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A CONVENIENT SYNTHESIS OF 2-(2-FURYL)-CYCLOALKANONES : AN APPLICATION TO BENZO[c]PHENANTHRIDONE RING FORMATION

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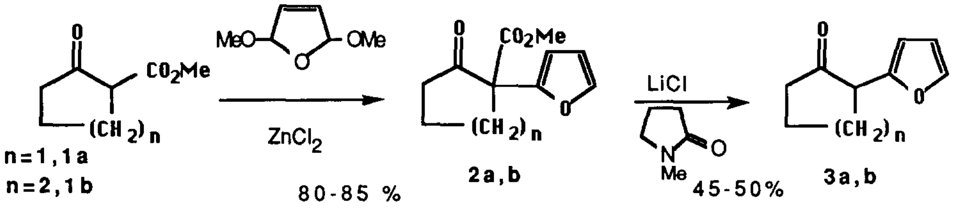
Abstract: An easy, high yield synthesis of 2-(2-furyl)-cycloalkanones is described in conjunction with an integrated strategy to a useful construction of benzo[c]phenanthridone alkaloid analogs.

In the course of our studies on furans as synthetic precursors, the synthesis of 2-(2-furyl)-cycloalkanones was achieved. The potential therapeutic interest associated with an important class of the isoquinoline alkaloid family, benzo[c]phenanthridines [1,2,3], prompted this work.

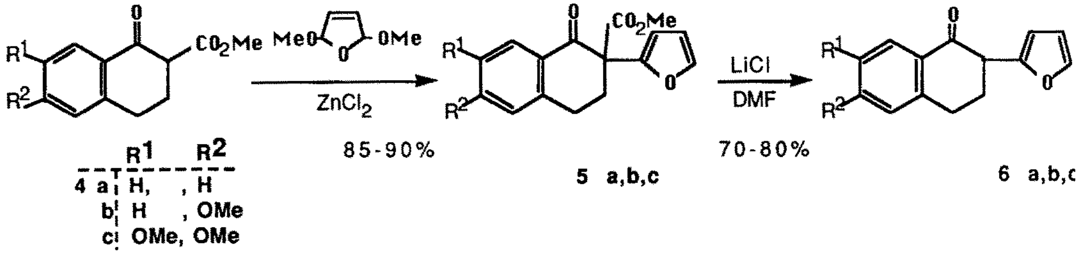
2-(2-Furyl)-cycloalkanones **3** [4] can generally be obtained in low yield either by nucleophilic substitution of nitrofurans with enamines [5] or as secondary products of [4+3] cycloadditions between polybromoketones and furan [6] or between cyclopentenylium-2-olate with furan derivatives [7]. Thus, for the synthesis of **3**, a decarbomethoxylation of 2-carbomethoxy-2-(2-furyl)-cyclanones **2** according to the modified method of Krapcho [8] was used. The compounds **2** were prepared by the condensation of 2,5-dihydro-2,5-dimethoxy-furan with ß-keto-esters **1**, in refluxing tetrahydrofuran in presence of zinc chloride and acetic acid [9]. (scheme 1)

Scheme 1

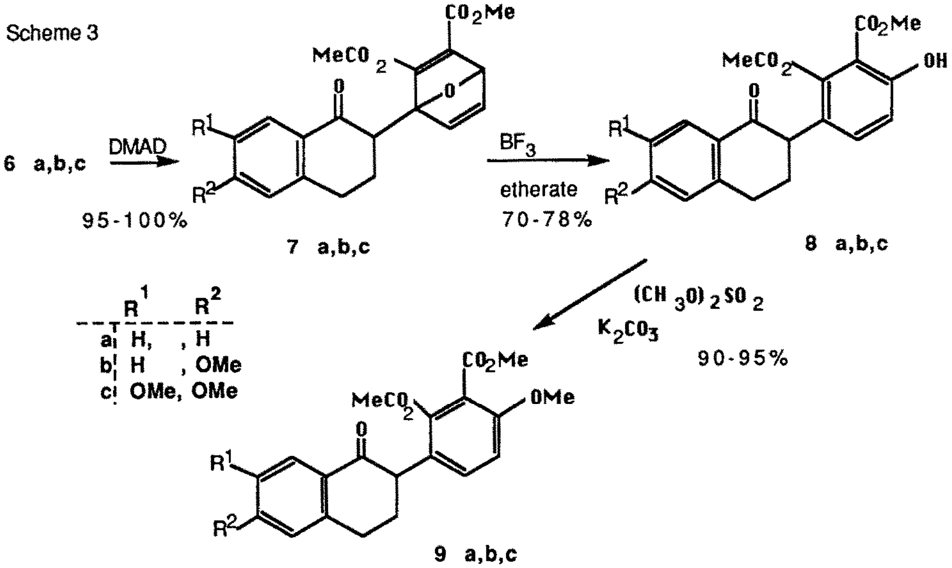


Under similar conditions, the substitued 1-tetralones **4** led to 2-(2-furyl)-1-tetralones **6** [10] via compounds **5** [11] (scheme 2). Diene synthesis between **6** and dimethyl acetylene dicarboxylate gave the cycloadducts **7** [12]. By an acid catalyzed aromatisation, the phenols **8** [13] were obtained, these were then next methylated to give compounds **9** [14]. (scheme 3)

Scheme 2

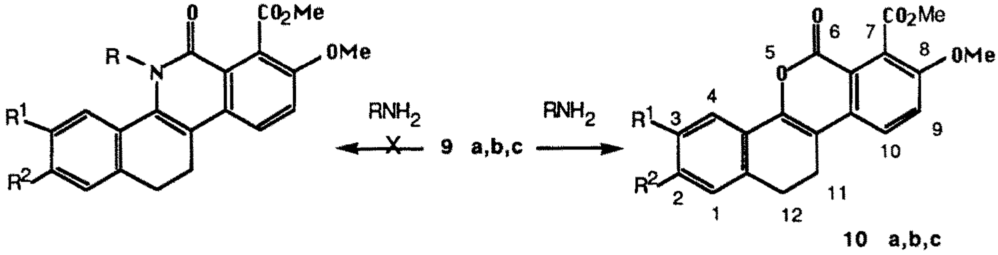


Scheme 3



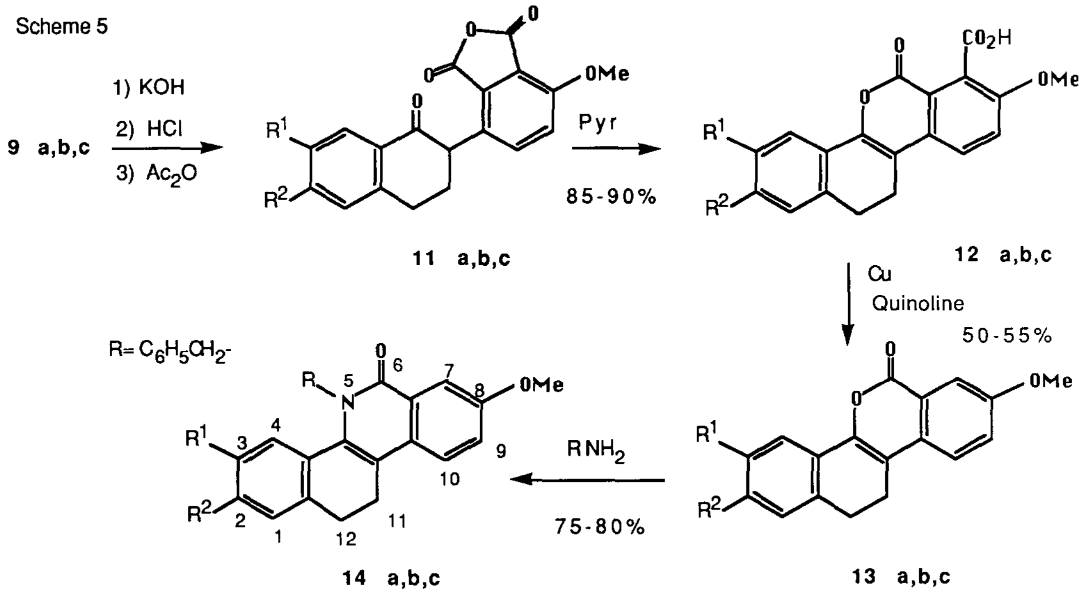
The attempted preparation of the benzo[c]phenanthridone ring by reaction of various primary amines in different solvents with **9** failed; only the benzo[d]dihydronaphtho[1,2-b] pyranones **10a,b,c** [15] were formed. (scheme 4)

scheme 4



So we planned to use the anhydrides **11** [16]; these were converted into their acid lactones **12** [17] by refluxing in pyridine. Decarboxylation of **12** yielded compounds **13** [18] which in the presence of high boiling primary amines reacted, and give the expected 11-12 dihydrobenzo[c]phenanthridones **14a,b,c** [19] in high yield. (scheme 5)

Scheme 5



Thus this new method involving furan derivatives has resulted in the synthesis in high yields of benzo[c]phenanthridines. The search for reaction conditions preserving the 7-carboxy group would bring about further chemical interest for these particular compounds.

References and notes:

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4. Analytical data **3b** : IR (cm^{-1})(KBr) : 1715. ^{1}H-NMR (CDCl$_3$, 60 MHz) : ∂ (ppm) 2.60-1.55 (m, 8H), 3.65 (m, 1H), 6.10 (d,1H, J = 2 Hz), 6.75 (dd, 1H, J = 1.0, 2.0 Hz), 7.3 (d, 1H, J = 1.0 Hz). bp (10 mm Hg) 125°C. n^{D}_{21} 1059,1.
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10. **6a** : IR (cm^{-1})(KBr) : 1685 . ^{1}H-NMR ($CDCl_3$, 60 MHz) : ∂ (ppm) 2.73-2.15 (m, 2H), 3.03 (t, 2H), 3.90 (t, 1H, J = 7.0 Hz), 6.20 (d, 1H, J = 3 Hz), 6.35 (dd,1H, J = 2.0, 3.0 Hz), 7.70-7.13 (m,3H), 7.43 (d, 1H, J = 2 Hz), 8.16 (dd,1H, J=7.50 Hz). bp (13mm Hg) 192°C. $n^{D}21$ 1588.7 . **6b** mp 75°C . **6c** mp 119°C.

11. **5a** : IR (cm^{-1})(KBr) : 1670, 1735 . ^{1}H-NMR ($CDCl_3$, 60 MHz) : ∂ (ppm) 2.86 (s,4H), 3.75 (s,3H), 6.21 (d,1H,J=3.5 Hz), 6.38 (dd,1H,J=2.0, 3.5 Hz), 7.81-7.16 (m,3H), 7.50 (d,1H,J=2.0 Hz), 8.26 (dd,1H, J=2.0, 8.0 Hz). mp 92°C. **5b**: mp 88 °C. **5c**: mp 132 °C

12. **7a** : IR (cm^{-1})(KBr) : 1725, 1705 . ^{1}H-NMR ($CDCl_3$, 60 MHz) : ∂ (ppm) 3.06-1.93 (m,4H), 3.65-3.78 (m,1H), 3.78 (s,3H), 3.81 (s,3H), 5.65 (dd,1H, J=8.00,1.50 Hz), 7.55-7.04 (m,5H), 8.03 (dd,1H, J=8.00,1.5 Hz). mp 135°C. **7b** mp 117°C. **7c** mp 161°C.

13. **8a** : IR (cm^{-1})(KBr) : 3380, 1730, 1715, 1675 . ^{1}H-NMR ($CDCl_3$, 60 MHz) : ∂ (ppm) 2.53-2.10 (m,2H), 3.28-2.86 (m,2H), 3.50-3.60 (m,1H), 3.80 (s,3H), 3.86 (s,3H), 6.96 (d,1H, J= 9.00 Hz), 7.23 (d,1H, J= 9 Hz), 7.58-7.16 (m,3H), 8.00 (dd,1H, J= 7.00,2.00), mp 133. **8b** mp 196°C. **8c** mp 258°C.

14. **9a** : IR (cm^{-1})(KBr) : 1740, 1730, 1690 . ^{1}H-NMR ($CDCl_3$, 60 MHz) : δ (ppm) 2.66-2.23 (m,2H), 3.33-2.80 (m,2H), 3.76 (s,3H), 3.86 (s,3H), 3.93 (s,3H), 4.33-4.00 (m,1H), 7.70-7.00 (m,5H), 8.11 (dd,1H, J= 1.5, 7.0 Hz). mp 153°C. **9b** mp 132°C. **9c** mp 223°C.

15. **10a** : IR (cm^{-1})(KBr) : 1740, 1720, 1635 . ^{1}H-NMR ($CDCl_3$ + CF_3CO_2H: 1/1,60 MHz) : ∂ (ppm) 3.00 (s,4H), 3.98 (s,3H), 4.16 (s,3H), 7.48-7.17 (m,4H), 7.61 (d,1H, J=10 Hz), 7.91 (d,H, J=10 Hz) . mp 232°C. **10b** mp 241°C. **10c** mp 253°C.

16. **11a** : IR (cm^{-1})(KBr) : 1840, 1755, 1680. ^{1}H-NMR ($CDCl_3$ + CF_3CO_2H: 1/1, 60 MHz) : ∂ (ppm) 8.26-7.16 (m, 6H), 4.96-4.50 (m, 1H), 4.06 (s, 3H), 3.53-2.16 (m, 4H). mp 218°C. **11b** mp 258°C. **11c** mp 233°C.

17. **12a** : IR (cm^{-1})(KBr) : 1715. ^{1}H-NMR ($CDCl_3$ + CF_3CO_2H: 1/1, 60 MHz) : ∂ (ppm) 8.03-7.16 (m, 6H), 4.00 (s, 3H), 3.00 (s, 4H). mp 295°C. **12b** mp 310°C. **12c** mp 284°C.

18. **13a** (R= C_6H_6-CH_2-) : IR (cm^{-1})(KBr) : 1710 . ^{1}H-NMR ($CDCl_3$, 60 MHz) : ∂ (ppm) 8.10-7.14 (m, 7H), 3.90 (s, 3H), 3.13-2.80 (m, 4H). mp 152°C. **13b** mp 180°C. **13c** mp 192°C.

19. **14a** (R= C_6H_6-CH_2-) : IR (cm^{-1})(KBr) : 1635. ^{1}H-NMR ($CDCl_3$, 60 MHz) : ∂ (ppm) 2.87 (s, 4H), 3.96 (s, 3H), 5.66 (s, 2H), 8.13-7.10 (m, 12H). mp 190°C. **14b** mp 112°C. **14c** mp 169°C.

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