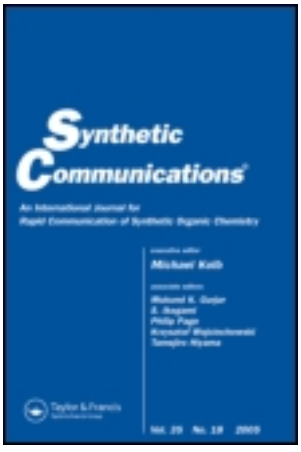

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Concise Synthesis of the Angular Dihydrofuroquinoline Alkaloids via Cyclopropane Opening in the Presence of Polyphosphoric Acid

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Abstract: We report a concise method for synthesis of dihydrofuroquinolinone alkaloids, in which the cyclopropane opening and closure was the key step. The only angluar type product was obtained in fairly high yields. IR, UV, ^{1}H NMR, ^{13}C NMR, and MS were used to confirm the structure. A possible mechanism in also described.

Keywords: Angluar, cyclopropane, furoquinolinone, ring opening and closure

Dihydrofuroquinolinones are an extremely diverse set of natural products which are the most widely distributed of quinoline alkaloids, as well as furoquinoline alkaloids[1] (Figure 1). They are primarily isolated from *Rutaceae* and often incorporate a terpenoid fragment. Their wide range of biological properties has stimulated interest in the synthesis of dihydrofuroquinolinone derivatives.[2]

Although they are of relatively modest complexity by today's standards of organic synthesis, a few number of synthetic approaches to the dihydrofuroquinolinone alkaloids have been reported.[3] Most of the methods were

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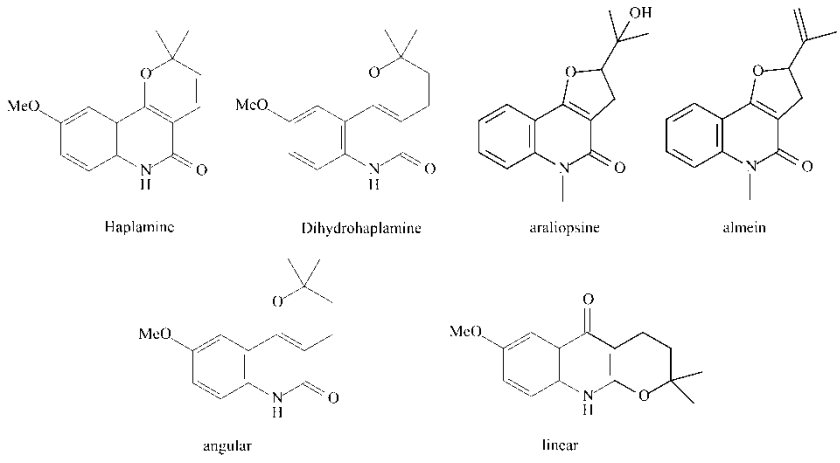


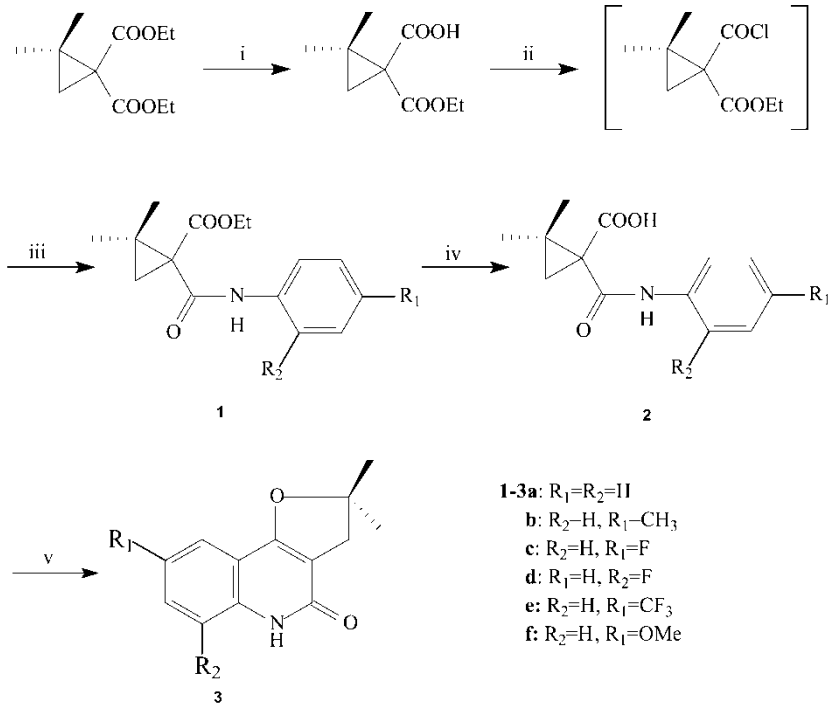
Figure 1. Furoquinoline alkaloids existed in nature and two types in the structure.

involved in the alkylation at the C-3 situation of quinolinone and then formation of furan ring. A mixture of angular and linear regioisomers was obtained. The procedure of these two steps was hitherto needed in the synthesis of this kind of compound. Now we reported a new method that forms the quinolinone ring and furan ring in one step. The only angular furoquinoline was obtained.

During our design and synthesis of the spiro-3,3-diallylquinoline system, which was regarded as analogous quinoline alkaloids, we became interested in the strained ring in C-3 situation in which cleavage or enlargement easily happens. When the cyclopropane was considered, opening and then closing were observed as expected.

The route started from the 2,2-dimethylcyclopropanedicarboxylate, which was synthesized by a Michael initiated ring closure (MIRC) reaction.[4] Then, a monoester was obtained after monosaponification in a 1 N NaOH/ethanol (1.1 eq) solution at room temperature for 12 h. Conversion of monocarboxylic acid with thionyl chloride provided cyclopropanecarbonyl chlorides, and subsequent treatment with substituted aniline gave amides 1 in 50–60% yield. After hydrolyzation of **1** in the 1 N NaOH/methanol (1.1 eq) solution at refluxing for 4 h, **2** was obtained. Treatment of **2** in the polyphosphoric acid (PPA) at 100–110°C for 2 h afforded dihydrofuroquinolin-one as a white solid in moderate yield (Scheme 1).

The assignment of **1** and **2** was confirmed by ^{1}H NMR analysis of the expected chemical shifts (see Table 1) and geminal coupling constants associated with the methylene group (J_{AB}) in the cyclopropane ring, which disappeared when the ring opened in the molecule **3**. Only a single product **3** was observed, and the assignment was confirmed by ^{1}H and ^{13}C NMR analysis. The regiochemistry of the linear and angular adduct was



i: 1 N NaOH, EtOH, 12 h. ii: $SOCl_2$, reflux, 0.5 h. iii: $ArNH_2$, Et_3N, THF, 2 h. iv: 1 N NaOH, MeOH, reflux, 4 h. v: PPA, 100-110 °C, 2 h.

Scheme 1. Synthesis of the angular dihydrofuroquinoline alkaloids via cyclopropane opening in the presence of polyphosphoric acid.

characterized in IR spectrum 1620–1660 cm^{-1} (amide in the angular type) and intense ultraviolet absorption at 270–290 nm. As a result of regioselective ring opening, the angular regioisomer **3** was the single product (see Table 2).

The mechanism investigated by Pirrung and Blume[3b] resembled this procedure, which involves initial cyclopropanation in the C-3 situation of quinoline ring, cyclopropane ring opening to a zwitterion, and then cyclopropane ring closure, but no selectivity for cyclopropane ring closure. The explanation mentioned by the authors was that the reaction was under kinetic control and balanced electron density at C-2 and C-4 oxygen in the putative zwitterions affected the production of similar amounts of the angular and linear regioisomers.[3b] In our procedure, formation of the quinolinone ring and cyclopropane ring opening occurred at the same time. The intermediate in Friedel–Crafts reaction changed the electron density at C-4 oxygen that affected the formation of furan ring. The angular regioisomer was the exclusive product (Figure 2).

Table 1.

Compound	Mp (°C)	^{1}H NMR ($CDCl_3$, 300 MHz, ppm)	Yield (%)
1a	53–55	1.23 (s, 3H, $-CH_3$), 1.24 (s, 3H, $-CH_3$), 1.64 (d, $J_{AB} = 5.1$, 1H, $-CH_2-$), 1.90 (d, $J_{AB} = 5.1$, 1H, $-CH_2-$), 1.32 (t, $J = 6.9$, 3H, $-CH_2CH_3$), 4.23 (q, $J = 7.5$, 2H, $-CH_2CH_3$), 7.06–7.11 (m, 1H, ArH), 7.29–7.34 (m, 2H, ArH), 7.56–7.58 (m, 2H, ArH), 9.86 (s, 1H, –NH–).	62.26
1b	59–60	1.23 (s, 3H, $-CH_3$), 1.22 (s, 3H, $-CH_3$), 1.62 (d, $J_{AB} = 4.8$, 1H, $-CH_2-$), 1.88 (d, $J_{AB} = 4.8$, 1H, $-CH_2-$), 1.31 (t, $J = 7.2$, 3H, $-CH_2CH_3$), 2.31 (s, 3H, $ArCH_3$), 4.22 (q, $J = 7.2$, 2H, $-CH_2CH_3$), 7.12 (d, $J = 8.1$, 2H, ArH), 7.45 (d, $J = 8.1$, 2H), 9.77 (s, 1H, –NH–).	68.9
1c	46	1.24 (s, 3H, $-CH_3$), 1.23 (s, 3H, $-CH_3$), 1.65 (d, $J_{AB} = 5.1$, 1H, $-CH_2-$), 1.89 (d, $J_{AB} = 5.1$, 1H, $-CH_2-$), 1.32 (t, $J = 6.9$, 3H, $-CH_2CH_3$), 4.23 (q, $J = 6.9$, 2H, $-CH_2CH_3$), 7.01–7.04 (m, 2H, ArH), 7.50–7.55 (m, 2H, ArH), 9.89 (s, 1H, –NH–).	43.5
1d	77–78	1.31 (s, 3H, $-CH_3$), 1.25 (s, 3H, $-CH_3$), 1.65 (d, $J_{AB} = 5.1$, 1H, $-CH_2-$), 1.90 (d, $J_{AB} = 5.1$, 1H, $-CH_2-$), 1.33 (t, $J = 7.2$, 3H, $-CH_2CH_3$), 4.26 (q, $J = 6.9$, 2H, $-CH_2CH_3$), 7.04–7.14 (m, 3H, ArH), 8.32 (t, 1H, ArH), 10.14 (s, 1H, –NH–).	63.7
1e	49–50	1.24 (s, 3H, $-CH_3$), 1.25 (s, 3H, $-CH_3$), 1.69 (d, $J_{AB} = 5.4$, 1H, $-CH_2-$), 1.92 (d, $J_{AB} = 5.4$, 1H, $-CH_2-$), 1.32 (t, $J = 7.2$, 3H, $-CH_2CH_3$), 4.24 (q, $J = 7.2$, 2H, $-CH_2CH_3$), 7.57 (m, 2H, ArH), 7.71 (m, 2H, ArH), 10.20 (s, 1H, –NH–).	65

1f	47–49	1.24 (s, 3H, $-CH_3$), 1.22 (s, 3H, $-CH_3$), 1.62 (d, $J_{AB} = 5.4$, 1H, $-CH_2-$), 1.88 (d, $J_{AB} = 5.4$, 1H, $-CH_2-$), 1.31 (t, $J = 7.2$, 3H, $-CH_2CH_3$), 4.22 (q, $J = 7.2$, 2H, $-CH_2CH_3$), 3.79 (s, 3H, $-ArOCH_3$), 7.47 (m, 2H, ArH), 6.86 (m, 2H, ArH), 9.72 (s, 1H, −NH−).	79.4
2a	134–136	1.29 (s, 3H, $-CH_3$), 1.35 (s, 3H, $-CH_3$), 1.76 (d, $J_{AB} = 4.8$, 1H, $-CH_2-$), 1.88 (d, $J_{AB} = 4.8$, 1H, $-CH_2-$), 7.10–7.15 (m, 1H, ArH), 7.31–7.36 (m, 2H, ArH), 7.52–7.55 (m, 2H, ArH), 9.17 (s, 1H, −NH−).	66.9
2b	149–150	1.28 (s, 3H, $-CH_3$), 1.34 (s, 3H, $-CH_3$), 1.75 (d, $J_{AB} = 5.1$, 1H, $-CH_2-$), 1.84 (d, $J_{AB} = 5.1$, 1H, $-CH_2-$), 2.32 (s, 3H, $ArCH_3$), 7.13 (d, $J = 8.1$, 2H, ArH), 7.40 (d, $J = 8.1$, 2H, ArH), 9.06(s, 1H, −NH−).	99.3
2c	142–144	1.28 (s, 3H, $-CH_3$), 1.35 (s, 3H, $-CH_3$), 1.76 (d, $J_{AB} = 5.1$, 1H, $-CH_2-$), 1.90 (d, $J_{AB} = 5.1$, 1H, $-CH_2-$), 6.99–7.05 (m, 2H, ArH), 7.47–7.52 (m, 2H, ArH), 9.26 (s, 1H, −NH−).	80.5
2d	106–109	1.29 (s, 3H, $-CH_3$), 1.37 (s, 3H, $-CH_3$), 1.77 (d, $J_{AB} = 5.1$, 1H, $-CH_2-$), 1.96 (d, $J_{AB} = 5.1$, 1H, $-CH_2-$), 7.02–7.14 (m, 4H, ArH), 8.23–8.28 (m, 1H, ArH), 9.70 (s, 1H, −NH−).	79.7
2e	138–141	1.29 (s, 3H, $-CH_3$), 1.38 (s, 3H, $-CH_3$), 1.79 (d, $J_{AB} = 5.1$, 1H, $-CH_2-$), 1.99 (d, $J_{AB} = 5.1$, 1H, $-CH_2-$), 7.58 (m, 2H, ArH), 7.69 (m, 2H, ArH), 9.66 (s, 1H, −NH−).	94.1
2f	117–118	1.28 (s, 3H, $-CH_3$), 1.34 (s, 3H, $-CH_3$), 1.76 (d, $J_{AB} = 5.1$, 1H, $-CH_2-$), 1.82 (d, $J_{AB} = 5.1$, 1H, $-CH_2-$), 3.79 (s, 3H, $-ArOCH_3$), 6.86 (m, 2H, ArH), 7.42 (m, 2H, ArH), 8.95 (s, 1H, −NH−).	85.4

Table 2.

Compound	Mp (°C)	IR(KBr) cm^{-1}	^1H and ^{13}C NMR ($CDCl_3$, 300 MHz, ppm)	MS (IE)m/z	Yield (%)
3a	228–229	3114, 2990, 1659, 1620	^1H NMR: 1.60 (s, 6H, 2 × $-CH_3$), 3.08 (s, 2H, $-CH_2-$), 7.18–7.72 (m, 4H, Ar-H), 11.86 (s, 1H, –NH–). ^{13}C NMR: 28.9, 40.4, 91.4, 107.6, 112.2, 116.6, 122.1, 122.6, 130.9, 139.7, 163.7, 163.8.	214.2	53.5
3b	241–242	3114, 2990, 1659, 1620	^1H NMR: 1.60 (s, 6H, 2 × $-CH_3$), 2.41 (s, 3H, $-CH_3$), 3.08 (s, 2H, $-CH_2-$), 7.30–7.49 (m, 4H, Ar-H), 12.10 (s, 1H, –NH–). ^{13}C NMR: 21.2, 28.8, 40.4, 91.2, 107.6, 112.1, 116.5, 122.0, 131.7, 132.3, 137.8, 163.5, 163.7.	230.2	12
3c	253–254	3394, 2999, 1659, 1626	^1H NMR: 1.60 (s, 6H, 2 × $-CH_3$), 3.08 (s, 2H, $-CH_2-$), 7.22–7.48 (m, 4H, Ar-H), 12.35 (s, 1H, –NH–). ^{13}C NMR: 28.74, 40.41, 91.71	232.1	69
3d	249–251	3154, 2978, 1661, 1626	^1H NMR: 1.60 (s, 6H, 2 × $-CH_3$), 3.04 (s, 2H, $-CH_2-$), 7.13–7.18 (m, 1H, Ar-H), 7.26–7.32 (m, 1H, Ar-H), 7.49–7.52 (m, 1H, Ar-H), 12.35 (s, 1H, –NH–).	232.2	21
3e	267–269	3154, 2978, 1662, 1627	^1H NMR: 1.63 (s, 6H, 2 × $-CH_3$), 3.09 (s, 2H, $-CH_2-$), 7.28–7.44 (m, 1H, Ar-H), 7.70–7.76 (m, 1H, Ar-H), 10.75 (s, 1H, –NH–).	282.2	5
3f	234	3154, 2978, 1662, 1626	^1H NMR: 1.60 (s, 6H, 2 × $-CH_3$), 3.09 (s, 2H, $-CH_2-$), 3.86 (s, 3H, $-CH_3$), 7.08–7.26 (m, 1H, Ar-H), 7.40–7.43 (m, 1H, Ar-H), 12.34 (s, 1H, –NH–). ^{13}C NMR: 28.9, 40.8, 56.0, 91.3, 102.9, 108.0, 112.5, 118.1, 121.1, 134.5, 154.9, 163.2, 163.3.	246.1	35.8

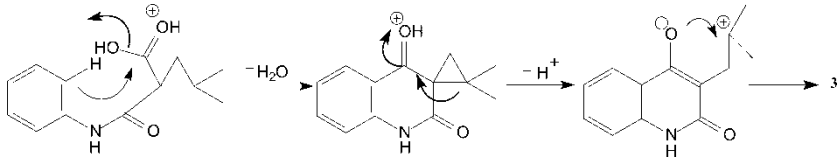


Figure 2. Mechanism of formation of quinolinone ring and furan ring in one step.

TYPICAL PROCEDURE

$SOCl_2$ was added to the solution of monoester in petroleum ester and then refluxed for 1–2 h. The mixture was concentrated in vacuo, and the solvent was removed. The solution of substituted anline and Et_3N in THF was added dropwise at 0°C and stirred at room temperature for 1.5 h after the dropping finished. The THF was removed, water was added, and then the mixture was extracted by EtOAc. The organic layer was dried and concentrated. The product **1** was obtained after purification by column chromatogram (PE/EtOAc).

A suspension of **1** in MeOH and 1 N NaOH was stirred under refluxing for 2 h. The resulting clear solution was condensed in vacuo. The residue was acidified by addition of an excess of 0.5 M HCl and extracted with ethyl acetate. The organic layer was washed by water, dried by $MgSO_4$, filtered, and evaporated in vacuo to give pure **2** as a solid.

The mixture of **2** in PPA was heated at 100–110°C for 1 h. The mixture was poured into cold water and extracted with ethyl acetate. After drying, the organic layer was concentrated in vacuo, and the crude product **3** was obtained. Purification could be done by ethanol.

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