Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Ultrasound-Promoted Synthesis of Quinolone and Isoquinolone Derivatives

Micheline Grignon-Dubois [a] & Alain Meola [a]
[a] Laboratoire de Chimie Organique et Organométallique, Université Bordeaux I, 351, Cours de la Libération, 33405, Talence, Cedex, France
Published online: 16 Feb 2007.

To cite this article: Micheline Grignon-Dubois & Alain Meola (1995) Ultrasound-Promoted Synthesis of Quinolone and Isoquinolone Derivatives, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 25:19, 2999-3006, DOI: 10.1080/00397919508011432

To link to this article: http://dx.doi.org/10.1080/00397919508011432

SYNTHETIC COMMUNICATIONS, 25(19), 2999-3006 (1995)

ULTRASOUND-PROMOTED SYNTHESIS OF QUINOLONE AND ISOQUINOLONE DERIVATIVES

Micheline Grignon-Dubois* and Alain Meola

Laboratoire de Chimie Organique et Organométallique, Université Bordeaux I, 351, Cours de la Libération, 33405 Talence-Cedex, France

Abstract : quinolinium and isoquinolinium salts are easily oxidized by potassium *tert*-butylate in *tert*-butanol under ultrasonic irradiation yielding quinolones and isoquinolones. Compared to the methods previously known, the main advantages of our process are shorter reaction times, easier work-up and good to quantitative yields.

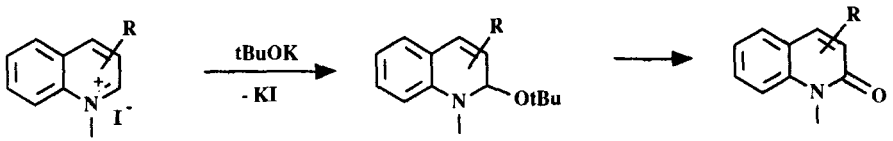
The quinolone and isoquinolone ring systems are the parent substances of many plant alkaloids and drugs.[1] They are generally obtained by oxidation of isoquinolinium and quinolinium iodides or chlorides in basic medium.[2] However, these reactions lead to a pseudobase intermediate, and competition can occur between its oxidation and disproportionation leading to a mixture of the corresponding amide and amine. Rabbit liver aldehyde oxidase has also been used to oxidize alkylquinolinium compounds in moderate yields,[3] but the reaction gave mixture of 4-oxo and 2-oxo compounds.

We report here a new one-step synthesis of isoquinolones and 2-oxoquinolones. We found that under sonication, potassium *tert*-butylate in

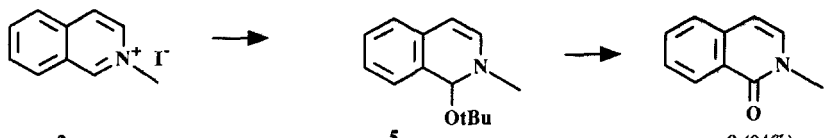
* To whom correspondence should be addressed

tert-butanol can be effectively used for the oxidation of quinolinium and isoqui--nolinium salts to the corresponding quinolones. Since no excess of base is necessary to oxidise all the substrate, hydrolysis of the reaction mixture is not necessary and a simple filtration through celite is generally sufficient to isolate the crude product. The reaction is completed in 15 minutes. This significant rate enhancement agrees well with the efficiency of ultrasound to promote heterogeneous reactions.[4] The behaviour of alkyl iodides **1-3** has been studied (Scheme). The reaction proceeds through the nucleophilic attack of the methiodide leading to **4-6**, which are not systematically observed. Indeed, their oxidation yielding **7-9** is very easy, and the actual product isolated at the end of the reaction depends on structural factors. In the case of **1a**, **1b** and **1d**, oxidation takes place during the sonication and **7a** or **7d** are only detected in the crude product. On the contrary, **6** was isolated and characterized by ^{1}H NMR, but its great oxidability prevented more precise structural study. **2** led to **8** along with **5**, which is oxidized during purification. The 3-bromo methiodide **1c** has intermediate behaviour. Using technical grade solvent only led to **7c** in a 85% yield, but using synthesis grade solvent led mainly to **4c**. The latter is very unstable and often decomposed before or during the NMR analysis. After purification on silica gel, **7c** is only isolated in a 33 % yield along with **7a** (16 %), resulting in the loss of the bromine atom. Oxygen is responsible of the oxidation of the *tert*-butoxy adduct, as demonstrated by experiment conducted under argon atmosphere with **1d**. In this case, **4d** was quantitatively isolated, but rapidly led to **7d** on exposure to air. Dostál et al.[5] has also reported the very easy decomposition of 6-methoxy- and 6-ethoxy-N-methyl-dihydro-5,6--phenanthridine. It led to both phenanthridone and dihydrophenanthridine, but neither proportion nor yields were mentioned.

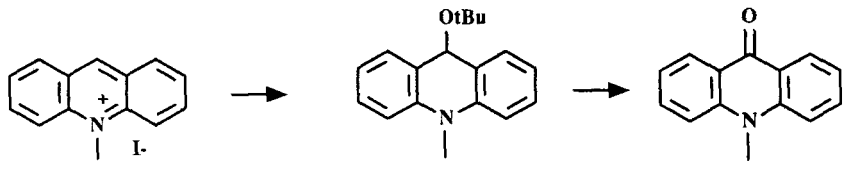
Oxidation of the intermediate *tert*-butoxy adduct took place simply by contact with air, but is better achieved by impregnation of the crude product on



R = H :	1a	4a	7a (98%)
2-Cl	1b	4b	7a (87%)
3-Br	1c	4c	7c (85%)
3,4-benzo	1d	4d	7d (96%)



2 5 8 (94%)



3 6 9 (95%)

silica gel (see experimental section). Compare to **4-5**, the relatively greater stability of **6** obtained from acridinium methiodide is probably due to the addition site, which is remote from the nitrogen atom.

The structure assignments of the final products are based on comparison of the melting points with literature and confirmed by satisfactory elemental analysis as well as physicochemical data (IR, mass and NMR spectrometries). In particular, acridone excepted, all the derivatives displayed an IR absorption in the range 1630-50 cm^{-1} and a ^{13}C NMR quaternary carbon resonance around 158-162 ppm, both typical of the amide moiety.[6] These data clearly show than the oxidation always take place in 2-position as previously observed with

potassium ferricyanide in basic medium[2a] or KOH in *tert*-butanol,[2b] and not in 4-position as reported in the case of quinolinium methosulfate.[2d]

Compared to the methods previously known, the main advantages of our process are shorter reaction times, easier work-up and good to quantitative yields.

Experimental Section

Melting points were determined on a Metler capillary apparatus and are uncorrected. IR spectra were obtained on a Perkin-Elmer 457 spectrophotometer. The NMR spectra were recorded on a Bruker AM 250 spectrometer ($CDCl_3$ solutions, TMS as internal standard) . Mass spectra were measured on an AEI MS 12 spectrometer. Elemental analyses were performed by service central d'analyse du CNRS (F-69390 Vernaison).

Flash column chromatography techniques (30 cm x 2 cm column) were employed to purify crude mixture using 230-400 mesh silica gel under positive air pressure. Ultrasound promoted reactions were carried out in a common ultrasonic laboratory cleaner (Brandsonic 321) filled with thermostated water at ambient temperature (15-20°C). The reaction flask was partially submerged in the sonicator water bath in a place that produced maximum agitation.

Materials. Reagent grade chemicals were used as received. Methiodides were prepared according to literature procedures[7] by alkylation of the appropriate quinoline with methyl iodide in acetone (**1a-c, 2**) or methylene chloride solution (**1d**, **3**). The mixture was maintained at room temperature until the substrate had completely reacted, as monitored by TLC (SiO_2; Et_2O/CH_2Cl_2, 30:70 v/v). The precipitated salts were filtered and recrystallized. All data for these compounds are identical to literature data.[7,8b]

Typical procedure - To a sonicated suspension of methiodide (22 mmol) in *tert*-butanol (30 ml), 3 g of potassium *tert*-butylate (27 mmol) was added within 5 minutes. The bright solution coloration immediately disappeared and a white

solid (KI) precipitate. The reaction was complete within 15 minutes as monitored by TLC (SiO_2; CH_2Cl_2/Et_2O, 50:50 v/v). The reaction mixture was filtered through celite and the *tert*-butanol solution was evaporated to dryness. In the cases of **1a**, **1b** and **1d**, the oxo-derivatives **7a** and **7d** were only detected (^1H NMR, TLC) in the crude product. They were purified by liquid chromatography (SiO_2, CH_2Cl_2) or crystallization. In all the other cases, the crude product was mainly constituted of the *tert*-butoxy adduct, or a mixture of *tert*-butoxy and quinolone. It was oxidized by treatment on silica gel (see below). During NMR analysis in $CDCl_3$ or C_6D_6 solution, decomposition of the *tert*-butoxy adduct occurred, and it was impossible to record their ^{13}C spectra.

Quinolone by oxidation of the *tert*-butoxy product: typical procedure. A chloroform solution of the *tert*-butoxy adduct (1g in 10 ml) was adsorbed on silica gel (1g, 70-230 mesh) then the solvent was removed by evaporation. The mixture was kept under an air atmosphere and allowed to stand at room temperature overnight. The organic material was extracted from the silica by adding 15 ml of methylene chloride and stirring the reaction mixture for 15 min. Silica gel was removed by filtration and the organic layer was evaporated to dryness yielding quantitatively the corresponding quinolone, which was analytically pure.

1,2-dihydro-2-*tert*-butoxy-3-bromo-1-methylquinoline (4c)

IR 1600 (s), 1500 (s), 1210 (s), 1055 (s), 1040 (s) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.3 (s, 9 H, tBu), 3.1 (s, 3 H, N-Me), 5.6 (s, 1 H, H-2), 7.0 (s, 1 H, H-4), 6.6-7.2 (m, 5 H, arom.).

5,6-dihydro-6-*tert*-butoxy-5-methylphenanthridine (4d)

^1H NMR (90 MHz, $CDCl_3$) δ 1.3 (s, 9 H, tBu), 3.2 (s, 3 H, N-Me), 5.5 (s, 1 H, H-6), 6.8-7.9 (m, 8 H, arom.).

9,10-dihydro-9-*tert*-butoxy-10-methylacridine (6)

m.p. 160°C; IR 1600 (vs), 1100 (s) cm^{-1}; ^1H NMR (90 MHz, C_3D_6O) δ 1.2 (s, 9 H, tBu), 3.3 (s, 3 H, N-Me), 5.3 (s, 1 H, H-9), 6.7-7.2 (m, 4 H, arom.)

1,2-dihydro-1-methylquinol-2-one (7a)

98 % yield from **1a** and 87% yield from **1b**; m.p. 73°C (C_6H_{12}), Lit[8b] 74°C; ^1H NMR (250 MHz, $CDCl_3$) δ 3.4 (s, 3 H, N-Me), 6.5 (d, 1 H, 9.4 Hz), 7.0 (dt, 1 H, 1.0, 7.4 Hz), 7.1 (d, 1 H, 8.4 Hz), 7.3 (m, 2 H), 7.4 (d, 1 H, 9.4 Hz); ^{13}C NMR (62.86 MHz, $CDCl_3$) CH_3 29.2, 6 CH 114.0, 121.4, 121.9, 128.6, 130.5, 138.8, 3 C 120.4, 139.8, 162.0; SM (m/e %) 160 (12.0), 159 (100).

Anal calc. for $C_{10}H_9NO$ C 75.45 , H 5.70 , N 8.80. Found C 75.65 , H 5.75 , N 8.71.

1,2-dihydro-3-bromo-1-methylquinol-2-one (7c)

85 % yield; m.p. 144°C (EtOH), Lit[8c] 146-7°C; IR 1645 (vs), 1600 (vs), 1500 (vs), 1210 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.7 (s, 3 H, N-Me), 7.17 (dt, 1 H, 0.8, 7.4 Hz), 7.25 (d, 1 H, 7.8 Hz), 7.4 (dd, 1 H, 1.3, 7.8 Hz), 7.52 (dt, 1 H, 1.3, 7.4 Hz), 8.0 (s, 1 H); ^{13}C NMR (62.86 MHz, $CDCl_3$) CH_3 30.9, 5 CH 114.2, 122.6, 127.7, 130.8, 140.4, 4 C 117.3, 120.2, 139.0, 158.2; SM (m/e %) : 240 (11.2), 239 (96.7), 238 (16.7), 237 (100).

Anal calc. for $C_{10}H_8BrNO$ C 50.45; H 3.39, N 5.88. Found C 50.36; H 3.42, N 5.63.

5-methyl-6-phenanthridone (7d)

96 % yield; m.p. 108°C (EtOH), Lit. [8d] 108°C; ^1H NMR (250 MHz, $CDCl_3$) δ 3.7 (s, 3 H, N-Me), 7.18 (dt, 1 H, 8.1, 1.0 Hz), 7.21 (dd, 1 H, 8.1, 1.0), 7.42 (dt, 1 H, 7.8, 1.4 Hz), 7.49 (dt, 1 H, 7.7, 1.0), 7.63 (dt, 1 H, 7.6, 1.4 Hz), 8.08 (d, 2 H, 8.1 Hz), 8.46 (dd, 1 H, 8.0, 1.4 Hz); ^{13}C NMR (62.86 MHz, $CDCl_3$) CH_3 29.9, 8 CH 114.9, 121.5, 122.3, 123.1, 127.8, 128.7, 129.4, 132.3, 5 C 119.1, 125.4, 133.4, 137.8, 161.5; SM (m/e %) : 210 (15.5), 209 (100).

Anal calc. for $C_{14}H_{11}NO$ C 80.36 , H 5.30 , N 6.69. Found C 80.52 , H 5.09 , N 6.63.

2-methyl-isoquinolone (8)

94 % yield; m.p. 40 ° (C_6H_{12}), Lit.[8b] 40 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 3.3 (s, 3 H, N-Me), 6.2 (d, 1 H, 7.3 Hz), 6.8 (d, 1 H, 7.3 Hz), 7.18 (t, 1 H, 7.3 Hz), 7.23

(d, 1 H, 7.3 Hz), 7.34 (dd, 1 H, 7.3, 8.0 Hz), 8.15 (d, 1 H, 8.0 Hz); ^{13}C NMR (62.86 MHz, $CDCl_3$) CH_3 36.5, 6 CH 105.4, 125.6, 126.3, 126.9, 131.6, 132.2, 3 C 125.5, 136.7, 162.0; SM (m/e %) : 160 (14), 159 (100).

Anal calc. for $C_{10}H_9NO$ C 75.45 , H 5.70 , N 8.80. Found C 75.69 , H 5.75 , N 8.69.

10-methyl-9-acridone (9)

95 % yield; m.p. 202°C (EtOH), Lit.[8b] 203 °C; ^1H NMR (250 MHz, $CDCl_3$) 3.82 (s, 3 H, N-Me),7.26 (m, 2H), 7.46 (d, 2 H, 7.7 Hz), 7.70 (m, 1 H), 8.53 (dd, 2 H, 8.0, 1.5 Hz); ^{13}C NMR (62.86 MHz, $CDCl_3$) CH_3 33.7, 4 CH 114.9, 121.3, 127.7, 133.9, 3 C 122.3, 142.3, 177.9; SM (m/e %) : 210 (16.0), 209 (100).

Anal calc. for $C_{14}H_{11}NO$ C 80.36 , H 5.30 , N 6.69. Found C 80.29 , H 5.22, N 6.58.

References

1. see for example : (a) Pelletier, S.W. "Chemistry of the Alkaloids", Van Nostrand Reinhold Co., New-York, 1970, p77. (b) Shamma, M.; Moniot, J.L. "Isoquinoline Alkaloid Research", Plenum Press, New-York, 1978, p57. (c) Dyke, S.F. *Tetrahedron*, **1971**, *27*, 281. (d) Brown, D.W.; Dyke, S.F. *Tetrahedron*, **1966**, *22*, 2429. (e) Iida, H.; Kawano, K.; Kihuchi, T.; Yoshimizu, F. *Yakugaku Zasshi*, **1976**, *96*, 176; Chem. Abstr., **1976**, *84*, 135898.(f) Sulkowski, T.S.; Wille, M.A. U.S. Patent 3 452 027 (1969); Chem. Abstr., **1969**, *71*, 112830. (g) Coyne, W.E.; Cusic, J.W. U.S. Patent 3 600 394; Chem. Abstr., **1971**, *75*, 118241f. (h) Kusner, E.J.; Buckner, K.C.; Dea, D.M.; DeHaas, C.J.; Marks, R.L.; Krell, R.D. *Eur. J. Pharmacol.*, **1994**, *257*, 285.

2. (a) Decker, H. *J. Pract. Chem.*, **1893**, *47*, 28. (b) Ruchirawat, S., Sunkul, S., Thebtaranonth, Y., Thirasasna, N. *Tetrahedron Lett.*, **1977**, *27*, 2335. (c) Ruchirawat, S.; Borvornvinyanant, U.; Hantawong, K.; Thebtaranonth, Y.

Heterocycles, **1977**, *6* (8), 1119. (d) Suzuki, N., Kazui, Y., Tsukamoto, T., Kato, M., Izawa, Y. *Bull. Chem. Soc. Jpn.*, **1983**, *56*, 1519.

3. Angelino, S.A.G.F., van Valkengoed, B.H., Buurman, D.J., van der Plas, H.C., Müller, F.J. *Heterocyclic. Chem.*, **1984**, *21*, 107.

4. for reviews, see:

(a) Boudjouk, P. *J. Chem. Educ.*, **1986**, *63*, 427. (b) Suslick, K.S. "Modern Synthetic Methods", Springer-Verlag: New-York, **1986**, Vol 4, p 1. (c) Luche, J-L. *Ultrasonics*, **1987**, *25*, 40. (d) Goldberg, Y; Sturkovich, R; Lukevics, E. *Heterocycles,* **1989**, *29*, 597.

5. Dostál, J.; Potáček, M; Nechvátal, M. *Collect. Czech. Chem. Commun.*, **1993**, *58*, 395.

6. (a) Osborne, A.G.; Buley, J.M.; Clarke, H.; Dakin, R.C.H.; Price, P.I. *J. Chem. Soc. Perkin Trans. I*, **1993**, 2747. (b) Duddeck, H; Kaiser, M. *Spectrochim. Acta*, **1985**, *41A*, 913. (c) Spassov, S.L.; Atanassova, I.A.; Haimova, M.A. *Org. Magn. Reson.*, **1984**, *22 (3)*, 194. (d) Coppola, G.M.; Kahle, A.D.; Shapiro, M.J. *Org. Magn. Reson.*, **1981**, *17 (4)*, 242. (e) Brown, N.M.D.; Grundon, M.F.; Harrison, D.M.; Surgenor, S.A. *Tetrahedron,* **1980**, *36*, 3579.

7. (a) Doebner, O. *Ber.*, **1883**, *16*, 2464. (b) Marchwald, W; Meijer, E. *Ber.*, **1884**, *33*, 1990. (c) Gurevitch, A.I.; Sheinker, Yu.N. *Zhur. Fiz. Chim.*, **1959**, *33*, 883; Chem. Abstr., **1960**, *54*, 8285b. (d) Zanker, V.; Cnobloch, H. *Z. Naturforsch., B Chem. Sci.*, **1962**, *17*, 819. (e) Duffin, C.F. *Advances in Heterocyclic Chemistry,* **1964**, *3*, 1.

8. (a) Späth, E; Galinoosky, F. *Ber.*, **1936**, *69*, 2059. (b) Pollock, J.R.; Stevens, R. "Dictionary of Organic Compounds", 4th ed., London 1965. (c) La Coste, W. *Ber.*, **1882**, *15*, 186. (d) *Beilstein 21*, 339.

(Received in The Netherlands 16 February 1995)