Convenient, tandem and one-reaction vessel synthesis of mixed dialkylated 2-naphthols from 2-tetralone

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Abstract: A convenient acid-catalyzed method for the synthesis of 1-alkyl-2-alkoxynaphthalenes by one-reaction vessel mixed alkylation of 2-tetralone, using aryl or alkyl aldehydes and alcohols followed by aromatization, is described.

Key words: ethers, aromatization, rearrangement, alkylation, 2-alkoxynaphthalenes.

Résumé : On décrit une méthode pratique de synthèse acidocatalysée des 1-alkyl-2-alkoxynaphtalènes impliquant une réaction monotope d'alkylation mixte de la 2-tétralone à l'aide d'alcools et d'aldéhydes aliphatiques ou aromatiques suivie d'une aromatisation.

Mots clés : éthers, aromatisation, réarrangement, alkylation, 2-alkoxynaphtalènes.

Introduction

A variety of methods are known for the synthesis of 2-alkoxy-1-arylmethylnaphthalenes (**1**, R = aryl), including the reduction of 1-(2-alkoxynaphthyl) aryl ketones (1) or the reduction of 1-(2-alkoxynaphthyl) aryl carbinols (2), Pd(II)-catalyzed C—C bond formation among 2-alkoxy-1-halonaphthalenes and substituted toluenes (3), and other procedures that are cumbersome (4, 5). The C-1 alkylation and etherfication of 2-naphthol using dialkyl sulfates leading to 2-alkoxy-1-alkylnaphthalenes (**1**, R = H, R′ = CH_3; R = CH_3, R′ = C_2H_5) is known (6). This procedure has at least two limitations: (*i*) the synthesis of the corresponding mixed dialkyl derivatives is not possible; and (*ii*) the unavailability of dialkyl sulfates limits the wider utility of this procedure. Another compound belonging to this class, namely 1-butyl-2-methoxynaphthlene (**1**, R = *n*-C_3H_7, R′ = CH_3), was made by a very lengthy and unwieldy procedure (7).

2-Alkoxy-1-arylmethylnaphthalenes (**1**, R = aryl, R′= alkyl) may also be obtained by the etherification of the corresponding 1-arylmethyl-2-naphthols (**1**, R = aryl, R′ = H), for which a number of methods are known. These include a Fries-type rearrangement of 2-benzyloxynaphthalene (8), a base-catalyzed reaction between benzyl chloride or benzyl alcohol and 2-naphthol (9–12), as well as Zn-catalyzed transfer of a benzyl group from various benzyl aryl ethers to 2-naphthol (8). Some of these reactions yield side products (5, 8, 9, 11).

Recently this research group reported a novel synthetic route to this class of compounds, which involved two simple reaction steps (13). 1-Arylmethylene-2-tetralones (**A**, R = aryl) (14) were converted to 2-alkoxy-1-arylmethylnaphthalenes (**1**, R = aryl, R′ = alkyl) under anhydrous acidic conditions in common alcohols and the yields were generally satisfactory (13). As the synthesis of 1-arylmethylene-2-tetralones (**A**, R = aryl) can be carried out under anhydrous acidic conditions (13–15) and the subsequent reactions yielding the title compounds were also carried out under anhydrous acidic conditions (13), we thought that it should be possible to carry out these two reactions in the same pot, without isolating the corresponding intermediate 1-arylmethylene-2-tetralones (**A**, R = aryl). It was also realized that the success of this three-component reaction would depend on the sequence of occurrence of the two competing reactions, viz. condensation of the aldehyde group with the active methylene of 2-tetralone and the vinyl ether formation between the alcohol and the enolic form of 2-tetralone based on the reaction mechanism described previously (13) (and later in this paper). This could easily be verified by performing the reactions.

The formation of 2-alkoxy-1-alkylnaphthalenes **1a**–**1i** (Fig. 1) from a mixture of 2-tetralone, aryl or alkyl aldehydes, and an absolute alcohol under anhydrous acidic conditions (Scheme 1) is reported herein.

Received 18 November 2002. Published on the NRC Research Press Web site at http://canjchem.nrc.ca on 2 May 2003.

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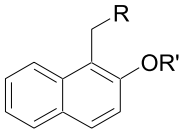
Experimental section

General

2-Tetralone and the substituted aldehydes were obtained from Aldrich Chemical Co. Column chromatography purifications were undertaken using silica gel (60–230 mesh) obtained from Aldrich Chemical Co. Hydrogen chloride gas was freshly generated in the laboratory by the action of con-

 doi: 10.1139/V03-064

Fig. 1. Chemical structures of compounds **1a**–**1i**.



1a-1i

a R = phenyl, R' = methyl
b R = phenyl, R' = ethyl
c R = phenyl, R' = *n*-butyl
d R = 4-nitrophenyl, R' = methyl
e R = 4-chlorophenyl, R' = methyl
f R = 4-methylphenyl, R' = methyl
g R = 4-carbomethoxyphenyl, R' = methyl
h R = ethyl, R' = methyl
i R = hexyl, R' = methyl

centrated sulfuric acid on the mixture of sodium chloride in concentrated hydrochloric acid in an appropriate apparatus. ^{1}H NMR spectra were recorded on a Bruker AMX 300 NMR spectrometer at 300 MHz and HR-MS spectra were obtained on VG-Analytical (Manchester, U.K.) VG-70 SEQ spectrometer. Melting points were recorded on an electrothermal apparatus and are uncorrected.

Syntheses of 2-alkoxy-1-alkylnaphthalenes (1a–1i)

General procedure

A mixture of 2-tetralone (3 mmol) and an appropriate aldehyde (3 mmol) in absolute alcohol (10 mL) was cooled by an ice bath to 0–5°C. Under anhydrous conditions, freshly generated dry hydrogen chloride gas was passed briskly through the solution for 20 min. The reaction mixture was stirred at room temperature for 24 h. Thin layer chromatography using precoated fluorescent silica gel and a developing solvent of hexane:chloroform (1:4) showed the formation of a faster moving product. The reaction mixture was evaporated to dryness under vacuum. Products (**1a**–**1c**, **1e**, **1f**, **1h**, **1i**) were purified using a silica gel (230–400 mesh) column with hexane as the eluent. Compounds **1d** and **1g** were obtained as solid powders from the reaction and were quite pure after filtration as viewed on TLC.

2-Methoxy-1-phenylmethylnaphthalene (1a)

White crystalline solid (yield: 76%). R_f = 0.59 (10% EtOAc – hexane), mp 91 to 92°C (Lit. value (1) 81 to 82°C. ^{1}H NMR (300 MHz, CDCl3) δ: 3.95 (3H, s, -OCH_3), 4.50 (2H, s, Ar-CH_2-Ar′), 7.10–7.22 (5H, m, Ar′-Hs), 7.30–7.36 (2H, m, H-3, 6), 7.38–7.42 (1H, m, H-7), 7.79–7.82 (2H, m, H-4, 5), 7.91 (1H, d, J = 8.6 Hz, H-8). HR-MS calcd. for $C_{18}H_{16}O$: 248.1201; found: 248.1196. EI-MS (70 eV) *m*/*z* (% int.): 248 (100), 233 (16), 215 (39), 202 (24), 171 (21), 141 (17), 91 (14).

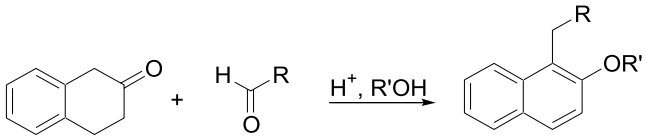
2-Ethoxy-1-phenylmethylnaphthalene (1b)

White crystalline solid (yield: 71%). R_f = 0.67 (10% EtOAc – hexane), mp 74–76°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.40 (3H, t, J = 7.0 Hz, CH_3), 4.17 (2H, q, J = 7.0 Hz, OCH_2), 4.49 (2H, s, Ar-CH_2-Ar′), 7.10–7.21 (5H, m, Ar′-Hs), 7.29–7.34 (2H, m, H-3, 6), 7.38–7.41 (1H, m, H-7), 7.75–7.80 (2H, m, H-4, 5), 7.92 (1H, d, J = 8.4 Hz, H-8). HR-MS calcd. for $C_{19}H_{18}O$: 262.1357; found: 262.1354. EI-MS (70 eV) *m*/*z* (% int.): 262 (100), 233 (44), 215 (34), 156 (19), 128 (21), 91 (31).

2-Butoxy-1-phenylmethylnaphthalene (1c)

White crystalline solid (yield: 76%). R_f = 0.78 (10% EtOAc – hexane), mp 30–32°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.95 (3H, t, J = 7.4 Hz, CH_2CH_3), 1.44–1.54 (2H, m, CH_2), 1.73–1.82 (2H, m, CH_2), 4.11 (2H, t, J = 6.4 Hz, OCH_2), 4.50 (2H, s, Ar-CH_2-Ar′), 7.10–7.22 (5H, m, Ar′-Hs), 7.30–7.34 (2H, m, H-3, 6), 7.38–7.42 (1H, m, H-7), 7.76–7.80 (2H, m, H-4, 5), 7.93 (1H, d, J = 8.5 Hz, H-8). HR-MS calcd. for $C_{21}H_{22}O$: 290.1670; found: 290.1677. EI-MS (70 eV) *m*/*z* (% int.): 290 (100), 234 (89), 215 (36), 202 (30), 156 (29), 128 (24), 91 (47).

Scheme 1.



2-Methoxy-1-(4-nitrophenylmethyl)naphthalene (1d)

White solid (yield: 87%). R_f = 0.41 (10% EtOAc – hexane), mp 103–105°C (Lit. value (3) 106–108°C). ^{1}H NMR data was found to be identical to that of the literature report (3). HR-MS calcd. for $C_{18}H_{15}NO_3$: 293.1052; found: 293.1058. EI-MS (70 eV) *m*/*z* (% int.): 293 (100), 278 (6), 262 (7), 231 (18), 215 (29), 202 (28), 171 (24), 141 (21), 128 (12), 101 (9).

1-(4-Chlorophenylmethyl)-2-methoxynaphthalene (1e)

White crystalline solid (yield: 92%). R_f = 0.49 (10% EtOAc – hexane), mp 51 to 52°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.94 (3H, s, OCH_3), 4.44 (2H, s, Ar-CH_2-Ar′), 7.10 (2H, d, J = 8.6 Hz, H-2′, 6′), 7.16 (2H, d, J = 8.6 Hz, H-3′, 5′), 7.32–7.36 (2H, m, H-3, 6), 7.39–7.47 (1H, m, H-7), 7.79–7.87 (3H, m, H-4, 5, 8). HR-MS calcd. for $C_{18}H_{15}ClO$: 282.0811; found: 282.0820. EI-MS (70 eV) *m*/*z* (% int.): 282 (100), 267 (13), 251 (20), 231 (26), 215 (49), 202 (31), 171 (29), 141 (20), 125 (18), 115 (14), 101 (17).

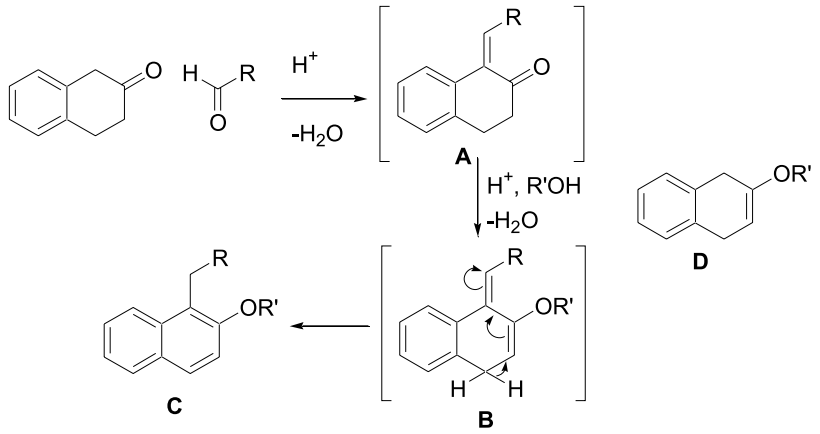
2-Methoxy-1-(4-methylphenylmethyl)naphthalene (1f)

White crystalline solid (yield: 84%). R_f = 0.47 (10% EtOAc – hexane), mp 58 to 59°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.27 (3H, s, Ar-CH_3), 3.95 (3H, s, OCH_3), 4.46 (2H, s, Ar-CH_2-Ar′), 7.02 (2H, d, J = 8.0 Hz, H-2′, 6′), 7.09 (2H, d, J = 8.2 Hz, H-3′, 5′) 7.30–7.37 (2H, m, H-3, 6), 7.38–7.43 (1H, m, H-7), 7.78–7.82 (2H, m, H-4, 5), 7.93 (1H, d, J = 8.6, H-8). HR-MS calcd. for $C_{19}H_{18}O$: 262.1357; found: 262.1363. EI-MS (70 eV) *m*/*z* (% int.): 262 (100), 247 (25), 231 (34), 215 (34), 202 (19), 189 (8), 171 (15), 158 (10), 141 (14), 115 (13), 105 (16).

1-(4-Carbomethoxyphenylmethyl)-2-methoxynaphthalene (1g)

White solid (yield: 90%). R_f = 0.28 (10% EtOAc – hexane), mp 88 to 89°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.86 (3H, s, CO_2CH_3), 3.94 (3H, s, OCH_3), 4.52 (2H, s, Ar-CH_2-Ar′), 7.21–7.25 (2H, d, J = 8.5 Hz, H-2′, 6′), 7.32–7.44 (3H, m, H-3′, 5′, 6), 7.78–7.89 (5H, m, Ar-Hs). HR-MS calcd. for $C_{20}H_{18}O$: 306.1256; found: 306.1266. EI-MS (70 eV) *m*/*z* (% int.): 306 (100), 291 (4), 275 (14), 231 (15), 215 (27), 202 (14), 171 (13), 141 (12), 101 (7), 83 (27).

Scheme 2.



2-Methoxy-1-propylnaphthalene (1h)

Light brown viscous oil (yield: 30%). R_f = 0.61 (10% EtOAc – hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.02 (3H, t, J = 7.3 Hz, CH_2CH_3), 1.63–1.70 (2H, m, $CH_2CH_2CH_3$), 3.07 (2H, t, J = 7.9 Hz, $ArCH_2$), 3.95 (3H, s, OCH_3), 7.25–7.37 (2H, m, H-3, 6), 7.44–7.51 (1H, m, H-7), 7.70–7.81 (2H, m, H-4, 5), 7.97 (1H, d, J = 8.6, H-8). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.70, 23.57, 27.20, 56.82, 113.75, 123.31, 123.64, 124.46, 126.26, 127.55, 128.70, 129.48, 133.28, 154.55. HR-MS calcd. for $C_{14}H_{16}O$: 200.1201; found: 200.1208. EI-MS (70 eV) *m*/*z* (% int.): 200 (44), 183 (26), 171 (100), 157 (96), 141 (66), 128 (56), 115 (24).

1-Heptyl-2-methoxynaphthalene (1i)

Colorless viscous oil (yield: 78%). R_f = 0.65 (10% EtOAc – hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.93 (3H, t, J = 6.8 Hz, CH_2CH_3), 1.30–1.53 (8H, m, $ArCH_2CH_2(CH_2)_4CH_3$), 1.63–1.69 (2H, m, $ArCH_2CH_2CH_2$), 3.11 (2H, t, J = 7.7 Hz, $ArCH_2$), 3.96 (3H, s, OCH_3), 7.29 (1H, d, J = 9.0 Hz, H-3), 7.33–7.39 (1H, m, H-6), 7.47–7.52 (1H, m, H-7), 7.73 (1H, d, J = 9.0 Hz, H-4), 7.81 (1H, d, J = 8.1, H-5), 8.0 (1H, d, J = 8.5, H-8). HR-MS calcd. for $C_{18}H_{24}O$: 256.1827; found: 256.1825. EI-MS (70 eV) *m*/*z* (% int.): 256 (51), 171 (100), 141 (31), 115 (7).

Results and discussion

It was found that when dry hydrogen gas was passed through a solution of 2-tetralone and benzaldehyde in absolute methanol for 20 min, and the reaction stirred at room temperature for 24 h, the TLC showed the formation of a faster moving spot. This product upon workup was characterized as 2-methoxy-1-phenylmethylnaphthalene (**1a**) in good yield.

The initial reactions in the present study were carried out in methyl alcohol (**1a**, **1d**–**1g**), but to confirm the generality of this procedure, one reaction in each of ethyl alcohol and *n*-butyl alcohol were also carried out under similar conditions. These attempts with 2-tetralone and benzaldehyde successfully yielded the compounds **1b** and **1c**. In the case of the reaction of 2-tetralone with 4-carboxybenzaldehyde in methanol, the obtained product (**1g**) had the carbomethoxy group as expected. We also found that this reaction worked for aliphatic aldehydes also and using propionaldehyde and heptaldehyde in methanol, we were able to make 2-methoxy-1-propylnapthalene **1h** and 1-heptyl-2-methoxynapthalene **1i** in 30 and 78% yield, respectively.

The likely mechanism of formation of these compounds seems similar to what was proposed in our previous paper (13) except that 1-arylidene-2-tetralone (**A**, R = Ar) or 1-alkylidene-2-tetralone (**A**, R = alkyl) are intermediates here. The formation of the enol ether **B** and subsequent rearrangement to **C** makes use of the extended conjugation (Scheme 2). Formation of an α,β-unsaturated species from the corresponding active methylene compound and aldehyde is very common in anhydrous acidic conditions (14, 15). Enol ethers are also easily formed under similar conditions especially when the ketone has an α-hydrogen atom (16), while hydronaphthalenes are quite amenable to aromatization (13, 17). Aromatization reactions usually require catalysts and harsh conditions (17), though highly facile aromatizations in different structural moieties are known (18). It was demonstrated by isotopic labeling studies in our previous work (13) that the rearrangement of protons does not take place by the less likely concerted 1,5-sigmatropic type rearrangement (for which a *cisoid* conformation is a prerequisite (19)) but follows the more favorable dissociation mechanism.

Based on these results, it can also be concluded that the condensation of the aldehyde group with the active methylene of 2-tetralone leading to the formation of **A** was favored over the formation of vinyl ether **D** as the highly predominant (or exclusive) intermediate. No efforts were made to detect the formation of **D** in the reaction mixture.

Conclusions

In conclusion, we have devised an exceptionally simple method to perform efficient and selective mixed *C*- and *O*-alkylation leading to 2-alkoxy-1-alkylnaphthalenes from 2-tetralone using an aldehyde and an alcohol under anhydrous acidic conditions. This transformation could be of importance to synthetic and combinatorial chemists. We are working towards widening the scope of this procedure.

Acknowledgement

Purdue Neuroscience Company, U.S.A., supported this work.

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