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A Convenient Approach to the Synthesis of Benzo[*c*]phenanthridines *via* Intramolecular Cyclization of Enamides

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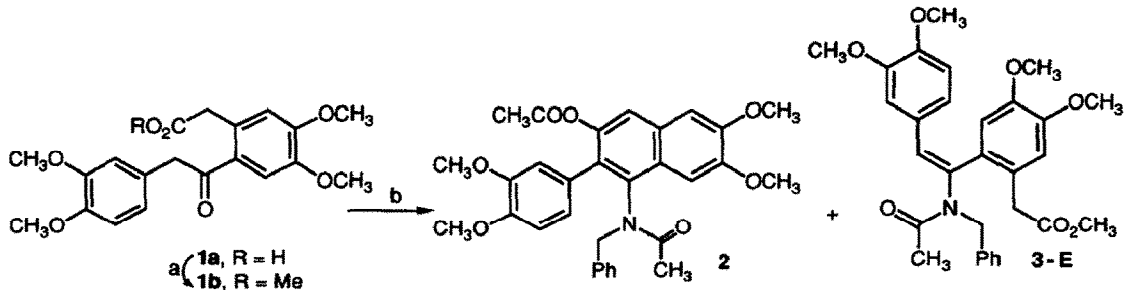
Abstract: A new synthetic route towards planar 8,9-disubstituted benzo[*c*]phenanthridinium salts *via* Bischler-Napieralski cyclization of enamides is reported. Treatment of ketoester **1b** with benzylamine/$TiCl_4$ in dimethoxyethane, followed by acetylation with acetyl chloride afforded a mixture of naphthylamide **2** and E-enamide **3**. Both enamides were efficiently cyclized by $POCl_3$ in acetonitrile under reflux. While the planar benzo[*c*]phenanthridinium salt **4** was directly produced from **2**, the E-enamide **3** gave the 3-arylisoquinolinium salt **5**, which was reduced and intramolecular cyclized to yield the tetracyclic nucleus of these alkaloids.

The benzo[*c*]phenanthridine alkaloids constitute a large group of metabolites which occur in the *Fumariaceae*, *Papaveraceae*, and *Rutaceae* and possess, in many cases, strong pharmacological activities.[1] Thus, nitidine and other 8,9-disubstituted planar benzophenanthridinium salts such as fagaronine have been shown to have antitumor activity in animal tumor models, an activity which could be related to inhibition of DNA topoisomerase.[2] Interestingly, 7,8-disubstituted benzophenanthridine alkaloids such as chelerythrine have not generally been found to have antitumor activity.[3] However, the toxicological problems associated with the most active members of this group have led to develop new synthetic methods of these compounds, in order to study the structure-activity relationship.[4]

There are many classical methods by which this heterocycle can be constructed[1] and especially attractive are those procedures which involve 3-arylisoquinoline intermediates, because these synthons could also be involved in the synthesis of other alkaloid skeletons, such as protoberberines and spirobenzylisoquinolines. The biomimetic approach which implies the cleavage and recyclization of their biogenetic precursors (protoberberines or protopines), as illustrated by the work of Hanoaka,[5] has so far been exploited most often. However, few reports on the preparation of C-2' substituted 3-arylisoquinolines are known. In fact, the most important approaches are the ammonolysis of benzopyrylium salts,[6] the condensation of Schiff bases with homophthalic anhydrides,[7] the cycloaddition of lithiated toluamides and benzaldimines,[8] and the $S_{RN}1$ reactions of iodobenzamides with enolates of 2-acylhomoveratric acid.[9] Recently, during the preparation of this paper, a new synthesis of 3-styrylisoquinolines by base-induced intramolecular cyclization of *N*-(2-ethenylbenzoyl)-*N*,2-dimethylbenzamide derivatives has been published.[10]

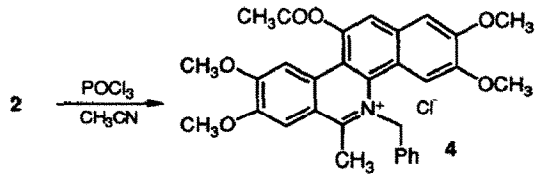
We recently reported the synthesis of 3-arylisoquinolinium salts *via* enamides.[11] The overall strategy involved the synthesis and intramolecular cyclization of appropriately functionalized *N*-1,2-diarylethyleneamides. This offers an extremely rapid and elegant entry into the benzo[*c*]phenanthridine skeleton and we were interested to try this methodology to simplify the synthesis of planar 8,9-disubstituted benzophenanthridinium. salts.

The starting ketoester **1b** was prepared by esterification of ketoacid **1a**[12] with methyl iodide in acetone using potassium carbonate. Treatment of the ketoester **1a** with benzylamine in the presence of triethylamine and titanium tetrachloride in dimethoxyethane as solvent and operating under strictly anhydrous conditions at -83°C, led to an intermediate imine, which was *in situ* acetylated with acetyl chloride to afford a 1:1.1 mixture of naphthylamide **2** and the E-enamide **3** (overall yield 60%).[13] These products were separated by HPLC (hexane/ethyl acetate 60%)) and the stereochemistry of **3** assigned on the basis of NOE difference experiments.[13] Thus, the large NOE from the enamidic proton to the methyl protons of the acetyl group, and *vice versa*, is only compatible with an E configuration for this compound. Presumably, **2** is formed by intramolecular acylation of the initially formed Z-isomer of **3** to give the corresponding naphthol and subsequent acetylation of the generated hydroxyl functionality would lead to **2**.



Scheme 1. Synthesis of naphthylamide **2** and E-enamide **3** from ketoacid **1a.** (a) MeI, K_2CO_3, acetone, 40-50°C, 1 h; (b) $PhCH_2NH_2$, NEt_3, $TiCl_4$, DME, -83°C to r.t., 0.5 h ; then CH_3COCl, $TiCl_4$, r.t., 2 h.

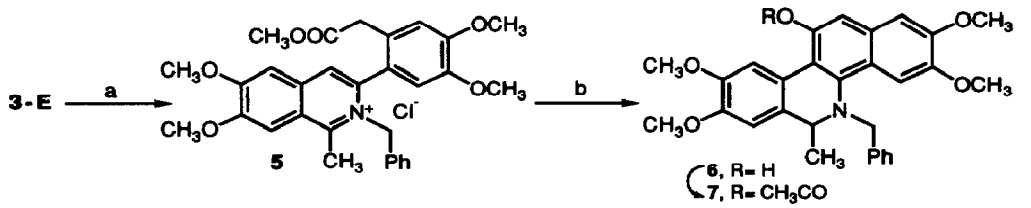
Treatment of **2** with $POCl_3$ in acetonitrile under reflux provided the benzophenanthridinium salt **4** in high yield (80%).[15] Previous syntheses of benzophenanthridines from naphthylamine derivatives have used several strategies for the preparation of the precursors, which involved complex and lengthy synthetic sequences.[1] For instance, the synthesis of sanguilutine of Ishii[16] requires the preparation of a naphthylamide from a 2-aryltetralone (4 steps), which were obtained by the Robinson method[17] (5 steps). Bisagni and Janin have recently reported[18] a new access to benzophenanthridines through thermal cyclization of ethyl carbamates of 2-aryl-1-naphthylamines, but the requisite urethanes for the key cyclization step were also prepared from 2-aryltetralones. Our methodology considerably reduces the number of steps and simplifies therefore the synthesis of this type of alkaloid.



Scheme 2. Synthesis of benzo[*c*]phenanthridinium salt **4** from naphthylamide **2**

On the other hand, under the same cyclization conditions the E-enamide **3** was isomerized to the Z diastereomer (^{1}H-NMR monitoring), which readily cyclized to the 3-arylisoquinolinium salt **5**. Due to its instability, **5** was transformed into the dihydrobenzophenanthridine **7** without further purification. Thus, reduction of **5** with $NaBH_4$ in THF at room temperature, followed by intramolecular acylation (HCl/MeOH)[6] of the resulting enamine, a 1,2-dihydroisoquinoline, led to **6** (overall yield 35%, from enamide **3-E**). Since this

phenolic benzophenanthridine also decomposed rapidily, it was *O*-acetylated (Ac_2O/pyridine) to give quantitatively **7**.[19]



Scheme 3. Synthesis of dihydrobenzo[*c*]phenanthridines **6** and **7** from enamide **3-E**. (a) $POCl_3$, CH_3CN, reflux, 3 h; (b) $NaBH_4$, THF, 0°C, 1h; then 12M HCl, MeOH, reflux, 2 h; (c) $(AcO)_2O$, pyridine, 60-70°C, 1 h

Fortunately, we discovered that treatment of the mixture of naphthylamide **2** and E-enamide **3** with $POCl_3$ in acetonitrile under reflux gave a mixture of the benzophenanthridine **4** and the 3-arylisoquinoline **5**, which was subjected to the above described synthetic sequence: (a) reduction ($NaBH_4$, THF), (b) intramolecular acylation (HCl/MeOH), and (c) acylation of the phenolic hydroxyl group (Ac_2O, pyridine) to afford **7**. This considerably improved the overall yield of the process (60% *vs.* 35%).

A convenient approach to the targeted planar 8,9-dialkoxylated benzo[*c*]phenanthridinium salts has been developed. Our strategy offers a very direct route into this alkaloid skeleton with attractive synthetic advantages : simplicity and high overall yields, availability of starting materials, versatility, since its allows the synthesis of C-6-substituted benzo[*c*]phenanthridines by changing the acyl halide in the first step, and easy functionalization at the C-11 position.

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13. Physical and spectroscopic data of:
    2: mp 186-188°C (hexane/ethyl acetate. IR (KBr): 1655, 1770 cm^{-1}. ^{1}H-RMN ($CDCl_3$): δ = 1.99 (s, 3H, CH_3CO_2); 2.09 (s, 3H, CH_3CON); 3.58 (d, J = 14.5, 1H, $PhCH_aH_bN$); 3.86 (s, 3H, OCH_3); 3.94 (s, 3H, OCH_3); 3.96 (s, 3H, OCH_3); 3.98 (s, 3H, OCH_3); 5.27 (d, J = 14.5, 1H, $PhCH_aH_bN$); 6.78-6.83 (m, 2H, H_{arom}); 6.92-6.99 (m, 3H, H_{arom}); 7.08 (s, 1H, H_{arom}); 7.14-7.23 (m, 5H, H_{arom}). ^{13}C-RMN ($CDCl_3$): δ = 20.38 (CH_3COO); 22.81 (CH_3CON); 51.74 (CH_2N); 55.63; 55.74; 55.79 (OCH_3); 99.86; 106.19; 110.92; 112.56; 121.86 (C_{arom}-H); 122.31; 126.10 (C_{arom}-C); 125.10; 127.03; 128.07; 128.69 (C_{arom}-H); 128.81; 137.09; 137.16; 144.32 (C_{arom}-C); 148.48; 150.49; 150.20 (C-6, C-7, C-8', and/or C-4'); 168.76; 170.51 (CH_3CO_2 and/or CH_3CON). MS (CI): m/z = 529 (M^+, 57).
    3-E: oil. IR ($CHCl_3$): 1650, 1740 cm^{-1}. ^{1}H-RMN ($CDCl_3$): δ = 2.41 (s, 3H, CH_3CO); 3.25 (broad s, 2H, $ArCH_2CO_2CH_3$); 3.49 (s, 3H, CO_2CH_3); 3.51 (s, 3H, OCH_3); 3.70 (s, 3H, OCH_3); 3.81 (s, 3H, OCH_3); 3.89 (s, 3H, OCH_3); 4.53 (broad s, 2H, $PhCH_2N$); 6.32 (s, 1H, CH=CN); 6.37 (s, 1H, H-2'); 6.53-6.55 (m, 2H, H-6' and H-6); 6.65 (d, J = 8.3, 1H, H-5'); 6.81 (s, 1H, H-3); 7.18-7.28 (m, 5H, Ph). ^{13}C-RMN ($CDCl_3$): δ = 22.54 (CH_3CO); 36.94 (CH_2-CO_2CH_3); 48.44 (NCH_2Ph); 51.82 (CO_2CH_3); 55.31; 55.77; 55.97 (4 x OCH_3); 110.76; 111.08; 112.54; 113.52 (C-2', C-3, C-5', and/or C-6); 122.35; 126.36; 127.06; 127.59 (PhC_{arom}-C and/or CH=CN); 128.24; 129.67 (C-6', PhC_{arom}-H and/or CH=CN); 135.76; 137.80; 148.63; 149.55 (C-3, C-4, C-3', and/or C-4'); 171.03 (CO_2CH_3); 171.70 (CON). MS (CI): m/z = 520 (M^++1, 100).
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15. Physical and spectroscopic data of **4**: mp >380°C (dec.) (ethyl acetate/methanol). IR ($CHCl_3$): 1610, 1770 cm^{-1}. ^{1}H-RMN ($CDCl_3$): δ = 2.71 (s, 3H, CH_3CO_2); 3.31 (s, 3H, CH_3C-6); 4.04 (s, 3H, OCH_3); 4.14 (s, 3H, OCH_3); 4.10 (s, 3H, OCH_3); 4.14 (s, 3H, OCH_3); 4.27 (s, 3H, OCH_3); 6.27 (broad s, 2H, $PhCH_2N$); 7.16-7.18 (m, 3H, H_{arom}); 7.25 (s, 1H, H-7); 7.43-7.46 (m, 3H, H_{arom}); 7.80 (s, 1H, H-10); 8.33 (s, 1H, H-12); 8.73 (s, 1H, H-4). ^{13}C-RMN ($CDCl_3$): δ = 19.51; 21.40 (CH_3-CO and/or CH_3C-6); 56.15; 56.34; 56.43; 56.79 (4 x OCH_3); 57.25 ($PhCH_2N$); 98.56; 106.13; 106.95; 109.15; 114.26 (C-1, C-4, C-7, C-10, and/or C-12); 125.18; 129.17; 130.00 (PhC_{arom}-H); 121.16; 123.60; 130.53; 130.97; 131.57 (C-6a, C-10a, C-14, and/or PhC_{arom}-C); 142.46 (C-11); 150.87; 152.77; 153.11; 158.02 (C-2, C-3, C-8, and/or C-9); 161.54 (C-6); 169.47 (CO_2). MS (CI): m/z = 511 (M^+-1, 86).
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19. Physical and spectroscopic data of **7**: IR ($CHCl_3$): 1770 cm^{-1}. ^{1}H-RMN ($CDCl_3$): δ = 1.15 (d, J = 6.5, 3H, CH_3C-6); 2.40 (s, 3H, CH_3CO_2); 3.88 (s, 3H, OCH_3); 3.96 (s, 3H, OCH_3); 3.96 (s, 6H, 2 x OCH_3); 4.21 (q, J = 6.5, 1H, H-6); 4.35 (d, J = 15.0, 1H, $PhCH_aH_bN$); 4.74 (d, J = 15.0, 1H, $PhCH_aH_bN$); 6.58 (s, 1H, H-1); 6.81 (s, 1H, H-10); 6.90 (s, 1H, H-12); 6.99 (s, 1H, H-7); 7.29-7.41 (m, 5H, H_{arom}); 7.78 (s, 1H, H-4). ^{13}C-RMN ($CDCl_3$): δ = 16.73; 21.29 (CH_3CO and/or CH_3C-6); 53.68 ($PhCH_2$-N); 55.82; 56.04 (4 x OCH_3); 57.58 (C-6); 100.30; 105.50; 106.80; 108.23; 110.11 (C-1, C-4, C-7, C-10, and/or C-12); 127.13; 127.56; 128.60 (PhC_{arom}-H); 116.39; 116.95; 121.07; 130.23; 134.75; 137.97; 141.74; 142.10 (C-4a, C-6a, C-10a, C-11, C-13, C-14, and/or PhC_{arom}-C); 147.68; 147.90; 148.43; 150.17 (C-8, C-9, C-2', and/or C-3); 168.57 (CO_2). MS (CI): m/z = 513 (M^+, 12).

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