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A catalytic versus stoichiometric photoinduced electron transfer promoted selective C_{16}–C_{21} bond cleavage of catharanthine

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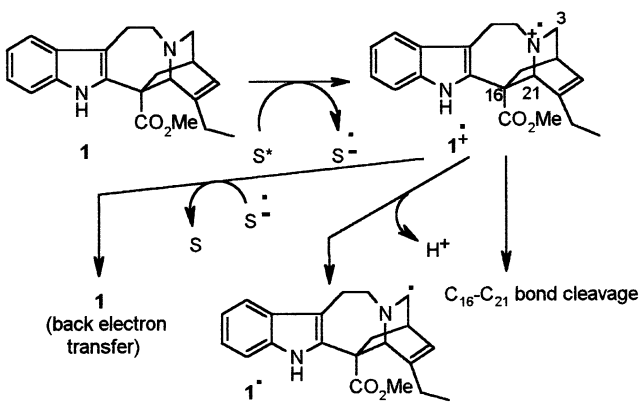
Abstract—A clean and efficient access to the cleavamine skeleton is described through the selective oxidative C_{16}–C_{21} bond cleavage of catharanthine. The best result is obtained by the use of catalytic quantities of β-lapachone as photosensitizer, which permits the successful control of competition between the back electron transfer, the deprotonation and the fragmentation pathway.

The field of green chemistry requires a significant rethinking of the ways in which chemists design organic reactions, of particular importance are the subset of reactions that employ toxic reagents in stoichiometric quantities and their replacement by catalysts.[1] Some of the most important unsolved technological problems in both selectivity and green chemistry involve oxidation. Among the candidates as reagents for benign oxidation chemistry are the photochemical transformations involving photoinduced electron transfer. In this communication, we applied this methodology to a selective transformation in the alkaloid series.

Vinblastine (VLB) and vincristine (VCR), vinca alkaloids isolated from the Madagascan periwinkle *Catharanthus roseus*, are well-known useful anticancer agents.[2] One of the most interesting pathways to these dimeric compounds involves an oxidative fragmentation of catharanthine **1** followed by the coupling with the vindoline moiety.[3] Our ongoing interest in photooxidation by visible light prompted us to try to realize photochemically such a cleavage by SET. Oxidation of catharanthine **1** achieved by irradiation with visible light in the presence of a photosensitizer (S) leads to a radical ion pair ($\mathbf{1}^{+\bullet}$, $S^{-\bullet}$). Once formed, the radical ion pair can decay via three pathways (Scheme 1). Firstly, the favourable thermodynamically back electron transfer (BET) gives the starting material. Secondly, a deprotonation reaction of the radical cation by the semi-reduced form $S^{-\bullet}$ can occur to give an α-amino-radical $\mathbf{1}^{\bullet}$, which after oxidation can finally lead to the 3β-cyanocatharanthine **2**.[3] We have already described photochemical conditions allowing such a selective evolution.[4] Lastly a previously observed C_{16}–C_{21} bond fragmentation can occur leading to the cleavamine skeleton.[5]

In this paper we report new photooxidative conditions with catalytic quantities of photosensitizer resulting in a selective decay of the radical ion pair via this third pathway.



Scheme 1.

Keywords: oxygen; singlet; photochemistry; oxidation; alkaloids; cleavage reactions.

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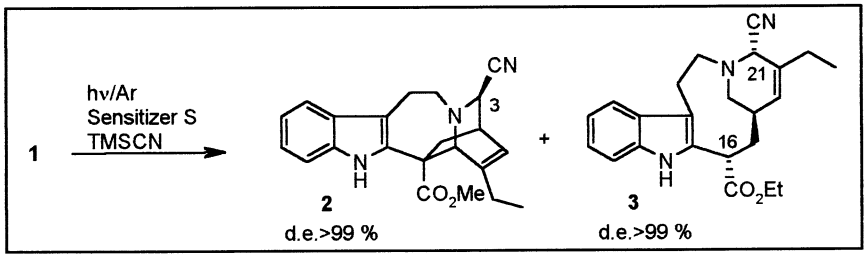
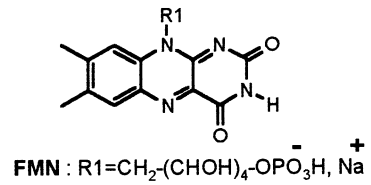
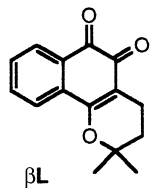


S	equiv.	2 : 3	Yield %
DCA	1	0 : 10	70
FMN	0,1	1 : 9	91
βL	0,03	0 : 10	88





Scheme 2.

Irradiation of catharanthine **1** (Scheme 2) under an argon atmosphere by visible light (λ>420 nm) in the presence of a stoichiometric amount of 9,10-dicyanoanthracene (DCA) as photosensitizer,[6] a small amount of water and trimethylsilyl cyanide (TMSCN), yields 21α-cyano-16α-(methoxycarbonyl)cleavamine **3** quantitatively (d.e.>99%). This product is obtained in 70% yield after crystallization.

The mechanism involved under these conditions requires a stoichiometric amount of DCA, a well-known photosensitizer which initiates electron transfer in the singlet excited state.[6,7] In this case, the BET is particularly rapid as this decay is an allowed spin transition (Scheme 3). An efficient way to avoid this fast BET is to quench the semi-reduced form of the photosensitizer ($DCA^{-\bullet}$) by protonation with trace amounts of water. We have isolated one equivalent of reduced sensitizer ($DCAH_2$) whose spectroscopic data are in agreement with the Farid's data.[7] When the irradiation is performed in anhydrous solvent, no oxidation product is formed. In this case the rate of BET is so fast that no other decay pathway of the radical ion pair can occur.

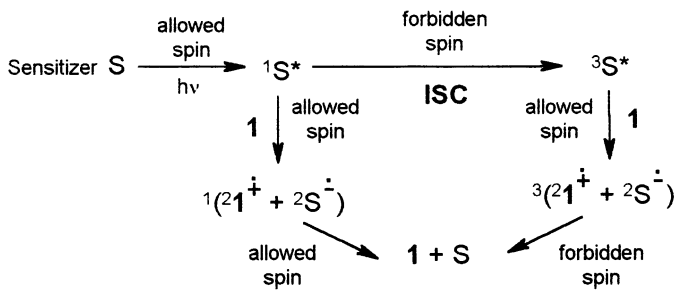
In order to perform this reaction with a catalytic amount of photosensitizer it is useful to slow down the BET without consuming the semi-reduced formed $S^{-\bullet}$. A sensitizer which presents a high intersystems crossing (ISC) mainly promotes electron transfer in the triplet excited state. Then, the triplet radical ion pair formed decays slower because of the forbidden spin transition (Scheme 3). So riboflavin 5′-phosphate sodium salt dihydrate (FMN), a derivative from the 3-methyllumiflavin was chosen (phosphorescence quantum yield = 0.55). This sensitizer was previously used in photooxidation to cleave the α,β carbon–carbon bond of an aminium radical cation.[8] The irradiation (λ>400 nm) of catharanthine **1** is performed in methanol under anaerobic conditions in the presence of TMSCN and a catalytic quantity of FMN (0.10 equiv.). Two oxidation products are obtained (Scheme 2) in 91% overall yield: 21α-cyano-16α-(methoxycarbonyl)cleavamine **3** resulting from the C_{16}–C_{21} bond cleavage and 3β-cyanocatharanthine **2** resulting from the deprotonation pathway in a 90:10 ratio, respectively.

As expected the photochemical process is catalytic but we observed the presence of a small amount of the by-product **2** which is the direct consequence of the intrinsic basicity of the semi-reduced form $FMN^{-\bullet}$.

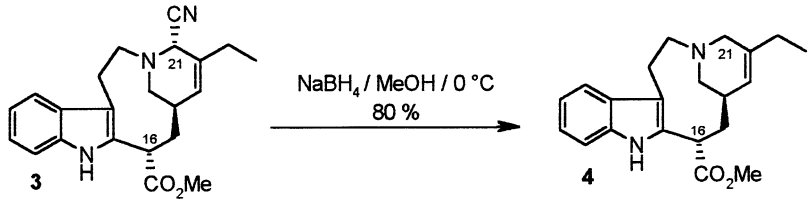
In order to circumvent the decay of the radical ion pair via the deprotonation, β-lapachone (βL), an orthoquinone known to initiate photoinduced SET[9] mainly in the triplet excited state (Scheme 3) was chosen. Thus the irradiation (λ>430 nm) of catharanthine **1** in methanol under anaerobic conditions in the presence of a catalytic quantity of βL (0.03 equiv.) leads selectively to the α-aminonitrile **3** in 88% yield (Scheme 2). In this case the photooxidation also proceeds with a catalytic amount of photosensitizer and the lower basicity of the semi-reduced form $\beta L^{-\bullet}$ compared to $FMN^{-\bullet}$ permits total selectivity.

We have fully characterized[10] the 21α-cyano-16α-(methoxycarbonyl)cleavamine **3**. Moreover, as chemical proof of the structure,[11] reduction at 0°C of this compound with sodium borohydride in methanol leads to the expected 16α-(methoxycarbonyl)cleavamine **4**[10] in 80% yield (Scheme 4).

In conclusion, we have presented photochemical conditions allowing the selective oxidative C_{16}–C_{21} bond cleavage of catharanthine by SET. Moreover, our understanding of the decay of the radical ion pair allowed us to control successfully the competition between BET and the fragmentation pathway. As a consequence we have found conditions which employ catalytic rather



Scheme 3.



Scheme 4.

than stoichiometric amounts of photosensitizer. The best result is observed in the case of the use of β-lapachone which leads very cleanly and efficiently to the cleavamine skeleton. A further report concerning this C_{16}–C_{21} bond cleavage mechanism will be published shortly.

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10. The 21α-cyano-16α-(methoxycarbonyl)cleavamine **3** was obtained as a crystalline white solid; mp 151°C; $[\alpha]_D^{25}=+40$ (*c* 1, $CHCl_3$); IR (KBr): 3380, 2950, 2220, 1730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.11 (t, $J=7.3$, 3H, H-18), 2.28 (m, 6H, H-14$_\alpha$, H-19, H-3, H-17), 2.54 (m, 1H, H-5), 2.77 (m, 1H, H-3), 2.93 (m, 3H, H-6, H-5), 3.69 (s, 3H, OCH_3), 4.15 (s, 1H, H-21$_\beta$), 4.81 (d, $J=9.1$, 1H, H-16$_\beta$), 5.56 (m, 1H, H-15), 7.13 (m, 1H, H-10), 7.20 (m, 1H, H-11), 7.36 (m, 1H, H-12), 7.54 (m, 1H, H-9), 8.66 (s, 1H, N$_a$-H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 11.92 (C-18), 25.67 (C-6), 26.09 (C-19), 33.57 (C-14), 37.25 (C-17), 38.25 (C-16), 49.29 (C-3), 51.76 (C-5), 52.18 ($CO_2\underline{C}H_3$), 55.57 (C-21), 110.65 (C-12), 110.79 (C-7), 117.77 (CN), 118.13 (C-9), 119.22 (C-10), 121.87 (C-11), 126.30 (C-15), 127.48 (C-8), 133.84 (C-13), 135.74 (C-2), 135.92 (C-20), 174.92 (C=O); MS (CI) *m*/*z* (rel. intensity) 364 (MH^+, 78), 337 (100); anal. calcd for $C_{22}H_{25}N_3O_2$: C, 72.70; H, 6.93; N, 11.56. Found: C, 72.85; H, 6.75; N, 11.28. The 16α-(methoxycarbonyl)cleavamine **4** (262 mg, 0.77 mmol, 80%) was obtained as a white solid after recrystallization in MeOH; mp 118°C (lit.[3] 121°C); $[\alpha]_D^{25}=+42$ (*c* 1, $CHCl_3$); IR (KBr): 3370, 2920, 1720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.11 (t, $J=7.3$, 3H, H-18), 2.10 (m, 3H, H-19, H-14$_\alpha$), 2.20 (m, 1H, H-3), 2.39 (m, 4H, H-17, H-5, H-3), 2.76 (m, 1H, H-5), 2.90 (m, 2H, H-6), 3.16 (m, 2H, H-21), 3.69 (s, 3H, OCH_3), 5.21 (d, $J=9.6$, 1H, H-16$_\beta$), 5.32 (m, 1H, H-15), 7.11 (m, 1H, H-10), 7.18 (m, 1H, H-11), 7.36 (m, 1H, H-12), 7.54 (m, 1H, H-9), 8.67 (s, 1H, N$_a$-H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 12.53 (C-18), 26.27 (C-6), 27.56 (C-19), 34.61 (C-14), 38.13 (C-17), 38.54 (C-16), 51.99 ($CO_2\underline{C}H_3$), 53.00 (C-5), 53.63 (C-3), 55.19 (C-21), 110.50 (C-12), 111.50 (C-7), 118.12 (C-9), 118.83 (C-10), 121.40 (C-11), 121.73 (C-15), 127.84 (C-8), 134.52 (C-13), 135.66 (C-2), 141.38 (C-20), 175.68 (C=O); MS (EI) *m*/*z* (rel. intensity) 338 ($M^{+\bullet}$, 79), 323 (7), 307 (3), 279 (4), 251 (4), 215 (100), 208 (8), 180 (6), 169 (22), 154 (13), 136 (78), 124 (54), 122 (31), 108 (14), 95 (23), 79 (11); anal. calcd for $C_{21}H_{26}N_2O_2$: C, 74.52; H, 7.74; N, 8.28. Found: C, 74.25; H, 7.58; N, 7.96.
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