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A 'one pot' microwave-mediated synthesis of the basic canthine skeleton: expedient access to unnatural β-carboline alkaloids

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Abstract—In a 'one pot' microwave reaction, an acyl hydrazide-tethered indole underwent a 3-component condensation to form a triazine, followed by an inverse-electron demand Diels–Alder reaction and subsequent chelotropic expulsion of N_2 to deliver novel, unnatural β-carboline alkaloids in good isolated yields.

Canthines represent a tetracyclic subclass of β-carboline alkaloids that possess an additional D-ring (Fig. 1).[1] Since the isolation of the parent canthine in 1952 from *Pentaceras australis*, over forty members of this class of alkaloids have been isolated and characterized.[2] Moreover, members of the canthine family have been shown to exhibit a wide range of pharmacological activities including antifungal, antiviral and antitumor properties.[1–3]

A number of synthetic approaches to access the canthine skeleton have been reported and typically employ Pictet–Spengler or Bischler–Napieralski strategies.[4] In 1992, Snyder disclosed an elegant strategy to access the canthine skeleton utilizing indole as a dienophile in an intramolecular inverse electron demand Diels–Alder (IEDDA) reaction (Scheme 1).[5] Treatment of acyl hydrazide-tethered indole **1** with a 1,2-diketone **2** and excess of ammonium acetate in refluxing acetic acid for several hours provided the triazine-tethered indole **3**. After purification, **3** was refluxed in triisopropylbenzene (232°C) for 1.5–20 h to provide the basic canthine skeleton **4** in 45–56% overall yield. Despite this notable synthetic advance, limited diversity exists at the C1/C2 positions of natural and unnatural canthine alkaloids reported to date.[1–5]

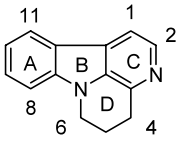
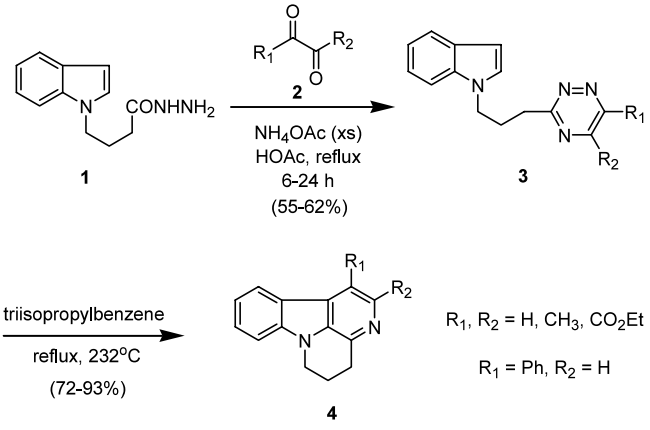


Figure 1. Canthine alkaloid tetracyclic skeleton.

In a recent letter, our laboratory reported on a new microwave-mediated protocol for the rapid synthesis of diverse 3,5,6-trisubstituted-1,2,4-triazines in high yields.[6] During the course of this work, readily available acyl hydrazide **1** was subjected to our standard microwave conditions. In the event, heating a 1:1 ratio of **1** and benzil **5** in the presence of 10 equiv. of NH_4OAc in a single-mode microwave at 180°C for 5 min delivered not only the desired triazine **6**, but also the 1,2-diphenyl canthine derivative **7** (Scheme 2).[7] LCMS and NMR analysis indicated a 9:1 ratio of **6**:**7** with isolated yields of 83% and 6%, respectively. Sig-



Scheme 1.

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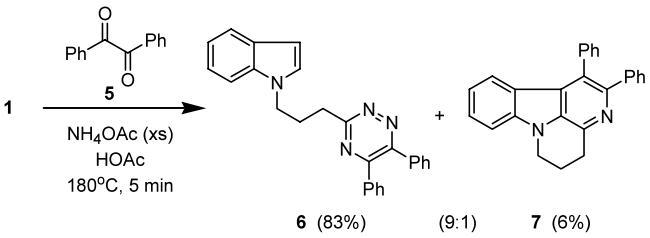


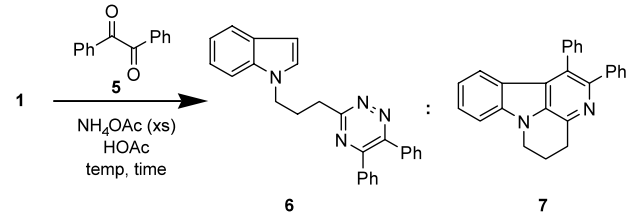
Scheme 2.

nificantly, in a single 'pot', **1** underwent a three component condensation to generate triazine **6**, followed by an intramolecular IEDDA reaction and subsequent chelotropic expulsion of N_2 to generate the previously unknown 1,2-diphenyl canthine **7**.

With this result in hand, our efforts centered on the optimization of this 'one pot' reaction to deliver **7** exclusively. Reaction parameters were quickly evaluated in an automated fashion on a single-mode microwave (Table 1).[7a] By simply increasing the reaction time from 5 to 60 min at 180°C, the ratio of **6**:**7** could be increased from 9:1 to 1:2, as determined by analytical LCMS. Further increasing the temperature to 220°C, 100°C above the boiling point of HOAc, for 40 min altered the selectivity to 0.5:9.5, in favor of **7**. Under these optimal reaction conditions, the pressure inside the microwave vessel reached 12 PSI, well within the safety limits of the instrument.

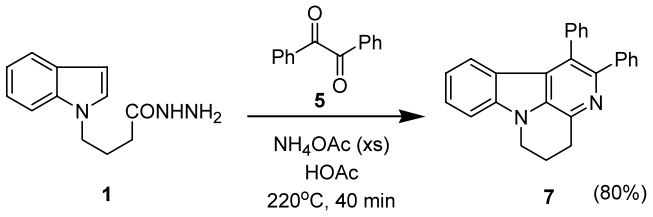
Application of these optimal conditions on a 0.5 mmol scale reaction that employed a 1:1 ratio of **1** to **5** with an excess of NH_4OAc for 40 min at 220°C delivered **7** in 80% isolated yield.[8] Analysis of the crude reaction by LCMS and NMR failed to detect any trace of triazine **6** (Scheme 3). With a 'one pot' protocol for the expedient synthesis of the basic canthine skeleton in hand, attention was now directed at probing the generality of this reaction with respect to other 1,2-diketones.

Table 1. Optimization of 'one pot' synthesis of **7**

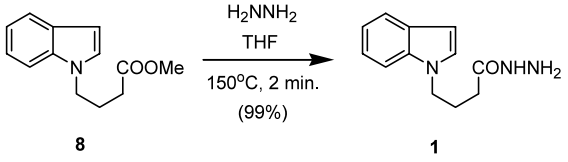


Entry	Time (min)	Temp. (°C)	**6**:**7**[a]
1	5	180	9:1
2	10	180	7:3
3	20	180	2:1
4	40	180	1:1
5	60	180	1:2
6	40	200	1:5
7	40	220	0.5:9.5

[a] Ratios determined by analytical LCMS.



Scheme 3.



Scheme 4.

In order to probe the reaction's generality, large quantities of **1** were required. Following literature preparations, **1** could be made on multigram scales; however, **1** was found to decompose upon storage at room temperature. Therefore, a microwave-accelerated variant of Laasko's thermal protocol was developed whereby **1** was prepared only as needed, and used immediately (Scheme 4).[5,9] In this instance, microwave heating of commercially available ester **8** with hydrazine at 150°C in THF for only 2 min afforded **1** in quantitative yield.[10] Isolation simply involved evaporation of the solvent, and subsequent reactions could be conducted in the same microwave reaction vessel.

Treatment of a variety of 1,2-diketones and **1** under our standard 'one pot' procedure delivered unnatural canthine alkaloids in moderate to excellent isolated yields (Fig. 2). Functionalized aryl analogs such as **9** and **10** provided the best yields (>80%), while heteroaryl congeners, exemplified by **11** and **12** afforded reasonable yields (~60%). In general, dialkyl derivatives afforded lower overall yields (~30%) under this protocol, as illustrated by **13** and the novel pentacyclic congener **14**. However, replacement of one alkyl group with a phenyl subtituent increased the yield to 62%, though a 1:1 mixture **15a**:**15b** of regioisomers resulted. Preparative mass-guided HPLC on a custom Agilent 1100 instrument smoothly separated the regioisomers.[11]

All attempts to modify reaction parameters to increase the 'one pot' yields of C1/C2 dialkyl analogs failed. Ultimately, improved yields were achieved by a 'two pot' microwave-accelerated procedure that required only 35 min total reaction time (Scheme 5). In the event, our standard triazine protocol was employed to deliver **17** in 5 min at 180°C.[6] After isolation, **17** was dissolved in 1.8 mL of dry DMF and heated at 250°C, almost 100°C above the boiling point of DMF, for 30 min in a single-mode microwave to provide **18** in 55% overall yield from **1**.[7a] Caution, this reaction generated 15 PSI of pressure, just below the safety threshold of the microwave. A number of solvents (dichloroethane, dioxane, toluene and ethanol) were examined for the

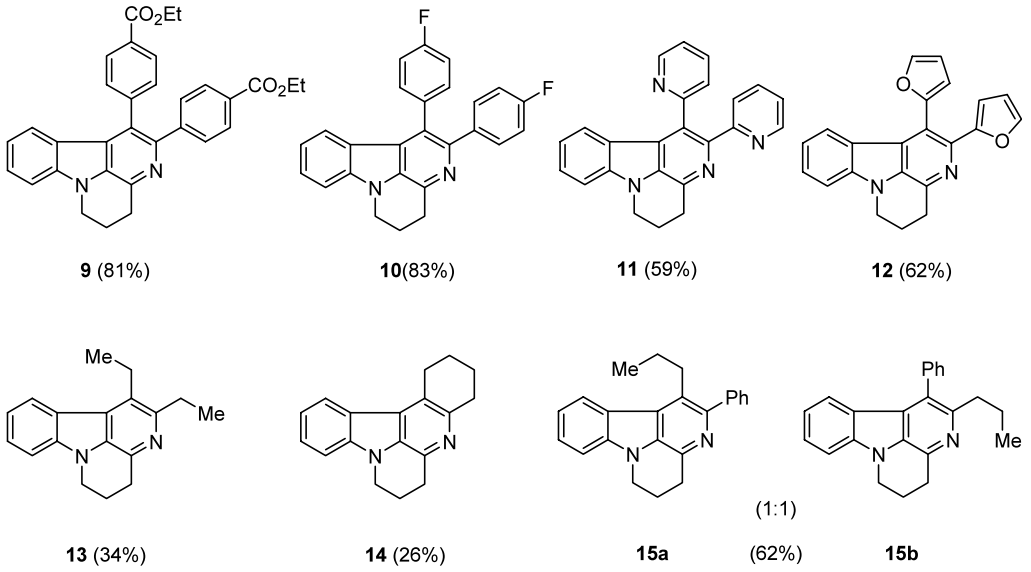
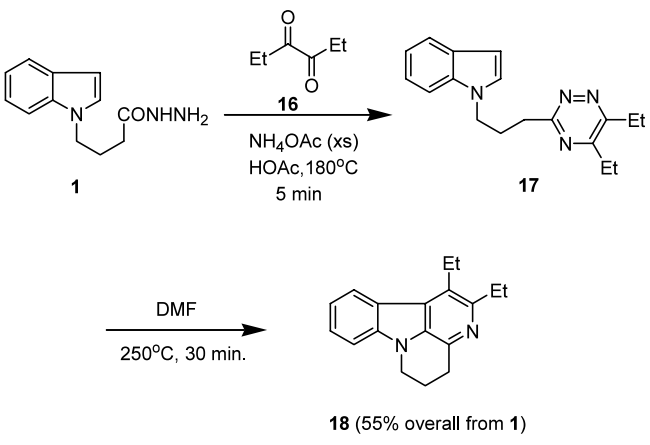
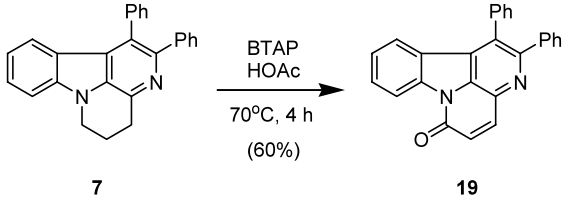


Figure 2. Representative unnatural canthine alkaloids.



Scheme 5.



Scheme 6.

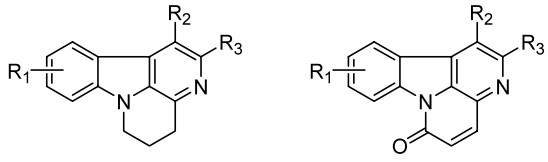


Figure 3. Generic unnatural canthine alkaloid library.

conversion of **17** to **18** at a variety of temperatures, but only DMF provided the desired canthine core.

Unnatural canthin-6-one alkaloid congeners could also be obtained by selective oxidation following the procedure prescribed by Snyder.[12] In this instance, treatment of canthine **7** with BTAP (triethylbenzylammonium permanganate) in CH_2Cl_2/HOAc delivers previously unknown 1,2-diphenyl canthin-6-one **19** in 60% isolated yield (Scheme 6). All attempts to oxidize **11** to the analogous canthin-6-one under this protocol were unsuccessful. In this case, oxidation at the C1/C2 pyridyl ring nitrogens occurred quickly and led to complex mixtures.

Recently, diversity-oriented synthesis has garnered a great deal of attention as unnatural analogs of natural products have been shown to possess novel biological activity.[13] Relatively few canthine alkaloids have been discovered or synthesized, yet possess a wide range of biological activities. For these reasons, in addition to a simple 'one pot' protocol for 3-position diversity, the preparation of a library of unnatural canthine alkaloids coupled with biological screening is in progress (Fig. 3).

In summary, a microwave-mediated protocol for the 'one pot' synthesis of the basic canthine alkaloid skeleton has been developed on a single-mode microwave synthesizer.[7a] This new 'one pot' procedure was found to be general for the synthesis of C1/C2 diaryl canthines. A complimentary 'two pot' microwave-accelerated procedure was also developed to productively deliver C1/C2 dialkyl canthine congeners. In addition to providing high yielding access to a number of previously unknown canthine and canthin-6-one alkaloids, reaction times have been reduced 10- to 700-fold over conventional thermal methods. Applications of this 'one pot' procedure for diversity-oriented organic syn-

thesis of unnatural canthine alkaloids coupled with biological screening is in progress and will be reported in due course.

Acknowledgements

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7. (a) The single-mode microwave synthesizer empoyed for this work was a Smithsynthesizer™, a unit now refered to and sold under the name Emrys Liberator™ by Personal Chemistry. For information on Personal Chemistry's microwave technology for organic synthesis, including the Emrys Liberator™, see: http://www.personalchemistry.com; (b) *Experimental procedure for* ***6****/****7***: To a 5 mL Emrys Liberator™ reaction vial (Part # 351521) with a stir bar was placed benzil, **5**, (105 mg, 0.5 mol) the indole-tethered acyl hydrazide, **1**, (109 mg, 0.5 mmol), ammonium acetate (385 mg, 5.0 mmol) and 2 mL of glacial HOAc. The reaction vessel was heated in the Emrys Liberator™ reactor cavity for 5 min at 180°C. After 5 min, the vessel was rapidly cooled to 40°C by the unit. Upon removal from the reactor cavity, the homogeneous solution was concentrated on a nitrogen evaporator and analyzed by LCMS. Two peaks in a 9:1 ratio were detected corresponding to **6** (3.84 min.) and **7** (2.71 min.), respectively. The sample was purified by preparative mass guided HPLC to deliver 162 mg (83%) of pure **6** and 10.8 mg (6.3%) of pure **7**.
Analytical data for ***6***: Analytical LCMS indicated a single peak (3.843 min, CH_3CN/H_2O/0.1%TFA, 4 min gradient) >98% pure by UV (214 nm) and 100% pure by ELSD. (^{1}H NMR, 300 mHz, $CDCl_3$): δ 7.49 (m, 3H), 7.39 (m, 5H), 7.29 (s, 2H), 7.27 (d, $J=3$ Hz, 1H), 7.19 (m, 2H), 7.08 (m, 2H), 6.32 (dd, $J=0.9$, 3.2 Hz, 1H), 4.36 (t, $J=6.3$ Hz, 2H), 3.32 (t, $J=6.9$ Hz, 2H), 2.61 (quint. $J=6.9$ Hz, 2H); HRMS calcd for $C_{26}H_{22}N_4$(M+H), 391.1917; found 391.1915 (M+H).
8. *Experimental procedure for 'one pot' synthesis of* **7**: To a 5 mL Emrys Liberator™ reaction vial (Part # 351521) with a stir bar was placed benzil, **5**, (105 mg, 0.5 mol) the indole-tethered acyl hydrazide, **1**, (109 mg, 0.5 mmol), ammonium acetate (385 mg, 5.0 mmol) and 2 mL of glacial HOAc. The reaction vessel was heated in the Emrys Liberator™ reactor cavity for 40 min at 220°C. Quickly, ~12 PSI of pressure was generated in the reaction vessel and detected by the instrument. After 40 min, the vessel was rapidly cooled to 40°C by the unit. Upon removal from the reactor cavity, the homogeneous solution was concentrated on a nitrogen evaporator and analyzed by LCMS. A major peak corresponding to **7** (2.708 min.) was observed—no peak (3.84 min.) corresponding to **6** was detected. The crude LCMS purity for **7** was 77% (214 nm and ELSD). The sample was purified by preparative mass guided HPLC to deliver 144 mg (80%) of pure **7**. Analytical LCMS indicated a single peak (2.711 min, CH_3CN/H_2O/0.1%TFA, 4 min gradient) >98% pure by UV (214 nm) and 100% pure by ELSD. (^{1}H NMR, 300 mHz, $CDCl_3$): δ 7.69 (m, 1H), 7.59 (m, 1H), 7.44 (m, 2H), 7.31 (m, 9H), 7.16 (m, 1H), 4.42 (t, $J=5.7$ Hz, 2H), 3.71 (t, $J=5.7$ Hz, 2H), 2.61 (t, $J=5.7$ Hz, 2H); HRMS calcd for $C_{26}H_{20}N_2$(M+H), 361.1699; found 361.1705 (M+H).
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