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Convenient synthesis of novel 2,2-dialkyl-1,2-dihydronaphtho[2,1-*b*]furans

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ABSTRACT

Reaction of 2,2-dialkylacetaldehydes with electron-rich 2-naphthols in presence of *p*-TSA under closed-vessel solvent-free microwave irradiation conditions resulted in formation of corresponding dihydronaphtho[2,1-*b*]furans in good to excellent yields. In several cases, small amounts of 14-alkyl-14*H*-dibenzo[*a*,*j*]xanthenes were also formed.

Benzofuran and naphthofuran frameworks are found abundantly in a number of biologically relevant natural products[1] and therefore their chemical syntheses have attracted considerable attention.[2] A plethora of biological activities have also been associated with a large number of synthetic benzofuran and naphthofuran analogs.[3]

Since this investigation deals with a new synthetic approach to prepare 1,2-dihydronaphtho[2,1-*b*]furans, it is imperative to review common and important literature procedures employed to construct this type of compounds. Claisen rearrangement of substituted allyl phenyl ethers followed by subsequent cyclization is a widely studied route to prepare dihydrobenzofurans and naphtho[2,1-*b*]furans.[4] 2-Allyl phenols formed after the first step in this process are often isolated as a side product.[4] Recently, an Ir(III)-catalyzed tandem Claisen rearrangement-intramolecular hydroaryloxylation to produce dihydrobenzofurans was developed.[5] Alternatively, direct synthesis of 2-allyl phenols by Lewis acid-catalyzed alkylation of phenols followed by acid-catalyzed cyclization also led to dihydrobenzofurans.[6] Pochini et al. reported *ortho*-condensation between magnesium phenolates and carbonyl compounds to produce alkylidene-bisphenols, 2-alkenyl-phenols, and 2,3-dihydrobenzofurans in varying ratios.[7] A simple dihydronaphtho[2,1-*b*]furan was produced by *o*-allylation of 6-bromo-2-naphthol followed by ozonolysis and reduction sequence to produce 6-bromo-1-(2-hydroxyethyl)naphthalen-2-ol and finally the ring closure was affected under acid-catalyzed conditions.[8] A mechanistically interesting approach involves a three-step protocol where the phenol is condensed with two molar equivalents of an allene in presence of a Pd(0) catalyst to produce *O*-dienyl derivative which undergoes Claisen rearrangement to *ortho*-*C*-dienyl derivative, which in turn undergoes acid-catalyzed intramolecular cyclization to produce dihydrobenzopyran (major) and dihydrobenzofuran (minor) derivatives.[9] Similar outcomes were achieved when phenols were reacted with conjugated dienes using 5 mol % silver triflate.[10] The product distribution between the dihydrobenzopyran and dihydrobenzofuran depended upon the diene used.[10] Another interesting synthetic conversion employs rearrangement of dihydronaphtho[1,2]dioxines (prepared from 1-formyl naphthalene) to 1-(β-keto)-2-naphthols which reacted with methyl(triphenylphosphoranylidene)acetate to afford 2,2-disubstituted 1,2-dihydronaphtho[2,1-*b*]furans.[11] Articulated dihydrobenzofurans were also prepared in one operation by reacting a vinyl sulfoxide with phenols.[12] Lithiation of 2,2-dialkyl-4*H*-benzo[*d*][1,3]dioxine resulted in formation of the corresponding homobenzylic alcohol which cyclized in presence of phosphoric acid to 2,2-dialkyl-2,3-dihydrobenzofurans.[13] $PdCl_2$-catalyzed intramolecular activation of electroneutral cyclopropane ring of 1-(2-ethylcyclopropyl)naphthalen-2-ol resulted in cleavage of the cyclopropane ring followed by formation of 2-ethyl, 2-methyl-1,2-dihydronaphtho[2,1-*b*]furan.[14] Another study reports Pd-catalyzed alkane arylation of tertiary alkyl 2-bromophenyl ethers resulting in formation of dihydrobenzofurans and dihydronaphthofurans.[15] Buchwald[16] and Hartwig[17] have also reported formation of 2,2-dialkyl-2,3-dihydrobenzofurans from 2-1,1-dialkyl-(2-bromophenyl)ethanols employing their protocol of Pd-catalyzed C–O coupling on aryl halides.

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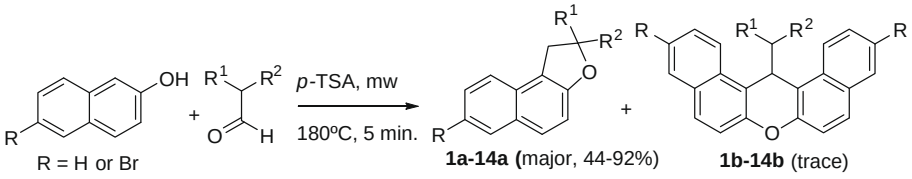


Scheme 1. Synthetic scheme followed to produce compounds **1a–14a** and **1b–14b**. Substituents are reported in Table 1.

Although the preceding discussion portrays several elegant methodologies, it also makes it abundantly clear that the existing procedures are inefficient, and involve multiple steps, expensive reagents and non-commercial starting materials. We herein report a simple, facile, and cost-effective formation of 2,2-dialkyl-1,2-dihydronaphtho[2,1-*b*]furans by reacting 2-naphthol analogs and 2,2-dialkyl acetaldehydes in the presence of catalytic amounts of *p*-toluene sulfonic acid (*p*-TSA) under solvent-free microwave irradiation conditions. Certain reactions also yielded 14-alkyl-14*H*-dibenzo[*a,j*]xanthenes in small quantities (Scheme 1).

One of the interests of our research group lies in development of novel structural frameworks from 2-naphthol analogs.[18] Reaction of 2-naphthol with non-enolizable aromatic aldehydes is a widely studied reaction that produces 14-aryl-14*H*-dibenzo[*a,j*]xanthenes in near quantitative yields.[19] On the contrary, aliphatic aldehydes with two enolizable protons produce a complex mixture of products in the form of tarry masses when reacted with 2-naphthol, understandably owing to a number of possible competing reactions such as aldol condensations, C-alkylation of 2-naphthol by aldehydes and aldol products and dehydrated secondary products. We were curious as to how aliphatic aldehydes with one enolizable proton will behave when reacted with 2-naphthol; the availability of a single enolizable proton should limit any possible competing reactions. Reaction of equimolar ratio of isobutyraldehyde with 2-naphthol in the presence of a catalytic amount of *p*-TSA under solvent-free microwave irradiation conditions resulted in formation of 2,2-dimethyl-1,2-dihydronaphtho[2,1-*b*]furan as the major product. Encouraged by the results we decided to test the generality and scope of the reaction by employing a variety of 2,2-dialkylacetaldehydes, 2-naphthol analogs, and other phenols.[20] Our literature search indicated that such a synthetic procedure to dihydronaphthofuran is novel and resulting compounds with general structure 2,2-dialkyl-1,2-dihydronaphtho[2,1-*b*]furan have not been reported in the chemical literature with the exception of 2,2-dimethyl-1,2-dihydronaphtho[2,1-*b*]furan[4d,7,15] and 2-ethyl,2-methyl-1,2-dihydronaphtho[2,1-*b*]furan.[14] Our reactions and the physical data for compounds **1-14** are summarized in Table 1.

The mechanism of formation of naphthofuran products appears to be straightforward. The proposed mechanism using isobutyraldehyde and 2-naphthol as starting materials is shown in Scheme 2. Nucleophilic C attack of 2-naphthol led to formation of a secondary alcohol intermediate which formed a secondary benzylic carbocation through corresponding oxonium ion under catalytic amount of *p*-TSA. 1,2-Hydride shift leading a tertiary carbocation followed by nucleophilic attack by the naphthol oxygen led to formation of a stable furan ring.

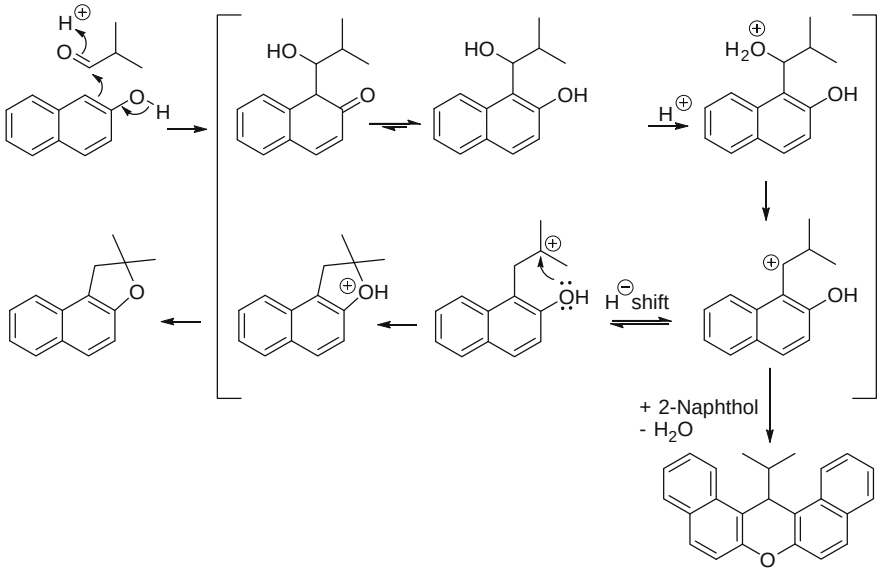
This reaction appears to work excellently with 2-naphthol and analogs, but with simpler phenols it appears to behave differently. Reaction of 4-*tert*-butylphenol with isobutyraldehyde led to formation of three products (based on TLC) under the same reaction conditions (Scheme 3). The reaction mixture was analyzed by GC–MS. The GC–MS indicated four peaks in the chromatograms one of which corresponded to the starting phenol [M^+ 150]. The molecular ions of the remaining three peaks were 204, 408, and 462. These were tentatively identified as 4-*tert*-butyl-2-(2-methylprop-1-enyl)phenol (**15**), 4-*tert*-butyl-1-(1-(4-*tert*-butylphenoxy)-2-methylpropoxy)-2-(2-methylprop-1-enyl)benzene (**16**), and 4,4′-(2-methylpropane-1,1-diyl)bis(oxy)bis(1-*tert*-butyl-3-(2-methylprop-1-enyl)benzene) (**17**), respectively. The compound with M^+ at 204 was identified as 4-*tert*-butyl-2-(2-methylprop-1-enyl)phenol and not as isomeric 5-*tert*-butyl-2,2-dimethyl-2,3-dihydrobenzofuran due to the presence of 4,4′-(2-methylpropane-1,1-diyl)bis(oxy)bis(1-*tert*-butyl-3-(2-methylprop-1-enyl)benzene) for which 4-*tert*-butyl-2-(2-methylprop-1-enyl)phenol serves as the intermediate. Extensive studies on 4-*tert*-butylphenol and other phenols will be reported subsequently.

In conclusion, we have developed a simple, facile, and efficient microwave-assisted reaction for the synthesis of 2,2-dialkyl-1,2-dihydronaphtho[2,1-*b*]furans from 2-naphthol analogs, 2,2-dialkylacetaldehydes, and catalytic amount of *p*-TSA. Our preliminary

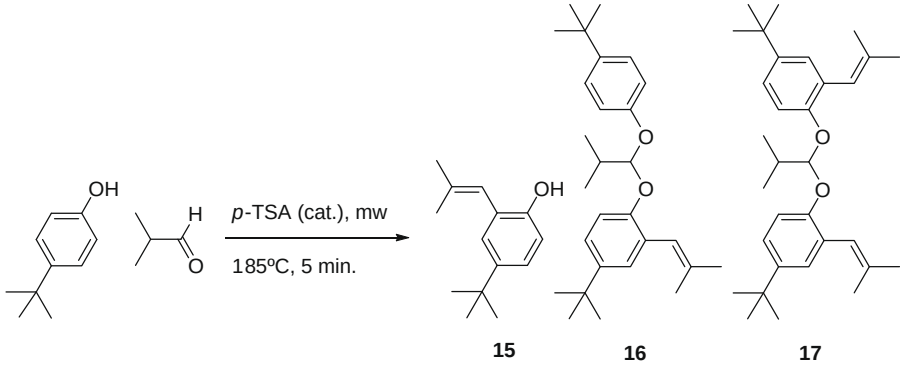
Table 1
Physical data for compounds **1–14**

Entry	R	R^1	R^2	Naphtho[2,1-*b*]furans (**a**)		Dibenzo[*a,j*]xanthenes (**b**)	
				% Yield	Mp	% Yield	Mp
1	H	Me	Me	48	Liquid[a]	8	128–136
2	H	Me	Et	80	Liquid	2	Liquid
3	H	Me	*n*-Pr	46	Liquid	2	Liquid
4	H	Me	Ph	73	76–78	NI	Liquid
5	H	Et	Et	71	Liquid	NI	Liquid
6	H	Et	*n*-Bu	44	Liquid	5	Liquid
7	H	$-(CH_2)_5-$		90	Liquid	5	Liquid
8	Br	Me	Me	74	60–64	4	188–180
9	Br	Me	Et	73	Liquid	NI	—
10	Br	Me	*n*-Pr	65	Liquid	NI	—
11	Br	Me	Ph	79	Liquid	NI	—
12	Br	Et	Et	83	Liquid	NI	—
13	Br	Et	*n*-Bu	91	Liquid	NI	—
14	Br	$-(CH_2)_5-$		92	80–83	NI	—

NI: not isolated.
[a] Lit. mp 42–43 °C.[7]



Scheme 2. Proposed mechanism of formation of 2,2-dimethyl-1,2-dihydronaphtho[2,1-*b*]furan and 14-isopropyl-14*H*-dibenzo[*a,j*]xanthenes from 2-naphthol and isobutyraldehyde.



Scheme 3. Reaction between 4-*tert*-butylphenol and isobutyraldehyde. Products were analyzed based on GC–MS data.

results indicate that this reaction is specific to 2-naphthol analogs; other phenols lead to formation of different type of products.

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20. In a typical procedure 2-naphthol (10 mmol) and cyclohexane carboxaldehyde (10 mmol) are combined in a microwave vial with a catalytic amount of 4-

toluene sulfonic acid (~50 mg), and are heated at 185 °C for 5 min in a CEM Discover S-Class microwave reactor. Subsequent purification of the compound via column chromatography yielded 1′*H*-spiro[cyclohexane-1,2′-naphtho[2,1-*b*]furan] as a light-brown viscous liquid in 90% yield. Spectroscopic data are presented here.[1] ^{1}H NMR: δ 1.82–1.90 (m, 10H, CH_2), 3.26 (s, 2H, Ar–CH_2), 7.11 (d, J = 8.8, 1H, Ar–H), 7.31 (d, J = 7.9, 1H, Ar–H), 7.44 (t, J = 7.2, 1H, Ar–H), 7.59 (d, J = 8.2, 1H, Ar–H), 7.69 (d, J = 8.8, 1H, Ar–H), 7.79 (d, J = 8.2, 1H, Ar–H). ^{13}C NMR: δ 23.15, 25.29, 37.54, 39.96, 89.51, 112.56, 117.96, 122.51, 124.05, 126.51, 128.01, 128.77, 128.86, 131.27, 156.40. UV–vis (λ_{max}): 235 nm. IR (NaCl; ν_{max}): 3057, 2926, 2855, 1600, 1465, 1261, 1205, 808. EIMS (amu): 238 [M^+, 100%].