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Oxidative radical cyclization on enamide systems using *n*-Bu_3SnH and dilauroyl peroxide

Miguel A. Guerrero, Raymundo Cruz-Almanza and Luis D. Miranda*

Instituto de Química, Universidad Nacional Autónoma de México, Circuito Exterior S.N., Ciudad Universitaria, Coyoacán, México, D.F. 04510, Mexico

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Abstract—Efficient 5-*endo* and 6-*endo* oxidative radical cyclizations on enamide systems are described using nBu_3SnH and dilauroyl peroxide both as initiator and oxidant. Dibenzoyl peroxide and dicumyl peroxide were also tested in the same reaction and the product yields were very similar to those obtained with dilauroyl peroxide. The erythrina ring system was constructed in a two-step sequence featuring this novel process.

1. Introduction

The 5-*endo-trig* cyclization of carbamoylmethyl radicals of enamides has been extensively explored, most notably by Ishibashi and co-workers.[1–5] This unusual 5-*endo* cyclization, reported as a highly efficient process, has been applied to the synthesis of various natural products and related compounds. Several methods have been devised to effect such cyclizations, most of them being *n*-Bu_3SnH-mediated reactions, whereby the stabilized radical intermediate **3** is ultimately reduced affording saturated γ-lactams **4** (Scheme 1).[2] In contrast, oxidative termination of the radical sequence has also been accomplished using metallic Ni-,[3] Mn(III)-[4] and Cu(II)-based reagents.[5]

Recently, Zard's group[6] reported an unexpected oxidative radical cyclization on the enamide **1a** using xanthates as the radical source and dilauroyl peroxide (DLP) as the initiator. The olefin mixture **7a**–**8a** formed in good yield from **1a** (Scheme 1) was suggested to arise by either a xanthate transfer/thermal elimination process (Scheme 3, path ii) or by direct oxidation by DLP (Scheme 1, path i). In an apparently similar process, lactams **7b**–**9b** (Scheme 1) were recently isolated in moderate yields (11–54%) from the radical cyclization of chloroacetamide **1b** using *n*-Bu_3SnH and a large excess (5 equiv.) of *n*-Bu_3SnX (X=F, OAc, Cl, or I).[2s] In the absence of a formal oxidant, the products were proposed to be formed by either a single electron transfer mechanism from the α-amidoyl radical **3** to the starting α-halo amides or by an halogen transfer/thermal elimination process.[2s,8]

The many synthetic applications of tin based radical chemistry, drew our attention to the possible use of an organic peroxide in a tin-mediated radical cyclization onto enamide systems. Thus, we wondered if using *n*-Bu_3SnH and a stoichiometric amount of DLP as the initiator, rather than AIBN, oxidized products would be obtained. Additionally, such experiments might yield information to clarify the oxidative role of the DLP in the xanthate mediated reaction (Scheme 1).[6] This publication describes the results of such an investigation (Scheme 3, path ii).

2. Results and discussion

Chloroacetamides **1b**[2s] and **1c**[6] were synthesized by the previously reported method. Thus a mixture of *n*-Bu_3SnH/DLP in benzene was then added slowly (over a four-hour period) to a solution of chloroacetamide **1b** in refluxing benzene. As expected, a mixture of two isomeric lactams **7a** and **8a** (8:2) was isolated in 92% yield together with traces of isomer **9a** (Table 1, entry 1), similar to that reported before using xanthate chemistry.[6] Longer reaction periods gave increasingly larger amounts of the most stable compound **9a**. This substance was also produced thermally from a mixture of **7a** and **8a**. A similar result was obtained starting with **1c** under the same reaction conditions (Table 1, entry 2).

In the light of the above observations, the effectiveness of dibenzoyl peroxide (DBP)[9] and dicumyl peroxide (DCP)[10] in this process, was also examined (Table 1). The combined product yields were very similar to those obtained with

Keywords: dilauroyl peroxide; radical cyclization; oxidation; enamide; erythrina.

* Corresponding author. Tel.: +52-55-56-22-44-40; fax: +52-55-56-16-22-17; e-mail: mirandald@correo.unam.mx

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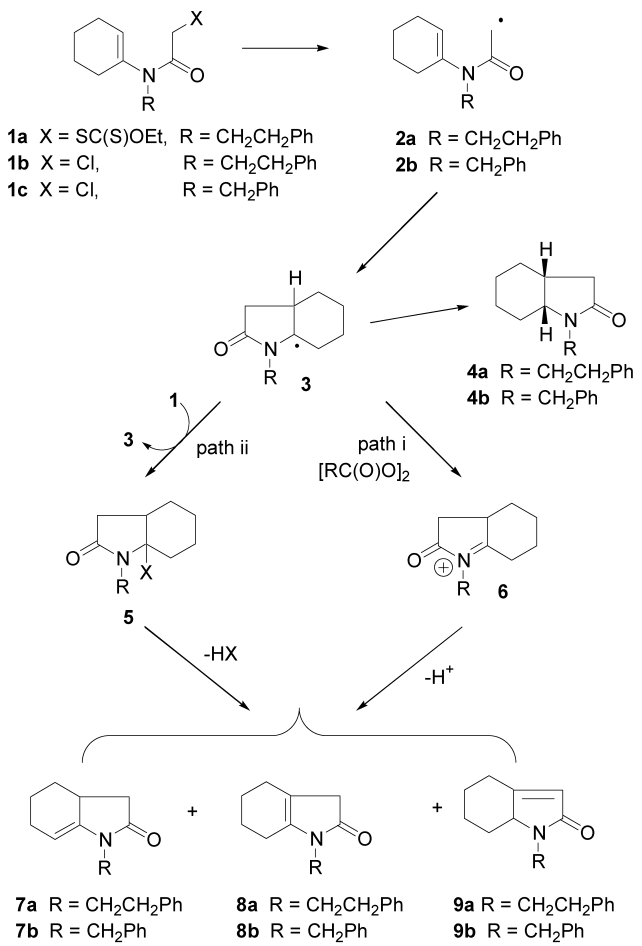


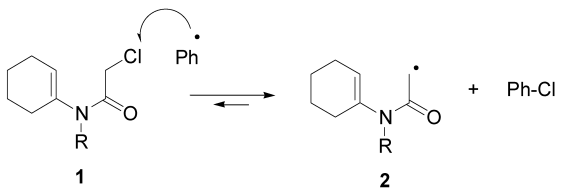
Scheme 1.

lauroyl peroxide but, the product distribution was rather different in the reaction mediated by dibenzoyl peroxide (Table 1, entry 3,4). The tendency for the latter reaction to give mainly the most stable olefin **9** may be explicable by a faster conversion of **7** and **8** into **9** by the more acidic benzoic acid produced in this reaction. The DCP-mediated reactions (Table 1, entry 5,6) were performed in refluxing chlorobenzene (132°C),[10] and good yields of **7** and **8** were

Table 1. Radical cyclization of α-halo amides **1b–c**

Entry	Amide	R	Cond.	Peroxide	Yield (%)		
					7+8[a]	**9**	**4**
1	**1b**	$(CH_2)_2Ph$	A	DLP[b]	92	Traces	
2	**1c**	CH_2Ph	A	DLP[b]	93	Traces	
3	**1b**	$(CH_2)_2Ph$	A	DBP[c]	5	86	
4	**1c**	CH_2Ph	A	DBP[c]	6	88	
5	**1b**	$(CH_2)_2Ph$	A	DCP[d]	89	Traces	
6	**1c**	CH_2Ph	A	DCP[d]	88	Traces	
7	**1c**	CH_2Ph	B	DBP	5	89	
8	**1b**	$(CH_2)_2Ph$	B	DBP	5	87	
9	**1c**	CH_2Ph	C	DLP	23	Traces	35

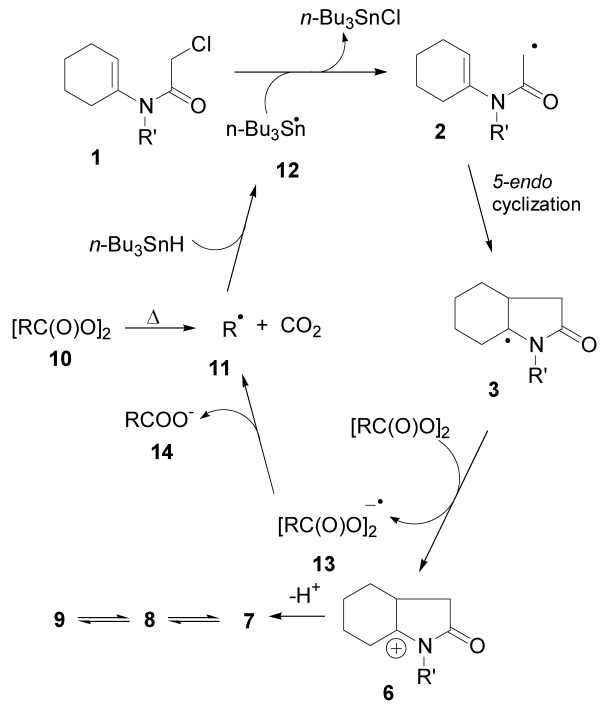
[10]Conditions: A. *n*-Bu_3SnH (1.1 equiv.), organic peroxide (2.0 equiv.). B. Dibenzoyl peroxide (1.5 equiv.), toluene, 95°C, 2 h. C. *n*-Bu_3SnH (1.5 equiv.), dilauroyl peroxide (0.9 equiv.), C_6H_6, reflux, 2 h.
[a] Ratio (~8:2) based on the ^1H NMR spectrum of an isolated mixture.
[b] In benzene, reflux.
[c] In toluene at 95°C.
[d] In chlorobenzene, reflux, 4 h.



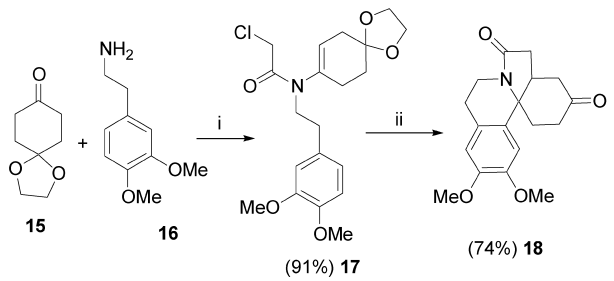
Scheme 2.

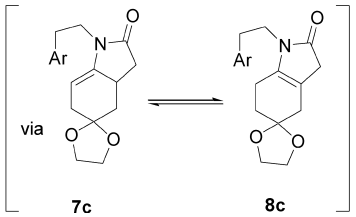
also observed. Generally, the product yields were better than those obtained in reactions performed with *n*-Bu_3SnX (X=F, OAc, Cl, or I), described before.[2s]

Fast consumption of the starting material was observed using dibenzoyl peroxide. Indeed, acetamide **1b** was entirely consumed before addition of the *n*-Bu_3SnH/DLP mixture was completed. This observation led us speculate that the process could be carried out by using dibenzoyl peroxide in absence of the tin reagent. In this case, abstraction of chlorine atom from **1** by the phenyl radical would generate the stabilized radical **2** (Scheme 2), a process which is expected to be very favorable.[11] Thus, upon a portionwise addition of dibenzoyl peroxide to a solution of either chloroacetamides **1b** or **1c** in toluene (at 95°C), lactams **9a** and **9b** respectively were isolated in good yield (Table 1, entry 7, 8). On the other hand, a competition between the oxidant (peroxide) and the relatively high concentration of the reductant (tin reagent), was observed in the process when, an excess of tin hydride (1.5 equiv.) was utilized in the reaction (Table 1, entry 9). Saturated lactam **4b** was afforded in 35% yield, together with 23% yield of the mixture **7b–8b** along with a considerable amount of recovered starting material (35%).

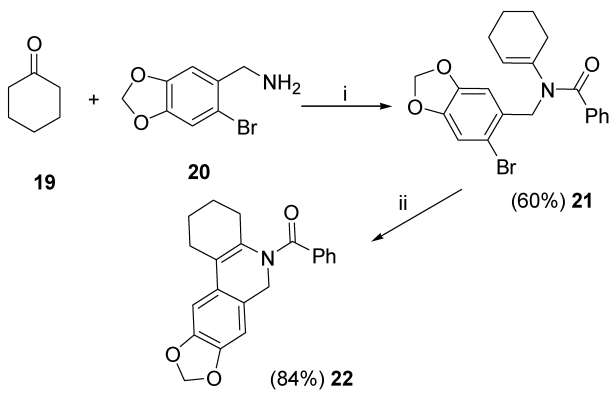


Scheme 3. Proposed mechanism for the oxidative radical cyclization under *n*-Bu_3SnH/DLP conditions.





Scheme 4. Short synthesis to the erythrina framework alkaloids. *Conditions*: (i) toluene, reflux, then chloroacetylchloride, pyridine CH_2Cl_2, rt, (ii) *n*-Bu_3SnH (1.1 equiv.), DLP (2.0 equiv.) benzene, reflux, 4 h, then catalytic *p*-toluenesulfonic acid.



Scheme 5. *Conditions*: (i) toluene, reflux, then benzoyl chloride, pyridine CH_2Cl_2, rt, (ii) *n*-Bu_3SnH (1.1 equiv.), DLP (2.0 equiv.) benzene, reflux, 4 h.

A reasonable mechanism for the *n*-Bu_3SnH/DLP mediated-reaction is depicted in Scheme 3. The reaction is initiated by the well-known thermal fragmentation/homolytic decarboxylation process of the peroxide **10**, affording two radicals **11** which produce the stannyl radical **12** by reacting with tin hydride (Scheme 3). The results described herein support a mechanism in which the organic peroxide functions as the oxidant generating the iminium ion **6** by a single electron transfer from radical **3** (Scheme 3). The generation of **6** by a chlorine atom transfer mechanism is expected to be difficult given that the cyclization of chloroacetamide **1c** under nBu_3-SnH/AIBN conditions gave mainly the reduced product **4b** (Scheme 1).[2a] Peroxyl radical-anion **13** formed in the process would undergo a heterolytic fragmentation to afford the carboxylate **14** and the carboxyl radical which by loss CO_2 would produce the intermediate radical **11** to continue the chain (Scheme 3). Consistent with this mechanism, lauric acid, which comes from the protonation of **14**, was isolated in yields ranging between 1 and 1.2 equiv. in DLP-mediated reactions. In addition, benzoic acid and 2-phenyl propan-2-ol were produced in similar yields (120 and 110%) in the dibenzoyl and dicumyl mediated reactions. In the light of the above observations, it is likely that a similar mechanism is involved in the DLP mediated xanthate reactions where oxidized products are obtained (Scheme 1, path i).[6] The ability of the DLP to effect oxidation of stabilized radicals to cations has been recently invoked in radical additions onto aromatic systems.[7]

The above observations opened up the possibility for a very short entry to the pharmacologically important erythrina alkaloids.[12] The skeleton of these alkaloids could be assembled combining oxidative radical cyclization with intramolecular in situ Friedel–Crafts type cyclization of the intermediate iminium ion as described recently by Zard et al.[6] (Scheme 4). Thus, chloroacetamide **17** was prepared in a two-step process from commercially available ketone **15** and amine **16**. For reasons which we do not understand, the dibenzoyl peroxide mediated reaction failed to effect cyclization of **17**, in the absence of *n*-Bu_3SnH (Condition B, Table 1). However, erythrina derivative **18** was ultimately isolated in 74% yield upon addition of a catalytic amount of *p*-toluenesulfonic acid to the reaction mixture after **17** had been consumed in the *n*-Bu_3SnH/DLP mediated radical cyclization. There was no need to isolate the mixture of the isomeric, intermediate, unsaturated lactams **7c** and **8c** since they both give the same iminium ion in the presence of acid. The dioxolane protective group was lost under these acidic reaction conditions. This sequence represents one of the shortest routes to an erythrina alkaloid derivative published to date.

The new *n*-Bu_3SnH/DLP oxidative radical cyclization process was extended to an aryl bromide. Thus, bromide **21** was prepared in two steps from the piperonal derived amine **20**[3d] in moderate yield. Reaction of **21** under the above-described oxidative radical conditions afforded the thermodynamically stable olefin **22**, exclusively in good yield. The phenanthridine system present in this product is found in many alkaloids, some of which exhibit interesting pharmacological activity (Scheme 5).[13]

3. Conclusions

Novel and efficient oxidative radical cyclizations are described using *n*-Bu_3SnH and an organic peroxide which serves both as the initiator and the oxidant in cyclizations onto enamide systems. This novel process opens up new applications in tin hydride-mediated free radical reactions, and the present route to the erythrina ring system and the phenanthridine derivative **22**, underscores its synthetic potential. Extension to more complex structures using this methodology is currently under investigation.

4. Experimental

4.1. General

Proton magnetic resonance spectra were recorded at 200 and 300 MHz as $CDCl_3$ solutions and are reported in ppm (Varian Unity instrument) downfield from internal tetramethylsilane. IR spectra were obtained on a Nicolet FT-IR Magna 750 spectrometer. Chromatography was carried out using silica gel. Mass spectra were recorded at JEOEL JEM-AX505HA instrument at voltage of 70 eV.

4.1.1. *N*-(6-Bromo-benzo[1,3]dioxol-5-ylmethyl)-*N*-cyclohex-1-enyl-benzamide (21) (general procedure). A solution of cyclohexanone (0.5 g, 5.1 mmol), and amine (1.17 g, 5.1 mmol) in toluene was heated to reflux for 4 h in a Dean–Stark apparatus. After evaporation of the solvent, the residue was dissolved in dry toluene and cooled to 0°C. Triethylamine (0.62 g, 6.1 mmol) was added, followed by a dropwise addition of benzoyl chloride (0.72 g, 5.1 mmol). The solution was then stirred for 3 hours at room temperature. Water was added and the resulting mixture extracted with ether, the organic layer was dried over magnesium sulfate and concentrated in vacuum. The residue was purified by silica gel column chromatography to give 1.26 g (60%) of the benzamide **21**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54–7.49 (m, 2H), 7.39–7.29 (m, 3H), 7.04 (s, 1H), 6.97 (s, 1H), 5.96 (s, 2H), 5.32–5.26 (m, 1H), 4.88 (s, 2H), 2.0–1.88 (m, 2H), 1.86–1.77 (m, 2H), 1.86–1.77 (m, 2H), 1.54–1.42 (m, 2H), 1.4–1.3 (m, 2H). ^{13}C NMR (50 MHz) δ 170.60, 147.58, 147.48, 138.39, 136.77, 130.38, 130.05, 129.60, 128.45, 127.72, 127.43, 112.36, 109.66, 101.69, 49.76, 28.62, 24.70, 22.48, 21.16. IR (cm^{-1}) ν: 2938, 1704, 1661.9, 15515.8, 1479.4. MS (EI) m/z=254 (100%), 413 (M^+ weak), 415 (M^++2), HRMS (FAB+): calcd for $C_{21}H_{21}O_3NBr$: 414.0709, found: 414.0705.

Chloroacetamides **1b–c** and **17** were synthesized according to the procedure described previously (see text).

4.1.2. 2-Chloro-*N*-cyclohex-1-enyl-*N*-phenethyl-cetamide (1b). Spectra data were identical with those reported previously.[6] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31–7.17 (m, 5H), 5.61–5.58 (m, 1H), 4.08 (s, 2H), 3.65–3.60 (m, 2H), 2.87 (dd, J_1=J_2=7.9 Hz, 2H), 2.14–2.04 (m, 4H), 1.76–1.68 (m, 2H), 1.63–1.59 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.3, 22.6, 24.7, 27.6, 33.8, 41.7, 47.6, 126.3, 128.4, 128.7, 137.9, 138.0, 165.6. IR (cm^{-1}) ν: 2942.1, 2863.14, 2840.2, 1641.8, 1451.5, 1409.1, 1356.6, 1140.4. MS (EI) m/z=242 (100%; M^+ –Cl), 277 (M^+ weak).

4.1.3. *N*-Benzyl-2-chloro-*N*-(cyclohex-1-enyl)acetamide (1c). The NMR spectra data were identical with those reported before.[2s] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26–7.30 (m, 5H), 5.47 (br s, 1H), 4.63 (s, 2H), 4.13 (s, 2H), 2.03 (br s, 4H), 1.52–1.70 (m, 4H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 165.8, 137.4, 137.1, 129.3, 128.7, 128.3, 127.4, 49.9, 41.7, 27.9, 24.7, 22.6, 21.3.

4.1.4. 2-Chloro-*N*-[2-(3,4-dimethoxy-phenyl)-ethyl]-*N*-(1,4-dioxa-spiro[4.5]dec-7-en-8-yl)-acetamide (17).[6] ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.81–6.72 (m, 3H), 5.48–5.5.46 (m, 1H), 4.09 (s, 2H),3.99 (s, 4H), 3.87 (s, 3H), 3.85 (s, 3H), 3.65–3.71 (m, 2H), 2.83 (dd, J_1=J_2=7.8 Hz, 2H), 2.34–2.25 (m, 4H), 1.85 (t, J=6.3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 149.2, 147.8, 137.8, 131.4, 125.9, 120.9, 120.8, 112.3, 111.5, 106.9, 64.8, 56.17, 56.12, 48.0, 41.9, 35.4, 33.6, 31.2, 29.97. IR (cm^{-1}) ν: 2960.2, 2936.5, 2838.7, 1731.7, 1654.9, 1515.3, 1462.7, 1446.37, 1415.5, 1260.9, 1154.4, 1119.6, 1030.7. MS (EI) m/z=164 (100% M^+ –Cl), 395 (M^+ weak).

4.2. Cyclization reaction

Conditions A (general procedure): a solution of dilauroyl peroxide (2.0 equiv.) (0.038 mmol/mL of benzene), Bu_3SnH (1.1equiv) in benzene was added dropwise (syringe pump) to a degassed solution of the chloride (1 equiv.) in refluxing benzene (0.025 mmol/mL) over 4 h. The reaction mixture was then cooled and the solvent removed under reduced pressure. The residues were partitioned between hexane (10 mL) and acetonitrile (15 mL). The polar layer was washed with hexane (4×10). The solvent was evaporated and the crude product was purified by silica gel column chromatography (hex/AcOEt) to furnish a mixture of isomers.

Reaction with dibenzoyl peroxide was carried out in toluene at 95°C. Procedure was identical to that described for the DLP-mediated reaction; however, the reaction mixture was washed with a saturated aqueous solution of $NaHCO_3$ before solvent was removed in the workup.

Reaction with dicumyl peroxide was carried out in refluxing chlorobenzene, and the procedure was identical to that described for the DLP-mediated reaction.

Conditions B: a solution of dibenzoyl peroxide (1.5 equiv.) in benzene was added dropwise to a degassed solution of the chloride **1b** or **1c** (1 equiv.) in toluene at 95°C over 3 h. The reaction mixture was then cooled and washed with a saturated aqueous solution of $NaHCO_3$. Solvent was removed under reduced pressure and crude product was purified by a silica gel column chromatography (Hep/AcOEt) to furnish olefin isomers (**7–9**).

Conditions C: A solution of dilauroyl peroxide (0.136 g, 0.34 mmol), and Bu_3SnH (0.16 g, 0.568 mmol) in benzene (9 mL) was added dropwise (syringe pump) to a degassed solution of the chloride **1c** (0.1 g, 0.38 mmol) in refluxing benzene (15 mL) over 4.5 h. Workup was identical to that described for conditions A. Affording 0.029 g of **4b** (35%) and 0.020 g of the mixture **7b–9b** (23%), along with 0.035 of recovered starting material g (35%).

4.2.1. *cis*-1-Benzyl-octahydroindol-2-ona (4b).[2s] The NMR spectra data were identical with those reported previously. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21–7.33 (m, 5H), 4.93 (d, 1H, J=15 Hz), 3.97 (d, 1H, J=15 Hz), 3.39 (q, 1H, J=5.6 Hz), 2.19–2.47 (m, 3H), 1.56–1.72 (m, 3H), 1.23–1.52 (m, 5H).

4.2.2. 1-Phenethyl-1,3,3a,4,5,6-hexahydro-indol-2-one (7a).[6] This product was very sensitive to isomerization and was fully characterized as its more stable isomer **9**.[6]

Isomer **7a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.3–7.1 (m, 5H), 4.85 (m, 1H, C=C–H), 3.81 (ddd, 1H, J=6.9 Hz, 9.4 Hz, 13.5 Hz, NCH–H), 3.51 (ddd, 1H, J=6.9 Hz, 9.4 Hz, 13.5 Hz, NCH–H), 2.8–2.9 (m, 2H, $PhCH_2$), 2.75–1.5 (m, 8H). MS (EI): M^+ m/z=241.

Isomer **8a** This product was very sensitive to isomerization as well and was observed only in mixtures with the other isomers. It was fully characterized as its more stable isomer **9a**.

Isomer **9a** The NMR spectra data were identical with those reported previously.[6] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20–7.30 (m, 5H), 3.90 (ddd, J=14.0, 8.4, 6.7 Hz, 1H, NCH–H), 3.54–3.27 (m, 1H, NCH), 3.33 (ddd, J=14.0, 8.4, 6.8 Hz, 1H, NCH–H), 2.91–2.84 (m, 2H, $PhCH_2$), 2.67–2.73 (m, 1H), 1.78–2.34 (m, 4H), 1.40–1.10 (m, 2H), 1.0–0.92 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 7171.5, 161.9, 139.1, 128.8, 128.5, 126.4, 62.3, 41.6, 35.3, 33.1, 28.3, 27.4, 23.08. IR (cm^{-1}) ν: 2941.7, 2861.3, 1670.3, 1449.8, 1411.9, 1327.9. EM: M^+ m/z=241.

4.2.3. Isomer 7b and 8b. This products were very sensitive to isomerization and was observed only in mixtures. It was characterized as its more stable isomer **9b**.

4.2.4. 1-Benzyl-1,4,5,6,7,7a-hexahydroindol-2-one (9b). Spectra data were identical with those reported previously.[2s] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.21 (m, 5H), 5.80 (s, 1H), 4.99 (d, J=15.1 Hz, 1H), 4.17 (d, J=15.1 Hz, 1H), 3.58 (dd, J=11.2, 5.9 Hz, 1H), 2.72 (br d J=11.2 Hz, 1H), 1.39–1.17 (m, 4H), 1.43–1.19 (m, 2H), 1.11–0.92 (m, 1H).

4.2.5. Phenyl-(2,3,4,6-tetrahydro-1*H*-[1,3]dioxolo[4,5-*j*]phenanthridin-5-yl)-methanone (22). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03–7.93 (m, 2H), 7.61–7.49 (m, 3H), 6.89 (s, 1H), 5.96 (dd, J_1=1.47 Hz, J_2=6.9 Hz, 2H), 5.30 (d, J=17.58 Hz, 1H), 4.30 (d, J=17.5 Hz, 1H), 2.82–2.75 (m, 1H), 2.49–2.38 (m, 2H), 2.1–1.9 (m, 3H), 1.81–1.57 (m, 2H), 1.41–1.15 (m, 2H). ^{13}C (75 MHz, $CDCl_3$) δ 165.81, 150.47, 147.47, 146.40, 131.89, 130.82, 128.28, 127.49, 125.53, 124.19, 123.98, 106.19, 103.13, 101.14, 40.98, 28.91, 25.41, 22.08, 19.02. IR (cm^{-1}) ν: 2932.5, 1678, 1486, 1042. EM: M^+ m/z=333. HRMS (IE): calcd for $C_{21}H_{19}O_3N$: 333.1365, found: 333.1362.

4.2.6. Erythrina derivative (18). A solution of dilauroyl peroxide (0.18 g, 0.45 mmol) and Bu_3SnH (0.08 g, 0.27 mmol) in benzene was added dropwise to a benzene solution of the chloride (0.10 g, 0.25 mmol) in refluxing benzene over a 4 h period. After no more starting material was detected by TLC a catalytic amount of *p*-toluenesulphonic acid was added to the reaction mixture. After additional 40 min reflux, the reaction mixture was cooled to room temperature and solvent removed under reduced pressure, the residues were partitioned between hexane (10 mL) and acetonitrile (15 mL). The polar layer was washed with hexane (4×10 mL). The solvent was evaporated and the crude product was purified by silica gel column chromatography (AcOEt) to furnish 59 mg (74%)of the product as a solid with mp: 162–164°C (lit. 162–165°C). Spectra data were identical with those reported previously.[6] ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.69 (s, 1H), 6.58 (s, 1H), 4.41–4.35 (m, 1H), 3.88 (s, 3H, OMe), 3.86 (s, 3H, OMe), 3.15–2.93 (m, 4H), 2.77–2.59 (m, 3H), 2.49–2.08 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): 210.0, 172.11, 148.4, 148.2, 134.3, 125.4, 111.7, 107.2, 62.4, 56.3, 55.9, 53.4, 43.2, 37.7, 37.4, 35.2, 34.7, 33.5, 27.5. IR (cm^{-1}) ν: 2956, 2939, 2850, 1718, 1680, 1514, 1463, 1424, 1285. EM: M^+ m/z=315. HRMS (IE): calcd for $C_{18}H_{21}O_4N$: 315.1471, found: 315.1458.

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