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$Sc(OTf)_3$-catalyzed diastereoselective synthesis of 3,4-dihydro-4-amino-2*H*-1-benzopyrans[†]

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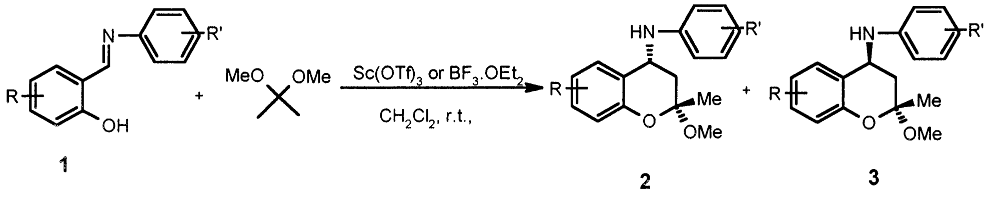
Abstract—2,2-Dimethoxypropane reacts with a variety of *o*-hydroxybenzaldimines in the presence of a catalytic amount of scandium triflate at ambient temperature to afford a series of new compounds, 3,4-dihydro-4-amino-2-methoxy-2-methyl-2*H*-1-benzopyrans, in high yields, with good diastereoselectivity. $BF_3{\cdot}OEt_2$ is also found to mediate this transformation under mild reaction conditions. © 2001 Elsevier Science Ltd. All rights reserved.

3,4-Dihydro-4-amino-2*H*-1-benzopyrans and their derivatives are known to exhibit a vast range of biological activities[1] such as antihypertensive and antiischemic behavior. They also act as modulators of potassium and calcium channels[2] influencing the activity of the heart and blood pressure. Currently there is a growing interest in the therapeutic potential of substances that modulate potassium channels.[3] As a result, there have been some reports[4,5] on the synthesis of 3,4-dihydro-2*H*-1-benzopyrans, which involve complex multi-step procedures, harsh reaction conditions, unsatisfactory yields, long reaction times and low diastereoselectivities. Therefore, the development of new methods that lead to convenient procedures and better yields is desirable. In recent years, lanthanide triflates have emerged as powerful Lewis acids[6] imparting high regio-, diastereo- and chemo-selectivities in various chemical transformations. These triflates have also been found to be effective, water-tolerant Lewis acids in several carbon–carbon bond forming reactions, and in some cases the presence of water even improves their activity. The unique catalytic properties inherent to lanthanide triflates prompted us to investigate the use of $Sc(OTf)_3$ in new carbon–carbon bond formation. In continuation of our work on the applications of $Sc(OTf)_3$ for various transformations,[7] we here report a novel and efficient protocol for the synthesis of 3,4-dihydro-4-amino-2*H*-1-benzopyrans using a catalytic amount of scandium triflate in dichloromethane. The reaction of salicylaldehyde Schiff's base with 2,2-dimethoxypropane in the presence of 10 mol% $Sc(OTf)_3$ at ambient temperature affords 3,4-dihydro-4-amino-2*H*-1-benzopyran, as a mixture of **2** and **3** ($R=R'=H$) in 88% yield (Scheme 1).

Similarly, the treatment of several substituted *o*-hydroxybenzylideneanilines with 2,2-dimethoxypropane gave the corresponding 3,4-dihydro-4-amino-2*H*-1-benzopyran derivatives in 70–89% yield. The reaction proceeded smoothly at ambient temperature in the presence of $Sc(OTf)_3$ to give predominantly isomer **2** with a trace amount of **3**. However, no reaction took place in the absence of catalyst. Similar yields and selectivity of the products were also obtained with 30



Scheme 1.

Keywords: scandium triflate; Schiff's base; 3,4-dihydro-4-amino-2*H*-1-benzopyrans.

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mol% $BF_3{\cdot}OEt_2$ under the same reaction conditions.[10] The ratio of diastereomers did not depend on the type of Lewis acid or solvent used. The conversions were clean and the products were obtained in good yields. The two diastereomers were formed in each reaction, the structures of which were confirmed by ^{1}H NMR and ^{13}C NMR studies. The assignment of stereochemistry was based on the chemical shifts as well as the coupling constants of the protons at the C_3 and C_4 positions. The coupling constants of the benzylic hydrogen, 4-H (δ 4.66, d, $^3J_{ae}=6.0$ Hz) as well as the hydrogens on the carbon adjacent to benzylic position 3-H and 3-H′ (δ 2.40, d, $^2J=14.5$ Hz and δ 2.10, dd, $^2J=14.5$, $^3J_{ae}=6.0$ Hz) in the proton NMR spectrum of product **2** indicated that the amino moiety and OMe group are in a diaxial orientation (Fig. 1). In the other isomer **3**, the coupling constants of the benzylic hydrogen 4-H (δ 5.03, dd, $^3J_{aa}=9.3$, $^3J_{ae}=4.6$ Hz) and the hydrogens on the carbon adjacent to benzylic position 3-H and 3-H′ (δ 2.57, dd, $^2J=10.3$, $^3J_{ae}=4.6$ Hz and δ 1.70, dd, $^2J=10.3$, $^3J_{aa}=9.3$ Hz) showed a structure with the amino moiety oriented in an equatorial position (Fig. 2).

The global energy minimum (GEM) for the two possible diastereomers **2** and **3** was studied using CONFLEX technique[8] and the missing MM2 parameters were adopted from the PC MODEL.[9] The diastereomer **2** (Fig. 1) is lower in energy with respect to diastereomer **3** (Fig. 2) by 0.9 kcal/mol and was also found to be stabilized by hydrogen bonding between the NH and OMe group. The ratio of **2** and **3** was determined from the ^{1}H NMR spectra of the products. The reaction was successful only with the dimethyl acetal of acetone and *o*-hydroxybenzylideneanilines (Schiff's bases). The imines, derived from salicylaldehydes and anilines carrying electron withdrawing substituents such as nitro or cyano groups on the aromatic ring failed to react with 2,2-dimethoxypropane under the reaction conditions. This synthetic protocol utilizes easily available starting materials and a reusable catalyst, i.e. scandium triflate. Among various lanthanide triflates, for example, $Yb(OTf)_3$, $Y(OTf)_3$, used in this reaction, $Sc(OTf)_3$ was found to be the superior Lewis acid in terms of yields, selectivity and reaction time. Furthermore, $Sc(OTf)_3$ was easily recovered from the aqueous layer during work-up and reused without significant loss of activity. Several examples illustrating this novel and one-pot procedure for the synthesis of 3,4-dihydro-4-amino-2*H*-1-benzopyrans are listed in the Table 1.

In summary, we have demonstrated a new and efficient protocol for the synthesis of 3,4-dihydro-4-amino-2-methoxy-2-methyl-2*H*-1-benzopyrans using a catalytic amount of scandium triflate. In addition to its simplicity and mild reaction conditions, the procedure is compatible with various substrates bearing electron

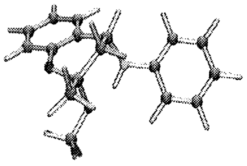

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Figure 1.

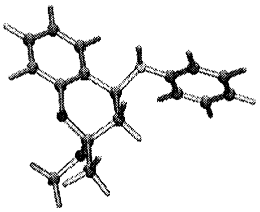

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Figure 2.

Table 1. Conversion of 2-hydroxybenzaldimines to 3,4-dihydro-4-amino-2*H*-1-benzopyrans[a]

Entry	R	R′	$Sc(OTf)_3$		$BF_3{\cdot}OEt_2$		Product ratio[c]
			Time (h)	Yield[b] (%)	Time (h)	Yield[b] (%)	**2**:**3**
a	H	H	3.0	88	5.0	83	60:40
b	H	4-Cl	4.5	86	3.5	78	95:05
c	5-Cl	H	6.0	87	7.5	81	85:15
d	H	4-OMe	3.0	89	5.5	84	90:10
e	3-OEt	H	4.5	84	6.0	80	100:00
f	3-OMe	H	4.0	81	5.5	77	95:05
g	H	4-Me	3.5	83	5.0	75	98:02
h	H	4-CN	7.5	75	8.0	71	65:35
i	3-OEt	4-Me	4.5	87	6.0	83	50:50
j	3-OEt	4-Cl	5.0	85	7.5	78	90:10
k	3-OMe	4-Me	3.5	89	5.0	87	97:03
l	3-OMe	4-Me	5.5	80	7.0	75	90:10
m	5-Cl	4-Cl	7.0	74	8.0	70	85:15
n	5-Cl	4-Me	5.0	83	7.5	81	60:40

[a] All products were characterized by ^{1}H NMR, IR and mass spectra.

[b] Isolated and unoptimized yields.

[c] Ratio of **2** and **3** was based on the ^{1}H NMR spectrum of product mixture (400 MHz).

donating as well as electron withdrawing substituents on the aromatic ring.

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9. PC MODEL, Serena Software BOX 3076, Bloomington, IN.
10. **General procedure**: A mixture of *o*-hydroxybenzylideneaniline (5 mmol), 2,2-dimethoxypropane (20 mmol), scandium triflate (10 mol%) or $BF_3 \cdot OEt_2$ (30 mol%) in dichloromethane (15 ml) was stirred at ambient temperature for an appropriate time (Table 1). After completion of the reaction, as indicated by TLC, the reaction mixture was quenched with water (10 ml) and extracted with dichloromethane (2×15 ml). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by column chromatography on silica-gel (Merck, 100–200 mesh, ethyl acetate–hexane, 0.5:95) to afford pure product. Representative spectroscopic data for product **2a**: ^{1}H NMR ($CDCl_3$): δ 1.60 (s, 3H), 2.10 (dd, 1H, $J=14.5$ and 6.0 Hz), 2.40 (d, 1H, $J=14.5$ Hz), 3.25 (s, 3H), 3.50 (brs, NH), 4.66 (d, 1H, $J=6.0$ Hz), 6.70 (m, 2H), 6.90 (m, 2H), 7.15–7.25 (m, 4H), 7.40 (d, 1H, $J=8.0$ Hz). ^{13}C ($CDCl_3$, proton decoupled) δ 22.9, 38.15, 45.4, 48.9, 99.3, 113.1, 116.8, 117.5, 121.1, 124.2, 126.8, 128.7, 129.4, 147.4, 151.5. EIMS m/z: 269$^+$, 237, 197, 177, 145, 118, 77. **3a**: ^{1}H NMR ($CDCl_3$): δ 1.60 (s, 3H), 1.65 (dd, 1H, $J=10.3$ and 9.3 Hz), 2.60 (dd, 1H, $J=10.3$ and 4.6 Hz), 3.30 (s, 3H), 3.65 (brs, NH), 5.02 (dd, 1H, $J=9.3$ and 4.6 Hz), 6.75 (m, 2H), 6.95 (m, 2H), 7.15 (m, 4H), 7.50 (d, 1H, $J=8.0$ Hz). ^{13}C ($CDCl_3$, proton decoupled) δ 23.0, 39.1, 46.2, 48.98, 99.9, 114.0, 117.3, 117.6, 121.3, 125.4, 128.4, 129.3, 130.1, 147.6, 152.2. **2g**: ^{1}H NMR ($CDCl_3$): δ 1.60 (s, 3H), 2.15 (dd, 1H, $J=14.2$ and 5.8 Hz), 2.30 (s, 3H), 2.45 (d, 1H, $J=14.2$ Hz), 3.25 (s, 3H), 3.50 (brs, NH), 4.60 (d, 1H, $J=5.8$ Hz), 6.60 (m, 2H), 6.95 (m, 3H), 7.00 (m, 2H), 7.40 (d, 1H, $J=8.2$ Hz). EIMS m/z: 283M$^+$, 251, 211, 177, 145, 107, 91. **3g**: ^{1}H NMR ($CDCl_3$): δ 1.65 (s, 3H), 1.75 (dd, 1H, $J=10.5$ and 9.5 Hz), 2.30 (s, 3H), 2.55 (dd, 1H, $J=10.5$ and 4.5 Hz), 3.30 (s, 3H), 3.70 (brs, NH), 5.05 (d, 1H, $J=9.5$ and 4.5 Hz), 6.65 (m, 2H), 6.90 (m, 2H), 7.05 (m, 3H), 7.60 (d, 1H, $J=8.2$ Hz).