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An elegant and unprecedented approach to 2-methylbenzofurans

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Abstract—An effective route for the synthesis of a variety of 2-methylbenzofurans is reported via DBU catalyzed dehydroiodination of easily accessible 2-iodomethyl-2,3-dihydrobenzofurans. The latter could be easily obtained by water mediated iodocyclization of allyl phenols.

In Nature's collection of biologically active heterocycles and in synthetic compounds, the benzofuran ring system is a common structural feature.[1–4] Benzofuran derivatives have been reported as estrogen receptor (ER) ligands,[5] H3 receptor antagonists,[6] selective ligands for the dopamine D3 receptor subtype,[7] metalloproteinase-13 inhibitors[8] and antifungal agents.[9] Furocoumarins (psoralens, 7*H*-furo[3,2-*g*]-1-benzopyran-7-ones) are widely used in PUVA therapy (psoralen plus UVA irradiation) as photoreactive drugs in the treatment of various skin diseases such as psoriasis, mycosis fungoides, vitiligo[10–12] and in photopheresis, an extracorporal form of photochemotherapy.[13,14] The derivatives, which are usually employed for both PUVA and photopheresis, are 8-methoxypsoralen (8-MOP), 5-methoxypsoralen (5-MOP) and 4,5,8-trimethylpsoralen (TMP).[15] The structures of a few of these compounds are listed below (Fig. 1), including Euparin,[16a] dehydrotremetone[16b] and Cicerfuran.[16c]

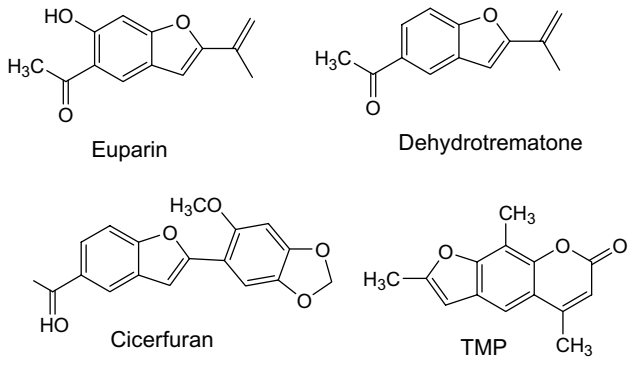

Figure 1. Selected biologically active benzofurans.

Consequently, various methods have been developed for the synthesis of benzofurans.[17] These methods utilize strongly acidic or basic conditions or organometallic catalysts.[18] The 2-methylbenzofuran moiety is a common constituent of many biologically active compounds and has recently been synthesized by Pd^{II} catalyzed oxidative cyclization of allyloxy phenols. Most of the methods developed so far suffer from one or more drawbacks including low yields, use of toxic and expensive reagents, long reaction times, hazardous (strongly acidic or basic reaction conditions) and environmental pollution. Recently, Fousteris et al.[19] developed an elegant, green process for the synthesis of 2-(iodomethyl)dihydrobenzofurans via water promoted iodocyclization of 2-allylphenols.

In continuation of our quest to develop new antitubercular agents and based on reports of antitubercular activities in purines[20] and benzofurans[21,22] we were interested in the synthesis of dihydrobenzofuryl purines and pyrimidines by replacing the iodine of iodomethyl dihydrobenzofurans in the presence of a base. Thus 2-allyl-4-chlorophenol (**1a**) on reaction with 1.1 mol of iodine in water at 50 °C gave the required intermediate 5-chloro-2-(iodomethyl)-2,3-dihydrobenzofuran (**2a**) in 75% yield. Compound **2a** was reacted with imidazole or benzimidazole under different experimental conditions (Scheme 1) in the presence of various inorganic and organic bases and the progress of the reaction was monitored by TLC.

Keywords: Benzofurans; Allyl phenols; Iodocyclization; DBU.
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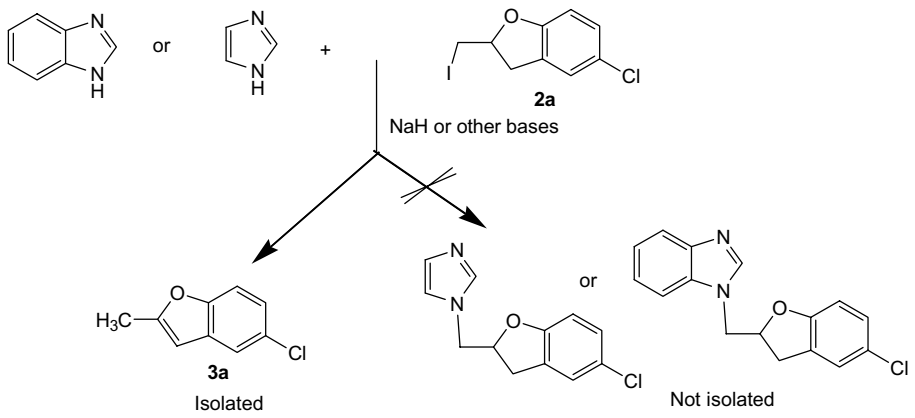


Scheme 1.

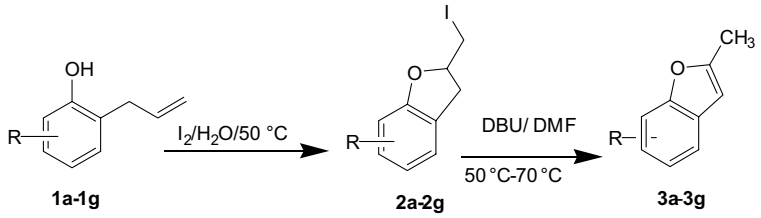
Table 1. Reaction of 5-chloro-2-iodomethyl-2,3-dihydrobenzofuran **2a** with imidazole and benzimidazole in the presence of different inorganic and organic bases

Entry	Reaction conditions	Time	% Yield of **3a**
1	NaH/DMF, 50 °C	6 h	20
2	Imidazole/NaH/DMF, 50 °C	2 h	70
3	Benzimidazole/NaH/DMF, 50 °C	2 d	65
4	Benzimidazole/Cs_2CO_3/DMF, 50 °C	3 d	<10
5	Benzimidazole/DBU/DMF, 50 °C	2 h	80
6	DBU/DMF, 50 °C	1 h	85
7	DABCO/DMF, 50 °C	4 h	82

A fast moving compound was observed in each of the above reactions (TLC), which was isolated in varying yields and identified as 5-chloro-2-methylbenzofuran (**3a**). Unreacted imidazole and benzimidazole were recovered. The structure of compound **3a** was established on the basis of spectroscopic data. Thus, instead of the expected 1-(5-chloro-2,3-dihydrobenzofuran-2-ylmethyl)-1*H*-imidazole/benzimidazole, the product was 5-chloro-2-methylbenzofuran (**3a**). DBU, a hindered organic base proved to be the best catalyst for conversion of 5-chloro-2-iodomethyl-2,3-dihydrobenzofuran to 5-chloro-2-methylbenzofuran (85%, 1 h). DABCO, another hindered base, although affording an 82% yield of **3a**, required a longer reaction time of 4 h (Table 1).

Similarly, reaction of 2-(iodomethyl)dihydrobenzofurans **2b**–**2g**, obtained by water mediated iodocyclization of 2-allylphenols **1a**–**1g**, with DBU resulted in the corresponding 2-methylbenzofurans **3b**–**3g** in good yields (Scheme 2). The results are presented in Table 2 and the structures were established on the basis of spectroscopic data and elemental analysis.

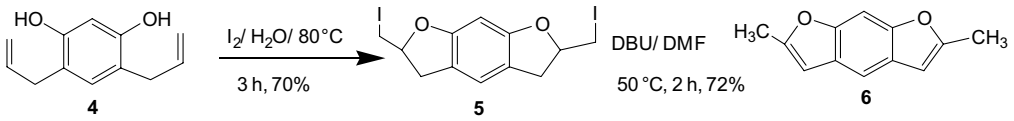
The method was also used for the synthesis of bis-benzofuran. Thus, reaction of 4,6-diallyl-benzene-1,3-diol (**4**) with iodine in water resulted in the formation of the intermediate 2-(iodomethyl)dihydrobenzofuran **5** in 70% yield. The latter on treatment with DBU as above gave the required product, 2,6-dimethylbenzo[1,2-*b*;



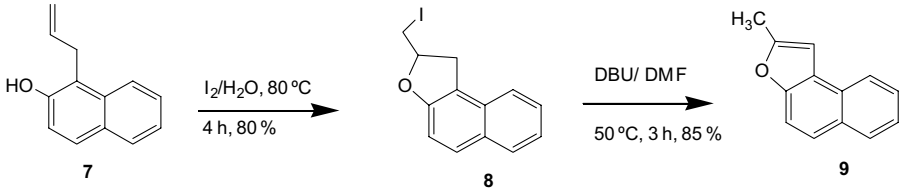
Scheme 2. Synthesis of 2-methylbenzofurans from 2-allylphenols.

Table 2. Synthesis of benzofurans **3a**–**3g** from allyl phenols **1a**–**1g**

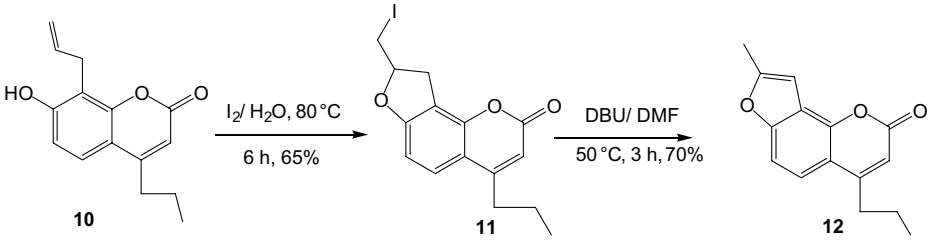
Entry	Allyl phenol	R	Dihydrobenzofuran	Time (h)	% Yield	2-Methylbenzofuran	Time (h)	% Yield
1	**1a**	4-Cl	**2a**	1	75	**3a**	1	85
2	**1b**	2,4-Di-Cl	**2b**	2	81	**3b**	1	82
3	**1c**	2,3-Di-Me	**2c**	2	76	**3c**	4	80
4	**1d**	2,5-Di-Me	**2d**	1.5	80	**3d**	3.5	78
5	**1e**	3-Me-4-Cl	**2e**	15	81	**3e**	8	76
6	**1f**	4-CN	**2f**	2	71	**3f**	2	85
7	**1g**	4-CHO	**2g**	10	78	**3g**	2	84



Scheme 3.



Scheme 4.



Scheme 5.

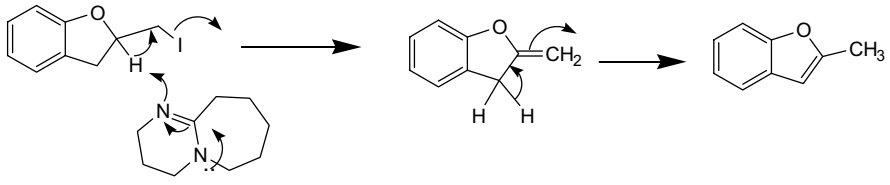


Figure 2. Proposed reaction mechanism.

5,4-*b*′]furan (**6**) in 72% yield (Scheme 3). Similar reaction of 2-allyl-1-naphthol (**7**) with iodine/water followed by treatment of the intermediate dihydrobenzofuran **8** with DBU gave naphthofuran **9** in good yield (Scheme 4).

Finally, this reaction was extended to the synthesis of 4-propylbenzofuranocoumarins as 4-propyl coumarins are known to possess antitubercular and anti HIV activities.[23,24] Thus 8-allyl-7-hydroxy-4-propyl-2*H*-1-benzopyran-2-one (**10**)[25] on iodocyclization gave 8-iodomethyl-4-propyl-8,9-dihydrofuro[2,3-*h*]-chromen-2-one **11** in good yield. Dehydroiodination of **11** with DBU gave the corresponding 8-methyl-4-propyl-furo[2,3-*h*]chromen-2-one **12** in good yield (Scheme 5). The structures of all the products were established on the basis of spectroscopic data and elemental analysis.[26]

A plausible reaction mechanism is proposed where the base may abstract a proton to give the exomethylene benzofuran, which isomerizes to the more stable 2-methylbenzofuran (Fig. 2).

In conclusion, we have developed an efficient and effective method for the preparation of benzofurans with or without functional groups on the benzene ring via dehydroiodination of 2-iodomethyl dihydrobenzofuran with DBU. The method is simple and economical.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.07.118.

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26. *Typical experimental procedure for iodocyclization:* A mixture of allylated phenol (1.0 mmol) and iodine (1.1 mmol) in water was stirred at 50 °C for the desired time. After completion, the reaction mixture was extracted with ethyl acetate and washed with water. The organic fraction was washed with aqueous sodium thiosulphate, dried (anhyd Na_2SO_4) and evaporated to furnish the crude product, which was purified by column chromatography (hexane–EtOAc) over silica gel to provide pure iodo products.
Typical experimental procedure for the synthesis of 2-methylbenzofuran: To a magnetically stirred solution of iodo compound (1.0 mmol) in DMF (5.0 mL), DBU (1.0 mmol) was added and stirring was continued for the desired time at 50 °C. After completion, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed several times with water, dried (anhyd Na_2SO_4) and evaporated to furnish the crude product, which was purified by column chromatography (hexane–EtOAc, 19:1) over silica gel to provide pure 2-methylbenzofurans.
Physical data of Prototype compounds: 5-Chloro-2-iodomethyl-2,3-dihydrobenzofuran (**2a**): Yield 75%; colourless solid; mp 44 °C, IR (KBr) ν_{max}: 2040, 1857, 1742, 1595 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.96, 3.07 (two d, $J = 6.5$ Hz, 1H), 3.25–3.45 (m, 3H), 4.83–4.93 (m, 1H), 6.64 (d, $J = 8.3$ Hz, 1H), 7.04–7.09 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 8.7, 36.4, 82.4, 110.8, 125.4, 126.0, 127.9, 128.5, 158; MS (ESI): *m/z* 317 $(M+Na)^+$. 5-Chloro-2-methylbenzofuran (**3a**): Yield 85%; light yellow oil;, IR (Neat) ν_{max}: 1600, 1449 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.43 (s, 3H), 6.28 (s, 1H) 7.09–7.40 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.5, 102.7, 111.9, 120.1, 123.6, 128.4, 130.9, 153.5, 157.2. Anal. Calcd For

C_9H_7OCl: C, 64.9; H, 4.2. Found C, 64.6; H, 4.1. MS (ESI): m/z 189.5 $(M+Na)^+$. 2,6-Bis-iodomethyl-2,3,5,6-tetrahydro-benzo[1,2-*b*;5,4-*b*′]difuran (**5**): Yield 70%; IR (KBr) ν_{max}: 1614, 1473 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.86, 2.90 (two d, 2H, $J = 6.4$ Hz), 3.21–3.44 (m, 6H), 4.79–5.08 (m, 2H), 6.21 (s, 1H), 6.85 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 9.16, 9.25, 36.0 (2C), 77.3, 82.9, 83.0, 93.4, 117.8, 120.9, 159.9 (2C); MS (ESI): m/z 442 (M^+). 8-Iodomethyl-4-propyl-8,9-dihydro-[2,3-*h*]-chromene-2-one (**11**): Yield 65%; colourless solid; mp 138 °C; IR (KBr) ν_{max}: 2363, 1702 cm^{-1}, ^1H NMR (200 MHz, $CDCl_3$) δ 1.05 (t, $J = 7.3$ Hz, 3H) 1.67–1.78 (m, 2H), 2.69 (t, $J = 7.3$ Hz, 2H), 3.13, 3.22 (two d, $J = 6.4$ Hz, 1H), 3.34–3.60 (m, 3H), 4.99–5.06 (m, 1H), 6.07 (s, 1H), 6.70 (d, $J = 8.5$ Hz, 1H), 7.4 (d, $J = 8.5$ Hz, 1H) ^{13}C NMR (50 MHz, $CDCl_3$) δ 8.4, 14.3, 22.0, 31.2, 33.6, 34.4, 83.8, 106.8, 110.8, 113.3, 125.7, 151.5, 156.7, 161.0, 163.1; MS (ESI): m/z 371 $(M+H^+)$. 2,6-Dimethyl benzo[1,2-*b*;5,4-*b*′]difuran (**6**): Yield 72%; colourless solid; mp 175 °C IR (KBr) ν_{max}: 1611, 1438 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.44 (s, 6H), 6.32 (s, 2H), 7.35 (s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.8, 29.5, 36.4, 99.2, 123.8, 125.3, 129.1, 138.2, 154.7, 155.9; MS (ESI): m/z 186 $(M)^+$ 198. Anal. Calcd for $C_{12}H_{10}O_2$: C, 77.4; H, 5.4. Found C, 77.2, H, 5.3. 8-Methyl-4-propyl furo[2,3-*h*] chromen-2-one (**12**): Yield 70%; colourless solid; mp 114 °C; IR (KBr) ν_{max}: 1723 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.07 (t, $J = 7.3$ Hz, 3H), 1.69–1.81 (m, 2H), 2.49 (s, 3H), 2.74 (t, $J = 7.4$ Hz, 2H), 6.16 (s, 1H), 6.67 (s, 1H), 7.23 (d, $J = 8.7$ Hz, 1H), 7.36 (d, $J = 8.7$ Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.02, 14.09, 21.6, 34.4, 100.2, 107.5, 111.5, 113.6, 118.5, 118.9, 147.3, 156.3, 156.7, 156.9, 160.8; MS (ESI): m/z 243 $(M+H)^+$. Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.3; H, 5.8. Found C, 74.1, H, 5.7.