This article was downloaded by: [Purdue University] On: 15 March 2013, At: 06:43 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



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

Novel Transformation of Methoxy Tetralones During Demethylation with Boron Trifluoride Etherate and Acetic Anhydride

Ajoy K. Banerjee^a, Liadis Bedoya^a, William J. Vera^a, Carlos Melean^a, Henry Mora^a, Manuel S. Laya^a & Miguel Alonso^b

^a Centro de Química, IVIC, Apartado 21827, Caracas, 1020-A, Venezuela

^b Química Ecológica, Universidad de Los Andes, Departamento de Química, Facultad de Ciencias, Mérida, Venezuela Version of record first published: 10 Jan 2011.

To cite this article: Ajoy K. Banerjee , Liadis Bedoya , William J. Vera , Carlos Melean , Henry Mora , Manuel S. Laya & Miguel Alonso (2004): Novel Transformation of Methoxy Tetralones During Demethylation with Boron Trifluoride Etherate and Acetic Anhydride, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 34:18, 3399-3408

To link to this article: http://dx.doi.org/10.1081/SCC-200030639

Full terms and conditions of use: <u>http://www.tandfonline.com/page/terms-and-conditions</u>

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, 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.

Novel Transformation of Methoxy Tetralones During Demethylation with Boron Trifluoride Etherate and Acetic Anhydride

Ajoy K. Banerjee,^{1,*} Liadis Bedoya,¹ William J. Vera,¹ Carlos Melean,¹ Henry Mora,¹ Manuel S. Laya,¹ and Miguel Alonso²

¹Centro de Química, IVIC, Caracas, Venezuela ²Química Ecológica, Universidad de Los Andes, Departamento de Química, Facultad de Ciencias, Mérida, Venezuela

ABSTRACT

Tetralones 3 and 9 on treatment with a mixture of boron trifluoride etherate and acetic anhydride underwent molecular transformations yielding the fully aromatized products 6 and 10, respectively, Oxidation of dimethoxy tetralin 13 with chromic acid and acetic acid afforded 6-methoxy- α -tetralone 12.

Key Words: Demethylation; Aromatization; Boron trifluoride etherate; Acetic anhydride; Chromic acid; Acetic acid; Water; Transformations.

3399

DOI: 10.1081/SCC-200030639 Copyright © 2004 by Marcel Dekker, Inc. 0039-7911 (Print); 1532-2432 (Online) www.dekker.com

Request Permissions / Order Reprints powered by **RIGHTSLINK**

^{*}Correspondence: Ajoy K. Banerjee, Centro de Química, IVIC, Apartado 21827, Caracas 1020-A, Venezuela; E-mail: abanerje@ivic.ve.

INTRODUCTION

The use of boron trifluoride etherate and acetic anhydride^[1] to cleave different types of steroidal methyl ethers to the corresponding acetates in high yield encouraged us to synthesize dimethoxy tetralones **3** and achieve its transformation to acetoxy tetralone **4**, which can easily be converted by standard organic reactions to 8-methoxy-2-tetralone^[2] **5**. (Sch. 1). This is an important starting material in the syntheses of compounds for the study of dopamine (DA) and serotonin (5-HT) receptors. Tetralone **3**, prepared from the 5-methoxy- α -tetralone **1**, underwent an unexpected transformation upon treatment with boron trifluoride etherate and acetic anhydride. This observation prompted us to synthesize dimethoxy tetralones **9** and **14** and examine their reactions with the same reagent. The present paper documents the results of our investigation.

RESULTS AND DISCUSSIONS

Reduction of commercially available 5-methoxy- α -tetralone 1 (Sch. 1) with sodium borohydride yielded an alcohol that was methylated by using sodium hydride and methyl iodide to obtain dimethoxy tetralin 2. This, on oxidation with chromic acid, acetic acid, and water, afforded tetralone 3 in 35% yield. Unfortunately, attempted oxidation of tetralin 2 under a variety of conditions (changing the amount of chromic acid and acetic acid, time period) failed to improve the yield of tetralone 3. It appears that the



Scheme 1.

Novel Transformation of Methoxy Tetralones During Demethylation 3401

methoxy group at aromatic ring partially inhibited the process of oxidation. The latter event supports this assumption.

Tetralone **3** upon treatment with boron trifluoride and acetic anhydride at room temperature underwent rearrangement to afford a solid compound (50%) whose spectroscopic properties indicated a structure far removed from the desired product **4**. Absorption at 1750 and 1650 cm⁻¹ in the infrared (IR) spectrum indicated the presence of ester and carbonyl group. Its mass spectrum displayed parent peak at m/z 258 (M⁺). The ¹H NMR spectrum showed signals at δ 2.35 (s, OAc), 2.67 (s, COMe), 3.97 (s, OMe), and 8.82–6.80 ppm (5H, aromatic protons). These spectral data led us to assume the formation of product **6** during the demethylation of tetralone **3**. The presence of COMe group was revealed in the ¹³C NMR spectrum by a resonance at δ 170.10 ppm. The rearrangement from **3** to **6** is a mechanistically novel process, a step-wise description of which is described in Sch. 2.



Scheme 2.

Tetralone **3** forms the carbocation (i) by the elimination of OMe group, which produces intermediate (iii) by boron trifluoride etherate. This reacts with acetic anhydride to form the ketone (iv) that leads the formation of compound **6**.

By addition of compound 6, dimethoxy tetralone 3 (12%) whose identity was confirmed by comparing its spectral data with an authentic specimen already prepared was recovered.

The demethylation study was then attempted on dimethoxy- α -tetralone **9**, prepared from the commercially available 7-methoxy- α -tetralone **7** by a procedure similar to that described in Sch. 1. Demethylation of **9** with the same reagent afforded a crystalline material (60%) that was homogeneous on thin layer chromotography (TLC) in several systems. It had molecular ion m/z 216 (M⁺) and 173 (M⁺-COMe) in mass spectrum and exhibited absorption 1745 (CO) cm⁻¹ in the IR spectrum. The singlet signals at δ 3.95 (3H) and 2.62 (3H) indicated the presence of methoxy and acetate group. The signals at δ 7.74 (d, J = 9 Hz), 7.61 (d, J = 8 Hz), (1H), 7.39 (t, J = 7 Hz), (1H), 7.16–7.07 (m, 3H), and 7.08 (s, 1H) ppm were assignable to six aromatic protons. These spectroscopic data led us to assign the structure **10** for the solid compound obtained during the demethylation of tetralone **9**. The formation of **10** may be rationalized by the reaction path, as depicted in Sch. 3.



Scheme 3.

Novel Transformation of Methoxy Tetralones During Demethylation 3403

The formation of intermediate (ii) from **9** can be explained by the mechanism already described in Sch. 2. The intermediate (ii) with acetic anhydride produces compound **10**.

With addition of compound **10**, a small amount of oily material was also obtained, which contained a mixture of products (by TLC). It had a molecular ion m/z 258 (M⁺) and exhibited in IR spectrum absorption at 1738 and 1680 cm⁻¹ (carbonyl). These data led us to believe the presence of product **11** in the reaction mixture. However, no attempt was made to isolate and characterize compound **11** owing to the small amount of material contaminated with other products.

The above findings led us to examine the demethylation of tetralone 14, which was expected to be obtained easily from 6-methoxy- α -tetralone 12 by the process already described. Metal hydride reduction of tetralone 12 followed by methylation yielded compound 13. An interesting transformation occurred when oxidation of 13 was attempted with chromic acid and acetic acid. Instead of expected tetralone 14, 6-methoxy- α -tetralone 12 was obtained in high yield, whose identity was confirmed by comparison of M.P., mixed, M.P., NMR, IR, and mass spectral properties as well as TLC mobility with an authentic specimen (Aldrich) of 6-methoxy- α -tetralone. A probable interpretation of this unexpected transformation is shown in Sch. 4. It is likely that the effect of resonance facilitates the formation of diene intermediate (ii), which is converted to intermediate (iv) by nucleophilic attack of water to the intermediate (iii). This undergoes further oxidation to yield tetralone 12.



Scheme 4.

Tetralins 2 and 8 do not experience a similar type of transformation during oxidation because of the absence of such resonance effect.

In conclusion, we have described interesting transformations of methoxy tetralones during demethylation with boron trifluoride etherate and acetic anhydride. The chemical literature reveals that many organic compounds undergo molecular transformations^[3-5] with boron trifluoride etherate. To the best of our knowledge, the boron trifluoride-acetic anhydride mediated transformations during demethylation have not been reported. A novel transformation of methoxy tetralin **13** during oxidation has been reported. It can also be observed that the yield of tetralone **9** was more satisfactory than tetralone **3**. This observation indicates that the absence of 8-methoxy group in tetralin **8** facilitates in oxidation reaction, whereas its presence causes partial hindrance in oxidative attack.

EXPERIMENTAL

Unless otherwise stated, IR spectra were taken on Nicolet FT instrument. ¹H NMR spectra were recorded on Brucker AM 300 Hz in CDCl₃. Mass spectra were run on gas chromatography Hewlett Packard 5890 Quadrupolar 5972 Serie S. The expression workup indicates that the solution is diluted with water, extracted with ether, washed with brine, dried (MgSO₄), and evaporated under reduced pressure. Column chromatography was performed on silica gel (Merck grade 60, 70–230 mesh). The spectral and analytical data of all new compounds have been reported in the Experimental Section. Microanalyses were carried out at the Chemistry Department, IVIC, Caracas.

1,5-Dimethoxy Tetralin 2

A mixture of tetralone **1** (1.25 g, 0.006 mol) and sodium borohydride (645 mg, 0.011 mol) in ethanol (100 mL) was stirred at 0°C for 1 hr. The mixture was diluted with aqueous ammonium chloride (25 mL) and extracted with ether. The organic extract was washed, dried, and evaporated to give an alcohol (1.24 g), v_{max} 3262 cm⁻¹ (OH) that, being completely free from tetralone (by TLC), was used for the methylation.

A solution of alcohol (1.24 g) in tetrahydrofuran (25 mL) was added dropwise to a suspension of sodium hydride (50% mineral oil, 1.92 g, 0.08 mol) in tetrahydrofuran (20 mL) under nitrogen. The mixture was warmed for 10 min, followed by the addition of methyl iodide (14 mL) and then heated under reflux for 6 hr. The usual workup afforded a viscous oil that, on chromatographic purification (eluant hexane : ether, 9:1), afforded the oily tetralin **2**

Novel Transformation of Methoxy Tetralones During Demethylation 3405

(1.18 g, 87%); m/z 192 (M⁺) and 160 (M⁺-MeOH); δ 7.14 (m, 1H), 6.96 (d, J = 8 Hz, 1H), 6.96 (d, J = 8 Hz, 1H) (aromatic protons), 4.28 (m, 1H), 3.79 (s, 3H, OMe), 3.47 (s, 3H, OMe), 1.72–2.53 (m, 6H, methylene protons) (Found: C, 75.23; H, 8.57. C₁₂H₁₆O₂ requires C, 74.97; H, 8.39%).

4,8-Dimethoxy-α-tetralone 3

To a solution of tetralin **2** (500 mg, 0.002 mol) in acetic acid (5 mL), cooled to 0°C, was added a solution of chromic acid (1 g, 0.01 mol) in water (1 mL) and acetic acid (10 mL). The reaction mixture was stirred at room temperature, and the progress of the reaction was monitored by tlc. After this mixture had been stirred for 5 hr, water (20 mL) was added and extracted with dichloromethane. The dried extract on evaporation yielded a dark red material that was chromatographed. Hexane : ether (6 : 4) elute yielded tetralone **3** (187 mg, 35%); m/z 206 (M⁺) and 162 (C₁₀H₁₀O₂); v_{max} 1680 cm⁻¹ (CO), δ 7.47 (m, 1H), 7.02 (d, J = 7 Hz, 1H), 6.95 (d, J = 8 Hz, 1H) (aromatic protons); 4.34 (m, 1H), 3.89 (s, 3H) (OMe), 3.36 (s, 3H, OMe), 2.91–2.23 (m, 6H, methylene protons); ¹³C NMR: δ 196.17 (C-1), 159.54 (C-8), 144.66 (C-10), 133.51 (C-6), 120.77 (C-9), 119.70 (C-5), 111.80 (C-7), 76.39 (C-4), 55.90 (C-12), 55.67 (C-11), 34.94 (C-2), and 26.79 (C-3) (Found: C, 70.11; H, 6.96. C₁₂H₁₄O₃ requires C, 69.88; H, 6.84%).

1-Acetyl-4-ketomethyl-8-methoxy Naphthalene 6

A solution of tetralone **3** (185 mg, 0.0008 mol) in acetic anhydride (8 mL) was cooled to 0°C and to this added freshly distilled boron trifluoride etherate (1.5 mL), which had been previously cooled to 0°C. The reaction mixture was stirred (15 hr) till no further progress was observed in tlc monitoring and then poured into ice cold water, stirred for 1 hr, and then extracted with ether. The ether extract was washed, dried, and evaporated. Purification of the residue from hexane : ether (7 : 3) afforded methoxy naphthalene **6** (1.16 mg, 50%); M.P. 138°C-140°C (from ether); m/z 258 (M⁺), v_{max} 1750, 1650 cm⁻¹ (CO); δ 8.82 (dd, J = 1 Hz), 8.12 (dd, J = 1 Hz), (1H), 7.94 (d, J = 8 Hz, 1H), 7.55 (dd, J = 7 Hz) 7.53 (dd, J = 7 Hz) (1H), 7.11 (dd, J = 1 Hz), 7.10 (dd, J = 1 Hz) (1H), 6. 80 (d, J = 8 Hz, 1H) (aromatic protons), 3.97 (s, 3H, OMe), 2.67 (s, 3H, COMe), and 2.35 (s, 3H, OCOMe), ¹³C NMR: δ 200.17 (C-5), 170.10 (C-4), 158.78 (C-7), 146.57 (C-6), 134.19 (C-8), 131.19 (C-12), 128.24 (C-10, C-14), 124.01 (C-15), 120.29 (C-11), 119.51 (C-9), 104.06 (C-13), 56.25 (C-3), 29.68 (C-2), and 20.91 (C-1), (Found: C, 70.01;

H, 5.60. $C_{15}H_{14}O_4$ requires C, 69.75; H, 5.46%). Hexane : ether (6:4) elute furnished tetralone (3) (27 mg 12%) whose identity was confirmed by comparing (spectral data and tlc) with an authentic specimen of (3) whose synthesis has already been described.

1,6-Dimethoxy Tetralin 8

A mixture of tetralone 7 (1.52 g, 0.008 mol) and sodium borohydride (755 mg, 0.022 mol) in ethanol (100 mL) was stirred at 0°C for 1 hr. The mixture was diluted with aqueous solution of ammonium chloride (25 mL) and extracted with ether. The extract was washed, dried, and evaporated to afford an alcohol (1.55 g), v_{max} 3420 cm⁻¹ (OH) that was completely free from tetralone 7, as evidenced by TLC, and therefore was directly used without further purification.

A solution of alcohol (1.53 g) in tetrahydrofuran (30 mL) was added drop-wise to a suspension of sodium hydride (50% mineral oil, 2.02 g) in tetrahydrofuran (25 mL) under nitrogen. The mixture was warmed for 10 min, followed by the addition of methyl iodide and then heated under reflux for 6 hr. The reaction mixture was cooled, diluted with water, and extracted with ether. The dried extract was evaporated and the resulting residue was chromatographed; elution with hexane : ether (9 : 1) afforded the oily tetralin **8** (1.45 g, 88%); m/z 192 (M⁺) and 160 (M⁺-MeOH); δ 7.03 (d, J = 8 Hz, 1H), 6.93 (d, J = 2.6 Hz, 1H), 6.78 (d, J = 8.4 Hz, 1H) (aromatic protons), 4.31 (m, 1H), 3.82 (s, 3H, OMe), 3.47 (s, 3H, OMe), 1.74–2.76 (m, 6H, methylene protons), (Found: C, 75.18; H, 8.55. C₁₂H₁₆O₂ requires C, 74.97; H, 8.39%).

4,6-Dimethoxy-α-tetralone 9

To a solution of tetralin **8** (850 mg, 0.004 mol) in acetic acid (10 mL), cooled to 0°C, was added a solution of chromic acid (2 g, 0.002 mol) in water (3 mL) and acetic acid (15 mL). The reaction mixture was stirred at room temperature and the progress of the reaction was monitored by TLC. After this mixture had been stirred for 6 hr, water (25 mL) was added and extracted with dichloromethane. The dried extract was evaporated and the residual oil on chromatographic purification (eluant hexane : ether, 6 : 4) yielded tetralone **9** (546 mg, 60%); m/z 206 (M⁺) and 162 (C₁₀H₁₀O₂); v_{max} 1685 cm⁻¹ (CO); δ 8.04 (d, J = 8.7 Hz, 1H), 7.01 (d, J = 8.6 Hz, 1H), 6.95 (m, 1H) (aromatic protons), 4.44 (m, 1H), 3.92 (s, 3H, OMe), 3.51 (s, 3H, 1H), 2.95–2.24 (m, 6H, methylene protons); ¹³C NMR: δ 196.32

(C-1), 163.76 (C-6), 145.35 (C-10), 129.77 (C-8), 125.18 (C-9), 114.39 (C-7), 112.04 (C-5), 77.16 (C-4), 56.49 (C-11), 55.49 (C-12), 34.43 (C-2), and 27.90 (C-3), (Found: C, 70.14; H, 6.95. C₁₂H₁₄O₃ requires C, 69.88; H, 6.84%).

1-Acetyl-6-methoxy Naphthalene 10

A solution of tetralone **9** (512 mg, 0.002 mol) in acetic anhydride (22 mL) was cooled to 0°C and to this added freshly distilled boron trifluoride etherate (3.8 mL), which had been previously cooled to 0°C. The reaction mixture was stirred (18 hr) till no further progress was observed in the monitoring and then poured into ice cold water, stirred for 1 hr, and then extracted with ether. The ether extract was washed, dried, and evaporated to yield an oily residue, which was chromatographed. Hexane : ether (8 : 2) elute contained compound **10** (321 mg, 60%), M.P. 72°C-73°C (from ether); m/z 216 (M⁺) and 173 (M⁺-MeCO); v_{max} 1745 cm⁻¹ (CO); δ 7.74 (d, J = 9 Hz, 1H), 7.61 (d, J = 8 Hz, 1H), 7.39 (t, J = 7 Hz, 1H), 7.16-7.07 (m, 3H), and 7.08 (s, 1H) (aromatic protons), 3.95 (s, 3H, OMe) and 2.62 (s, 3H, OCOMe); 1³C NMR: δ 169.47 (CO), 158.02 (C-7), 146.75 (C-4), 136.05 (C-10), 126.13 (C-2), 124.81 (C-1), 122.77 (C-9), 122.09 (C-5), 119.33 (C-6), 115.81 (C-3), and 105.89 (C-8), (Found: C, 72.42; H, 5.75. C₁₃H₁₂O₃ requires C, 72.21; H, 5.59%).

1,6-Dimethoxy Tetralin 13

To tretalone **12** (302 mg, 0.001 mol), in ethanol (12 mL), sodium borohydride (170 mg, 0.006 mol) was added portionwise and stirred for 4 hr at room temperature. The mixture was diluted with water and thoroughly extracted with ether. The combined extracts were washed, dried, and evaporated to yield alcohol (304 mg); v_{max} 3257 cm⁻¹ (OH). This was completely free from tetralone **12** (by TLC) and IR spectrum and thus used for methylation without purification.

A solution of alcohol (302 mg) in tetrahydrofuran (10 mL) was added drop-wise to a stirred suspension of sodium hydride (50% mineral oil, 410 mg) in tetrahydrofuran (10 mL) under nitrogen. The mixture was warmed for 10 min, followed by the addition of methyl iodide (5 mL) and then heated under reflux for 6 hr. The reaction mixture was cooled, diluted with water, extracted with ether, dried, and evaporated. The oily residue on chromatographic purification (hexane : ether, 9:1) yielded dimethoxy tetralin **13** (289 mg; 88%); m/z 192 (M⁺) and 160 (M⁺-MeOH); δ 7.23 (s, 1H), 6.72 (d, 1H, J = 8 Hz), 6.59 (d, 1H, J = 2 Hz) (aromatic protons), 4.24 (m, 1H, 1-H), 2.68–1.71 (m, 6H), 3.86 (s, 3H, OMe), and 3.75 (s, 3H, OMe), (Found: C, 75.24; H, 8.58. C₁₂H₁₆O₂ requires C, 74.97; H, 8.39%).

6-Methoxy-α-tetralone 12

To a solution of tetralin **13** (305 mg, 0.001 mol) in acetic acid (2 mL), cooled to 0°C, was added a solution of water (1 mL) and chromic acid (1.51 g, 0.015 mol). The reaction mixture was stirred (6 hr) till no further progress was observed in TLC monitoring, diluted with water, and extracted with dichloromethane. The dried extract on evaporation yielded a semisolid material that, on crystallization with ether, afforded 6-methoxy-1-tetralone **12** (245 mg, 88%); M.P. $78^{\circ}-79^{\circ}$ C (77° C -79° C) (lit. values from Aldrich Chemical Company), m/z 176 (M⁺); v_{max} 1670 cm⁻¹ (CO); δ 8.48 (d, 1H, J = 8 Hz), 6.79 (d, J = 8 Hz), 6.78 (d, J = 3 Hz), (1H), 6.65 (d, J = 3 Hz, 1H), (aromatic protons), 2.91 (t, 2H, J = 2.5), 2.58 (t, 2H, J = 2.9), 2.13–2.04 (m, 1H); ¹³C NMR: δ 197.21 (C-1), 163.52 (C-6), 146.94 (C-10), 129.63 (C-8), 126.32 (C-9), 113.01 (C-5), 112.60 (C-7), 55.39 (C-11) 38.88 (C-2), 30.15 (C-4), and 23.35 (C-3), (Found: C, 75.21; H, 6.69. C₁₁H₁₂O₂ requires C, 74.97; H, 6.86%).

REFERENCES

- Narayan, C.R.; Iyer, K.N. Regeneration of steroidal alcohols from their methyl ethers. J. Org. Chem. 1965, 30, 1734.
- Lee, S.; Frescas, S.P.; Nicholas, D.E. A new simple procedure for the preparation of 8-methoxy-2-tetralone. Synth. Commun. 1995, 25, 2775 (and related references cited therein).
- Boyer, J.; Krum, J.; Myers, M.; Fazal, A.; Wigal, C. Synthetic utility and mechanistic implication of Fries rearrangement of hydroquinone diester in boron trifluoride complexes. J. Org. Chem. 2000, 65, 4712.
- Pelliccari, R.; Natalini, B.; Sadeghpour, B.; Marinozzi, M.; Snyder, J.; Williamson, B.; Kuethe, J.; Padwa, A. The reaction of a-diazo-b-hydroxy esters with boron trifluoride etherate: Generation and rearrangement of destabilized vinyl cations. A detailed experimental and theoretical study. J. Am. Chem. Soc. **1996**, *118*, 1.
- Anilkumar, R.; Chandrasekhar, S. Improved procedure for Beckman rearrangement: The reaction of ketoxime carbonates with boron trifluoride etherates. Tetrahedron Lett. 2000, 41, 5427.

Received in the USA June 2, 2004