH).[15] The yield was not optimized, but our preliminary result showed that similar yields (49% unoptimized yield) could be obtained using the nontoxic germanium alternative reagent. Bu_3GeH also has the advantages of long shelf life and clean reaction workups.[15]

A crystal structure of imidoyl selanide **21** was obtained showing the *Z*-configuration of the C=N bond (Figure 1). Therefore, abstraction of the phenylselanyl group yields an imidoyl radical with the correct stereochemistry (as shown in **13**, Scheme 3) for cyclization and does not require isomerization of the radical intermediate. Modeling studies showed that the S_H2 transition state for the homolytic cleavage of the carbon−selenium bond (e.g., **10** to **13**, Scheme 3) is sterically hindered, which probably accounts for the unusually slow reactions observed for the cascade cyclizations.

In conclusion, we have demonstrated a novel radical cascade protocol for the synthesis of aryl- and heteroaryl-fused[*b*]carbazoles, thereby enabling the synthesis of this

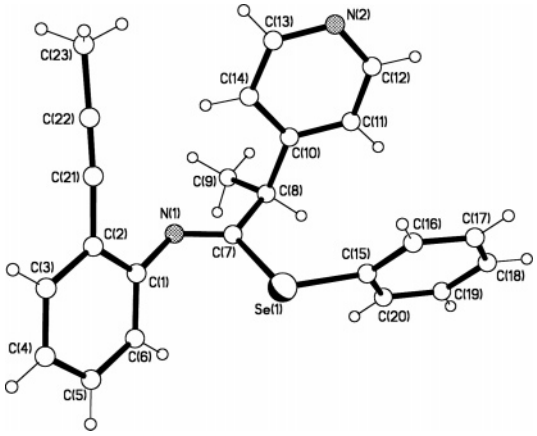


FIGURE 1. X-ray crystal structure of the imidoyl selanide 21.

important class of compounds in just two steps from easily available amides. The protocol was successfully applied to the total synthesis of the anticancer alkaloid ellipticine **1**. The protocol allows for easy incorporation of diversity for the synthesis of libraries of analogues. Further studies are aimed at adapting the protocol for the synthesis of other biologically active heteroarenes.

Experimental Section

General Procedure for the Conversion of Amides to Imidoyl Selanides. The amide (3.00 mmol) was dissolved in dry DCM (50 mL) followed by addition of DMF (6 drops) and dropwise addition of a 20% phosgene solution in toluene (4.76 mL, 9.00 mmol) at 0 °C. The reaction mixture was stirred overnight at room temperature and evaporated under reduced pressure. This residue was immediately dissolved in anhydrous THF (50 mL) and transferred into a suspension of $(PhSe)_2$ (0.47 g, 1.50 mmol) and K-selectride (1 M solution in THF) (3.30 mL, 3.30 mmol) in THF (20 mL). The reaction mixture was stirred until homogeneous at room temperature and evaporated under reduced pressure. The residue was dissolved in DCM, washed with water, dried, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel with EtOAc in light petroleum (20%) as eluent to yield the required imidoyl selanide.

Typical Experiment: (*Z*)-Phenyl *N*-2-(Prop-1-ynyl)phenyl-2-(pyridin-4-yl)propaneselenoimidate 21. Yellow crystals (48%), mp 90−92 °C. (Found: C, 68.52; H, 4.87; N, 6.70. $C_{23}H_{20}N_2Se$ requires C, 68.48; H, 5.00; N, 6.94%). ν_{max}(film)/cm^{-1} 3052, 2982, 2926, 1630. 742, 692; δ_H ($CDCl_3$, 400 MHz) 1.51 (3 H, d, J = 6.9), 2.07 (3 H, s), 3.91 (1 H, q, J = 6.9), 6.87 (1 H, bd, J = 7.9), 7.04−7.06 (2 H, m), 7.10 (1 H, dd, J = 7.7, 1.3), 7.20−7.31 (3 H, m), 7.35−7.40 (3 H, m), 7.45 (1 H, dd, J = 8.1, 1.4,), 8.41−8.43 (2 H, m); δ_C ($CDCl_3$, 100 MHz) 4.7 (CH_3), 21.8 (CH_3), 48.3 (CH), 77.3, 90.0 (C), 114.2 (C), 118.8, 123.1, 124.5 (CH), 126.9 (C), 128.4, 129.2, 129.3, 133.0, 137.6, 149.6 (CH), 151.4, 152.0 (C), 167.7 (C); *m/z* (LSIMS) 405.0866 [(M + H)$^+$, $C_{23}H_{21}N_2$-Se requires 405.0864], 405 (41%), 249 (85), 108 (100). The structure of **18** was confirmed by X-ray crystallography.

General Procedure for Radical Cascade Reactions. Ellipticine 1. (*Z*)-Phenyl *N*-2-(prop-1-ynyl)phenyl-2-(pyridin-4-yl)propane selenoimidate **21** (0.25 g, 0.62 mmol) and tributyltin hydride (0.36 mL, 1.36 mmol) were dissolved in toluene (20 mL), and the solution was flushed with argon for 15 min. Triethylborane (18.6 mL, 18.6 mmol) was added in three portions, once every 24 h (preceded by deoxygenation). The reaction mixture was stirred for 72 h, allowing oxygen (in air) to bleed in through a needle. The solution was evaporated under reduced pressure, the residue was dissolved in DCM, extracted three times with dilute HCl, and washed with petrol, and the aqueous phase was basified using concentrated NaOH. The resulting dispersion was

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extracted five times with DCM, and the organic phase was evaporated under reduced pressure. The resulting residue was purified using column chromatography using silica gel as absorbent and THF/EtOAc (1:1) as eluent to give ellipticine **1** (93 mg, 61%) as yellow crystals, mp 310−314 °C (Lit.,[16] 311−315 °C) IR 3422, 3153, 3090, 2925, 2870, 2363, 2341, 1600, 1463, 1407, 1383, 1262, 1242, 1027, 811, 743, 604 cm^{-1}; ^1H NMR (400 MHz, d_6-DMSO) δ 11.42 (1 H, s), 9.70 (1 H, s), 8.43 (1 H, d, J = 6.0 Hz), 8.39 (1 H, d, J = 8.0 Hz), 7.92 (1 H, d, J = 6.0 Hz), 7.51−7.59 (2 H, m), 7.27 (1 H, ddd, J = 8.0, 6.9, 1.4 Hz), 3.26 (3 H, s), 2.79 (3 H, s); ^{13}C NMR (100 MHz, DMSO) δ 149.6, 142.6, 140.5, 140.4, 132.4, 128.0, 127.1, 123.8, 123.3, 123.1, 121.9, 119.1, 115.9, 110.7, 108.0, 14.3, 11.9. The data were identical to those reported in the literature.[16]

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

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