UNEXPECTED IODINE CATALYZED CYCLIZATION FOR SYNTHESIS OF 2,2-DIALKYL-2,3-DIHYDROBENZOFURANS

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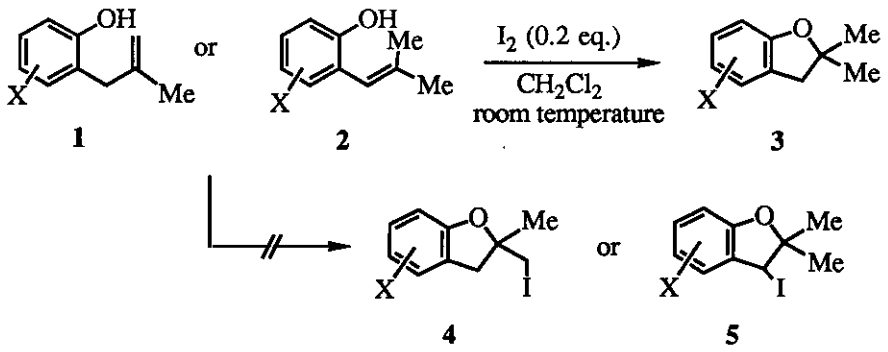
Abstract - 2-(β-Methylallyl)phenol and 2-isobutenylphenol derivatives were easily cyclized to 2,2-dimethyl-2,3-dihydrobenzofurans in the presence of a catalytic amount of iodine without any formation of iodinated products.

2,3-Dihydrobenzofurans are important precursors for the synthesis of a variety of natural products and pesticides, and many methods for the preparation of these compounds have been developed.[1] The halo-cyclization of 2-allylphenols or 2-(α-methylallyl)phenols by an electrophilic halogenating agents, such as iodine monochloride, bromine and NBS, has been known to produce the corresponding 2-halomethyl-2,3-dihydrobenzofurans.[2]

In the course of our program to synthesize various 2,3-dihydrobenzofuran derivatives, we observed an unexpected iodine catalyzed cyclization reaction. The reaction of 2-(β-methylallyl)phenols (**1**) and 2-isobutenylphenols (**2**) in the presence of a catalytic amount of iodine gave 2,2-dimethyl-2,3-dihydrobenzofurans (**3**) without any detection of the normally expected 2-iodomethyl-2-methyl-2,3-dihydrobenzofurans (**4**) or 2,2-dimethyl-3-iodo-2,3-dihydrobenzofurans (**5**) (**Scheme 1**). Typically, the reaction of 2-(β-methylallyl)-3,5,6-trimethylphenol (**1a**) with iodine (0.2 equiv.) in dry methylene chloride at room temperature for 30 min resulted in clean conversion to 2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran (**3a**). The reaction mixture was washed with 5% aqueous sodium thiosulfate and purified by column chromatography to give a 98 % yield of pure product (**3a**). This reaction was found to be clean, easy to work-up, and gave good to excellent yields of **3** without formation of iodine containing compounds and polymeric resins.



X for Compound **1** or **2** :

a = 3,5,6-Me_3	**e** = 6-CHO
b = 6-Cl-3,4-Me_2	**f** = H
c = 6-Me	**g** = 6-OH
d = 6-Cl	**h** = 6-NO_2

X for Compound **3**, **4** or **5** :

a = 4,6,7-Me_3	**e** = 7-CHO
b = 7-Cl-4,5-Me_2	**f** = H
c = 7-Me	**g** = 7-OH
d = 7-Cl	**h** = 7-NO_2

Scheme 1

The representative results are summarized in **Table 1**. Analogously, 2-isobutenylphenols (**2**)[1a] gave also good yields of 2,2-dimethyl-2,3-dihydrobenzofurans (**3**) but needed longer reaction period to complete the reaction (Entries 8, 9 and 10). The reaction was conducted in dry carbon tetrachloride or methylene chloride to avoid the external proton source which may generate HI with iodine. The use of 0.2 equiv. of iodine completed the reaction within 30 min whereas the use of less than 0.2 equiv. (e.g, 0.1 eq.) required somewhat longer reaction time (Entry 2). However, the use of larger amounts of iodine found not to affect the yields.

The reaction of 2-(β-methylallyl)-3,5,6- trimethylphenol (**1a**) with iodine monochloride (0.2 eq. / CCl_4 / room temperature, 30 min) gave the similiar result (98 %), but with chlorine (2 M in DMF, 0.2 eq./ CH_2Cl_2 / room temperature, 24 h) afforded somewhat lower yield (63 %) without any detection of halogenated products, whereas bromine (0.2 eq./ CH_2Cl_2 / room temperature, 30 min) gave a mixture of 2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran (**3a**) (68 %) and 3-bromo-2,2,4,6,7-pentamethyl-2,3-dihydro-benzofuran (24 %). Cyclization of 2-(β-methylallyl)-3,5,6-trimethylphenol (**1a**) with HI (99.9%, 0.2 eq. / CH_2Cl_2 / room temperature, 30 min) gave 2,2,4,6,7-pentamethyl- 2,3-dihydrobenzofuran (**3a**) in 21 % yield. The results indicated that iodine is very effective reagent as a catalyst to generate 2,2-dimethyl-2,3-dihydrobenzofuran.

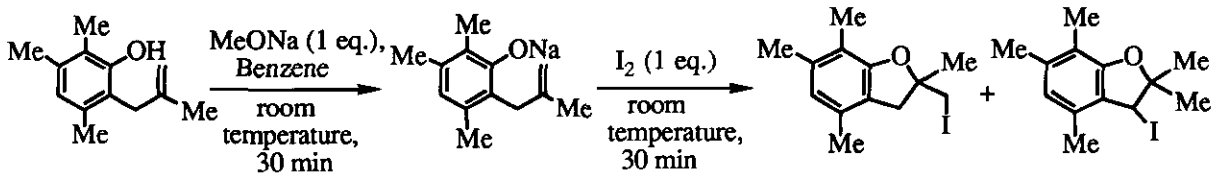
Table 1. Iodine Catalyzed Cyclization of 2-(β-Methylallyl)phenols and 2-Isobutenylphenols.

Entry	Phenol	Reaction Conditions	Product[a]	Yield (%)
1	**1a**	I_2 (0.2 eq.) / CH_2Cl_2 / room temperature, 30 min	**3a**	98
2	**1a**	I_2 (0.1 eq.) / CH_2Cl_2 / room temperature, 6 h	**3a**	100
3	**1b**	I_2 (0.2 eq.) / CH_2Cl_2 / room temperature, 30 min	**3b**	97
4	**1d**	I_2 (0.2 eq.) / CH_2Cl_2 / room temperature, 30 min	**3d**	96
5	**1e**	I_2 (0.2 eq.) / CH_2Cl_2 / room temperature, 30 min	**3e**	63
6	**1g**	I_2 (0.2 eq.) / CH_2Cl_2 / room temperature, 30 min	**3g**	84
7	**1h**	I_2 (0.2 eq.) / CH_2Cl_2 / room temperature, 30 min	**3h**	no reaction
8	**2a**	I_2 (0.2 eq.) / CH_2Cl_2 / room temperature, 4 h	**3a**	97
9	**2c**	I_2 (0.2 eq.) / CH_2Cl_2 / room temperature, 1 h	**3c**	80
10	**2f**	I_2 (0.2 eq.) / CH_2Cl_2 / room temperature, 1 h	**3f**	80

[a] All compounds gave the satisfactory spectral data and physical properties (see ref. 1h).

The electron-withdrawing substituents on the phenyl moiety as in 2-(β-methylallyl)phenol-6-carboxaldehyde (**1e**) decreased the yield of 2,2-dimethyl-2,3-dihydrobenzofuran-7-carboxaldehyde (**3e**) (Entry 5). Strong electron-withdrawing nitro group as in 6-nitro-2-(β-methylallyl)phenol (**1h**) failed to give the desired product (**3h**) (Entry 7). It could be assumed that the tight hydrogen bond between phenolic hydrogen atom and the oxygen atom of nitro group should prohibit the cyclization reaction.

We also examined the cyclization of **1a** with iodine in the presence of sodium methoxide in dry benzene in order to prohibit the participation of the acidic proton of phenol in the reaction (**Scheme 2**). A mixture of



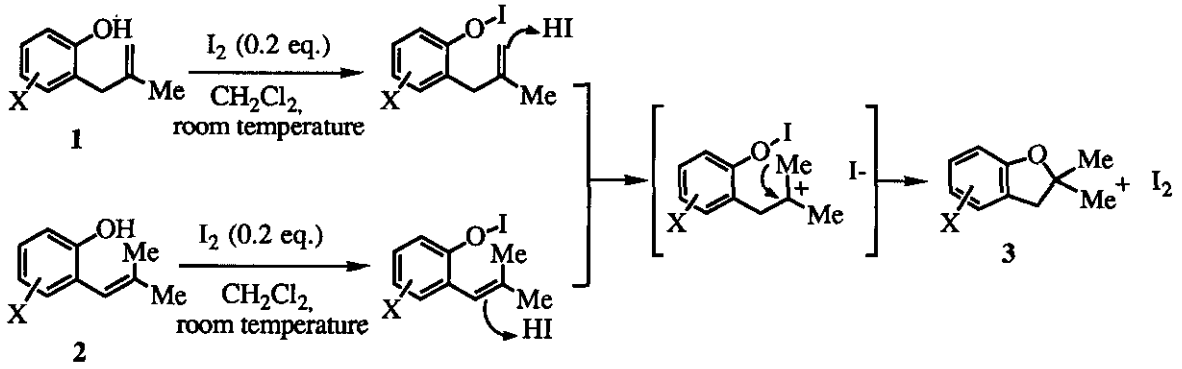
1a **4a** **5a**

Scheme 2

2-iodomethyl-2,4,6,7-tetramethyl-2,3-dihydrobenzofuran (**4a**)[3] and 2,2,4,6,7-pentamethyl-3-iodo-2,3-dihydrobenzofuran (**5a**)[4] was obtained in a ratio of 4 : 3 in total 83% yield. Iodocyclization of **1a** by the literature[5] (aq. $NaHCO_3$, 2 eq. / I_2, 1 eq. / MeCN) resulted in **4a** in 63% yield without detection of **3a** and **5a**. The results showed that the free phenolic hydrogen atom is crucial to generate 2,2-dimethyl-2,3-dihydrobenzofurans.

The attempted reactions of iodocyclized product(**4a**)to **3a** with HI or I_2 proved to be ineffective. Thus, the possibility of the formation of **3a** *via* the normal iodocyclization followed by reduction should be apparently excluded.

We tentatively propose a plausible mechanism for the reaction as shown in **Scheme 3** on the basis of our observations. Iodine may interact initially with phenolic hydrogen to generate HI, followed by generation of tertiary carbonium ion, and then intramolecular cyclization to afford 2,3-dihydro-2,2-dimethylbenzofurans.



Scheme 3

In summary, we found that the free phenolic hydrogen atom and alkyl moiety at the olefinic double bond to form tertiary carbonium ion (**Scheme 3**) are essential for **1** and **2** to undergo the intramolecular cyclization reaction, which shows quite different mode of reaction from the known iodocyclization.[2,5] The unpresented iodine catalyzed reaction should be very useful for the preparation of 2,2-dimethyl-2,3-dihydrofurans(**3**)under very mild condition.

Typical experimental procedure for the synthesis of 2,3-dihydro-2,2-dimethylbenzofurans (**3**) : Iodine (0.51 g, 2 mmol) was added to a stirred solution of **1a** or **2a** (1.90 g, 10 mmol) in dry methylene

chloride (20 ml). The solution was stirred for 30 min and quenched with 5 % aqueous sodium thiosulfate. After usual extractive workup, the crude product was purified by silica gel column chromatography using n-hexane as an eluent to give **3a**.

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3. 2-Iodomethyl-2,4,6,7-tetramethyl-2,3-dihydrobenzofuran (**4a**) ; white solid. mp = 55 °C ; ^{1}H nmr (200 MHz, $CDCl_3$) ; δ 1.66 (s, 3H), 2.08 (s, 3H), 2.16 (s, 3H), 2.20 (s, 3H), 2.95(d, J=15.7, 1H), 3.20 (d, J=15.7, 1H), 3.41 (s, 2H), 6.51 (s, 1H). ; ms (70 eV) m/z (rel. intensity) 316 (M^+, 100), 189 (96), 174 (43).

4. 2,2,4,6,7-Pentamethyl-3-iodo-2,3-dihydrobenzofuran (**5a**) was identified from ^{1}H nmr spectra with a mixture **4a** ; ^{1}H nmr (200 MHz, $CDCl_3$) ; δ 1.46 (s, 6H), 2.06 (s, 3H), 2.14 (s, 3H), 2.18 (s, 3H), 2.89 (s, 1H), 6.46 (s, 1H).

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