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A facile synthesis of indeno[1,2-*b*]chromanes catalyzed by scandium triflate

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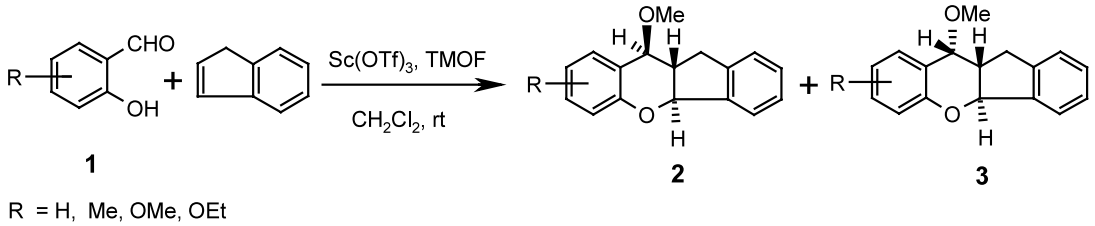
Abstract—Scandium triflate efficiently catalyzes the cyclocondensation of *o*-hydroxybenzaldehydes with alkenes such as indene, styrene and allyltrimethylsilane in the presence of trimethyl orthoformate at ambient temperature to afford a new class of compounds, 2,4-disubstitued chromanes in high yields with high diastereoselectivity.

2-Substituted 3,4-dihydro-2*H*-1-benzopyrans (chromanes) are an important class of biologically active compounds.[1] *o*-Quinonemethides are particularly versatile intermediates for the synthesis of a variety of oxygenated heterocycles.[2,3] Fused indenobenzopyrans are frequently found in naturally occuring bioactive molecules and direct methods for their synthesis are highly desired.[4] The synthesis of fused pyranobenzopyrans by intramolecular cycloaddition of *o*-quinonemethides generated from salicylaldehydes and unsaturated alcohols using a protic acid as a catalyst[5] has recently been reported. However, there are no reports on the synthesis of fused indenobenzopyrans from *o*-hydroxybenzaldehydes and indene. Lanthanide triflates are unique Lewis acids that are currently of great research interest. They are quite stable to water and reusable and in addition, are highly efficient. Therefore, lanthanide triflates are unique catalysts compared to conventional Lewis acids in several carbon–carbon bond forming reactions and have found widespread applications in organic synthesis.[6]

In this report, we describe a new method for the synthesis of substituted benzopyrans from *o*-hydroxybenzaldehydes and alkenes using a catalytic amount of $Sc(OTf)_3$ under mild conditions.[7] The treatment of *o*-hydroxybenzaldehyde with an equimolar ratio of indene and trimethyl orthoformate (TMOF) in the presence of 5 mol% $Sc(OTf)_3$ resulted in the formation of fused indeno[1,2-*b*]benzopyran derivatives, **2** and **3** in high yields (Scheme 1).

The reactions proceeded efficiently in high yields at ambient temperature. The products were obtained as diastereoisomers **2** and **3**, which were separated by column chromatography on silica gel. The ratio of **2** and **3** was determined from the ^1H NMR spectrum of the crude product and the diastereoisomers were characterized by ^1H, ^{13}C and mass spectroscopy. The reactions were clean and diastereoselective, affording the corresponding *trans*-fused indeno benzopyran derivatives in high yields. The stereochemistry of the products was assigned on the basis of coupling constants and



Scheme 1.

Keywords: $Sc(OTf)_3$; *o*-quinonemethide; *o*-hydroxybenzaldehydes; indenochromanes.

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NOE studies. The large coupling constants $J_{a\text{-}b}=7.5$ Hz at δ 5.68 Ha, $J_{c\text{-}b}=5.7$ Hz at δ 4.75 Hb for product **2a** and the presence of weak NOE cross peaks between Ha–Hb, Hb–Hc and Ha–Hc indicate a structure with *trans*-fusion (Fig. 1).

The product **3a** differs from the product **2a** having a different configuration at C-3. Analogous to **2a**, the six-membered tetrahydropyran ring and five-membered cyclopentane rings in **3a** are *trans*-fused as deduced from the large coupling constant $J_{a\text{-}b}=6.4$ Hz at δ 5.60 Ha, and small coupling constant $J_{c\text{-}b}=2.8$ Hz at δ 4.25 Hb and the presence of a strong NOE cross peak between Hb–Hc and a weak cross peak between Ha–Hb in the NOESY spectrum (Fig. 2).

Furthermore, the reaction of salicylaldehydes with styrenes and trimethyl orthoformate in the presence of $Sc(OTf)_3$ gave the corresponding 4-methoxy-2-phenylchromanes in good yields (Scheme 2).

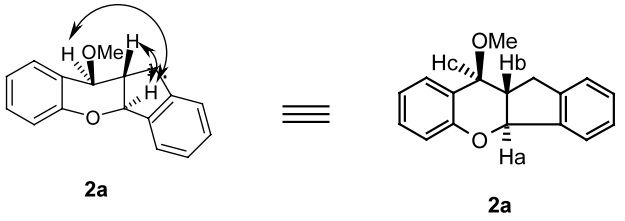


Figure 1. Important NOEs and chemical structure of **2a**.

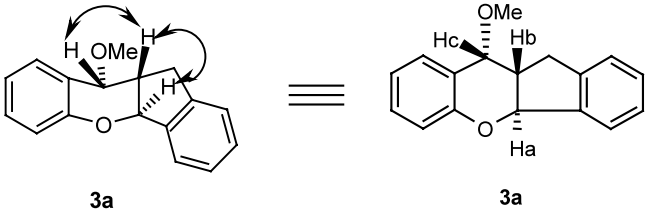


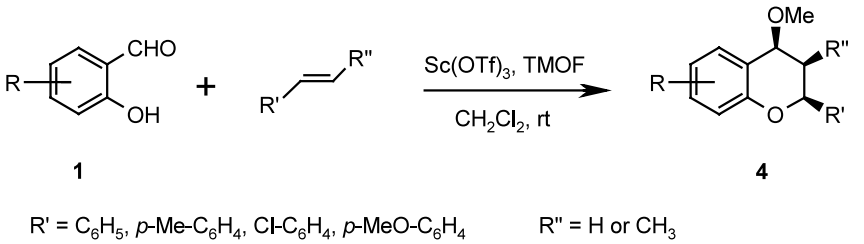
Figure 2. Important NOEs and chemical structure of **3a**.

In all cases, the reactions proceeded smoothly at ambient temperature with high diastereoselectivity. Only a single diastereoisomer was obtained in each reaction, the structure of which was established by ^{1}H NMR studies. The products are formed with high *syn*-selectivity. In a similar fashion, salicylaldehydes reacted smoothly with allyltrimethylsilane under typical reaction conditions to afford the respective 2,4-disubtituted chromanes in high yields (Scheme 3).

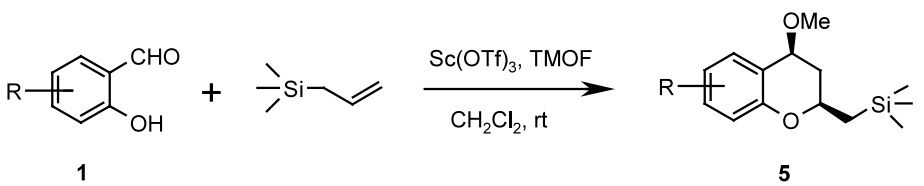
Several examples illustrating this novel and efficient procedure for the synthesis of substituted benzopyrans are listed in Table 1. Finally, the catalyst could be recovered from the aqueous layer during work-up and was reused in subsequent reactions with only a gradual decrease in activity, for example, salicylaldehyde and indene gave 90, 85 and 80% yields over three cycles. In addition, this method does not require any promoters and no precautions need to be taken to exclude moisture from the reaction media. The reaction may proceed through (4+2) cycloaddition of *o*-quinonemethides generated in situ from salicylaldehyde and trimethyl orthoformate as shown in Scheme 4.

Among the various metal triflates such as $Sc(OTf)_3$, $Yb(OTf)_3$, $Y(OTf)_3$ and $In(OTf)_3$ used for this reaction, scandium triflate was found to be most effective in terms of conversion and reaction time.[8]

In summary, we have described a new method for the synthesis of substituted benzopyrans involving [4+2] cycloaddition of *o*-quinonemethides with alkenes using catalytic amounts of $Sc(OTf)_3$. In addition to its simplicity, efficiency and mild reaction conditions, this method provides high yields of products with high selectivity, which makes it a useful and attractive process for the synthesis of 2,4-disubstituted benzopyrans.

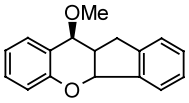
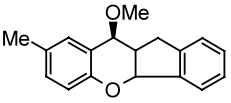
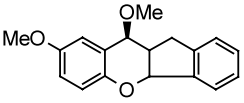
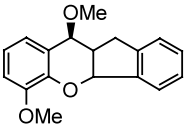
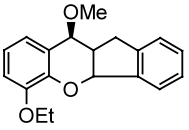
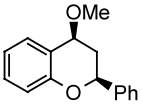
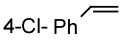
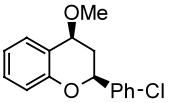
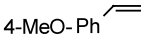
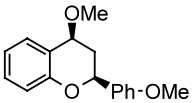
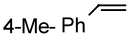
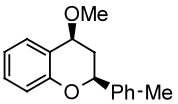
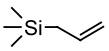
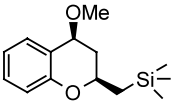
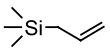
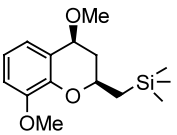
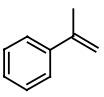
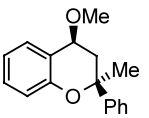
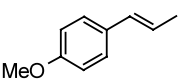
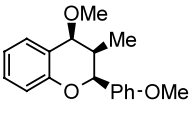


Scheme 2.

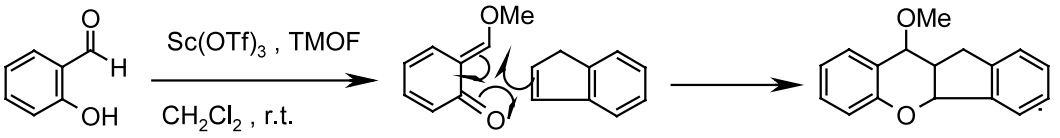


Scheme 3.

Table 1. $Sc(OTf)_3$-catalyzed synthesis of *trans*-fused 3,4-dihydro 2*H*-1-benzopyrans

Entry	R	Olefin	Product [a]	Time (h)	Yield (%)[b]
a	H			2.5	88 [c]
b	5-Me			3.0	85 [c]
c	5-MeO			2.0	90 [c]
d	3-MeO			2.5	89 [c]
e	3-EtO			2.0	90 [c]
f	H			4.5	85
g	H			6.0	78
h	H			3.5	87
i	H			4.0	83
j	H			2.5	80
k	3-MeO			2.0	85
l	H			3.5	82 [c]
m	H			3.0	90 [c]

a. All products were characterized by ^1H and ^{13}C NMR, IR and mass spectroscopy
b. Isolated and unoptimized yields
c. Diastereoisomers were isolated in a 1:1 ratio



Scheme 4.

Acknowledgements

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8. *Experimental procedure*: A mixture of *o*-hydroxybenzaldehyde (2 mmol), indene (2 mmol), trimethylorthoformate (3 mmol) and $Sc(OTf)_3$ (0.12 mmol) in dichloromethane (10 mL) was stirred at room temperature for an appropriate time (Table 1). After completion of the reaction, as indicated by TLC, the reaction mixture was diluted with water (15 mL) and extracted with dichloromethane (2×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by column chromatography on silica gel to afford pure product. **2a**: Solid, mp 95–96°C. ^{1}H NMR ($CDCl_3$) δ: 2.85, (ddd, 2H, J=8.4, 12.6, 16.7 Hz), 3.53 (m, 1H), 3.60 (s, 3H), 4.74 (d, 1H, J=5.7 Hz), 5.68 (d, 1H, J=7.5 Hz), 6.75 (d, 1H, J=8.0 Hz), 6.98 (t, 1H, J=7.8 Hz), 7.18–7.20 (m, 1H), 7.25–7.30 (m, 3H), 7.43 (d, 1H, J=8.0 Hz), 7.50–7.55 (m, 1H). ^{13}C NMR ($CDCl_3$) δ: 31.9, 41.5, 56.8, 74.6, 82.2, 117.1, 120.9, 124.6, 125.4, 125.6, 126.5, 127.7, 128.9, 141.7, 143.4, 154.2. EIMS: m/z: 252 M$^+$. **3a**: Solid, mp 108°C. ^{1}H NMR ($CDCl_3$) δ: 2.73 (dd, 1H, J=8.7, 15.8 Hz), 3.04 (dd, 1H, J=8.7, 15.6 Hz), 3.15 (m, 1H), 3.38 (s, 3H), 4.25 (d, 1H, J=2.8 Hz), 5.60 (d, 1H, J=6.4 Hz), 6.78 (d, 1H, J=8.0 Hz), 6.85 (d, 1H, J=8.0 Hz), 7.15–7.25 (m, 5H), 7.50–7.60 (m, 1H). ^{13}C NMR ($CDCl_3$) δ: 34.7, 44.0, 56.3, 75.9, 79.3, 117.4, 120.1, 121.3, 124.8, 125.6, 126.9, 128.9, 129.4, 129.8, 142.2, 155.1. EIMS: m/z: 252 M$^+$. **2k**: Liquid. ^{1}H NMR ($CDCl_3$) δ: 0.01 (s, 9H), 0.90 (dd, 1H, J=7.3, 13.9 Hz), 1.30 (dd, 1H, J=7.3, 13.9 Hz), 1.65 (dt, 1H, J=2.9, 3.6, 11.7 Hz), 1.98 (dt, 1H, J=1.4, 2.2 Hz), 3.28 (s, 3H), 3.70 (s, 3H), 4.05 (t, 1H, J=2.9 Hz), 4.28 (m, 1H), 6.65 (m, 3H). ^{13}C NMR ($CDCl_3$) δ: –0.79, 24.4, 35.1, 55.9, 70.3, 72.8, 111.3, 119.0, 121.7, 122.5, 148.5. EIMS: m/z: 280 M$^+$. **2f**: Solid, mp 101°C. ^{1}H NMR ($CDCl_3$) δ: 2.30 (dd, 1H, J=11.7, 2.4 Hz), 2.50 (ddd, 1H, J=1.4, 5.8, 12.4 Hz), 3.48 (s, 3H), 4.80 (dd, 1H, J=5.8, 10.9 Hz), 5.18 (dd, 1H, J=1.4, 12.4 Hz), 6.85 (d, 1H, J=8.2 Hz), 6.93 (t, 1H, J=8.0 Hz), 7.20 (t, 1H, J=8.0 Hz), 7.28–7.48 (m, 6H). ^{13}C NMR ($CDCl_3$) δ: 35.2, 55.5, 73.6, 76.8, 116.5, 120.6, 123.4, 126.0, 127.2, 128.0, 128.5, 128.8, 140.7, 154.7. EIMS: m/z: 240 M$^+$. **2h**: Solid, mp 85°C. ^{1}H NMR ($CDCl_3$) δ: 2.18 (dd, 1H, J=11.7, 12.4 Hz), 2.50 (ddd, 1H, J=1.4, 5.8, 12.4 Hz), 3.48 (s, 3H), 3.78 (s, 3H), 4.70 (dd, 1H, J=5.8, 10.7 Hz), 5.05 (dd, 1H, J=1.4, 12.4 Hz), 7.0–7.18 (m, 4H), 7.38–7.40 (m, 1H), 7.58–7.63 (m, 3H). ^{13}C NMR ($CDCl_3$) δ: 34.8, 55.4, 72.7, 73.5, 76.3, 113.8, 116.3, 120.4, 123.4, 127.1, 127.3, 128.6, 129.6, 130.7, 132.7, 154.7. EIMS: m/z: 270 M$^+$.