PERKIN 1

A new and efficient synthesis of 2,2-disubstituted-3,4-dihydro-2*H*-1-benzopyrans †‡

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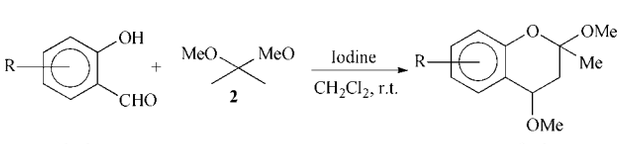
3,4-Dihydro-2,4-dimethoxy-2-methyl-2*H*-1-benzopyrans are formed in high yields by the cyclocondensation of *o*-hydroxybenzaldehydes with 2,2-dimethoxypropane catalysed by elemental iodine at room temperature.

Introduction

2*H*-1-Benzopyrans and their derivatives have wide applications in the perfume, cosmetic and pharmaceutical industry.[1] Benzopyran analogues have attracted considerable interest as modulators of potassium channels influencing the activity of the heart and blood pressure.[2] In addition, the 2*H*-1-benzopyran ring system is present in a number of natural products, including flavonoids, that interact with various enzymes and receptor systems of pharmacological significance.[3] Further, these compounds are the precursors for the synthesis of 4-hydroxycoumarins and chromones. Very few methods[4] are reported for the synthesis of 2*H*-1-benzopyrans under various reaction conditions. Even though the synthesis of 2,4-diethoxychromanes has been reported using Friedel–Crafts methodology,[5] this involves a stoichiometric amount of the catalyst, harsh reaction conditions, long reaction times, unsatisfactory yields and low diastereoselectivity. Due to their biological significance, there is a need to develop a new and high yielding protocol for the synthesis of these compounds. Furthermore, the development of new methods with greater efficacy, convenient procedures and better yields is of interest. The use of iodine as catalyst in various transformations[6] is well documented in the literature.

Results and discussion

Herein, we wish to report a new, efficient and practical method for the synthesis of 2,2-disubstituted-3,4-dihydro-2*H*-1-benzopyrans through the one-pot cyclocondensation of salicylaldehydes with 2,2-dimethoxypropane using a catalytic amount of elemental iodine in dichloromethane (Scheme 1). The reaction



1a-l **3a-l**

Scheme 1

of *o*-hydroxybenzaldehyde with 2,2-dimethoxypropane proceeded smoothly at room temperature to give 90% yield of the 2,4-dimethoxy-2-methylbenzopyran derivative. In a similar fashion, several substituted salicylaldehydes were reacted with

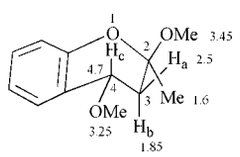
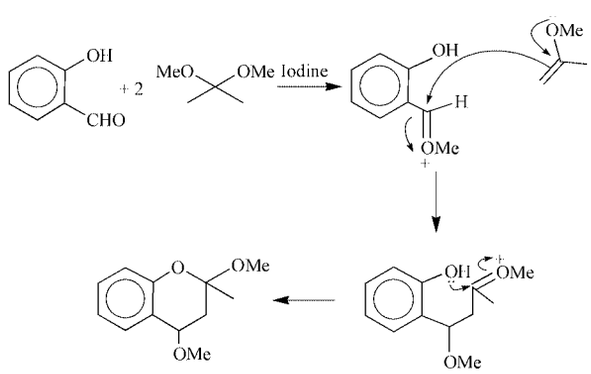


Fig. 1 Relative stereochemistry of compound **3a** as determined from the NOE data.

2,2-dimethoxypropane (DMP) at room temperature in the presence of iodine to afford 2*H*-1-benzopyrans in good yields in a short reaction time. The reactions were clean and completed within 0.5–1.5 h of reaction time with high diastereoselectivity. Only one diastereomer was obtained in the reaction, which was confirmed by ^{1}H, ^{13}C NMR, and NOE experiments. The relative stereochemistry of **3a** was established by NOE studies as shown in Fig. 1.

The 4H_c proton at δ 4.70 (1H, dd) showed correlation with the methoxy protons at δ 3.45 (s, 3H, 2-OCH_3, 5.22%) but did not show any correlation with the methyl protons at δ 1.60 (s, 3H, CH_3). Further, the methyl protons at δ 1.6 exhibited NOE correlation with the methoxy protons at δ 3.25 (s, 3H, 4-OCH_3, 2.85%), and the methoxy protons at δ 3.45 (s, 1H, 2-OCH_3) showed strong correlation with the proton at δ 4.7 (1H, dd, 4H_c, 1.90%) indicating that the two methoxy groups are in a *trans* orientation. The formation of the products may be explained by the mechanism shown in Scheme 2.



Scheme 2

However, the reaction of aromatic aldehydes without an *o*-hydroxy group gave only the aldol product *i.e.*, 4-aryl-4-methoxybutan-2-one whereas aliphatic aldehydes afforded the corresponding acetals in good yields. Ketones did not yield any condensation product even after long reaction times. When the reactions were carried out with different acetals such as

† Spectroscopic data for compounds **3b**–**k** and **3m** are available as supplementary data. For direct electronic access see http://www.rsc.org/suppdata/p1/b0/b004683n/
‡ IICT Communication No. 4429.

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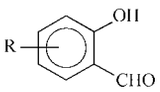
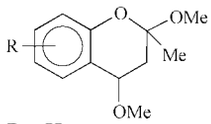
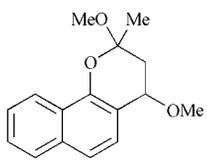
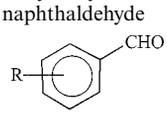
Table 1 Conversion of *o*-hydroxybenzaldehydes into 2*H*-1-benzopyrans

Entry	Aldehyde **1**	Benzopyran[a] **3**	Reaction time/h	Yield (%)[b]
				
a	R = H	R = H	0.5	90
b	R = 6-OMe	R = 8-OMe	1.0	86
c	R = 6-OEt	R = 8-OEt	1.0	82
d	R = 4-Me	R = 6-Me	0.5	88
e	R = 4-Pr^{i}	R = 6-Pr^{i}	0.5	90
f	R = 4-Bu^{t}	R = 6-Bu^{t}	0.5	83
g	R = 4-(1,1-Dimethylpropyl)	R = 6-(1,1-Dimethylpropyl)	1.0	88
h	R = 4-Cl	R = 6-Cl	1.0	81
i	R = 4-Br	R = 6-Br	1.0	84
j	R = 4-NO_2	R = 6-NO_2	2.0	75
k	1-Hydroxy-2-naphthaldehyde		1.5	78
				
l	R = 4-OMe	R = 4-OMe	1.0	85
m	R = 3,4-OCH_2O–	R = 3,4-OCH_2O–	1.0	87

[a] All products were characterised by IR, ^{1}H and ^{13}C NMR, mass spectra and elemental analysis. [b] Isolated yields after purification.

diethyl acetals of aromatic and aliphatic aldehydes, the corresponding carbonyl compounds were isolated in good yields. The reaction proceeded only with the dimethyl acetal of acetone and *o*-hydroxyaryl aldehydes. The results as summarized in Table 1, indicate the generality of the process with respect to various substrates containing both electron donating and electron withdrawing substituents in the aromatic ring. When the reactions were carried out with different protic acids such as HCl, HBr and HI, this resulted in the formation of undesired products along with the recovery of the starting aldehydes. Furthermore, to confirm the actual catalysis by elemental iodine, all the reactions were carried out using resublimed iodine free from acidic impurities, carefully excluding moisture by carrying out the reactions under a nitrogen atmosphere using dry dichloromethane (distilled over CaH_2). This synthetic protocol utilizes inexpensive and readily available starting materials. The mild reaction conditions, operational simplicity, clean reaction products and inexpensive reagents are the main advantages of this procedure.

In conclusion, we have described a new and efficient synthesis of 3,4-dihydro-2,4-dimethoxy-2-methyl-2*H*-1-benzopyrans by the cyclocondensation of *o*-hydroxybenzaldehydes with dimethoxypropane catalyzed by elemental iodine. The procedure is simple, rapid and high yielding, and will find many applications in organic synthesis.

Experimental

Melting points were recorded on a Büchi R-535 apparatus. IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectrophotometer with KBr optics. ^{1}H and ^{13}C NMR were recorded on Varian Gemini-200 spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Finning-MAT 1020 mass spectrometer operating at 70 eV. CHN analyses were recorded on a Vario EL analyzer. TLC was monitored on 0.25 mm E. Merck pre-coated silica gel plates (60F-254). Dichloromethane was distilled over CaH_2 and stored over activated molecular sieves. The starting *o*-hydroxybenzaldehydes were prepared by the Reimer–Tiemann procedure.[7]

General procedure

A mixture of *o*-hydroxybenzaldehyde (10 mmol), 2,2-dimethoxypropane (20 mmol) and iodine (0.2 mmol) in dry dichloromethane (20 ml) was stirred under a N_2 atmosphere for 0.5 h. After complete conversion, as indicated by TLC, the reaction mixture was diluted with water and extracted with dichloromethane (2 × 20 ml). The organic extracts were washed with 15% sodium thiosulfate (10 ml), brine and dried over anhydrous Na_2SO_4. Removal of solvent *in vacuo* gave a crude product which was purified by column chromatography on silica gel (100–200 mesh) and eluted with a gradient mixture of ethyl acetate–hexane (1 : 9) to afford a pure product as a colourless liquid. Representative examples of spectroscopic data are given below. Data for compounds **3b**–**k** and **3m** are available as supplementary data.†

Spectroscopic data for compound 3a. Colourless oil. ^{1}H NMR ($CDCl_3$) δ 1.60 (s, 3H, Me), 1.85 (dd, $1H_b$, J = 12.5 and 11.6 Hz), 2.50 (dd, $1H_a$, J = 12.5 Hz and 6.2 Hz), 3.25 (s, 3H, 4-OMe), 3.45 (s, 3H, 2-OMe), 4.70 (dd, $1H_c$, J = 11.6 and 6.2 Hz), 6.70 (d, 1H, J = 8.7 Hz, ArH), 6.85 (t, 1H, J = 8.7 Hz, $ArH_,$), 7.15 (t, 1H, J = 8.7 Hz, ArH), 7.40 (d, 1H, J = 8.7 Hz, ArH); ^{13}C (proton decoupled, $CDCl_3$) δ 23.0 (CH_3), 36.6 (CH_2), 48.6 (OCH_3), 55.7 (OCH_3), 71.12 (CH), 100.2 (C), 116.3, 120.7, 123.8, 126.8, 128.4, 151.5 (aromatic); IR (KBr) ν/cm^{-1} 3040, 2950, 1482, 1209, 1089, 1035; EI MS *m*/*z* (%) 208 M^+ (20), 177 (35), 161 (80), 145 (100), 121 (40), 101 (50), 91 (15). Analysis calcd. for $C_{12}H_{16}O_3$ (208.26) C, 69.21; H, 7.74. Found: C, 69.55; H, 7.65%.

Compound 3l. Pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 2.15 (s, 3H, CH_3), 2.50 (dd, $1H_b$, J = 15.6 and 4.4 Hz), 2.95 (dd, $1H_a$, J = 15.6 and 8.9 Hz), 3.15 (s, 3H, OMe), 3.89 (s, 3H, Ar-OMe), 4.55 (dd, $1H_c$, J = 8.9 and 4.4 Hz), 6.87 (d, 2H, J = 8.7 Hz, ArH), 7.25 (d, 2H, J = 8.7 Hz, ArH); ^{13}C (proton decoupled, $CDCl_3$) δ 31.58 (CH_3), 48.5 (CH_2), 56.67 (OCH_3), 55.14 ($ArOCH_3$), 77.0 (CH), 113.54, 130.35, 130.40, 133.15, 133.10, 159.8 (aromatic) 209.64 (CO); IR (KBr) ν/cm^{-1} 3040, 2933, 1715, 1460, 1248, 1173, 1065; EI MS *m*/*z* (%) 208 M^+ (30), 151 (100), 135 (40), 91 (20), 77 (20), 43 (60). Analysis calcd. for

$C_{12}H_{16}O_3$ (208.26) C, 69.21; H, 7.74. Found: C, 69.35; H, 7.15%.

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