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Iodine–Methanol-promoted Oxidation of 2-Aryl-1,2,3,4-tetrahydro-4-quinolones to 2-Aryl-4-methoxyquinolines†

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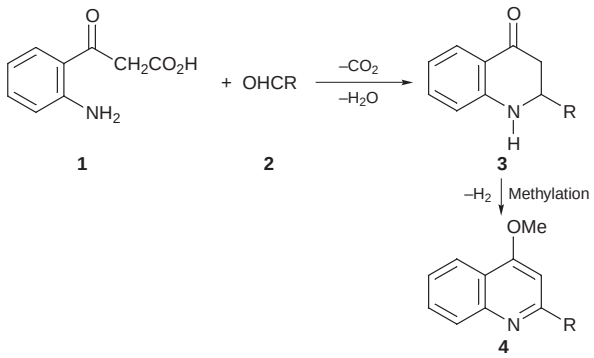
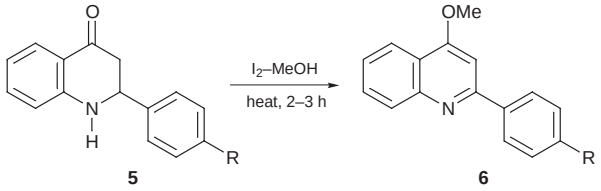
2-Aryl-1,2,3,4-tetrahydro-4-quinolones are converted in high yields to the corresponding 2-aryl-4-methoxyquinolines using molecular iodine in refluxing methanol; the structures of the quinoline derivatives are determined using ^{1}H and ^{13}C NMR spectroscopic techniques.

The pharmacological activity of benzopyridine derivatives such as quinolines is well documented, and a number of synthetic analogues are in clinical use as antimalarial agents.[1] Quinolines are widely distributed in the plant family *Rutaceae* and they are generally accessible in the laboratory *via* the reactions of aniline derivatives with carbonyl systems.[2] The synthesis of 4-alkoxy-2-arylquinolines continue to attract considerable attention in organic chemistry because of their striking biological activity.[3] 4-Methoxyquinoline alkaloids **4** are believed to be formed in plants by the reaction between 2-aminobenzoylacetic acid **1** and the appropriate aldehyde **2** followed by dehydrogenation and methylation (Scheme 1).[4] Only a limited number of methods for the synthesis of 4-alkoxy-2-arylquinolines have been reported in literature and most of them involve multiple steps.[5] As part of our research on heterocyclic compounds with medicinal potential, in this work, we have explored the oxidative aromatization of 2-aryl-1,2,3,4-tetrahydro-4-quinolones **5** to 2-aryl-4-methoxyquinolines **6** using relatively cheaper and safer reagents, iodine and methanol. To our knowledge, the only methods reported to-date for the oxidation of 2-aryl-1,2,3,4-tetrahydro-4-quinolones to 2-aryl-4-methoxyquinolines make use of either thallium(III) nitrate[6] or [hydroxy(tosyloxy)-iodo]benzene[7] in trimethyl orthoformate in the presence of catalytic amount of perchloric acid.

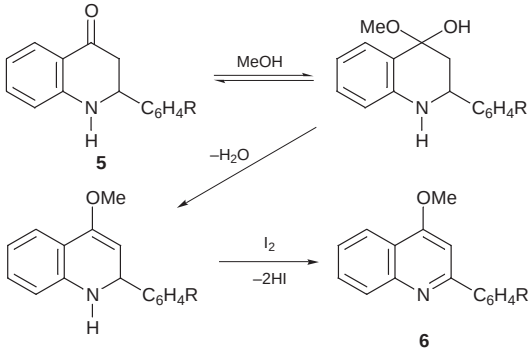


Scheme 1

In our previous communication, we reported the results of iodine–methanol promoted oxidation of 3-phosphonoalkylcyclohexenones to the corresponding *m*-anisole derivatives.[8] These reaction conditions were applied in this investigation to series of specially prepared 2-aryl-1,2,3,4-tetrahydro-4-quinolones **5** and in all cases we isolated the corresponding 2-aryl-4-methoxyquinoline derivatives **6**, as sole products (Scheme 2). As in the case of 3-cyclohexenone alkylphosphonates,[8] we interpret the results of iodine-promoted aromatization reaction described in Scheme 2 as a consequence of an initial carbonyl addition of methanol, followed by dehydration and oxidative aromatization (Scheme 3).



Scheme 2



Scheme 3 R = H, **a**; 4′-F, **b**; 4′-Cl, **c**; 4′-Br, **d**; 4′-OMe, **e** or 4′-NO_2 **f**.

The benzopyridine derivatives **6** exhibit spectral properties in accord with the assigned structures. Their ^{1}H NMR spectra are characterized by the presence of the methoxy and aromatic proton signals at δ ca. 4.50 and 7.00–9.20, respectively. On the other hand, their ^{13}C NMR spectra lack the carbonyl carbon, methylene and methine carbon resonances thus distinguishing themselves from the corresponding precursors **5**. Compounds **6a**, **c** and **e** prepared in this investigation were, however, found to exhibit higher melting points than the corresponding compounds described

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in the literature.[6,7] Nevertheless, the structures of all the prepared products were found by ^{1}H NMR, ^{13}C NMR and high-resolution mass spectroscopic techniques to correspond to the aromatic systems **6** and their molecular formulae represent, in each case, the closest fit (consistent with available atoms) to the experimentally determined accurate *m/z* values.

Iodine–methanol oxidative aromatization of 2-aryl-1,2,3,4-tetrahydro-4-quinolones described here represents a versatile, relatively mild and high yielding approach to 2- and 4-substituted quinoline derivatives. Systems **6** can serve as substrates for further studies of chemical transformation and for biological activity.

Experimental

Melting points were recorded on a Thermocouple digital melting point apparatus and are uncorrected. NMR spectra were obtained for $CDCl_3$ solutions on a Varian Gemini 200 MHz spectrometer and the chemical shifts are quoted relative to the solvent peaks (δ_H 7.25, δ_C 77.0). High-resolution mass spectra were recorded at Cape Technikon Mass Spectrometry Unit using a VG-70 SEQ MASPEC II[32] instrument (scanning at RP 10 000). The 2-aryl-1,2,3,4-tetrahydro-4-quinolones **5a**–**f** used as substrates in this investigation were prepared from the corresponding 1-(2-aminophenyl)-3-arylprop-2-en-1-ones following a method reported by Donnelly and Farrell.[9]

Synthesis of 2-*Aryl*-4-*Methoxyquinolines* **6**. *General Procedure.*—A stirred mixture of 2-aryl-1,2,3,4-tetrahydro-4-quinolone **5** (1 equiv.) and iodine (1 equiv.) in methanol (5 ml per mmol of **5**) was refluxed for 3 h and then allowed to cool. The product crystallized from the mother-liquor to afford 2-aryl-4-methoxyquinoline **6**.

4-*Methoxy*-2-*phenylquinoline* **6a**. Solid (73%), mp 166–169 °C (MeOH) (lit.,[6,7] 66–68 °C); δ_H (200 MHz, $CDCl_3$) 4.15 (3H, s, OCH_3), 7.15–7.32 (4H, m, 2′-H, 3′-H, 4′-H and 6′-H), 7.37 (1H, s, 3-H), 7.70 (1H, t, *J* 7.3 Hz, 6-H), 7.91 (1H, t, *J* 7.1 Hz, 7-H), 8.24 (1H, t, *J* 7.2 Hz, 5′-H), 8.27 (1H, d, *J* 7.2 Hz, 8-H) and 9.19 (1H, d, *J* 8.6 Hz, 5-H); δ_C (50 MHz, $CDCl_3$) 59.3 (OCH_3), 101.0 (C-3), 119.7 (C-4a), 121.1 (C-6), 122.6 (C-5), 128.4 (C-8), 129.0 (C-3′ and C-5′), 129.4 (C-1′), 129.8 (C-2′ and C-6′), 132.5 (C-4′), 134.3 (C-7), 139.3 (C-8a), 156.2 (C-2) and 168.5 (C-4); *m/z* 235 (M^+, 67.7), 205 (28.6), 193 (6.51) and 141 (100) (Found: M^+ 235.0990. $C_{16}H_{13}NO$ requires 235.0997).

2-(4′-*Fluorophenyl*)-4-*methoxyquinoline* **6b**. Solid (80%), mp 149–151 °C (MeOH); δ_H (200 MHz, $CDCl_3$) 4.50 (3H, s, OCH_3), 7.06 (2H, t, *J* 8.5 Hz, 3′-H and 5′-H), 7.31 (1H, s, 3-H), 7.72 (1H, t, *J* 7.8 Hz, 6-H), 7.96 (1H, t, *J* 7.9 Hz, 7-H), 8.26 (1H, dd, *J* 0.8 and 8.2 Hz, 8-H), 8.36 (2H, m, 2′-H and 6′-H) and 9.28 (1H, d, *J* 8.4 Hz, 5-H); δc (50 MHz, $CDCl_3$) 58.1 (OCH_3), 99.8 (C-3), 116.2 (d, $^2J_{CF}$ 22.5 Hz, C-3′ and C-5′), 119.9 (C-4a), 122.5 (C-6), 123.2 (C-5), 125.6 (d, $^4J_{CF}$ 3.0 Hz, C-1′), 127.9 (C-8), 131.8 (d, $^3J_{CF}$ 8.8 Hz, C-2′ and C-6′), 133.5 (C-7), 141.2 (C-8a), 156.0 (C-2), 162.5 (d, $^3J_{CF}$ 245 Hz, C-4′) and 167.5 (C-4); *m/z* 253 (M^+, 100), 252 (61.2), 224 (40.4), 223 (44.7), 222 (44.9), 208 (6.7) and 183 (12.1) (Found: M^+ 253.0894. $C_{16}H_{12}NOF$ requires 253.0903).

2-(4′-*Chlorophenyl*)-4-*methoxyquinoline* **6c**. Solid (91%), mp 155–157 °C (MeOH) (lit.,[6,7] 111–112 °C); δ_H (200 MHz, $CDCl_3$) 4.53 (3H, s, OCH_3), 7.26 (2H, d, *J* 8.6 Hz, 3′-H and 5′-H), 7.35 (1H, s, 3-H), 7.71 (1H, dt, *J* 1.2 and 7.7 Hz, 6-H), 7.94 (1H, dt, *J* 1.4 and 7.8 Hz, 7-H), 8.27 (2H, d, *J* 8.8 Hz, 2′-H and 6′-H), 8.24 (1H, d, *J* 8.2 Hz, 8-H) and 9.11 (1H, d, *J* 8.4 Hz, 5-H); δ_C (50 MHz, $CDCl_3$) 59.6 (OCH_3), 101.1 (C-3), 119.8 (C-4a), 120.8 (C-6), 122.9 (C-5), 127.7 (C-1′), 128.9 (C-8), 129.5 (C-3′ and C-5′), 131.4 (C-2′ and C-6′), 134.7 (C-7), 139.3 (C-4′), 139.9 (C-8a), 154.8 (C-2) and 168.7 (C-4); *m/z* 269 (M^+, 100), 240 (43.1), 204 (37.8) and 146 (8.7). (Found: M^+ 269.0602. $C_{16}H_{12}NO^{35}Cl$ requires 269.0607).

2-(4′-*Bromophenyl*)-4-*methoxyquinoline* **6d**. Solid (65%), mp 133–135 °C (MeOH); δ_H (200 MHz, $CDCl_3$) 4.49 (3H, s, OCH_3), 7.30 (1H, s, 3-H), 7.66 (2H, d, *J* 8.8 Hz, 2′-H and 6′-H), 7.85 (1H, dt, *J* 1.0 and 7.5 Hz, 6-H), 7.99 (2H, d, *J* 8.8 Hz, 3′-H and 5′-H), 8.08 (1H, dt, *J* 1.5 and 7.8 Hz, 7-H), 8.42 (1H, dt, *J* 1.0 and 8.4 Hz, 8-H) and 8.75 (1H, d, *J* 8.2 Hz, 5-H); δ_C (50 MHz, $CDCl_3$) 58.6 (OCH_3), 100.7 (C-3), 119.4 (C-4a), 120.1 (C-6), 122.9 (C-5), 127.5 (C-1′), 128.4 (C-8), 129.8 (C-4′), 130.3 (C-3′ and C-5′), 132.3 (C-2′ and C-6′), 134.6 (C-7), 138.9 (C-8a), 155.2 (C-2) and 168.6 (C-4); *m/z* 313 (M^+, 1000), 284 (33.8), 204 (44.3), 190 (24.9) and 117 (21.5) (Found: M^+ 313.0094. $C_{16}H_{12}NO^{79}Br$ requires 313.0102).

2-(4′-*Methoxyphenyl*)-4-*methoxyquinoline* **6e**. Solid (90%), mp 163–165 °C (MeOH) (lit.,[5,6] 93–95 °C); δ_H (200 MHz, $CDCl_3$) 3.63 (3H, s, 4′-OCH_3), 4.48 (3H, s, 4-OCH_3), 6.74 (2H, d, *J* 8.8 Hz, 3′-H and 5′-H), 7.30 (1H, s, 3-H), 7.64 (1H, t, *J* 7.5 Hz, 6-H), 7.89 (1H, t, *J* 7.3 Hz, 7-H), 8.16 (1H, d, *J* 8.4 Hz, 8-H), 8.34 (2H, d, *J* 9.0 Hz, 2′-H and 6′-H) and 9.16 (1H, d, *J* 8.6 Hz, 5-H); δ_C (50 MHz, $CDCl_3$) 55.4 (4′-OCH_3), 59.2 (4-OCH_3), 99.9 (C-3), 114.5 (C-3′ and C-5′), 119.4 (C-1′), 121.0 (C-6), 121.5 (C-4a), 122.5 (C-5), 127.8 (C-8), 131.9 (C-2′ and C-6′), 133.9 (C-7), 139.4 (C-8a), 155.6 (C-2), 163.4 (C-4′) and 167.8 (C-4); *m/z* 265 (M^+, 100), 264 (54.3), 236 (31.0), 235 (32.2), 220 (15.5), 191 (14.2), 178 (14.9) and 27 (17.6) (Found: M^+ 265.1097. $C_{17}H_{15}NO_2$ requires 265.1103).

4-*Methoxy*-2-(4′-*nitrophenyl*)*quinoline* **6f**. Solid (60%), mp 151–153 °C (MeOH); δ_H (200 MHz, $CDCl_3$) 4.54 (3H, s, OCH_3), 7.40 (1H, s, 3-H), 7.78 (1H, dt, *J* 1.1 and 7.8 Hz, 6-H), 8.00 (1H, dt, *J* 1.5 and 8.1 Hz, 7-H), 8.21 (2H, d, *J* 8.8 Hz, 2′-H and 6′-H), 8.35 (1H, dd, *J* 1.0 and 8.4 Hz, 8-H), 8.49 (2H, d, *J* 8.8 Hz, 3′-H and 5′-H) and 9.11 (1H, d, *J* 8.6 Hz, 5-H); δ_C (50 MHz, $CDCl_3$) 58.6 (OCH_3), 101.2 (C-3), 119.3 (C-6), 120.5 (C-4a), 122.4 (C-5), 123.4 (C-3′ and C-5′), 128.2 (C-8), 130.1 (C-2′ and C-6′), 134.1 (C-7), 136.6 (C-1′), 139.4 (C-8a), 149.0 (C-4′), 153.6 (C-2) and 168.2 (C-4); *m/z* 280 (M^+, 100), 250 (26.3), 219 (21.7) and 191 (26.5) (Found: M^+ 280.0846. $C_{16}H_{12}N_2O_3$ requires 280.0848).

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