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An elegant and unprecedented approach to 2-methyl benzofurans

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Abstract: An effective route towards the synthesis of 2-methylbenzofurans has been reported. This method allows the preparation of a variety of 2-methyl benzofurans by DBU catalysed dehydroiodination of easily accessible 2-iodomethyl-2,3-dihydrobenzofurans. The latter could be easily obtained by water mediated iodocylization of allyl phenols

Key Words: Benzofurans, allyl phenols, iodocyclization, DBU

In nature's collection of biologically active heterocycles and synthetic compounds benzofuran ring system is a common structural feature with a wide range of biological activities.[1-4] A variety of 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, *7H*-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] Few of the compounds are listed below (Figure 1). These compounds include hydroxylated benzofurans such as Euparin[16a], dehydrotremetone[16b], or Cicerfuran[16c].

Please Insert Figure 1

Consequently different methods have been developed for their synthesis.[17] These methods utilize strongly acidic or basic conditions or organometallic catalysts.[18] 2-Methyl benzofuran moiety is a common skeleton in many biologically active compounds and has recently been synthesised by Pd^{II} catalysed oxidative cyclization of allyloxy phenols.[19] Most of the methods developed so for suffer one or more drawbacks including low yields, use of toxic and expensive reagents, longer reaction time, hazardous (strongly acidic or basic reaction condition) and environmental malignancy. Recently Manolis Fousteris et al [20] have developed an elegant green chemistry process for the synthesis of 2-(iodomethyl) dihydrobenzofurans by water promoted iodocyclization of 2-allyl phenols. In continuation

of our quest to develop new molecular entities as antitubercular agents and the reports of antitubercular activities in purines[21] and benzofurans[22] we were interested in the synthesis of dihydrobenzofuryl purines and pyrimidines by replacing iodine of iodomethyl dihydrobenzofurans in presence of bases. Thus 2-allyl 4-chlorophenol (**1a**) on reaction with 1.1 mole of iodine in water at 50 °C gave the required intermediate 5-chloro-2-(iodomethyl)-2,3-dihydrobenzofuran (**2a**) in 75 % yield. The latter compound **2a** was reacted with imidazole and benzimidazole under different experimental conditions (Table 1) separately in presence of a variety of inorganic and organic bases and the progress of the reaction was monitored on TLC plate.

Please insert Scheme 1

Please Insert table 1

A faster moving compound was observed in each of the above reactions (TLC), it was isolated in varying yields and identified as 5-chloro-2-methyl-benzofuran (**3a**). Imidazole and benzimidazole were recovered as such. The structure of compound **3a** was established on the basis of spectroscopic data and analysis. Thus, instead of getting the expected 1-(5-chloro-2,3-dihydro-benzofuran-2-ylmethyl)-1*H*-imidazole/benzimidazoles, the product was 5-chloro-2-methyl benzofuran. DBU, a hindered organic base was proved to be the best catalyst for conversion of 2-iodomethyl dihydrobenzofuran to 2-methylbenzofuran. DABCO another hindered base although offered almost quantitative yield yet the reaction time was prolonged to 4 hr.

Similarly reaction of other 2-(iodomethyl) dihydrobenzofurans **2b**-**2g**, obtained by water mediated iodocyclization of respective 2-allyl phenols **1a**-**1g**, with DBU resulted in respective 2-methyl benzofurans **3b**-**3g** (Scheme 2) in good yields. The results are presented in Table 2. The structures of all the products were established on the basis of spectroscopic data and analysis.

The method was then used for the synthesis of *bis*-benzofuran (Scheme 3). 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 resulted in the required product 2,6-dimethyl-benzo[1,2-b; 5,4-b'] furan (**6**) in 72% yield. Similar reaction of 2-allyl-1 naphthol (**7**) with iodine water followed by treatment of the intermediate dihydrobenzofuran (**8**) with DBU gave the respective naphthofuran (**9**) in good yield.

Please insert Scheme 2a, 2b and 2c

Please insert Table 2

Lastly, the scope of this reaction was extended in the synthesis of 4-propyl benzofuranocoumarins as 4-propyl coumrins are known to possess antitubercular and anti HIV activities.[23,24] Thus 8-allyl-7-hydroxy-4-methyl (propyl)-2H-1-benzopyran-2-one (**10**)[25] on iodocyclization led to the formation of respective 8-iodomethyl- 4-propyl-8,9-dihydrofuro[2,3-*h*]-chromen-2-ones **11** respectively in good yield. The latter on dehydroiodination with DBU as above gave the corresponding 4,8-dimethyl furo[2,3-h] chromen-2-ones **12** in good yield. The structures of all the products were established on the basis of spectroscopic data and anlysis. [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-methyl benzofuran.

Please insert Figure 2

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

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26. **Typical experimental procedure for iodocyclization of C-allyl phenol:** A mixture of Allylated phenols (1 mmol) and iodine (1.1 mmol) in water was stirred at 50 °C for desired time. After completion, reaction mixture was extracted with ethylacetate and water. To remove iodine, ethylacetate layer was washed by sodium thiosulphate solution for several times. Organic layer was dried (Anhyd. Na_2SO_4) and evaporated to furnish crude product which was purified by column chromatography (hexane-EtOAc) over silicagel to provide pure iodo products

Typical experimental procedure for synthesis of 2-methylbenzofuran: To a magnetically stirred solution of iodo compound in DMF, DBU was added and stirring was continued for desired time at 50 °C. After completion reaction mixture was diluted with water and extracted by ethylacetate. Ethylacetate layer was washed several times by water, dried (Anhyd.Na_2SO_4) and evaporated to furnish crude product which was purified by a filter column over silicagel to provide pure 2-methylbenzofurans.

Physical data of selected compounds:

5-chloro-2-iodomethyl-2,3-dihydrobenzofuran (**2a)**. Yield 75%; Colourless solid; m.p. 44 °C IR (KBr) : 2040, 1857, 1742, 1595; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.96 (dd, 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 294 $(M+Na)^+$. *5,7-Dichloro-2-iodomethyl-2,3-dihydrobenzofuran* **(2b**) Yield 81%; Colourless oil; IR (Neat): 1585, 1460 cm^{-1}; ^{1}H NMR (200MHz, $CDCl_3$) δ 3.13 (dd, J= 6.7 Hz 1H) 3.29-3.52 (m, 3H), 4.94-4.99 (m, 1H) , 7.00 (s, 1H), 7.12 (s, 1H) ^{13}C NMR (50 MHz, $CDCl_3$) δ 8.12, 37.1, 83.0, 116.0, 123.8, 126.3, 128.6, 129.0. 154.5; MS (ESI): m/z 329. *6,7-Dimethyl-2-iodomethyl-2,3-dihydrobenzofuran* **(2c).** Yield 76%; Brown solid; m.p. 50 °C; IR (KBr): 1593,1456; ^{1}H NMR (200MHz, $CDCl_3$) δ 2.15 (s, 3H), 2.26 (s, 3H), 3.01 (dd, J= 6.5 Hz, 1H), 3.27-3.51 (m, 3H), 4.85-4.93 (m, 1H), 6.66 (d, J= 7.5 Hz, 1H), 6.87 (d, J= 7.4 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 9.5, 12.1, 19.8, 36.8, 81.7, 118.7, 121.8, 122.5, 137.1, 158.2; MS (ESI): m/z 289 $(M+H)^+$. *4,6-Dimethyl-2-iodomethyl-2,3-dihydrobenzofuran* **(2d):** yield 80%; Colourless oil; IR (Neat):1589; ^{1}H NMR (200MHz, $CDCl_3$) δ 2.14 (s, 3H), 2.24 (s, 3H), 3.0 (dd, J= 6.1 Hz, 1H), 3.21-3.45 (m,3H), 4.48 -4.51 (m, 1H), 6.52 (d, J= 7.6 Hz, 1H,), 6.78 (d, J= 7.5 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 8.72, 9.1, 15.0, 15.9, 18.7, 21.4, 25.9, 30.8, 35.5, 68.5, 71.8, 81.2,

116.7; MS(ESI): m/z 311 $(M+Na)^+$. *5-Chloro-4-methyl-2-iodomethyl-2,3-dihydrobenzofuran* **(2e):** Yield 81%; Colourless oil; IR (Neat): 1592, 1454 cm^{-1}; ^1H NMR (200MHz, $CDCl_3$) δ 2.25 (s, 3H), 2.90 (dd, J=6.2 Hz 1H), 3.24-3.46 (m, 3H), 4.81-4.93 (m, 1H) 6.50 (d, J=8.4 Hz, 1H), 7.05 (d, J=8.3Hz, 1H) ^{13}C NMR (50 MHz, $CDCl_3$) δ 9.0, 17.3, 20.8, 36.3, 82.4, 108.4, 112.0, 125.1, 126.8, 157.3; MS (ESI): m/z 308.5 $(M)^+$ *5-Cyano-2-iodomethyl-2,3-dihydrobenzofuran***(2f):** Yield 71%; Colourless crystals, m.p. 85 °C; IR:1716, 1609, 1483; ^1H NMR (200MHz, $CDCl_3$) δ 3.02 (dd, J=6.0 Hz, 1H), 3.31-3.50(m, 3H), 4.93-5.01(m, 1H), 6.80 (d, 8.7 Hz, 1H), 7.43-7.47 (m, 2H), ^{13}C NMR (50 MHz, $CDCl_3$) δ 8.21, 35.8, 82.9, 104.7, 110.8, 119.4, 127.8, 129.3, 134.1, 163.0; MS (ESI): m/z 286 $(M+H)^+$. *2-Iodomethyl-2,3-dihdro-benzofuran-5-carbaldehyde* **(2g)** Yield 78%; Light brown oil; IR (Neat): 1684; ^1H NMR (200MHz, $CDCl_3$) δ 3.03 (dd, J=6.5 Hz, 1H), 3.32-3.52 (m, 3H), 4.95-5.03 (m, 1H), 6.85 (d, J=8.1 Hz, 1H), 7.65 (d, 2H), 9.80 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 8.0, 35.3, 82.8, 109.8, 125.9, 127.2, 130.9, 133.0, 164.4, 190.0; MS (ESI): 289 $(M+H)^+$. *5-Chloro-2-methyl benzofuran* **(3a):** Yield 84%; light yellow oil;, IR(Neat): 1600, 1449; ^1H NMR (200MHz, $CDCl_3$) 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, 64.8; H, 4.2; Found C, 64.2; H, 4.1; MS (ESI):m/z 189.5 $(M+Na)^+$ *5,7-Dichloro-2-methyl benzofuran* **(3b).** Yield 82%; Colourless Solid; m.p.70 °C; IR:1606, 1433, 1366; ^1H NMR (200MHz, $CDCl_3$) δ 2.41 (s, 3H) 6.24 (s, 1H), 7.09 (s, 1H), 7.20(s, 1H) ^{13}C NMR (50 MHz, $CDCl_3$) δ 15.8, 101.7, 109.9, 117.1, 120.4, 122.0, 125.4, 128.6, 131.8; MS (ESI):m/z 202 ($M+H)^+$ Anal. Calcd for $C_9H_6OCl_2$: C, 53.7; H, 2.98; Found C, 53.2; 2.7. *6,7-Dimethyl-2-methyl benzofuran* **(3c)**: Yield 80%; colourless oil; IR (Neat): 1609 ; ^1H NMR(200MHz, $CDCl_3$) δ 2.33 (s, 3H), 2.38 (s,3H) 2.42 (s, 3H) , 6.24 (s, 1H) , 6.91 (d, J=7.8 Hz, 1H) 7.09 (d, J=7.8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.1, 14.5, 19.5, 25.1, 102.2 103.2, 117.0, 119.5, 124.8, 126.9, 131.5, 154.7; MS(ESI): m/z 183 $(M+Na)^+$ Anal. Calcd for $C_{11}H_{12}O$: C, 82.5; H, 7.5; Found C, 82.4; H, 7.2; *4,6-Dimethyl-2-methyl benzofuran***(3d)**.Yield 78 %; colourless oil, IR (Neat): 1651; ^1H NMR (200MHz, $CDCl_3$) δ 2.40 (s, 3H), 2.44 (s, 6H) 6 .31 (s, 1H), 6.83 (s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.2, 14.9, 18.3,101.5, 117.9, 122.7, 123.9, 127.0, 128.3, 153.3, 154.2; MS (ESI): 160 $(M)^+$; Anal. Calcd for $C_{11}H_{12}O$ C, 82.5, H, 7.5; Found C, 82.3, H, 7.1. *5-Chloro-2, 4-dimethyl- benzofuran* **(3e):** Yield 76%; colourless oil; ^1H NMR (200MHz, $CDCl_3$) δ 2.41 (s, 3H), 2.42 (s, 3H) 6.20 (s, 1H), 7.11(s, 1H), 7.36 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.3, 15.8, 18.0, 100.3, 103.9, 107.8, 111.1, 122.5, 125.8, 156.1; MS (ESI): m/z 181.5 $(M)^+$; Anal. Calcd for $C_{10}H_9OCl$: C, 66.1; H, 4.9; Found C, 66.3; H, 4.4. *5- Cyano-2-methyl benzofuran* **(3f):**Yield 85%; Colourless granules; m.p. 66 °C; IR: 1605, 1438 ,^1H NMR (200MHz, $CDCl_3$) δ 2.49 (s,3H), 6.42(s,1H), 7.45(s, 2H), 7.77(s, 1H), ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.4, 102.9, 106.8, 112.0, 119.7, 125.2, 127.2, 130.2, 156.7, 158.4; MS (ESI): 158 $(M+H)^+$; Anal. Calcd for $C_{10}H_7ON$: C, 76.4; H, 4.4; N, 8.9; Found C, 76.2, H, 4.3, N, 8.8; *2-Methylbenzofuran-5-carbaldehyde* **(3g):** Yield 84%; Colourless oil; IR (Neat): 1693; ^1H NMR (200MHz, $CDCl_3$) δ 2.48 (s, 3H), 6.45 (1H), 7.44 (d, J= 8.5Hz, 1H), 7.72 (d, J= 8.5Hz, 2H), 7.97 (s, 1H), 10.0 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.0, 103.1, 111.2, 123.0, 125.0, 129.7, 132.0, 157.4, 158.1, 191.3; MS (ESI): 161 $(M+H)^+$; Anal. Calcd for $C_{10}H_8O_2$ C, 75, H, 5; Found C, 74.8, H, 5.4; [1C] MS (ESI): m/z 294 $(M+Na)^+$;IR (KBr):2040, 1857, 1742, 1595; ^1H NMR (200 MHz, $CDCl_3$) δ 2.96 (dd,1H, J= 6.5 Hz), 3.25-3.45 (m, 3H), 4.83-4.93 (m, 1H), 6.64 (d, 1H, J= 8.3 Hz), 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, 158.2. *2,6-bis-iodomethyl-2,3,5,6-tetrahydro-benzo[1,2-b;5,4-b']difuran* **(5):** Yield 70%; IR (KBr): 1614, 1473; ^1H NMR (200MHz, $CDCl_3$) δ 2.86 (dd, 1H, J=6.4 Hz), 3.21-3.44 (m, 3H), 4.79-5.08 (m, 1H), 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; MS (ESI): m/z 442 $(M)^+$.*2,6-dimethyl- benzo[1,2-b;5,4-b']difuran* **(6)** Yield 72 %; Colourles solid; m.p. 175 ºC IR (KBr): 1611, 1438; ^1H NMR (200MHz, $CDCl_3$) δ 2.44 (s, 3H), 6.32 (s, 1H), 7.35 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.81, 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, 5.3; Found C, 77.2, H, 5.3 2-Methyl-naphtho[2,1-b] furan **(9):** Yield 85%; Colourless solid; m.p. 58 ºC; IR (KBr): 1589, 1439 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 2.54 (s, 3H), 6.80 (s, 1H), 7.34-7.60 (m, 4H), 7.83 (d, J= 7.5 Hz, 1H), 7.96 (d, J= 7.6 Hz, 1H), ^{13}C NMR (50 MHz, $CDCl_3$) 14.3, 101.89, 112.0, 123.45, 123.88, 124.10, 125.0, 125.8, 127.5, 128.7, 130.3, 152.0 154.1; MS (ESI): m/z 183 $(M+H)^+$ Anal. Calcd for $C_{15}H_{14}O_3$ C, 85.7; H, 5.4; Found C, 85.9, H, 5.1. *8-Iodomethyl-4-propyl-8,9-dihydro-[2.3-h]-chromene-2-one* **(11):** Yield 65%; Colourless solid; m.p. 138 ºC; IR: 2363, 1702, ^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 (dd, J=6.4Hz, 1H), 3.34-3.60 (m, 2H), 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 $(M+H)^+$ *8-Methyl-4-proppyl furo[2,3-h] chromen-2-one* (**12):** Yield 70%; colourless; m.p. 114 ºC ; IR:1723; ^{1}H NMR (200MHz, $CDCl_3$) 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 243.2 $(M)^+$ Anal. Calcd for $C_{15}H_{14}O_3$ C, 74.3; H, 5.7; Found C, 74.1, H, 5.3;