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Scandium triflate catalyzed formation of 2,4-dimethoxy-2-methylbenzopyrans†

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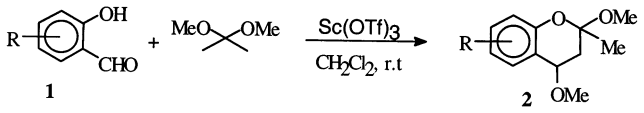
Abstract

Scandium trifluoromethanesulfonate is found to catalyze an unusual cyclocondensation of *o*-hydroxybenzaldehydes with 2,2-dimethoxypropane at room temperature to afford a class of new compounds, 2,4-dimethoxy-2-methylbenzopyrans, in high yields. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: scandium triflate; *o*-hydroxybenzaldehydes; 2,2-dimethoxypropane; benzopyran.

Chromans and their derivatives are versatile intermediates[1] in the fields of pharmaceuticals, cosmetics and perfumes. Chroman derivatives also act as modulators of potassium channels influencing the activity of the heart and blood pressure.[2] Further, the 2*H*-1-benzopyran ring system is found in a number of natural products including flavonoids, that interact with various enzymes and receptor systems of pharmacological significance.[3] In addition, these compounds are the precursors for the synthesis of chromans and 1-benzopyrylium salts. Although, the synthesis of 2,4-diethoxychromans has been reported using a Friedel–Crafts method,[4] this involves stoichiometric amounts of the catalyst, harsh reaction conditions, long reaction times unsatisfactory yields and low diasteroselectivity.

In recent years, lanthanide triflates have received considerable attention[5] due to their high catalytic nature, regeneration, low toxicity, water stability, reusability, high selectivity, non-corrosiveness and ease of isolation of the products. These special properties inherent to scandium triflate prompted us to disclose a mild and new protocol for the synthesis of substituted benzopyran derivatives.



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Herein we report a new and highly efficient procedure for the synthesis of 2,4-dimethoxy-2-methylbenzopyrans using a catalytic amount of scandium triflate in dichloromethane. The reaction of *o*-hydroxybenzaldehyde with 2,3-dimethoxypropane proceeds smoothly at room temperature to give a 92% yield of 2,4-dimethoxy-2-methylbenzopyran. Similarly, various substituted *o*-hydroxyl aryl aldehydes were reacted with 2,2-dimethoxypropane to afford the corresponding benzopyran derivatives.[6] The products were obtained in high to quantitative yields in short reaction times. The reactions were clean and complete within 0.5–1.0 h with high diastereoselectivity. Only one diastereomer was obtained in each reaction, the structure of which was confirmed by ^{1}H and ^{13}C NMR and NOE experiments. The relative stereochemistry of product **2a** was determined by NOE studies, as shown in Fig. 1.

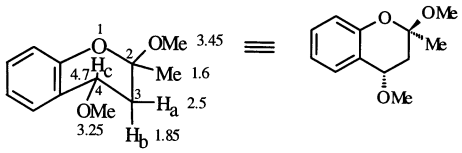
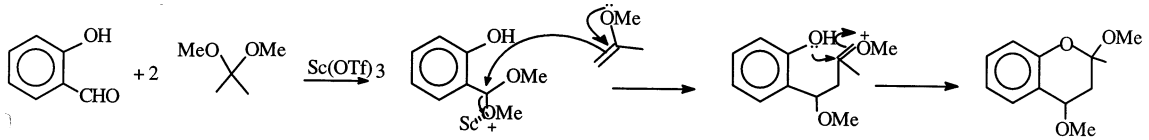


Figure 1.

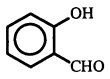
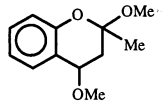
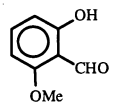
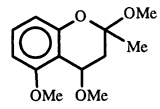
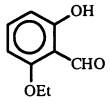
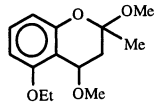
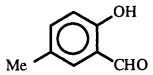
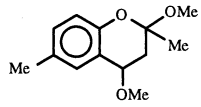
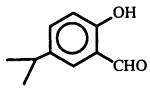
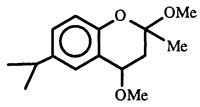
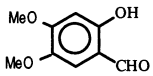
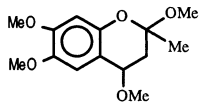
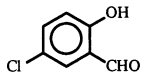
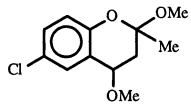
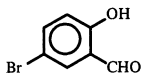
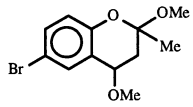
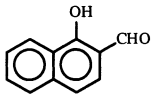
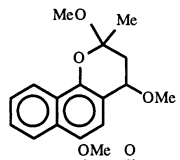
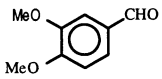
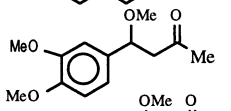
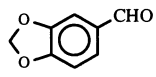
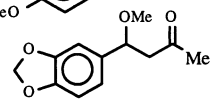
The 4Hc proton at δ 4.70 (1H, dd) showed correlation with the methoxy protons at δ 3.45 (s, 3H, 2-OMe), but did not show any correlation with the methyl protons at δ 1.60 (s, 3H, CH_3). Further, the methyl protons at δ 1.60 exhibited NOE correlation with the methoxy protons at δ 3.25 (s, 1H, 4-OMe) and no NOE correlation with protons at δ 4.70 (dd, 1H, 4Hc), indicating that the two methoxy groups are in a *trans* orientation. The formation of the products may be explained by the following mechanism.



The reaction of aromatic aldehydes without an *o*-hydroxyl group gave only the aldol product, i.e. 4-aryl-4-methoxy-2-butanone, while aliphatic aldehydes afforded the corresponding acetals in good yields. Ketones like acetophenone, cyclohexanone and benzophenone did not yield any condensation products even after longer reaction times. Further, the reaction of dimethylacetals of aromatic and aliphatic aldehydes with *o*-hydroxybenzaldehydes in the presence of $Sc(OTf)_3$ gave only the parent carbonyl compounds. The reaction proceeded only with the dimethylacetal of acetone and *o*-hydroxybenzaldehydes. The results, summarised in Table 1, indicate the scope of the reaction with respect to various substituted aryl aldehydes. This synthetic protocol utilizes easily available starting materials and a reusable catalyst, i.e. scandium triflate. Among various triflates such as $Yb(OTf)_3$, $Y(OTf)_3$ and $Cu(OTf)_2$ employed in this reaction, $Sc(OTf)_3$ is found to be more effective in terms of reaction time and yields than the others. The catalyst was easily recovered from the aqueous layer during work-up and reused without significant loss of activity.

In conclusion, the present protocol provides a novel and highly efficient procedure for the synthesis of a class of new compounds, 2,4-dimethoxy-2-methyl chromans, using a catalytic amount of scandium trifluoromethanesulfonate. The procedure offers several advantages including high yields, high diastereoselectivity, short reaction times, easily available starting materials, reusable catalyst and simple experimental/isolation procedures which makes it a useful procedure for the synthesis of substituted benzopyrans.

Table 1
Scandium triflate catalyzed conversion of *o*-hydroxybenzaldehydes to benzopyrans

Entry	Aldehyde (1)	Benzopyran[a] (2)	Reaction time (min)	Yield (%)[b]
a			20	92
b			25	93
c			20	95
d			30	90
e			25	88
f			30	90
g			40	86
h			45	85
i			30	90
j			50	85
k			60	88

[a] All products were characterised by ^{1}H, ^{13}C NMR, IR and Mass spectroscopy
[b] Isolated yields after purification

Acknowledgements

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6. Typical procedure: a mixture of *o*-hydroxybenzaldehyde (5 mmol), 2,2-dimethoxypropane (12.5 mmol) and scandium trifluoromethanesulfonate (5% w/w of aldehyde) in dichloromethane (15 ml) was stirred at room temperature for 0.5 h. After complete conversion, as indicated by TLC, the reaction mixture was diluted with water (10 ml) and extracted with dichloromethane (2×15 ml). The organic extracts were dried over anhydrous Na_2SO_4 and purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane 1:9) to afford pure 2,4-dimethoxy-2-methyl-2*H*-1-benzopyran in 92% yield as a colourless oil. ^{1}H NMR ($CDCl_3$) δ: 1.60 (s, 3H), 1.85 (dd, 1H, J=12.5 and 11.5 Hz), 2.50 (dd, 1H, J=12.5 and 6.5 Hz), 3.25 (s, 3H), 3.45 (s, 3H), 4.70 (dd, 1H, J=11.5 and 6.5 Hz), 6.70 (d, 1H, J=8.5 Hz), 6.85 (t, 1H, J=8.5 Hz), 7.15 (t, 1H, J=8.5 Hz), 7.40 (d, 1H, J=8.5 Hz). ^{13}C NMR (proton decoupled, $CDCl_3$) δ: 23.0 (CH_3), 36.6 (CH_2), 48.6 (OCH_3), 55.7 (OCH_3), 71.1 (CH), 100.2 (C), 116.3, 120.7, 126.7, 128.4, 151.5 (aromatic). IR (KBr) υ: 3030, 2980, 1490, 1470, 1225, 775. EIMS: m/z (%): 208 M^+ (20), 177 (35), 161 (80), 145 (100), 121 (40), 101 (50), 91 (20). Anal. calc. for $C_{12}H_{16}O_3$ (208.26): C, 69.55; H, 7.14; found: C, 69.35; H, 7.18.