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A NEW, SIMPLE PROCEDURE FOR THE PREPARATION OF 8-METHOXY-2-TETRALONE

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Abstract: 8-Methoxy-2-tetralone (**6**) can be easily prepared in approximately 50% overall yield starting from 2-bromophenylacetic acid (**1**), utilizing a Friedel-Crafts acylation/cyclization, ketone protection, copper(I)-catalyzed methoxylation of the aromatic bromide in the presence of an ester as a co-catalyst, and ketone deprotection.

8-Methoxy-2-tetralone (**6**) is an important starting material[1] in the syntheses of compounds for the study of dopamine (DA) and serotonin (5-HT) receptors, and has in the past been prepared from 1,7-dihydroxynaphthalene, through *O*-methylation followed by Birch reduction.[2] However, since 1,7-dihydroxynaphthalene is now difficult to obtain commercially, we sought an alternate synthesis for the preparation of this ketone.

McKervey et al.[3] originally reported that **6** could be prepared by Rh(II) acetate catalyzed cyclization of 1-diazo-4-(2-methoxyphenyl)-2-butanone. However, it was subsequently claimed[4] that the actual yield of this conversion was much lower (maximally around 20%).

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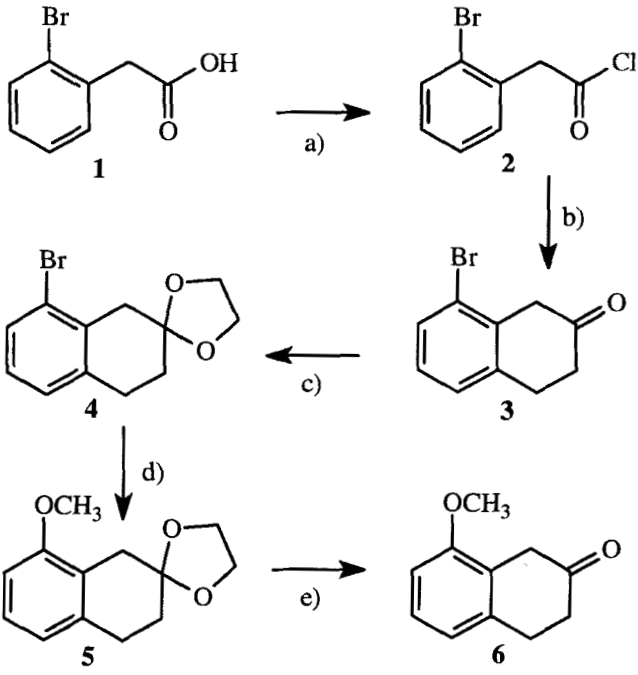
In addition to the methods mentioned above, 2-tetralones have been made either by transposition of the carbonyl group of 1-tetralones,[5] or annelation of phenylacetic acids with ethylene.[6] There have been several reports that 2-tetralones including chloro,[7] bromo,[8] methyl,[9] and methoxy[10] substituted analogs, were efficiently prepared according to the method of Burckhalter and Campbell[6] by Friedel-Crafts acylation of ethylene followed by intramolecular alkylation. We attempted to prepare **6** from 2-methoxyphenylacetyl chloride by this latter method but without success.

We then considered the copper(I)-catalyzed exchange reaction of bromide by methoxide, since 8-bromo-2-tetralone (**3**) can be prepared in good yield by straightforward methods.[11] However, this nucleophilic substitution reaction appeared to suffer from several problems such as a lack of selectivity, the need for high temperatures, and the requirement for solvents such as hexamethylphosphorous triamide (HMPT) and dimethylformamide (DMF) in the case of unactivated (devoid of electron withdrawing substituents) aryl bromides. Recently, however it has been reported that this exchange can be done under mild conditions in concentrated (3 to 5 M) methoxide solution, using esters as co-catalysts[12] to prevent the precipitation of copper(I) methoxide.

We thus prepared 8-methoxy-2-tetralone (**6**) by methoxylation of the 8-bromo compound **4** (Scheme 1). The 8-bromo-2-tetralone (**3**) was synthesized in 68% yield according to the published procedure[10] from 2-bromophenylacetic acid (**1**). Ketone **3** was protected with ethylene glycol, and the resulting ketal **4** was heated at reflux for 5 hours with copper(I) bromide and ethyl acetate in a 5 M solution of sodium methoxide in methanol to give a single spot on TLC analysis. After the usual workup, product **5** was heated with 50% aqueous acetic acid at 100 °C for deprotection. Finally, 8-methoxy-2-tetralone (**6**) was purified by Kügelrohr distillation, followed by crystallization from petroleum ether to afford a 72% overall yield, starting from crystalline 8-bromo-2-tetralone (**3**).

As described above, 8-methoxy-2-tetralone (**6**) was easily synthesized through a new synthetic pathway in an overall yield of about 50%, starting from commercially available 2-bromophenylacetic acid (**1**). These mild conditions and simple procedures offer a convenient alternative to the conventional method[2] that employs the virtually inaccessible[4] 1,7-dihydroxynaphthalene.



a) $(COCl)_2$, DMF, CH_2Cl_2, r.t., 6 h; b) $(CH_2)_2$, $AlCl_3$, CH_2Cl_2, -5 °C; c) $(CH_2OH)_2$, p-TsOH, C_6H_6, reflux, 1 h; d) 5M NaOMe/MeOH, CuBr, EtOAc, reflux, 3 h; e) $HOAc/H_2O$ (1:1), 100 °C, 3 h.

Scheme 1

Experimental Section

^1H NMR spectra were recorded using a Bruker ARX 300 NMR spectrometer in $CDCl_3$ solution with tetramethylsilane as an internal standard. Chemical shifts were reported in Hz. Melting points were determined with a Thomas-Hoover apparatus and are uncorrected.

8-Bromo-2-tetralone (3)

Oxalyl chloride (44.4 g, 350 mmol) was added slowly with stirring to a solution of 2-bromophenylacetic acid **1** (30 g, 140 mmol) and a few drops of dry DMF in CH_2Cl_2 (90 mL), cooled to 0°C in an ice bath. The reaction mixture was stirred under nitrogen at room temperature for 6 hours. The solvent and excess oxalyl chloride were removed by evaporation under reduced pressure to give a light yellow oil **2** which was not purified further.

A resin ketal reactor containing $AlCl_3$ (69 g, 520 mmol) in CH_2Cl_2 (1200 mL) was cooled to - 5 °C in an ice/salt bath with vigorous mechanical stirring. The crude acid chloride **2** in CH_2Cl_2 (120 mL) was slowly added via a dropping funnel, and then ethylene was introduced through a gas inlet tube for 1 hour. Stirring was continued for an additional 1 hour. The reaction mixture was poured over ice (2000 mL), stirred vigorously for a few minutes, and set aside until the ice melted. The CH_2Cl_2 layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic extracts were filtered through a pad of Celite, washed with 2N HCl (2 x 300 mL) and saturated $NaHCO_3$ (2 x 300mL), dried ($MgSO_4$), and concentrated *in vacuo*. The resulting oil was purified by Kügelrohr distillation (bp 86-95 °C, 0.01 mm Hg), and then crystallized from petroleum ether to give **3** as a white solid (21 g, 68 %).

^1H NMR ($CDCl_3$) ∂ 2.60 (t, J = 6.8 Hz, 2H), 3.10 (t, J = 6.8 Hz, 2H), 3.67 (s, 2H), 7.09 (t, J = 7.7Hz, 1H), 7.19 (d, J = 7.5 Hz, 1H), 7.30 (d, J = 7.8 Hz, 1H).

8'-Bromo-3',4'-dihydrospiro-[1,3,-dioxolane-2,2'(1H)-naphthalene] (4)

A solution of **3** (18 g, 80 mmol), ethylene glycol (9.9 g, 160 mmol) and p-toluenesulfonic acid (1.3 g, 6.7 mmol) in benzene (350 mL) was heated at reflux for 1 hour under nitrogen utilizing a Dean-Stark apparatus for water removal . The cooled solution was diluted with diethyl ether, washed with saturated $NaHCO_3$ (2 x 200 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give **4** as an oil (19.6 g, 91%).

^{1}H NMR ($CDCl_3$) ∂ 1.94 (t, J = 7.8 Hz, 2H), 2.9 (t, J = 7.7Hz, 2H), 3.0 (s, 2H), 4.0 (m, 4H), 7.0 (t, J = 7.7 Hz, 1H), 7.1(d, J = 7.4 Hz, 1H), 7.4 (t, J = 7.8 Hz, 1H).

8'-Methoxy-3',4'-dihydrospiro-[1,3-dioxolane-2,2'(1'H)-naphthalene] (5)

To a flame-dried, two-necked reaction flask (250 mL) were added **4** (19 g, 70 mmol), 5.0 M solution of sodium methoxide in methanol (220 mmol, 45 mL), ethyl acetate (3.64 g, 28 mmol) and CuBr (1.43 g, 10 mmol). The reaction mixture was heated at reflux for 5 hours, and after cooling, all volatiles were removed under reduced pressure. Water (800 mL) was added to the residue, which was then extracted with CH_2Cl_2 (3 x 100 mL). Extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give a pale yellow oil **5** (13g, 86%).

^{1}H NMR ($CDCl_3$) ∂ 1.9(t, J = 6.7Hz, 2H), 2.8 (s,2H), 2.98 (t, J = 6.5Hz, 2H), 3.77 (s, 3H, $-OCH_3$) 4.0 (m, 4H), 6.64 (d, J = 8.1Hz, 1H), 6.73 (d, J = 7.7Hz, 1H), 7.1 (t, 1H).

8-Methoxy-2-tetralone (6)

Ketal **5** (13 g, 59 mmol) was heated with stirring at 100 °C in 50% aqueous acetic acid (400 mL) for 3 hours. The reaction mixture was quenched with water (400 mL) and extracted with diethyl ether. Extracts were washed with 10% aqueous NaOH and water, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting oil was purified by Kügelrohr distillation (bp 90-100 °C, 0.01 mm Hg), followed by crystallization from petroleum ether to afford 8-methoxy-2-tetralone (**6**) as a white solid (9.5 g, 92%): mp 59 - 60 °C (Lit.[2] 58 -59 °C).

^{1}H NMR ($CDCl_3$) ∂ 2.5 (t, J = 6.7 Hz, 2H), 3.0 (t, J = 6.7 Hz, 2H), 3.5 (s, 2H), 3.8 (s, 3H) 6.76 (d, J = 8.1 Hz,1H), 6.83 (d, J = 7.5 Hz, 1H), 7.18 (t, J = 7.8 Hz, 1H).

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