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Selective Oxidation of Canthines to Canthin-6-ones with Triethylbenzylammonium Permanganate

Jia-He Li and John K. Snyder*

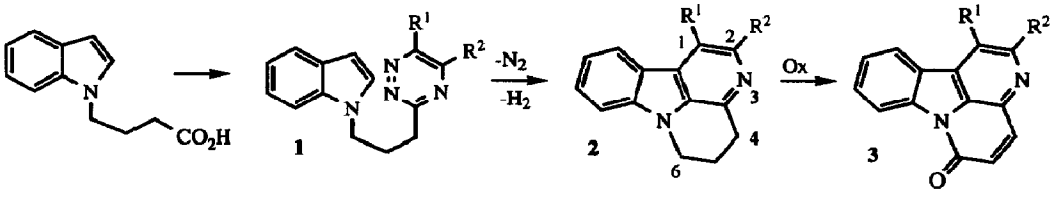
Department of Chemistry, Boston University, 590 Commonwealth Ave., Boston, MA 02215

Abstract: Oxidation of canthines, prepared from intramolecular inverse electron demand Diels-Alder reactions of indole with tethered triazines, produced the corresponding canthin-6-ones regiospecifically, with no detected canthin-4-ones.

The canthin-6-one alkaloids are a subclass of β-carboline alkaloids with an additional D-ring, the parent compound of which was first isolated from *Pentaceras australis*.[1] Since then, more than forty members of this class of alkaloids have been reported,[2] primarily from species of the Simaroubaceae family.[3] These alkaloids have been reported to be cytotoxic against various tumor cell lines,[4] and several members have also been shown to be antifungal,[2a,5] antiviral,[2a] and molluscicidal.[6] In specific enzyme/receptor assays, canthin-6-ones have been shown to inhibit adenosine 3',5'-cyclic monophosphate phosphodiesterase,[7] while 4,5-dihydrocanthin-6-one depressed CNS activity in mice;[8] synthetic 2-(methoxycarbonyl)canthin-6-one was also shown to bind to the benzodiazepine receptor,[9] though the mode of binding was thought to be inverted in comparison to the bindings of other β-carbolines.[10] Of equal interest is a recent report that the production of canthin-6-one alkaloids in *Ailanthus altissima* cell cultures can be stimulated by fungal elicitors,[11] suggesting a defensive role for these alkaloids. Previous syntheses of the canthin-6-ones have relied upon a Pictet-Spengler strategy to form the β-carboline structure from tryptamine or tryptophan followed by subsequent formation of the D-ring.[12]

We recently reported an intramolecular inverse electron demand cycloaddition route to the canthine skeleton **2** using indole as the dienophile with a 1,2,4-triazine constructed at the terminus of a trimethylene tether linking the triazinyl 3-position with the indole nitrogen (**1**, Scheme 1).[13] This cycloaddition route, which produces the aromatized C-ring subsequent to the cycloaddition, allows for easy access to various 1- and 2-position mono- and disubstituted canthines in good overall yields beginning with indole.

Scheme 1

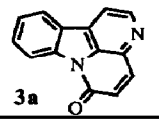
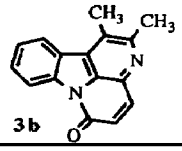
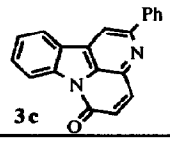
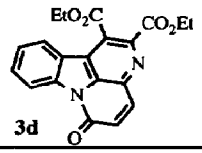
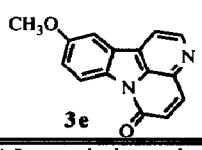


Completion of the canthin-6-one syntheses from the canthine cycloadducts requires the regioselective oxidation of C-6. Of particular concern was the potential oxidation of the canthine C-4[14] and N-3 sites (to produce canthin-4-ones and canthine ^{3}N-oxides), as well as possible oxidation of alkyl substituents such as the methyl groups in 1,2-dimethylcanthine [**2b**]. We now report the regioselective oxidation of various canthines to

canthin-6-ones with the phase transfer permanganate reagent triethylbenzylammonium permanganate (BTAP),[15a] used by Schaefer to oxidize amines to amides.[15b]

In optimization studies with **2b** (the most sensitive of the canthines to oxidation at other sites), the oxidation proved to be very sensitive to the solvent. With freshly prepared, anhydrous BTAP in anhydrous methylene chloride, no oxidation of **2b** occurred even after 3 days. An optimal yield (67%) of canthin-6-one **3b** was obtained using the mixed solvent system CH_2Cl_2:HOAc (1:5) employing 1.5 eq of BTAP at 70 °C (3 h) with no detectable oxidation at C-4, N-3, or the methyl substituents. Using these conditions, all canthines in hand were successfully oxidized to the canthin-6-ones (Table). In general, increasing amounts of CH_2Cl_2 slowed down the reactions while using pure glacial acetic acid as the solvent led only to intractable decomposition of the canthine (i.e. a mess) with only trace amounts of isolable canthin-6-ones.

Table. Canthin-6-ones Prepared by Canthine Oxidation with BTAP[a]

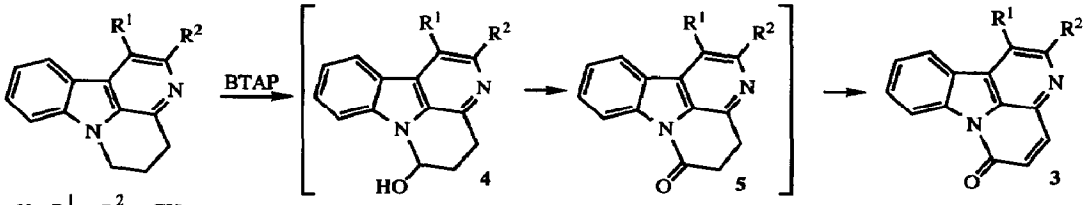
Canthinone	Yield (%)[b]	Time (h)	^{1}H NMR [$CDCl_3$: δ]
 **3a**	65	4	8.82 (d, *J* = 5.0 Hz, H-2); 8.67 (dd, *J* = 8.0, 1.0 Hz, H-8); 8.11 (dd, *J* = 7.7, 1.0 Hz, H-11); 8.05 (d, *J* = 9.8 Hz, H-4); 7.98 (d, *J* = 5.0 Hz, H-1); 7.71 (ddd, *J* = 8.0, 8.0, 1.0, Hz, H-9); 7.53 (ddd, *J* = 8.0, 7.7, 1.0 Hz, H-10); 6.98 (d, *J* = 9.8 Hz, H-5)
 **3b**	67	4	8.71 (d, *J* = 8.3 Hz); 8.18 (d, *J* = 7.8 Hz); 8.00 (d, *J* = 9.8 Hz); 7.68 (dd, *J* = 8.3, 7.7 Hz); 7.52 (*J* = 7.8, 7.7 Hz); 6.89 (d, *J* = 9.8 Hz); 2.85 (s, 3H); 2.80 (s, 3H)
 **3c**	58	3	8.64 (d, *J* = 7.9 Hz); 8.33 (s, H-1); 8.12 - 8.08 (m, 3H); 8.04 (d, *J* = 9.7 Hz); 7.68 (ddd, *J* = 7.9, 7.4, 1.3 Hz); 7.55 - 7.45 (m, 4H); 6.96 (d, *J* = 9.7 Hz)
 **3d**	67	3	8.68 (d, *J* = 8.5 Hz); 8.20 (d, *J* = 7.8 Hz); 8.20 (d, *J* = 10.0 Hz); 7.75 (dd, *J* = 8.5, 7.3 Hz); 7.54 (dd, *J* = 7.8, 7.3 Hz); 7.05 (d, *J* = 10.0 Hz); 4.60 (q, *J* = 7.2 Hz, 2H); 4.53 (q, *J* = 7.2 Hz, 2H); 1.47 (t, *J* = 7.2 Hz, 3H); 1.46 (t, *J* = 7.2 Hz, 3H)
 **3e**	64	4	8.80 (d, *J* = 5.0 Hz); 8.55 (d, *J* = 8.9 Hz); 8.00 (d, *J* = 9.9 Hz); 7.93 (d, *J* = 5.0 Hz); 7.56 (d, *J* = 2.5 Hz); 7.25 (dd, *J* = 8.9, 2.5 Hz); 6.97 (d, *J* = 9.9 Hz); 3.95 (s, 3H)

a) In a typical experiment, to a solution of the canthine **2** (0.5 mmol) and BTAP (0.75 mmol) in CH_2Cl_2 (1.0 mL) was slowly added glacial acetic acid (5.0 mL) with stirring over 5 minutes. The solution was maintained at 70 °C for 3 - 4 h. The reaction mixture was then evaporated in vacuo and the solid residue suspended in the biphasic system EtOAc/H_2O (2:1, 30 mL) and suction filtered. The organic layer was separated and the aqueous layer extracted with EtOAc. The combined EtOAc layers were washed with H_2O, dried over $MgSO_4$, and the solvent removed in vacuo. The residue was purified by flash chromatography to provide **3a** - **3e**.
b) Isolated yields.

All the canthin-6-ones were fully characterized by ^1H and ^{13}C NMR, HRMS, and IR. Of particular value was the appearance of the characteristic H-4/H-5 doublets of the α,β-unsaturated lactam D-ring (Table), and the carbonyl carbon in the ^{13}C NMR spectra (δ 159.2 - 159.5). In addition, the isolation of two 4,5-dihydrocanthin-6-one intermediates and comparison of the ^1H and ^{13}C chemical shifts with literature values for known canthinones **3a** and **3e** (vida infra) confirmed the regiospecificity of the oxidation.

While the mechanism of the oxidation remains unclear,[16] by lowering the reaction temperature to 60 °C with the mixed solvent system CH_2Cl_2:HOAc (1.5:5) intermediate carbinolamine **4b** (6%) and dihydrocanthin-6-one **5b** (21%) were isolated and characterized (Scheme 2) along with canthin-6-one **3b** (32%) and recovered canthine **2b** (35%). Both **4b** and **5b** were characterized by HRMS (**4b**: *m/z* 252.1259 [M+], calc'd for $C_{16}H_{16}N_2O$ 252.1263; **5b**: *m/z* 250.1104 [M+], calc'd for $C_{16}H_{14}N_2O$ 250.1106) and ^1H NMR. Similarly, the oxidation of 2-phenylcanthine **2c** with BTAP in CH_2Cl_2:HOAc (1:1, 70 °C, 4 h) produced dihydrocanthin-6-one **5c** (55%). The ^1H NMR spectra of **4b**, **5b**, and **5c** in comparison with those of the corresponding canthines **2b** and **2c** all showed the loss of the methylene triplet of the H-6 protons adjacent to the indole nitrogen (**2b**: δ 4.20, t, *J* = 5.8 Hz, 2H; **2c**: δ 4.26, t, *J* = 5.8 Hz, 2H). In carbinolamine **4b**, a new signal for H6 appeared at δ 6.15 (dd, *J* = 2.7, 2.7 Hz) along with the H-4 and H-5 methylene protons (δ 3.39, m, 1H, and 3.18, m, 1H: H-4; δ 2.51, m, 1H, and 2.12, m, 1H: H-5; assigned by COSY). The spectra of **5b** and **5c** showed only the H-4 and H-5 methylene triplets (**5b**: δ 3.39, t, *J* = 7.5 Hz, 2H, H-4; 3.18, t, *J* = 7.5 Hz, 2H, H-5; **5c**: δ 3.49, t, *J* = 7.6 Hz, 2H, H-4; 3.19, t, *J* = 7.6 Hz, 2H, H-5) with the H-5 triplets significantly deshielded by the C-6 carbonyl group relative to their respective chemical shifts in the corresponding canthines (**2b**: δ 2.41; **2c**: δ 2.44).[13] The appearance of the lactam carbonyl in **5b** and **5c** was indicated by the IR spectra (**5b**: ν_{CO} 1698 cm^{-1}; **5c**: ν_{CO} 1691 cm^{-1}) and the ^{13}C NMR spectrum of **5c** which revealed a carbonyl carbon (δ 166.6). Subjecting **4b**, **5b**, and **5c** either to oxidation with BTAP, or to DDQ in refluxing benzene produced the respective canthin-6-ones **3b** and **3c** (> 90% yields).

Scheme 2



2b: $R^1 = R^2 = CH_3$
2c: $R^1 = H$, $R^2 = Ph$

In conclusion, the phase transfer oxidant benzyltriethylammonium permanganate has proven to be highly regioselective for transforming canthines to canthin-6-ones in a one pot reaction. This simple oxidation procedure allows for straightforward syntheses of canthin-6-ones beginning with indole and proceeding through the corresponding canthines. Canthin-6-one [**3a**], isolated from numerous sources,[2a] and 10-methoxycanthin-6-one [**3e**], recently reported from *Aerva lanata*,[17] are natural products; **3a** has been previously synthesized though this is the first reported synthesis of **3e**. Spectroscopic data for **3a**[2a,4c] and **3e**[2g] are in agreement with

that reported in the literature. Work is continuing to find other oxidants which may accomplish this transformation in higher yields.

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16 Distinct routes initiated by either electron transfer or by N-oxide formation followed by immonium ion formation can be envisioned.

17 Ref. 2g. An earlier report of 10-methoxycanthin-6-one (ref. 4a) has since been shown to have been misassigned (ref. 2d).

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