A Practical and Cost-Effective Synthesis of 6,7-Dimethoxy-2-tetralone

Amjad M. Qandil, David W. Miller, David E. Nichols*

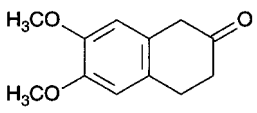
Department of Medicinal Chemistry and Molecular Pharmacology, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, IN 47907, USA

Received 26 June 1999; revised 1 September 1999

Abstract: The cyclic ketone, 6,7-dimethoxy-2-tetralone, a versatile starting material for many dopaminergic compounds, can be prepared practically, cost-effectively and in good overall yield. The synthesis starts from readily available 3,4-dimethoxyphenylacetic acid. Ring iodination gave the 2-iodo-4,5-dimethoxy acid, which was converted to its methyl ester. Palladium (II)-catalyzed Heck cross coupling afforded the expected unsaturated diester, which was then catalytically hydrogenated. Dieckmann condensation, followed by careful decarboxylation led to the desired 2-tetralone. Reagents used in subsequent reactions are inexpensive and readily available. This method appears practical for large-scale synthesis of the target tetralone, compared with other procedures reported in the literature.

Key words: 6,7-dimethoxy-2-tetralone, esterification, Heck cross coupling, Dieckmann condensation, decarboxylation

The cyclic ketone, 6,7-dimethoxy-2-tetralone **(1)** is a key starting material for the synthesis of the full dopamine agonist dihydrexidine and its derivatives.[1,2] It has also been used to synthesize various aminotetralins,[3-7] isoquinoline derived dopaminergic agents,[8] other catecholamine mimicking agents,[9,10] natural alkaloids,[11] and cyclic amino acids.[12] The accessibility of this material is hampered by high cost ($131/500 mg, Aldrich), and tedious and/or extremely low yielding synthetic pathways when prepared. There have been several syntheses reported for this compound, the most widely employed perhaps being the reaction of 3,4-dimethoxyphenylacetyl chloride with ethylene gas in the presence of aluminum chloride as a catalyst.[6,13,14] This method suffers from difficulty in optimizing reaction parameters (e.g. ethylene gas flow), a very tedious workup, and despite numerous reactions in our laboratory where we attempted to optimize each variable, always afforded yields of less than 30%. Ketone transposition[13-16] of the corresponding 1-tetralone has found limited success, but it is a multi-step synthesis that requires the preparation of the 1-tetralone starting material. Other reported methods employ silylenol ethers,[17] rhodium catalyzed cyclization of diazoketones,[18] or Pummerer rearrangement of a β-keto sulfoxide.[7,19] Based on our own experience with virtually all of these approaches, we concluded that no really efficient synthesis of this important material had been developed.



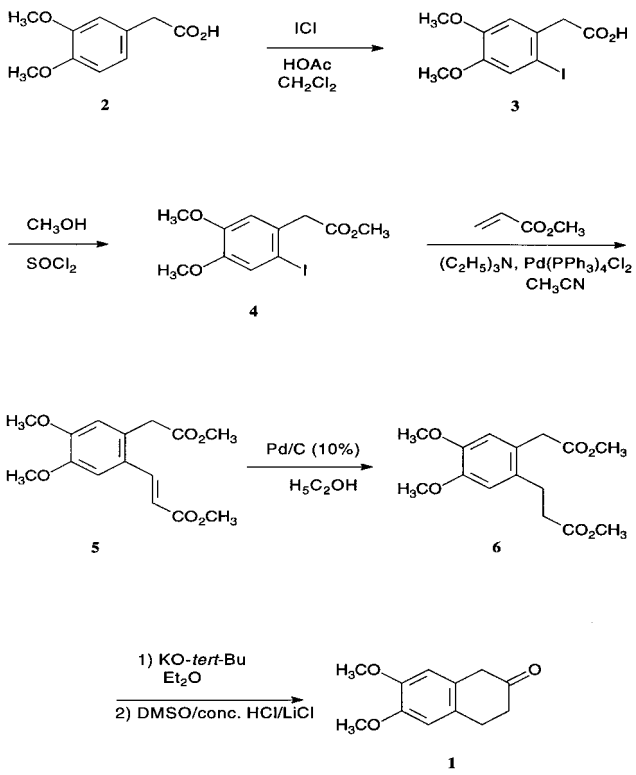
1

In this paper we report a practical, very cost-effective and overall high yielding methodology to prepare the desired tetralone. The method utilizes easily available and inexpensive starting material and reagents. The synthesis starts with the high-yielding iodination of 3,4-dimethoxyphenylacetic acid **(2)** with iodine monochloride to afford the iodoacid **3** that was then esterified to yield methyl 2-iodo-4,5-dimethoxyphenylacetate **(4)**. These two intermediates have been reported in the literature,[20-22] but our sequence affords a better overall yield using less expensive reagents. This ester was subjected to Heck cross coupling conditions[23-28] using only 1 mole% of dichlorobis-(triphenylphosphine)palladium(II), a highly stable low-cost form of palladium(II).[29] The cinnamate **5**, obtained in excellent yield, was catalytically reduced with hydrogen over 10% palladium on carbon. This reaction was extremely fast, and after filtration of the catalyst and evaporation of the solvent afforded analytically pure propionate **6** in quantitative yield. The diester was then treated with potassium *tert*-butoxide in Et_2O, and the precipitated potassium salt was filtered, dried and then decarboxylated using a DMSO/H_2O/LiCl reagent system.[30,31] The H_2O was added in the form of concentrated HCl to neutralize the potassium salt from the previous reaction. The 2-tetralone was purified as its bisulfite adduct, which upon treatment with sodium carbonate liberated to the ketone. The overall yield when starting from intermediate **5** is 59.5% while when starting from intermediate **2** is 47%. This methodology provides the option of synthesizing the tetralone and storing it either as the ketone or the bisulfite adduct, or accumulating the very stable cinnamate intermediate **5** in large quantities and synthesizing the tetralone from it on demand, in a fast and practical way.

Mps were determined with a Thomas-Hoover apparatus and are uncorrected. ^{1}H NMR spectra were obtained with a Varian VXR500 (500 MHz) or a Bruker AXR300 (300 MHz) NMR instrument in $CDCl_3$ and chemical shifts are reported in δ values (ppm) relative to an internal reference of $CHCl_3$ (δ 7.24). Chemical ionization (CI) mass spectra were obtained with a Finnegan 4000 quadrupole mass spectrometer. The ionization gas for CIMS was isobutane, unless otherwise noted. Elemental analyses were performed by the microanalysis laboratory in the Chemistry Department at Purdue University.

2-Iodo-4,5-dimethoxyphenylacetic Acid (3)

To a soln of 3,4-dimethoxyphenylacetic acid (100 g, 0.51 mol) in CH_2Cl_2 (600 mL) and HOAc (100 mL), iodine monochloride (27.6 mL, 87.76 g, 0.54 mol) in CH_2Cl_2 (500 mL) was added dropwise via a dropping funnel. The reaction mixture was stirred overnight and was then quenched with sat. sodium thiosulfate, and the organic lay-



Scheme

er was washed with brine (3 × 150 mL), dried ($MgSO_4$) and filtered. The solvent was then evaporated and the residue was triturated with Et_2O to yield 142.2 g (86%) of a light-orange solid, mp: 161-164 °C (Lit.[21] mp: 164–165 °C).

^{1}H NMR: δ = 3.74 (s, 2H, $ArCH_2CO$), 3.81 (s, 6H, OCH_3), 6.76 (s, 1H, ArH), 7.2 (s, 1H, ArH).

Methyl 2-Iodo-4,5-dimethoxyphenylacetate (4)

Thionyl chloride (75 mL) was added dropwise to a solution of 2-iodo-4,5-dimethoxyphenylacetic acid **(3)** (138.2 g, 0.43 mol) dissolved in anhyd MeOH (1 L). The reaction mixture was stirred overnight at r.t., then concentrated and the residue was taken up into CH_2Cl_2 and washed with H_2O and sat. aq $NaHCO_3$. The organic layer was dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was crystallized from EtOAc:hexane to afford 132.2 g (92%) of a white solid, mp: 76–78 °C (Lit.[21] mp: 72–73 °C).

^{1}H NMR: δ = 3.66 (s, 3H, OCH_3), 3.67 (s, 2H, $ArCH_2CO$), 3.79 (s, 6H, OCH_3), 6.76 (s, 1H, ArH), 7.15 (s, 1H, ArH).

Methyl (*E*)-3-[4,5-Dimethoxy-2-(2-methoxy-2-oxoethyl)phenyl]prop-2-enoate (5)

Methyl 2-iodo-4,5-dimethoxyphenyl acetate **(4)** (80 g, 0.238 mol) was dissolved in MeCN (300 mL) and placed under an Ar atm. To the solution was added Et_3N (99.50 mL, 72.25 g, 0.714 mol), methyl acrylate (85.91 mL, 81.96 g, 0.952 mol) and dichlorobis(triphenylphosphine)palladium(II) (1 g, 1 mol%). The reaction mixture was heated at reflux for 6 h. The cooled mixture was then concentrated and the residue was taken up into EtOAc (1 L) and washed twice with H_2O, several times with 2N HCl until the aqueous layer remained acidic, and finally with H_2O. The organic layer was dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was dissolved in boiling EtOH and decolorized with charcoal. After filtration to remove carbon, cooling afforded 67.24 g (96%) of a white crystalline solid, mp: 95–97 °C.

IR (film): ν = 2951, 1735, 1714, 1602, 1518, 1436, 1272, 1170 cm^{-1}.

^{1}H NMR: δ = 3.65 (s, 3H, OCH_3), 3.69 (s, 2H, $ArCH_2CO$), 3.75 (s, 3H, OCH_3), 3.85 (s, 6H, OCH_3), 6.24 (d, 1H, ArCH = C*H*CO, *J* = 15 Hz), 6.7 (s, 1H, ArH), 7.03 (s, 1H, ArH), 7.84 (d, 1H, ArC*H* = CHCO, *J* = 15 Hz).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 37.9, 51.6, 52.1, 55.8, 108.7, 113.4, 117.4, 125.9, 127.2, 141.3, 148.4, 150.7, 167.4, 171.5.

CIMS: 294/295 (47/13%), 263/264 (100/15%).

Anal. Calcd for $C_{15}H_{18}O_6$: C, 61.22, H, 6.16. Found: C, 61.31, H, 6.13.

Methyl 3-[4,5-Dimethoxy-2-(2-methoxy-2-oxoethyl)phenyl]-propanoate (6)

Cinnamate **5** (50 g, 0.17 mol) was dissolved in hot EtOH (1 L) and to it was added 10% palladium on carbon (5 g). The reaction mixture was shaken in a Parr hydrogenator at 50 psi until H_2 uptake ceased. The suspension was filtered over a thick pad of Celite and the solvent was evaporated to afford a colorless oil in quantitative yield.

IR (film): ν = 2952, 1731, 1609, 1520, 1436, 1276, 1197 cm^{-1}.

^{1}H NMR: δ = 2.52 (t, 2H, $ArCH_2CH_2$, *J* = 7 Hz), 2.86 (t, 2H, $ArCH_2CH_2CO$, *J* = 7 Hz), 3.56 (s, 2H, $ArCH_2CO$), 3.62 (s, 3H, OCH_3), 3.64 (s, 3H, OCH_3), 3.80 (s, 6H, OCH_3), 6.65 (s, 1H, ArH), 6.67 (s, 1H, ArH).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 27.3, 34.9, 37.5, 51.2, 51.7, 55.5, 112.0, 113.3, 123.6, 131.0, 147.0, 147.8, 171.8, 172.9.

CIMS: 297 (100%), 265 (17%), 237 (53%).

Anal. Calcd for $C_{15}H_{18}O_6$: C, 60.80, H, 6.80. Found: C, 60.91, H, 6.88.

6,7-Dimethoxy-2-tetralone (1)

Potassium *tert*-butoxide (Aldrich, 20 g, 0.178 mol) was stirred in dry Et_2O (1 L) under an Ar atm. To the suspension a solution of **6** (48 g, 0.162 mol) in anhyd Et_2O (500 mL) was added dropwise via a dropping funnel. After stirring for 30 min, the resulting suspension was filtered. The cake was washed repeatedly with Et_2O and dried under high vacuum to afford a quantitative yield of the potassium enolate as a tan solid. This potassium salt (10 g, 33.11 mmol) and LiCl (1.684 g, 39.73 mmol) were dissolved in DMSO (23 mL). While stirring, conc. HCl (3.3 mL, 40 mmol) was added rapidly and the flask was placed in an oil bath preheated to 125 °C and stirred under Ar for 5 h. The reaction mixture was cooled and diluted with EtOAc (500 mL). The organic layer was washed with H_2O (3 × 200 mL), dried ($MgSO_4$), filtered, and the solvent evaporated. The residue was dissolved in a minimum amount of Et_2O, a freshly prepared soln of sodium bisulfite (10.33 g, 10 mL of H_2O) was added and the biphasic mixture was vigorously stirred overnight. The precipitate was filtered, air dried, and then dissolved in H_2O. Excess solid Na_2CO_3 was added to the soln to precipitate **1**. The crystals were filtered and washed with H_2O to afford 4.23 g (62%) of white crystals, mp: 84–86 °C (Lit.[6] mp: 85.5–86.5 °C).

^{1}H NMR: δ = 2.56 (t, 2H, $ArCH_2CH_2$, *J* = 7 Hz), 3.00 (t, 2H, $ArCH_2CH_2CO$, *J* = 7 Hz), 3.51 (s, 2H, $ArCH_2CO$), 3.86 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 6.62 (s, 1H, ArH), 6.74 (s, 1H, ArH).

Acknowledgement

This work was supported by NIH grant MH42705 and by the Bristol-Myers Squibb Company.

References

(1) Brewster, W. K.; Nichols, D. E.; Riggs, R. M.; Mottola, D. M.; Lovenberg, T. W.; Lewis, M. H.; Mailman, R. B. *J. Med. Chem.* **1990**, *33*, 1756.
(2) Knoerzer, T. A.; Watts, V. J.; Nichols, D. E.; Mailman, R. B. *J. Med. Chem.* **1995**, *38*. 3062.
(3) Hall, A. W.; Taylor, J. K.; Simmonds, S. H.; Stange, P. G. *J. Med. Chem.* **1987**, *30*, 1879.
(4) Manitto, P.; Speranza, G.; Monti, D.; Fontana, G.; Panosetti, E. *Tetrahedron* **1995**, *51*, 11531.
(5) Kanao, M.; Hashizume, T.; Ichikawa, Y.; Irie, K.; Isoda, S. *J. Med. Chem.* **1982**, *25*, 1358.
(6) Horn, A. S.; Grol, C. J.; Dijkstra, D. *J. Med. Chem.* **1978**, *21*, 825.
(7) Canon, J. G.; Lee, T.; Goldman, H. D.; Costall, B.; Naylor, R. *J. Med. Chem.* **1977**, *20*, 1111.
(8) Cannon, J. G.; Lee, T.; Hsu, F.-L. *J. Med. Chem.* **1980**, *23*, 502.
(9) Atwal, K. S.; O'Reily, B. C.; Ruby, E. P.; Turk, C. F.; Aberg, G. *J. Med. Chem.* **1987**, *30*, 627.
(10) Gorczynski, R. J.; Anderson, W. G.; Stout, D. M. *J. Med. Chem.* **1981**, *24*, 835.
(11) Dreau, M.-A. L.; Desmaele, D.; Dumas, F.; d'Angelo, J. *J. Org. Chem.* **1993**, *58*, 2933.
(12) Obrecht, D.; Spiegler, C.; Schoenholzer, P.; Mueller, K.; Heimgartner, H.; Stierli, F. *Helv. Chim. Acta.* **1992**, *75*, 1666.
(13) Pendergast, W.; Johnson, J. V.; Dickerson, S. H.; Dev, K. I.; Duch, D. S.; Ferone, R.; Hall, W. R.; Humphreys, J.; Kelly, J. M.; Wilson, D. C. *J. Med. Chem.* **1993**, *36*, 2279.
(14) Cordi, A. A.; Lacoste, J.-M.; Descombes, J.-J.; Courchay, C.; Vanhoutee, P. M. *J. Med. Chem.* **1995**, *38*, 4056.
(15) Pryde, D. C.; Henry, S. S.; Myeres, A. I. *Tetrahedron Lett.* **1996**, *37*, 3243.
(16) Craig, J. C.; Torkelson, S. M.; Findell, P. R.; Weiner, R. L. *J. Med. Chem.* **1989**, *32*, 961.
(17) Pandey, G.; Krishna, A.; Girija, K.; Karthikeyan, M. *Tetrahedron Lett.* **1993**, *34*, 6631.
(18) McKervey, M. A.; Tuladhar, S. M.; Fiona, M. T. *J. Chem. Soc., Chem. Comm.* **1984**, 129.
(19) Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1974**, *30*, 2653.
(20) Aidhen, I. S.; Ahuja, J. R. *Tetrahedron Lett.* **1992**, *33*, 5431.
(21) Weisgraber, K. H.; Weiss, U. *J. Chem. Soc., Perkin. Trans. 1* **1972**, 83.
(22) Cromarie, R. I.; Harley-Mason, J.; Wannigama, D. G. *J. Chem. Soc.* **1958**, 1982.
(23) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581.
(24) Heck, R. F.; Nolley, J. P. *J. Org. Chem.* **1972**, *37*, 2320.
(25) Mori, K.; Mizoroki, T.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 1505.
(26) Dieck, H. A.; Heck, R. F. *J. Am. Chem. Soc.* **1974**, *96*, 1133.
(27) Plevyak, J. E.; Dickerson, J. E.; Heck, R. F. *J. Org. Chem.* **1979**, *44*, 4078.
(28) Chourdray, R. M.; Sarma, M. R.; Rao, K. K. *Tetrahedron Lett.* **1990**, *31*, 5781.
(29) Tsuji, J. *Palladium Reagents and Catalysts: Innovation in Organic Synthesis*,1st ed., Wiley: Chichester, 1996.
(30) Lin, C.-H.; Haadsma-Svensson, S. R.; Lahti, R. A.; McCall, R. B.; Piercey, M. F.; Schreur, P. J.; VonVoigtlander, P. F.; Chidester, C. G. *J. Med. Chem.* **1993**, *36*, 671.
(31) Kouvarakis, A.; Katerinopoulos, H. E. *Synth. Commun.* **1995**, *25*, 3035.

Article Identifier:
1437-210X,E;1999,0,12,2033,2035,ftx,en;M01599SS.pdf