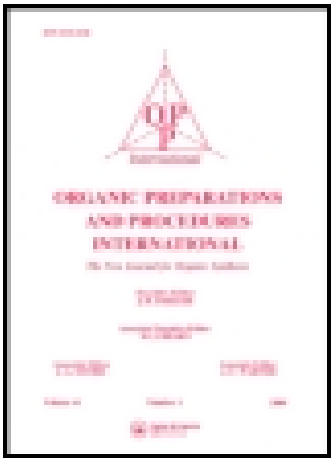

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SYNTHESIS OF SUBSTITUTED 1-TETRALONES

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SYNTHESIS OF SUBSTITUTED 1-TETRALONES

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(05/17/96)

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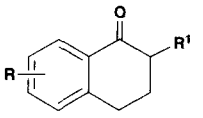
Substituted 1-tetralone derivatives (**1**) are valuable intermediates in organic synthesis. In fact, 6-methoxy-1-tetralone[1] (**2**), 1-tetralone[2] (**3**), and 5,6-methylenedioxy-1-tetralone[3] are the starting materials in the synthesis of several complex biologically active compounds. In 1972, Heck reported the conjugate addition of benzyl chloride to methyl acrylate, promoted by $Pd(OAc)_2$, leading to the formation of methyl 4-phenyl-3-butenoate (69%) and methyl 4 -phenyl- 2 -butenoate (9%)[4]. Since

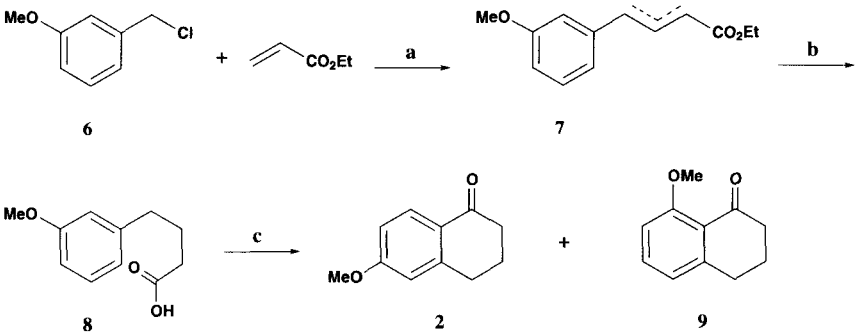


1

2) R = 6-Methoxy ; R^1 = H **4**) R = 5, 6-Dimethoxy ; R^1 = H
3) R = R^1 = H **5**) R = H ; R^1 = Methyl

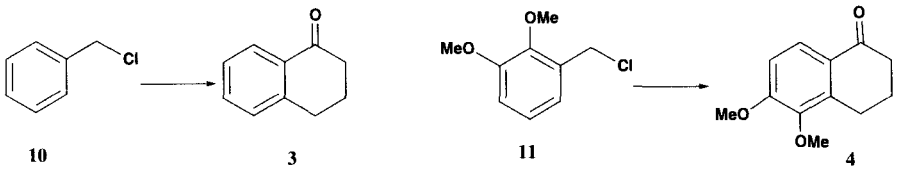
that time, relatively little interest has been shown in this reaction. The existing approaches[5] to the synthesis of substituted 1-tetralone derivatives require long or complex reaction sequences, sometimes leading to the formation of isomeric compounds. For instance, preparation of compound **5** by Friedel-Crafts acylation of benzene with methylsuccinic anhydride followed by reduction of one of the benzylic ketones leads to an isomeric mixture. As a part of our current interest in abortifacient drug Mifepristone[6] and ABT-200[3], a potent α-2 antagonist and norepinephrine uptake inhibitor currently undergoing testing at Abbot Labs, we developed an alternate process, based on the Heck reaction to prepare 6-methoxy-1-tetralone (**2**), 1-tetralone (**3**), 5,6-dimethoxy-1-tetralone (**4**) and 2-methyl-1-tetralone.

3-Methoxybenzyl chloride (**6**) and ethyl acrylate were heated at 100° in the presence of $Pd(OAc)_2$ and tributylamine for 9 h to give **7** in 85% yield. The ^1H NMR spectrum of **7** revealed the presence of 3- and 2-butenoates as regioisomers. Subsequent reduction of **7** over Pd-C in methanol at



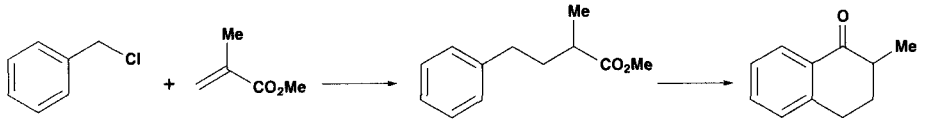
a) $Pd(OAc)_2$, Bu_3N, 100°, 9 h; b) i) H_2, Pd-C, MeOH, 50 psi, 5 h; ii) 6N, KOH, EtOH, Δ, 2 h;
c) PPE, $CHCl_3$, RT, 7 h.

50 psi followed by hydrolysis gave the acid **8**. Compound **8** was treated with polyphosphoric ester (PPE)[7] in $CHCl_3$ at room temperature to give **2** (77.8% overall yield) along with 8-methoxy-1-tetralone (**9**) (8%). Similarly, benzyl chloride (**10**) was converted into 1-tetralone (**3**) (overall yield 77%). The synthesis of 5,6-dimethoxy-1-tetralone (**4**) (overall yield 67%) was also completed by the above approach starting from 2,3-dimethoxybenzyl chloride (**11**)[8].



10 3 11 4

In order to prepare 2-methyl-1-tetralone (**5**), the reaction of benzyl chloride (**10**) and ethyl methacrylate in the presence of $Pd(OAc)_2$ at 100° for 11 h followed by catalytic reduction produced the product **12**. Subsequent ester hydrolysis of **12** and cyclization with PPE-$CHCl_3$ gave **5** (overall 51.6% yield).



10 12 5

EXPERIMENTAL SECTION

Proton magnetic resonance spectra were recorded in $CDCl_3$ on Varian FT-200 MHz (Gemini) spectrophotometer using TMS as the internal standard. Infra Red spectra were scanned on Shimadzu IR-470 with sodium chloride optics. Mass spectra were recorded on VG 7070 H. Melting points were recorded on Buchi 535 melting point apparatus and are uncorrected. All evaporations were carried under reduced pressure on rotary evaporators below 50°.

Ethyl 4-(3-Anisyl)-2-butenoate and Ethyl 4-(3-Anisyl)-3-butenoate (7).- A mixture of 3-methoxybenzylchloride (15.6 g, 100 mmol), $Pd(OAc)_2$ (0.24 g, 1 mmol), tri-*n*-butylamine (37.07 g, 200 mmol) and ethyl acrylate (15.0 g, 150 mmol) was heated at 100° for 9 h. The reaction mixture was poured in water and extracted with ethyl acetate. The organic layer was washed with 1N HCl, water, dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel by using ethyl acetate:light petroleum (5:95) to give **7** as a pale brown viscous oil, isolated in 85% yield (18.7 g). ^1H NMR: δ 1.28 (t, 3H, J = 7.3 Hz), 3.21 (d, 2H, J = 5.8 Hz), 3.80 (s, 3H), 4.16 (q, 2H, J = 7.3 Hz), 6.15-7.3 (m, 6H).

Anal. Calcd. for $C_{13}H_{16}O_3$: C, 70.88; H, 7.32. Found: C, 70.77; H, 7.34

6-Methoxy-1-tetralone (2).- Compound **7** (18.7 g, 84.09 mmol) and 10% Pd-C (2 g) in methanol (100 mL) was hydrogenated at 50 psi for 5 h. After the catalyst was filtered through celite, the filtrate was diluted with 6N KOH (50 mL) and heated under reflux for 2 h. The reaction was acidified with concentrated HCl and methanol was removed under reduced pressure. The aqueous layer was extracted with ethyl acetate, dried (Na_2SO_4) and concentrated. The residue was dissolved in chloro-

form (100 mL) and PPE (19 g) was added. The resulting mixture was stirred at room temperature for 7 h, decomposed with water. The chloroform layer was separated, dried (Na_2SO_4), concentrated and the residue was chromatographed on silica gel by using ethyl acetate:light petroleum (5:95) to give **2** as a white crystaline solid, mp. 76-76.6°; lit.[5f] mp. 75-77°, isolated in 92% yield (13.7 g). ^{1}H NMR: δ 2.04 (m, 2H), 2.50 (t, 2H, *J* = 6.3 Hz), 2.86 (t, 2H, *J* = 6.3 Hz), 3.77 (s, 3H), 6.61 (d, 1H, *J* = 1.5 Hz), 6.73 (dd, 1H, *J* = 1.5 Hz, 9.0 Hz), 7.93 (d, 1H, *J* = 9 Hz). IR ($CHCl_3$): 1670 cm^{-1}. MS: m/z 176 (M^+).

Further elution gave 8-methoxy-1-tetralone as a colorless liquid, bp. 96-98°/ 0.02 mm; lit.[9] bp. 94-96° / 0.02 mm isolated in 8% yield (1.1g). ^{1}H NMR: δ 2.06 (m, 2H), 2.61 (t, 2H, *J* = 6.2 Hz), 2.91 (t, 2H, *J* = 6.2 Hz), 3.89 (s, 3H), 6.78 (m, 2H), 7.34 (t, 1H, *J* = 8.0 Hz).

1-Tetralone (3), isolated as a light yellow liquid, bp. 136-138°/ 15 mm; lit.[10] bp. 135-137° / 15 mm in 77% yield. ^{1}H NMR: δ 2.06 (m, 2H), 2.56 (t, 2H, *J* = 6.8 Hz), 2.88 (t, 2H, *J* = 6.8 Hz), 7.13-7.24 (m, 2H), 7.36 (m, 1H), 7.95 (d, 1H, *J* = 8.1 Hz). IR (Neat): 1680 cm^{-1}; MS: m/z 146 (M^+).

5,6-Dimethoxy-1-tetralone (4), white crystaline solid, mp. 103-104.6°; lit.[11]mp. 104-105°, isolated in 67% yield. ^{1}H NMR: δ 2.02-2.17 (m, 2H), 2.56 (t, 2H, *J* = 6.4 Hz), 2.94 (t, 2H, *J* = 6.4 Hz), 3.79 (s, 3H), 3.90 (s, 3H), 6.82 (d, 1H, *J* = 8.6 Hz), 7.78 (d, 1H, *J* = 8.6 Hz). IR ($CHCl_3$): 1665 cm^{-1}; HRMS: 206.0944. Calcd. for $C_{12}H_{14}O_3$: 206.0942.

Ethyl 2-Methyl-4-phenylbutenoate (12).- A mixture of benzyl chloride (12.6 g, 100 mmol), $Pd(OAc)_2$ (0.24 g, 1 mmol) and ethyl methacrylate (20 mL, 183 mmol) tri-n-butylamine (37.07 g, 200 mmol) was heated at 100° for 11 h. After usual work-up, the residue was hydrogenated over 10% Pd-C (1.5 g) at 50 psi in methanol (50 mL) for 6 h to give **12** as a colourless viscous oil, isolated in 60% yield (12.1 g). ^{1}H NMR: δ 1.16 (d, 3H, *J* = 6.4 Hz), 1.25 (t, 3H, *J* = 6.4 Hz), 1.65 (m, 1H), 1.95 (m, 1H), 2.36 (m, 1H), 2.55 (t, 1H, *J* = 6.4 Hz), 4.08 (q, 2H, *J* = 6.4 Hz), 7.0-7.2 (m, 5H).

2-Methyl-1-tetralone (5).- Compound **12** (12.0 g, 58.2 mmol) was hydrolysed with 6N KOH (20 mL) and then cyclised with PPE (12 g) in chloroform (30 mL) as reported above to provide **5** as a colorless oil, isolated in 88% yield (8.26g). ^{1}H NMR: δ 1.30 (d, 3H, *J* = 6.0 Hz), 1.7-3.1 (m, 5H), 7.15-7.4 (m, 3H), 8.0 (d, 1H, *J* = 9 Hz). IR (Neat): 1680 cm^{-1}; HRMS: 160.0897. Calcd. for $C_{11}H_{12}O$: 160.0888.

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DETHIOACETALIZATION OF DITHIOLANES WITH FERRIC NITRATE AND SILICA GEL IN HEXANE

Submitted by (12/09/97)

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The importance of protection/deprotection processes for certain functionalities in the synthesis of organic compounds has led to the development of a large numbers of protective groups and of methods for their removal.[1] Of the typical deprotective procedures (*e.g.* chemically, photolyti-