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Metal Triflates: Efficient Catalysts for Oxa-Pictet-Spengler Reaction

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Abstract: A screening of different metal triflates as catalysts was performed to get isochromans through an oxa-Pictet-Spengler reaction. Good to high yields were obtained for various aliphatic or aromatic aldehydes and β-arylethanols. A mechanism involving catalysis by *in situ* liberated triflic acid to catalyse the isochroman ring formation is proposed.

Keywords: Metal triflate, oxa-Pictet-Spengler, catalysis.

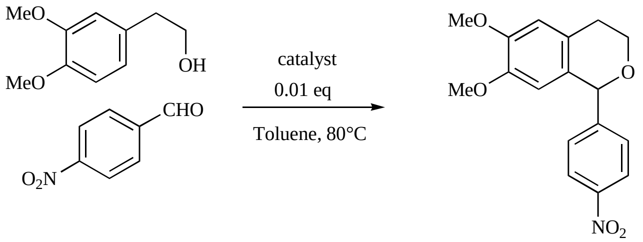
The oxygenated version of the Pictet-Spengler reaction, called Oxa-Pictet-Spengler, consists of a condensation of β-aryl ethanol with a carbonyl derivative to give the isochroman ring [1]. This reaction was reported for the first time by Wunsch *et al.* in 1992 [2]. Since then, different methods have been reported to prepare isochromans [3-5]. The isochroman template is present in structures of different drugs [1,6-8] or in natural products [1].

In the previous work, we described the synthesis of iso(thio)chromans from 2-phenylethanol derivatives or 2-phenylethanethiol and different aldehydes in the presence of catalytic amounts of bismuth(III) triflate [9]. The catalytic activity of $Bi(OTf)_3$ could be attributed to traces of triflic acid generated *in situ* [10]. The numerous advantages of metal catalysts make them highly attractive for chemical synthesis from environmental and economic points of view. In this study, we disclose the usefulness of metal triflate to provide isochroman from β-aryl ethanol. This work provides also insights into the catalytic role of metal triflates in the reaction. We have also examined the scope of the reaction in the presence of different reactants.

Initially, the condensation of 3,4-dimethoxyphenyl ethanol (1 eq) and 4-nitrobenzaldehyde (1 eq) was used as a model reaction for the screening of seven different metal triflate catalysts.

The reaction was carried out in toluene at 80°C in the presence of a catalytic amount (0.01 eq) of metal triflate. The reaction was monitored by TLC analysis following the disappearance of the starting alcohol. The reaction was completed in maximum 1.5h and isochroman was obtained in almost quantitative yield (entries 2-8, Table **1**) after work-up and silica gel purification. The same reaction was realized in the absence of metal to recover essentially the starting material and the isochroman product in 16% yield after 18 hours (entry 1, Table **1**).

Table 1. Synthesis of Isochroman Under Different Reaction Conditions



Entry	Catalyst	Time (h)	Yields[a] (%)
1	---	18	16
2	$Bi(OTf)_3$ 0.01 eq	1	>99
3	$In(OTf)_3$ 0.01 eq	1	>99
4	$Sc(OTf)_3$ 0.01 eq	1	>99
5	$Zn(OTf)_2$ 0.01 eq	1	91
6	$Yb(OTf)_3$ 0.01 eq	1	>99
7	$Y(OTf)_3$ 0.01 eq	1	>99
8	$Cu(OTf)_2$ 0.01 eq	1	94

[a]Yields for the isolated isochroman.

In order to get insights into the mechanism of the reaction, we explored different reaction conditions. We investigated first the catalytic role of each metal triflate. Dumeunier *et al.* have demonstrated in a related reaction acylation of alcohols in the presence of metal triflates that the true catalyst was the liberated triflic acid instead of the metal triflate [11]. In that respect, we conducted our reaction in the presence of 10% mol triflic acid in toluene at 80°C. After 1h, the reaction was completed affording the isochroman derivative in quantitative yield (entry 1, Table **2**). Thus the strong proton donating abilities of triflic acid (Brønsted acid properties) catalyzed the reaction very efficiently.

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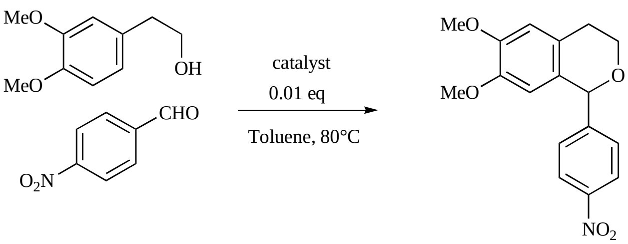
In order to investigate the role of traces of water in the mechanism of chroman formation, we conducted each reaction of metal triflate with the two same reagents in toluene and in the presence of molecular sieves (4Å) [12]. Under these conditions, only traces of isochroman were observed in the reaction mixture along with starting compounds (entry 3, Table **2**). This points out the importance of water molecules for the reaction to occur.

Table 2. Insights on the Catalytic Role of Metal Triflate



Entry	Catalyst	Time (h)	Yields[a] (%)
1	TfOH 0.1 eq	1	>99
2	$M(OTf)_n$ 0.01 eq	1	>99
3	$M(OTf)_n$ 0.01 eq 4 Å MS[b]	1	traces
4	$M(OTf)_n$ 0.01 eq 0.1 eq TTBP	1	0
5	$Cu(OTf)_2$ 0.01 eq , 4 Å MS[b] TfOH 0.05 eq	1	48

[a] Yields for the isolated isochroman.

[b] Molecular sieves (MS) were activated at 150°C under high vacuum.

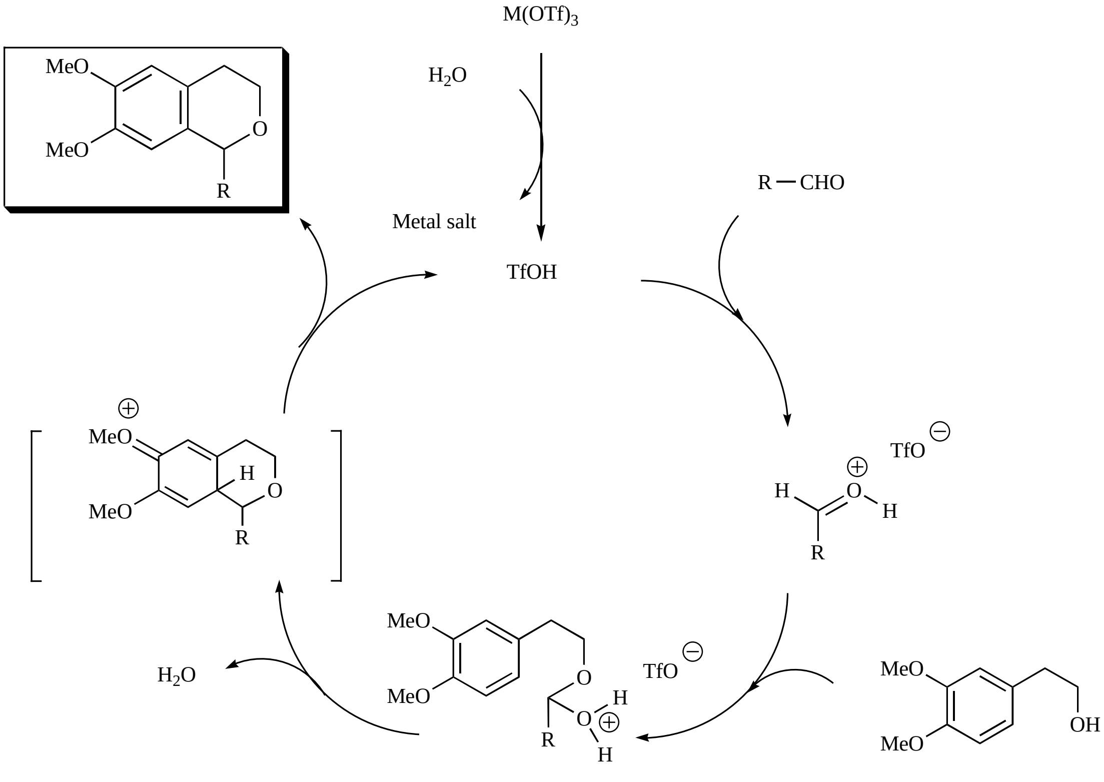
Next, in order to neutralize the traces of triflic acid, 2,4,6-tri-tert-butyl pyridine (TTBP), a very hindered base, was added to the reaction media. This base is known to not interact with metal catalysts [13]. Under these conditions, no product was observed in the presence of various metal triflates (Table **2**, entry 4).

These experiments taking together showed that metal triflates do not act as Lewis acids but as a source of triflic acid. Unlike triflic acid (corrosive and toxic), less toxic metal triflates are eco-friendly and easy-handled reagents.

In order to verify more precisely the role of residual water, we decided to add triflic acid to a solution of copper triflate and molecular sieves. The reaction resulted in a modest 48% yield. These findings proved that water impacts on the mechanism by two ways: 1) by hydrolyzing the metal triflate catalyst; 2) by acting as a base to remove the acidic hydrogen in the aromatic cycle. A possible mechanism is depicted in Scheme **1**.

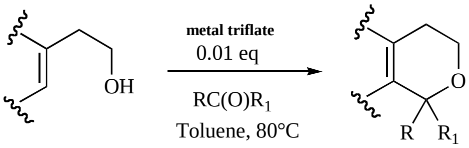
Traces of water molecules may provide the initial source of triflic acid. Then β-arylethanol condensates with the aldehyde activated by triflic acid to form a hemiacetal intermediate, which undergoes cyclization affording the isochroman ring.

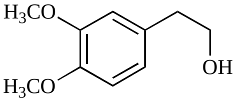
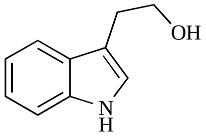
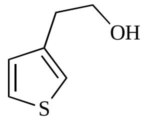
We next examined the generality of this methodology for the synthesis of isochromans from 3,4-dimethoxy-phenylethanol using different catalysts and carbonyl derivatives (Table **3**). Both aromatic (entries 1-4, Table **3**), aliphatic aldehydes (entries 5-6) or ethyl β-ketobutyrate (entries 7-8) were applicable to this reaction. Furthermore we found that the reaction is slower with copper (II) triflate (entries 3, 5 and 9, Table **3**). It should be noted that the



Scheme 1. Mechanism for the oxa-Pictet-Spengler reaction.

Table 3. Scope of the Reaction Catalyzed by Metal Triflate

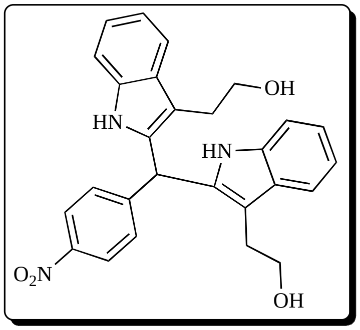


Entry	Substrate	RC(O)R$_1$	Metal Triflate	Time (h)	Yields[a] (%)
1		4-NO$_2$-Ph-CHO	Cu(OTf)$_2$	1.5	>99
2		4-NO$_2$-Ph-CHO	Bi(OTf)$_3$	1	>99
3		4-CH$_3$O-Ph-CHO	Cu(OTf)$_2$	3	86
4		4-CH$_3$O-Ph-CHO	Bi(OTf)$_3$	1.5	91
5		CH$_3$(CH$_2$)$_4$-CHO	Cu(OTf)$_2$	3	90
6		CH$_3$(CH$_2$)$_4$-CHO	Bi(OTf)$_3$	1	>99
7		CH$_3$COCH$_2$COOEt	Cu(OTf)$_2$	2	67
8		CH$_3$COCH$_2$COOEt	Bi(OTf)$_3$	2	91
9		4-NO$_2$-Ph-CHO	Cu(OTf)$_2$	3	40 (N/I)[b]
10		4-NO$_2$-Ph-CHO	Bi(OTf)$_3$	2	56 (N/I)[b]
11		4-NO$_2$-Ph-CHO	Sc(OTf)$_3$	2	48 (17)[b]
12		4-CH$_3$O-Ph-CHO	Sc(OTf)$_3$	1.5	66
13		4-CH$_3$O-Ph-CHO	Bi(OTf)$_3$	1	98
14		CH$_3$COCH$_2$COOEt	Sc(OTf)$_3$	2	85

[a] Yields for isolated compounds.
[b] Second product observed (N/I: not isolated).

reaction with benzaldehyde bearing electron-rich substituent such as *p*-methoxybenzaldehyde (entries 3-4) proceeds slower than for benzaldehyde bearing electron-poor substituent such as *p*-nitrobenzaldehyde (entries 1-2).

In the case of tryptophol (entries 9-11), the yields for the isochroman ring formation are around 50%. That could be explained by the presence of a second product. After different investigations by ^{1}H and ^{13}C NMR and mass spectrometry, we elucidated the structure as a 2,2'-bis(indoyl)-4-nitrophenylmethane derivative (See *note b* in Table **3**). Bis(indoyl)alkane derivatives are easily accessible in the presence of Lewis acid or Brønsted acid [14].



Furthermore, the reactions with 2-(3-thienyl)ethanol with 4-methoxybenzaldehyde or ethyl acetoacetate afforded the corresponding isochromans in good yields depending on the catalyst. In fact Sc(OTf)$_3$ was found to be less efficient by comparison with Bi(OTf)$_3$ with 4-methoxybenzaldehyde (entries 12-13).

In conclusion, an efficient, simple, and eco-friendly method has been described for the synthesis of isochromans by employing condensation reaction of different β-aryl ethanol, aldehydes, and β-diketones in toluene using metal triflates as a mild Brønsted acid precursor. The use of these easy-handled catalysts by comparison with triflic acid should find utility in the synthesis of natural products.

EXPERIMENTAL

All chemicals were obtained from Aldrich or Acros Organics and used without further purification. Nuclear magnetic resonance spectra were recorded on a Bruker AC 300 spectrometer (^{1}H and ^{13}C NMR), and mass spectra were measured on a Nermag R10-10C mass spectrometer.

Typical Procedure

To a solution of alcohol (1 eq, 0.37 mmol) and aldehyde (1 eq, 0.37 mmol) in toluene (3 mL), was added M(OTf)$_n$ (0.01 eq) at room temperature. The reaction mixture was warmed up to 80°C and stirred until completion followed by TLC. The mixture was cooled and concentrated under reduced pressure. Then ethyl acetate (20 mL) was added and the organic layer washed with water (2 x 20 mL), dried over MgSO$_4$ and concentrated under reduced pressure to give the isochroman derivative. In some cases, the products had to be purified by flash chromatography. Some compounds reported in Table **3** could be compared with those of the previously reported spectroscopic data (entries 1 [15], 3 [3]).

The spectral data of isochromans reported in Table **3** are summarized below.

3,4-dihydro-6,7-dimethoxy-1-pentyl-1H-isochromene (Entry 5)

Colorless oil. ^{1}H NMR ($CDCl_3$) δ 0.89 (m, 3H); 1.39 (m, 6H); 1.76 (m, 2H); 2.58 (m, 1H); 2.89 (m, 1H); 3.72 (m, 1H); 3.84 (s, 3H); 3.85 (s, 3H); 4.66 (dd, J = 8.1 Hz, J = 2.9 Hz, 1H); 6.54 (s, 1H); 6.58 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.0; 22.6; 24.9; 28.6; 31.9; 36.0; 55.8; 55.9; 63.1; 75.5; 107.9; 111.4; 125.9; 130.4; 147.3 (2C); LRMS : (DCI/NH_3, m/z) calc. for $C_{16}H_{24}O_3$: 264.2. Found: 282.1 ($M+NH_4^+$).

Ethyl 2-(3,4-dihydro-6,7-dimethoxy-1-methyl-1H-isochromen-1-yl)acetate (Entry 7)

Colorless liquid. ^{1}H NMR ($CDCl_3$) δ 1.18 (t, J = 7.1 Hz, 3H); 1.61 (s, 3H); 2.72 (m, 1H+2H); 2.88 (d, J = 13.7 Hz, 1H); 3.83 (s, 3H); 3.84 (s, 3H); 3.94 (m, 2H); 4.08 (m, 1H); 6.55 (d, J = 6.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.1; 27.7; 28.6; 46.5; 55.7; 56.0; 59.8; 60.1; 74.9; 108.3; 111.2; 125.4; 132.8; 147.4; 147.5; 170.1; LRMS: (DCI/NH_3, m/z) calc. for $C_{16}H_{22}O_5$: 294.2. Found: 295.1 ($M+H^+$).

1,3,4,9-tetrahydro-1-(4-nitrophenyl)pyrano[3,4-b]indole (Entry 11)

Yellow solid. ^{1}H NMR ($CDCl_3$) δ 2.87 (m, 1H); 3.12 (m, 1H); 4.02 (m, 1H); 4.31 (m, 1H); 5.91 (s, 1H); 7.18 (m, 2H); 7.27 (d, J = 7.1 Hz, 1H); 7.49 (br s, 1H); 7.57 (d, J = 8.7 Hz, 2H+1H); 8.22 (d, J = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 22.1; 64.9; 75.0; 109.3; 111.1; 118.5; 120.0; 122.5; 124.0; 126.8; 129.1; 131.9; 136.2; 146.7; 148.1; LRMS: (DCI/NH_3, m/z) calc. for $C_{17}H_{14}N_2O_3$: 294.1. Found: 295.1 (M+H).

2,2'-Bis(indoyl)-4-nitrophenylmethane (Entry 11, side product)

Yellow foam. ^{1}H NMR ($CDCl_3$) δ 2.16 (broad s, 2H); 2.85 (m, 4H); 3.86 (m, 4H); 6.35 (s, 1H); 7.15 (m, 4H); 7.25 (d, J = 7.3 Hz, 2H); 7.32 (d, J = 8.6 Hz, 2H); 7.54 (d, J = 7.2 Hz, 2H); 8.10 (d, J = 8.7 Hz, 2H); 8.71 (broad s, 2H); ^{13}C NMR ($CDCl_3$) : δ 27.3; 40.7; 62.3;110.1; 111.2; 118.6; 119.8; 122.3; 123.9; 128.1; 129.2;134.5; 136.0; 147.0; 148.1; LRMS: (DCI/NH_3, m/z) calc. for $C_{27}H_{25}N_3O$: 455.2. Found: 456.2 (M+H).

5,7-dihydro-7-(4-methoxyphenyl)-4H-thieno[2,3-c]pyran (Entry 12)

Brown crystal upon standing. ^{1}H NMR ($CDCl_3$) δ 2.71 (m, 1H); 2.98 (m, 1H); 3.82 (s, 3H); 3.92 (m, 1H); 4.24 (m, 1H); 5.76 (s, 1H); 6.86 (d, J = 5.1 Hz, 1H); 6.89 (d, J = 8.8 Hz, 2H); 7.17 (dd, J = 5.0 Hz, J = 0.8 Hz, 1H); 7.32 (d, J = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 26.2; 55.2; 64.2; 77.3; 113.8; 123.7; 126.8; 129.2; 133.8; 137.2; 159.7; LRMS: (DCI/NH_3, m/z) calc. for $C_{14}H_{12}O_2S$: 246.1. Found: 247.0 ($M+H^+$).

Ethyl 2-(5,7-dihydro-7-methyl-4H-thieno[2,3-c]pyran-7-yl)acetate (Entry 14)

Colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.22 (t, J = 7.1 Hz, 3H); 1.67 (s, 3H); 2.69 (t, J = 5.5 Hz, 2H); 2.75 (d, J = 13.9 Hz, 1H); 2.90 (d, J = 13.9 Hz, 1H); 3.98 (m, 2H); 4.13 (q, J = 7.2 Hz, 2H); 6.75 (d, J = 5.1 Hz, 1H); 7.14 (d, J = 5.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1; 26.1; 28.7; 47.2; 74.7; 122.7; 126.7; 132.9; 140.4, 169.7; LRMS: (DCI/NH_3, m/z) calc. for $C_{12}H_{16}O_3S$: 240.1. Found: 241.1 ($M+H^+$).

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