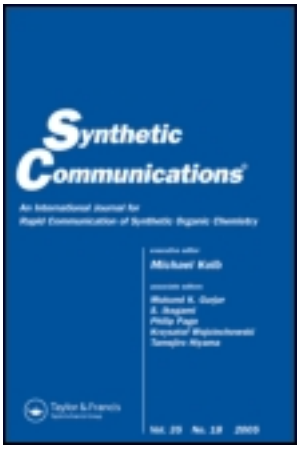

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Facile and Simple Route to the Synthesis of Condensed Acridine Systems

Periyasamy Murugan [a], Kuo Chu Hwang [a], Dhakshanamurthy Thirumalai [b] & Vayalakavoor T. Ramakrishnan [b]

[a] Department of Chemistry, National Tsing Hua University, Hsinchu, Taiwan, China

[b] Department of Organic Chemistry, University of Madras, Chennai, India

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Facile and Simple Route to the Synthesis of Condensed Acridine Systems

Periyasamy Murugan and Kuo Chu Hwang
Department of Chemistry, National Tsing Hua University, Hsinchu, Taiwan, China

Dhakshanamurthy Thirumalai and Vayalakavoor T. Ramakrishnan
Department of Organic Chemistry, University of Madras, Chennai, India

Abstract: Condensation of cyclohexane-1,3-dione or dimedone with *o*-nitrobenzaldehyde and ammonium acetate/acetic anhydride furnished the corresponding acridinedione/xanthene derivatives. The middle ring aromatization followed by reductive cyclization afforded the respective condensed acridine systems.

Keywords: Acridinedione, reductive cyclization, xanthene

The acridine skeleton fused with a five- or six-membered heterocyclic ring plays a vital role as a DNA-intercalating anticancer drug.[1] Pyridoacridine alkaloids are an important class of marine natural products with interesting biological properties.[2,3] Compounds of this class show both cytotoxic activity against L1210 leukemia cells and powerful calcium-releasing activity in the sarcoplasmic reticulam.[4,5] Other compounds with similar structures have enhanced selectivity for cerebral coronary and peripheral blood vessels.[6] The synthesis and biological evaluation of a number of condensed acridines has been extensively studied by Antonini and his

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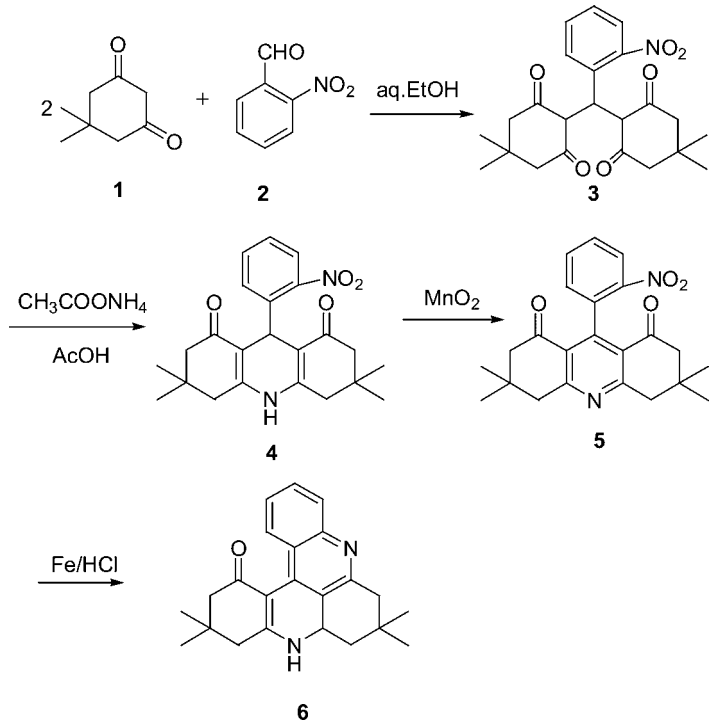
Address correspondence to Vayalakavoor T. Ramakrishnan, Department of Organic Chemistry, University of Madras, Guindy Campus, Chennai-600 025, India. Tel.: +91-44-24414247; Fax: +91-44-22352494; E-mail: vtrk28@yahoo.com

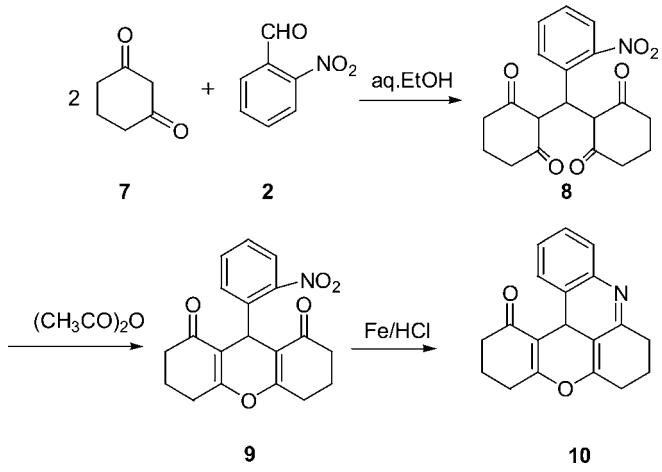
coworkers.[7] Moreover, the synthesis of a number of quino and pyrano acridine derivatives has been reported.[8]

In continuation with our interest in the acridinedione ring system,[9–11] we focused our attention on the synthesis of condensed acridine systems. Because of their biological importance, we report a simple and facile synthesis of quinoline, pyridine-containing condensed acridine systems. Condensation of dimedone **1** and *o*-nitrobenzaldehyde **2** in aq. ethanol furnished the tetraketone **3**,[12,13] which was then refluxed with ammonium acetate (excess) in acetic acid to give 9-(2-nitrophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro-1,8-(2H,5H) acridinedione **4** in 82% yield. Aromatization[14] of the compound **4** with active MnO_2 afforded 9-(2-nitrophenyl)-3,3,6,6-tetramethyl-3,4,5,6-tetrahydro-1,8-(2H, 7H)acridinedione **5** in 80% yield. Reductive cyclization of compound **5** with Fe/HCl in ethanol at 90°C for 4 h furnished 3,3,7,7-tetramethyl-1,3,4,5,5a,6,7,8-octahydroquino[2,3,4-*kl*]acridin-1-one **6** (Scheme 1).

Similarly, condensation of cyclohexane-1,3-dione **7** with *o*-nitrobenzaldehayde **2** afforded the teraketone **8**,[12,13] which was then refluxed in acetic anhydride to give the xanthene derivative **9**. Reductive cyclization of the compound **9** with Fe/HCl in ethanol furnished 13-oxo-6,7,8,10,11,12,13,13b-octahydro-benzopyrano[2,3,4-*kl*]acridine **10** (Scheme 2).



Scheme 1.

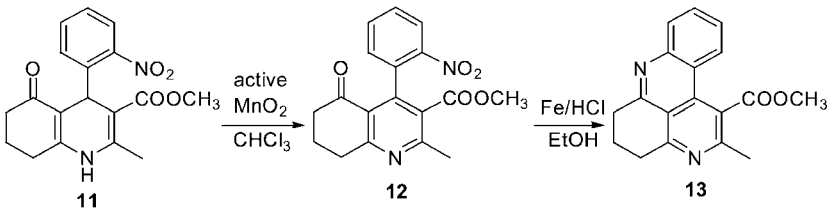


Scheme 2.

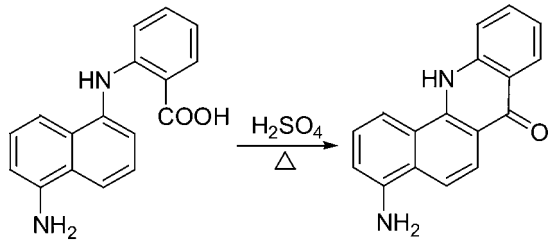
Next, the hexahydroquinoline derivative **11** was synthesized according to the literature procedure[15] and then was subjected to aromatization with active MnO_2 to afford methyl 2-methyl-4-(*o*-nitrophenyl)-5-oxo-5,6,7,8-teterahydroquinoline-3-carboxalate **12**. Treatment of **12** with Fe/HCl in ethanol at 90°C for 4 h furnished methyl 2-methyl-4,5-dihydro-6H-pyrido[4,3,2-*mn*]acridin-1-carboxylate **13** (Scheme 3).

Similarly, the reductive cyclization of the naphthyl derivative **14**[16] with con. H_2SO_4 at 90°C for 4 h furnished 4-amino-7,12-dihydrobenzo[*c*]acridin-7-one **15** (Scheme 4).

In summary, we have reported the synthesis of acridine derivatives fused with quinoline, pyran, pyridine, and benzene ring systems using a simple and convenient methodology. Also, in the case of reductive cyclization of the compounds **5**, **9**, and **12** to give the corresponding cyclized compounds **6**, **10**, and **13**, the use of other reducing agents such as $SnCl_2$/HCl, Sn/HCl, and Raney Ni results in the formation of an inseparable mixture. Thus, Fe/HCl in ethanol was found to be an efficient reagent for the reductive cyclization.



Scheme 3.



14 **15**

Scheme 4.

EXPERIMENTAL

Melting points are uncorrected. IR spectra were recorded on a Perkin Elmer 258 spectrophotometer. ^{1}H NMR spectra were recorded on JEOL GSX 400 (400 MHz) instrument. Mass spectra were measured on Hewlett-Packard 5985 GC/MS instrument. HRMS data was recorded on a Thermo Finnigan MAT 95XL instrument.

9-(*o*-Nitrophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro-1,8(2H,5H) acridinedione (4). A solution of tetraketone **3** (1.5 g, 3.6 mmol) and ammonium acetate (excess) in acetic acid (25 mL) was refluxed for 8 h. The reaction mixture was then cooled and poured onto crushed ice; the yellow solid obtained was filtered, dried, and recrystallized from a mixture of methanol and chloroform (1:2). Yield: 1.25 g (82%); mp 298–300°C; IR (KBr): 1630, 1509, 1350 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 and 1.08 (2s, 12H, *gem*-dimethyl), 2.01–2.22 (2d, 4H, C_4 and C_5-CH_2, $J = 16.2$ Hz), 2.34–2.46 (2d, 4H, C_2 and C_7-CH_2, $J = 16.9$ Hz), 5.75 (s, 1H, C_9-H), 7.29–7.70 (m, 4H, Ar-H), and 8.8 (bs, 1H, NH, exchangeable with D_2O); MS (EI) m/z (%): 394 (M^+, 8), 393 (6), 347 (3), 378 (4), 335 (2), 307 (3), 272 (4), 271 (2), 236 (5), 194 (100), 180 (26), 152 (10), 112 (12), 83 (9). Anal. calcd. for $C_{23}H_{26}N_2O_4$ (394.46): C, 70.03; H, 6.64; N, 7.10. Found: C, 70.12; H, 6.42; N, 7.29.

9-(*o*-Nitrophenyl)-3,3,6,6-tetramethyl-3,4,5,6-tetrahydro-1,8(2H,5H)acridinedione (5). The acridinedione **4** (1.5 g, 3.38 mmol) was dissolved in chloroform (150 mL) with a few drops of DMSO and stirred at room temperature with active MnO_2 (6.0 g) for 12 h. The residue was filtered off and the filtrate was concentrated. The solid obtained was recrystallized from methanol to afford the compound **5**. Yield: 1.2 g (80%); mp 248–250°C; IR (KBr): 1698, 1509, 1350 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.08 (s, 12H, *gem*-dimethyl), 2.39 and 3.11 (2s, 8H, C_2, C_4, C_5, C_7-CH_2), 6.89–8.20 (m, 4H, Ar-H). MS: m/z (%): 392 (M^+, 1), 377 (2), 347 (100), 346 (100), 300 (11), 316 (5), 290 (30), 262 (6), 247 (8), 232 (6), 204 (5), 83

(12), 55 (16). Anal. calcd. for $C_{23}H_{24}N_2O_4$ (392.44): C, 70.40; H, 6.16; N, 7.13. Found: C, 70.49; H, 6.28; N, 7.28.

3,3,7,7-Tetramethyl-1,3,4,5,5a,6,7,8-octahydro-2H-quino[2,3,4-*kl*]acridin-1-one (6). To a mixture of acridinedione **5** (2.5 g, 6.3 mmol) and iron powder (3.5 g) in ethanol (20 mL), a solution of con. HCl (1.8 mL) in ethanol (10 mL) was added slowly and the reaction mixture was refluxed for 4 h. The reaction mixture was filtered and the filtrate was concentrated to afford a solid, which was then purified by column chromatography over neutral alumina using a 1:1 mixture of chloroform methanol as eluant. Yield: 1.72 g (78%); mp 272–274°C; UV (λ_{max}): 361, 310 nm (MeOH); fluorescence (λ_{max}): 462 nm (MeOH). IR (KBr): 3250, 1610, 1580 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.99, 1.15, 1.16, 1.20 (4s, 12H *gem*-dimethyl), 1.95–2.05 (m, 2H, C_6-CH_2), 2.45–2.60 (2d, 2H, $J = 17.5$ Hz, C_2-CH_2), 2.75–2.95 (2d, 2H, $J = 17.5$ Hz, C_4-CH_2), 2.50 (bs, 2H, C_8-CH_2), 4.31–4.40 (m, 1H, C_{5a}-CH), 5.81 (bs, 1H, NH, exchangeable with D_2O), 7.31–7.92 (m, 4H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.87, 164.74, 154.20, 148.37, 136.33, 128.76, 128.40, 127.80, 124.13, 122.08, 119.80, 109.97, 51.42, 51.07, 46.31, 40.49, 31.72, 31.31, 30.37, 29.85, 26.92, 24.87. MS, m/z (%): 346 (100), 345 (45), 344 (40), 343 (30), 316 (10), 290 (50), 189 (10), 288 (25), 246 (10). Anal. calcd. for $C_{23}H_{26}N_2O$ (346.46): C, 79.73; H, 7.56; N, 8.08. Found: C, 79.89; H, 7.68; N, 8.22.

9-(2-Nitrophenyl)-3,4,6,7-tetrahydro-9H-xanthene-1,8(2H, 5H)-dione (9). A solution of the tetraketone **7** (1.0 g, 2.8 mmol) in acetic anhydride (20 mL) was refluxed for 7 h. After completion of the reaction, the reaction mixture was concentrated. The solid material obtained was recrystallized from methanol to give the xanthene derivative **9**. Yield: 0.85 g (78%); mp 248–250°C; IR (KBr): 1670, 1530, 1358, 1335 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.92–2.10 (m, 4H), 2.30–2.32 (m, 4H), 2.56–2.67 (m, 4H), 5.41(s, 1H, C_9-H), 7.40–7.63 (m, 3H, Ar-H), 7.79–7.81 (d, 1H, $J = 8.0$ Hz, Ar-H). Anal. calcd. for $C_{19}H_{17}NO_5$ (339.34): C, 67.25; H, 5.04; N, 4.12. Found: C, 67.52; H, 5.10; N, 4.29.

3-Oxo-6,7,8,10,11,12,13,13b-octahydro-benzopyrano[2,3,4-*kl*] acridine (10). To a mixture of xanthene derivative **9** (1.0 g, 2.9 mmol) and iron powder (1.4 g) in ethanol (20 mL), a solution of con. HCl (0.6 mL) in ethanol (5 mL) was added slowly and refluxed for 5 h. The reaction mixture was concentrated and the residue was purified by column chromatography over neutral alumina using a mixture of chloroform and methanol (3:1) as eluant. Yield: 0.52 g (60%); mp 220–222°C; IR (KBr): 1706, 1601, 1588 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 1.78–1.86 (m, C_7-CH_2, 2H), 1.89–1.96 (m, C_{11}-CH_2, 2H), 2.14–2.20 (m, C_6-CH_2, 2H), 2.23–2.30 (m, C_{12}-CH_2, 2H), 2.55–2.66 (m, C_8 and C_{10}-CH_2, 4H), 5.38 (s, C_{13b}, 1H), 7.31–7.76 (m, 4H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 190.82,

163.72, 162.17, 151.11, 148.27, 147.18, 136.32, 128.34, 127.18, 127.01, 118.48, 109.86, 51.27, 50.89, 41.98, 40.11, 34.07, 33.78, 31.61. MS, m/z (%): 291 (51), 262 (10), 260 (20), 236 (40), 235 (100), 217 (60), 197 (45), 183 (40), 180 (40), 168 (35), 167 (50), 141 (30), 140 (30), 108 (60), 91 (70), 83 (55). HRMS calcd. for $C_{19}H_{17}NO_2$: 291.3438. Found: 291.3441.

Methyl 2-methyl-4-(*o*-nitrophenyl)-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxylate (12). Aromatization of **11** was carried out by following the procedure described in the synthesis of the compound **5** to afford the ester **12**. Yield: 0.98 g (65%); mp 154–156°C; IR (KBr): 1729, 1690, 1510, 1369 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.14–2.18 (m, 2H, C_7-CH_2), 2.52–2.55 (m, 2H, C_8-CH_2), 2.60 (s, 3H, CH_3), 3.15–3.20 (m, 2H, C_6-CH_2), 3.39 (s, 3H, OCH_3), 7.02–7.04 (d, $J = 8.0$ Hz, 2H, Ar-H), 7.50–7.61 (m, 2H, Ar-H), 8.21–8.23 (d, $J = 8.0$ Hz, 2H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.21, 164.37, 152.65, 146.18, 141.08, 140.2, 134.07, 131.29, 129.11, 125.65, 124.48, 122.30, 115.18, 52.80, 32.68, 32.56, 22.89, 22.76. Anal. calcd. for $C_{18}H_{16}N_2O_5$ (340.33): C, 63.52; H, 4.74; N, 8.23. Found: C, 63.45; H, 4.82; N, 8.18.

Methyl 2-methyl-4,5-dihydro-6H-pyrido[4,3,2-*mn*]acridin-1-carboxylate (13). Reductive cyclization of **12** was carried out by following the procedure described for the synthesis of the compound **6** to afford the ester **13**. Yield: 0.21 g (4%); mp 225–227°C; IR (KBr): 1725, 1610, 1522 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.19–2.22 (m, C_5-CH_2, 2H), 2.57 (s, 3H, CH_3), 3.15–3.2 (m, C_4 and C_6-CH_2, 4H), 4.07 (s, 3H, CH_3), 7.67–7.88 (2t, 2H, Ar-H), 8.04–8.06 (m, 2H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.46, 162.46, 160.53, 153.59, 145.45, 133.60, 131.15, 129.72, 126.87, 124.14, 120.56, 119.83, 115.72, 53.40, 33.88, 33.54, 22.62, 22.14; MS, m/z (%): 292 (100), 277 (10), 261 (80), 260 (30), 233 (30), 232 (54), 231 (28), 218 (36), 217 (24), 216 (64), 206 (23), 192 (45), 191 (34), 189 (61), 164 (10), 140 (63), 130 (63), 102 (32), 95 (45), 88 (42). Anal. calcd. for $C_{18}H_{16}N_2O_2$ (292.33): C, 73.94; H, 5.51; N, 9.58. Found: C, 73.65; H, 5.87; N, 10.33.

4-Amino-7,12-dihydrobenzo[*c*]acridin-7-one (15). In a 50-mL round bottomed flask, a solution of **14** (0.5 g, 1.7 mmol) in con. H_2SO_4 (5 mL) was heated to 90°C for 5 h. Then, the reaction mixture was poured into boiling water (20 mL). The yellow solid obtained was filtered, dried, and purified by column chromatography over neutral alumina using a mixture of methanol and chloroform (1:3) as eluant. Yield: 0.24 g (52%); mp > 320°C; IR (KBr): 3410, 3369, 3120, 1640 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.92 (bs, NH_2, exchanged with D_2O), 6.93–6.95 (d, $J = 8.0$ Hz, 1H), 7.30–7.33 (m, 1H), 7.42–7.46 (m, 1H), 7.72–7.784 (m, 2H), 7.99–8.25 (m, 4H), 11.47 (bs, NH, exchanged with D_2O). ^{13}C NMR (100 MHz, DMSO-D_6) δ: 176.18, 145.78, 138.53, 132.70, 127.11, 125.43, 123.17, 121.87, 121.50,

121.48, 121.20, 119.35, 118.36, 116.73, 116.13, 115.50, 110.04; MS, m/z (%): 260 (100), 232 (5), 231 (6), 204 (8), 203 (5). Anal. calcd. for $C_{17}H_{12}N_2O$ (260.29): C, 78.44; H, 4.64; N, 10.77. Found: C, 78.69; H, 4.49; N, 10.51.

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