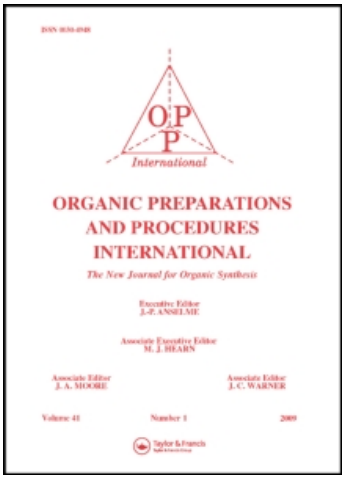
This article was downloaded by:
On: *26 January 2011*
Access details: *Access Details: Free Access*
Publisher *Taylor & Francis*
Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

A Simple Synthesis of 8-Methoxy-1-tetralone

Elvia V. Cabrera[a]; Ajoy K. Banerjee[a]
[a] Department of Chemistry, Faculty of Sciences, University of Zulia, Maracaibo, Venezuela

Online publication date: 01 October 2010

To cite this Article Cabrera, Elvia V. and Banerjee, Ajoy K.(2010) 'A Simple Synthesis of 8-Methoxy-1-tetralone', Organic Preparations and Procedures International, 42: 5, 499 — 502
To link to this Article: DOI: 10.1080/00304948.2010.514837
URL: http://dx.doi.org/10.1080/00304948.2010.514837

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: http://www.informaworld.com/terms-and-conditions-of-access.pdf

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

Organic Preparations and Procedures International, 42:499–502, 2010
Copyright © Taylor & Francis Group, LLC
ISSN: 0030-4948 print
DOI: 10.1080/00304948.2010.514837

Downloaded At: 17:26 26 January 2011

OPPI BRIEFS

A Simple Synthesis of 8-Methoxy-1-tetralone

Elvia V. Cabrera[1] and Ajoy K. Banerjee[1]

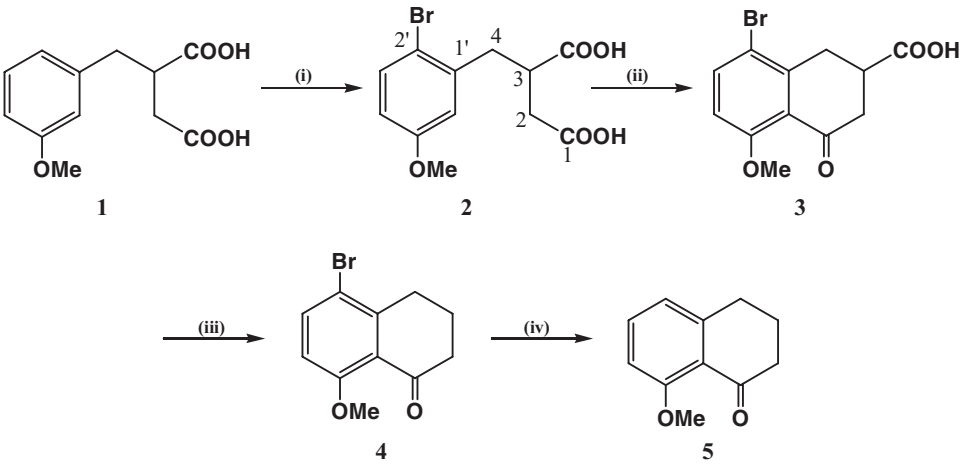
[1]Department of Chemistry, Faculty of Sciences, University of Zulia, Maracaibo, Venezuela
[2]Chemistry Center, Venezuelan Institute of Scientific Research (IVIC), Caracas, Venezuela

Substituted 1-tetralones play an important role in the synthesis of natural and non-natural products.[1] 8-Methoxy-1-tetralone **5** unlike 5-, 6-, and 7-methoxy-1 tetralones is not commercially available. It has recently been utilized for the synthesis[2] of ARQ-501, a metabolite of human blood. In addition, tetralone **5** has been used in the synthesis of compounds for the study of dopamine (DA) and serotonin (5-HT) receptors.[3] To the best of our knowledge, only four syntheses[4–7] of **5** have been reported. In addition to the route described in references 4 and 5, the other two routes[6,7] afford very poor yield of the tetralone **5**. The synthetic approach[5] which reports a good yield of tetralone **5** consists in the methylation of the 8-hydroxy-1-tetralone which was prepared[8] by the catalytic hydrogenation of the commercially available naphthalene 1,8-diol. We have developed a facile synthesis of tetralone **5** (*Scheme 1*) which is described in the present communication.

The previously reported[9] acid **1** on bromination with bromine and acetic acid led to the formation of the bromoacid **2** in 93% yield. The bromoacid was subjected to cyclization with conc. sulfuric acid. The resulting ketone **3**, obtained in 57% yield, underwent decarboxylation[10] on heating with a mixture of sodium persulfate and silver nitrate in acetonitrile affording the bromotetralone **4** in 77% yield. The conversion of the bromotetralone into 8-methoxy-1-tetralone (**5**) in 97% yield was accomplished by catalytic hydrogenation over Pd/C (5%) in absolute methanol. The spectroscopic data (IR, ^{1}H NMR, MS and ^{13}C NMR) of **5** were consistent with the structure assigned. The overall yield from **1** was 40%.

In conclusion, a convenient approach for the synthesis of 8-methoxy-1-tetralone has been developed. The starting material **1** can easily be prepared[9] in large quantity from the commercially available *m*-methoxybenzaldehyde. All the intermediates were obtained in satisfactory yield and properly characterized. The published route[4] describes a synthesis of the tetralone **5** in 41% yield from 2-methoxy-6-methylbenzoic acid *via* a clever use of tandem Michael-Dieckmann condensation and this is a noteworthy aspect of the synthesis

Received May 18, 2010.
Address correspondence to Ajoy K. Banerjee, Centro de Química, IVIC, Apartado 21827, Caracas-1020 A, Venezuela. E-mail: abanerje@ivic.gob.ve; aabanerje@gmail.com



1 2 3 4 5

Reagents: (i) Br_2, MeCOOH; (ii) conc. H_2SO_4; (iii) $Na_2S_2O_8$, $AgNO_3$, MeOH; (iv) H_2, Pd/C (5%)

Scheme 1

Downloaded At: 17:26 26 January 2011

but the procedure has the following drawbacks: (a) the synthesis of the starting material involves six steps; (b) the Michael acceptor methyl acrylate has a tendency to polymerize and thus should be purified before use; (c) the work-up process is not at all easy; (d) none of the intermediate products were characterized.

Experimental Section

Unless otherwise stated, all melting points are uncorrected and were determined on a Electrothermal melting point apparatus. Infrared (IR) spectra were taken on a Nicolet-Fourier transform (FT) instrument and NMR spectra were obtained on a Bruker AM-300 spectrometer in $CDCl_3$. Chemical shifts (δ) are expressed in ppm. Mass spectra (MS) were determined on a Dupont 21-492B instrument. Column chromatography was carried out on silica gel 60 (Merck). The expression work-up indicates that the solution was diluted with water, extracted with ether or chloroform, washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. Thin layer chromatography (TLC) plates were coated with silica gel and the spots were located by exposure to ultraviolet (UV) light. Elemental analyses were performed on a Carlo-Erba 1108 elemental analyzer.

2-(2-Bromo-5-methoxybenzyl)succinic Acid (2)

To a solution of acid **1** (13.01 g, 54.6 mmol) in glacial acetic acid (60 mL), cooled at 0°–5°C, was added dropwise bromine (2.8 mL, 54.2 mmol), stirred for 5 min at this temperature and then for 20 h at room temperature. To the resulting brown solution was added a solution of the sodium bisulfite (5%) till the brown color disappeared and then extracted with chloroform. The organic extract was washed with water, a solution of $NaHCO_3$ (5%), dried and evaporated to yield bromoacid **2** (14.47 g, 93%) as white solid, mp. 135–136°C (from ethyl acetate-hexane); IR (cm^{-1}): 3112, 1710, 1480, 1243; MS (m/z): 299 (M^+ -H_2O), 219 (M^+ -H_2O -Br); ^1H NMR (MeOD): δ 2.37–2.44 (m,1H), 2.58–2.67 (m,1H), (2H at

C-2), 2.89–2.92 (m, 1H), 3.06–3.12 (2H at C-4), 3.15–3.18 (m, 1H) (H at C3), 3.76 (s, 3H, OMe), 6.75 (dd, 1H, J = 8 Hz, J = 3 Hz) (H at C-4′), 6.85 (d, 1H, J = 3 Hz) (H at C-6′), 7.45 (d, 1H, J = 8 Hz) (H at C-3′); ^{13}C NMR (MeOD) δ: 176.18 (C-1), 173.84 (COOH), 159.10 (C-5′), 138.84 (C-1′), 133.13 (C-3′), 116.51 (C-6′), 114.35 (C-2′), 113.93 (C-4′), 54.42 (OMe), 41.32 (C-3), 37.39 (C-2), 34.6 (C-4) .

Anal. Calcd for $C_{12}H_{13}BrO_5$: C, 45.42; H, 4.11. Found : C, 45.65; H, 3.99

3-Carboxy-5-bromo-8-methoxy-1-tetralone (3)

A solution of acid **2** (5 g, 15.8 mmol) in sulfuric acid (50 mL) was stirred for 8 hr at room temperature and then slowly poured on ice. The precipitated solid was collected, washed with water and dried to afford ketone **3** (2.72 g, 57%) as a white solid, mp.189–190°C (from ethanol) which develops a color upon standing at room temperature for a week; IR (cm^{-1}): 3440, 2925, 1728, 1683, 1589, 1466; MS 299 (M^+); 220 (M^{+1} –Br); ^{1}H NMR (acetone-d_6): δ 2.72–2.78 (m, 2H) (H at C-2), 3.11–3.39 (m, 3H) (H at C-4, C-3), 3.81 (s, 3H, OMe), 7.01 (d, 1H, J = 9 Hz) (H at C-7), 7.74 (d, 1H, J = .9 Hz) (H at C-6); ^{13}C NMR (acetone-d_6): δ 192.62 (C-1), 173.54 (C-11), 159.70 (C-8), 142.48 (C-10), 137.46 (C-6), 123.52 (C-9), 114.03 (C-5), 112.60 (C-7), 55.46 (C-12), 41.42 (C-3), 38.22 (C-4), 32.97 (C-2).

Anal. Calcd for $C_{12}H_{11}BrO_4$: C, 48.16; H, 3.67. Found: C, 47.88; H, 3.85

5-Bromo-8-methoxy-1-tetralone (4)

To the ketone **3** (2 g, 6.7 mmol) dissolved in a mixture of acetone-water (77:26 mL) was added silver nitrate (20 mg, 0.128 mmol) and heated under reflux for 5 min. To the resulting deep yellow solution a solution of sodium persulfate (3.18 g, 13.4 mmol) in water (20 mL) was added, heated under reflux for 20 min. and then extracted with ether. The organic extract was washed, dried and evaporated to afford a oil which on chromatographic purification (eluent hexane:ether 8:2) afforded the bromotetralone **4** (1.31 g,77%) as a colorless oil whose color changes to pale yellow upon standing at room temperature, IR(cm^{-1}): 2933, 1712, 1585,1284; MS (m/z): 255 (M^+), 241(M^{+1} -Me); ^{1}H NMR: δ 2.05–2.37 (m, 2H) (H at C-3), 2.53–2.74 (m, 2H) (H at C-2), 3.21–3.33 (m, 2H) (H at C-4), 3.91 (s, 3H, OMe), 6.72 (d, 1H, J = 8 Hz) (H at C-7), 7.64 (d, 1H, J = 8 Hz) (H at C-6); ^{13}C NMR: δ 206.46 (C-1), 157.43 (C-8), 155.03 (C-10), 138.60 (C-6), 126.14 (C-9), 111.70 (C-5), 111.21 (C-7), 55.99 (C-11), 42.08 (C-2), 35.35 (C-4), 16.55 (C-3) .

Anal. Calcd for $C_{11}H_{11}BrO_2$: C, 51.76; H, 4.31. Found: C, 52.03; H, 4.13

8-Methoxy-1-tetralone (5)

A solution of the bromotetralone **4** (1 g, 3.9 mmol) in absolute ethanol (10 mL) was hydrogenated in presence of Pd-C (10%) at room temperature for 24 hr and atmospheric pressure. Removal of the catalyst and solvent left an oil which on distillation afforded the tetralone **5** as a colorless oil (670 mg, 97%) (bp. 141–142°C/0.10 mmHg) (*lit.*[5] bp. 140°C/0.9 mmHg) which develops a faint yellow color on standing at room temperature for a week; IR (cm^{-1}): 1674 (CO); MS (m/z): 176 (M^+); ^{1}H NMR: δ 2.01–2.07 (m, 2H) (H at C-3), 2.61 (t, 2H, J = 6 Hz) (H at C-4), 2.89 (t, 2H, J = 6 Hz) (H at C-2), 3.87 (s, 3H, OMe), 6.78 (d, 1H, J = 8.5 Hz) (H at C-5), 6.82 (d, 1H, J = 8 Hz) (H at C-7), 7.38 (dd, 1H, J = 8

Downloaded At: 17:26 26 January 2011

Hz, J = 7.9 Hz) (H at C-6); ^{13}C NMR: δ 197.55 (C-1), 160.34 (C-8), 147.11(C-10),133.87 (C-6), 122.21 (C-9), 120.67 (C-5), 109.89 (C-7), 55.92 (C-11), 40.89 (C-2), 30.78 (C-4), 22.80 (C-3) .

Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.97; H, 6.86. Found: C, 74.73; H, 7.01

References

1. Po. S. Poon, A. K. Banerjee, W. J. Vera, H. D. Mora, M. S. Laya, L. Bedoya, E. V. Cabrera and C. E. Melean, *J. Chem. Res.*, 181 (**2008**).
2. R.Yang, D. Kitzer, H. Wu, E. Volckova, X. Miao, S. Ali, M. Tandon, R. Savage, T. Chan and M. Ashwell, *Bioorg. Med. Chem.*, **16**, 5635 (2008).
3. S. Lee, S. Frescas and D. Nichols, *Synth. Commun.*, **25**, 2775 (1995).
4. B. Tarchompoo, C. Thebtaranonth and Y. Thebtaranonth, *Synthesis*, 785 (**1986**).
5. C. Bilger, P. Demerseman and R. Royer, *Euro. J. Med. Chem.*, **22**, 363 (1987).
6. M. Date, M. Watnabe and S. Furukawa, *Chem. Pharm. Bull.*, **38**, 902 (1990).
7. P. Kumar, *Org. Prep. Proced. Int.*, **29**, 477 (1997).
8. I. A. Kaye, R. S. Matthews and A. A. Scala, *J. Chem. Soc.*, 2816 (**1964**).
9. T. Yanagi, K. Kikuchi, H. Takeuchi, T. Ishikawa, T. Nishimura, T. Kamijo, I. Yamamoto, *Chem. Pharm. Bull.*, **49**, 340 (2001).
10. W. Fristad, M. Fry and F. Klang, *J. Org. Chem.*, **48**, 3575 (1983).

Downloaded At: 17:26 26 January 2011