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Bismuth triflate-catalyzed oxa- and thia-Pictet–Spengler reactions: access to iso- and isothio-chroman compounds

Christian Lherbet *, David Soupaya, Cécile Baudoin-Dehoux, Chantal André, Casimir Blonski, Pascal Hoffmann

Laboratoire de Synthèse et Physico-Chimie de Molécules d'Intêret Biologique, UMR CNRS 5068, Université Paul Sabatier Groupe de Chimie Organique Biologique 118, Route de Narbonne, 31062 Toulouse Cedex 9, France

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ABSTRACT

A new route to functionalized iso(thio)chromans is described. The compounds are accessible easily in a one pot-reaction by using different benzaldehydes and phenylethanethiol or phenylethanol in presence of bismuth triflate.

Many isochroman derivatives are of interest in several pharmaceutical areas, since they exhibit a variety of biological properties.[1,2] The isochromanic structure is obtained by a variety of synthetic methods, the oxa-Pictet–Spengler reaction, in which a β-arylethylalcohol undergoes ringclosure after condensation with an aldehyde, being one of the most convenient methods. Otherwise, the isothiochroman ring structure (1*H*-2-benzothiopyran) has proven to be a convenient precursor for the synthesis of isoquinolin, tetrahydronaphthalene or isochroman analogues[3,4] and to also exhibit pharmacological properties as glucose-6-phosphate inhibitors or estrogen receptor binding molecules. To access to isothiochroman compounds, a number of synthetic approaches have been developed including intramolecular cyclization of phenylethanethiol in the presence of catalytic amounts of Lewis acids,[5] intramolecular cyclization from thioacetal[6] or from phenylmethanethiol derivatives[7] or from enediynes under acidic conditions.[8] There are few reports describing the preparation of 1-arylated isothiochromans (1-aryl-3,4-dihydro-1*H*-benzothio-pyrans), for example, by reaction of 1-brominated isothiochroman compounds with aryl magnesium bromide.[9]

As part of a project that aims to discover novel inhibitors of coenzyme A-dependant enzymes, we prepared with moderate yields, a series of isothiochroman compounds by mixing arylethanethiol with formaldehyde in the presence of hydrogen bromide (unpublished results). Therefore, we envisaged to investigate whether other acid catalysts would improve our procedure for the preparation of the isothiochroman ring system through a 'Pictet–Spengler' like reaction (called thia-Pictet–Spengler), and considered the use of bismuth(III) salts for their preparation. Bismuth(III) salts as Lewis acids have been proved to efficiently catalyze a number of reactions like Michael reactions,[10] acylation reactions,[11] oxidation of α-ketols[12] or epoxides[13] and Diels–Alder reactions.[14] Additionally, Bi(III) salts have been found to catalyze Mannich reactions, the intermolecular variant of a Pictet–Spengler process.[15]

Moreover, compared to other Lewis acids such as $AlCl_3$, $ZnCl_2$ or $SnCl_4$, bismuth salts have been shown to be less toxic, and to be generally more stable in solution, particularly in protic solvents like water or methanol.

In this study, we report an efficient one-pot racemic synthesis of isothiochromans, or isochromans, by using $Bi(OTf)_3$ as Lewis acid catalyst (Table 1), and show that $Bi(OTf)_3$ catalyzes both formation of the dithioacetal intermediate and the subsequent intramolecular cyclization leading to the isothiochroman compounds.

In the presence of 0.1 equiv of bismuth triflate, phenylethanethiol reacted at room temperature with 3-nitrobenzaldehyde to yield almost quantitatively the corresponding dithioacetal, and only trace of the cyclized compound was observed, as evidenced by ^{1}H NMR (Table 1). A similar reaction was reported for the protection of aldehydes with ethanedithiol in the presence of catalytic amount of bismuth nitrate.[16] The S,S-acetalization of aldehydes

* Corresponding author. Tel.: +33 561 55 68 07; fax: +33 561 85 60 11.
E-mail address: lherbet@chimie.ups-tlse.fr (C. Lherbet).

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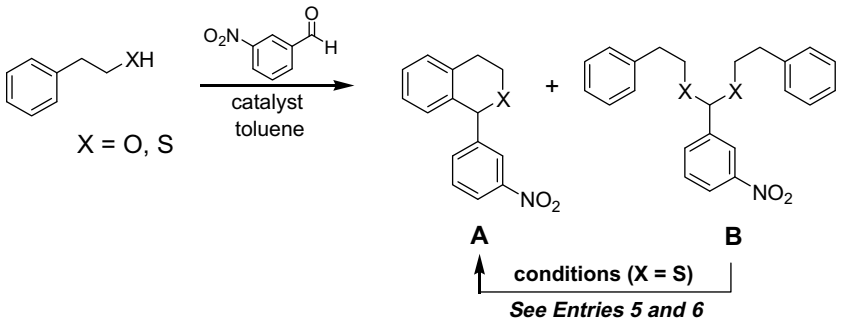
Table 1
Synthesis of isothiochroman (or isochroman) in a one-pot reaction



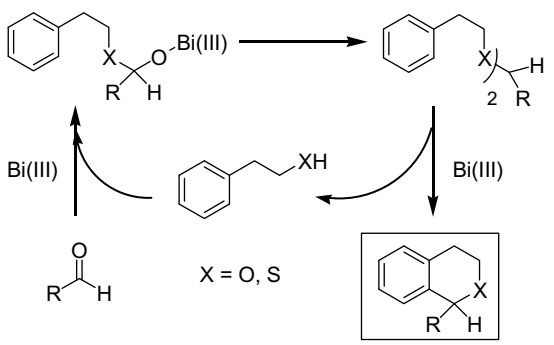
Entry	X	Catalyst	Conditions	Yields[a] *A*/*B*, (%)
1	S	$Bi(OTf)_3$ (0.1 equiv)	rt	Traces/96
2	S	$Bi(OTf)_3$ (0.1 equiv)	100 °C, 2 h	88/no
3	S	$Bi(OTf)_3$ (0.02 equiv)	100 °C, 2 h	75/25[b]
4	O	$Bi(OTf)_3$ (0.1 equiv)	110 °C, 6 h	80/0
5	S	—	100 °C, 2 h	Traces/95
6	S	$Bi(OTf)_3$ (0.1 equiv)	100 °C, 2 h	91/no

[a] Yields after purification by flash chromatography.
[b] Ratio observed by ^1H NMR of crude reaction mixture.

or ketones was also described by using BiX_3 (X = Cl, Br and I).[17] We examined a variety of reaction conditions to obtain isothiochromans and found that the process was usually most efficient in toluene at 100 °C. Using these conditions, the product was obtained in yields approaching 90% after routine purification by flash chromatography.[18]

In order to investigate the mechanism, the reaction was performed starting from the isolated thioacetal intermediate. In that case, no reaction was observed in the absence of Bi(III) (Table 1, entry 5), but cyclization to the expected isothiochroman occurred when the thioacetal was heated at 100 °C in the presence of the bismuth catalyst (0.1 equiv) for 2 h (Table 1, entry 6). The efficiency of bismuth to catalyze the reaction encouraged us to try the same conditions with phenylethanol instead of phenylethanethiol in order to see the impact of the heteroatom on the reaction (Table 1, entry 4). Optimization of reaction conditions resulted in yields up to 80% after heating at 110 °C for at least 6 h. As evidenced by ^1H, ^{13}C NMR and by TLC, the acetal product is the intermediate in the reaction.

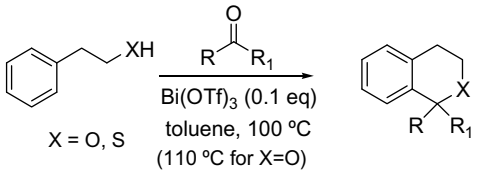
According to Guiso et al., a three-step reaction mechanism is observed involving an acid-catalyzed hemiacetal formation followed by dehydration to give the oxonium ion intermediate, and further cyclization.[19] In our case, the acetal is the result of the first step followed by an alcohol or thiol loss, thus leading to the oxonium or sulfonium ions. From our results, we conclude that Bi(III) catalyzes both the dithioacetal formation and the cyclization reaction leading to the isothiochroman, as proposed in Scheme 1.



Scheme 1.

Under optimal conditions, different isothiochroman or isochroman compounds were synthesized from phenylethanethiol or phenylethanol and a series of benzaldehydes (Table 2). Good yields in the range of 40–94% were obtained for all reactions, even with sterically hindered aldehydes such as 2-methoxybenzaldehyde or 2,6-dichlorobenzaldehyde (Table 2, entries 2 and 11). An X-ray structure was determined for the racemic isochroman compound (entry 11, see Supplementary data). It should be noted that in some cases (Table 2, entries 4 and 10) the reactions afforded an inseparable mixture of the expected compounds and the dithioacetal intermediates, as revealed by TLC and ^1H NMR spectroscopy. Consequently, in this case, the resulting isothiochroman (Table 2, entry 4) was isolated as a sulfone after its oxidation by hydrogen peroxide in the presence of acetic acid.

Table 2
Synthesis of isothiochroman from phenylethanethiol or phenylethanol

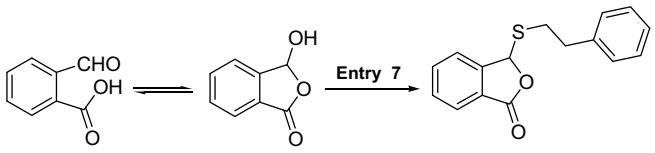


Entry	X	R	R_1	Reaction time (h)	Yields[a] (%)
1	S	3-NO_2–Ph–	H–	2	88
2	S	2-MeO–Ph–	H–	2.5	40
3	S	Ph–	H–	2	94
4	S	Naphthyl–	H–	2	68[b]
5	S	3-CHO–Ph–	H–	3	53[c]
6	S	Ph–	CH_3–	15	<25[d]
7	S	2-HO_2C–Ph–	H–	2	68[e]
8	O	3-NO_2–Ph–	H–	6	80
9	O	4-NO_2–Ph–	H–	6	84
10	O	Ph–	H–	6	Inseparable mixture
11	O	2,6-Cl_2–Ph–	H–	7	52[f]

[a] Products characterized by ^1H, ^{13}C NMR and MS.[20].
[b] Yield after two steps (product isolated as sulfone after oxidation with H_2O_2, AcOH).
[c] Yield for the di-isothiochroman product (2 equiv thiol was added).
[d] Yield in dithioacetal, estimated by ^1H NMR.
[e] Yield for the phthalide.
[f] Recrystallization in petroleum ether/cyclohexane.

Extension of this methodology to the preparation of 2-alkylated isothiochroman derivatives starting from ketones was then investigated. Contrary to expectations, in the same experimental conditions no isothiochroman was obtained from acetophenone after 15 h (Table 2, entry 6). In fact, control experiments revealed that $Bi(OTf)_3$ did not efficiently catalyze the formation of the dithioacetal intermediate. It should be noted that neither $BiCl_3$ nor other bismuth(III) salts were found to catalyze the reaction in our conditions, although these catalysts have proven to be efficient for the preparation of cyclic dithioacetal such as 1,3-dithiane from both aliphatic and aromatic aldehydes and ketones.[17]

When phthaldehydic acid was used as starting aldehyde (Table 2, entry 7), the corresponding thioether was observed as the sole isolated product in the presence of bismuth triflate. It should be noted that the same compound was obtained when *p*-toluenesulfonic acid was used as acid catalyst.[21]



In conclusion, it was demonstrated that iso(thio)chromans can be efficiently prepared from phenylethanethiol or phenylethanol and different benzaldehydes in the presence of $Bi(OTf)_3$. Bismuth(III) was shown to be essential both in the dithioacetal formation initial step and in the cyclization to form the isothiochroman derivative. The procedure was found to be highly efficient, giving the desired compounds in good to excellent yields. Finally, the established protocol will be extended to (substituted-phenyl)-ethanethiol derivatives.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.07.007.

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18. *General procedure to get isothiochroman derivatives from phenylethanethiol*: To a solution of aldehyde (1 equiv, 0.37 mmol) in toluene (5 mL) were added phenylethanethiol or phenylethanol (1 equiv) and $Bi(OTf)_3$ (0.1 equiv), successively. The reaction mixture was warmed up slowly to 100 °C (110 °C for phenylethanol) and stirred for 2 h. The mixture was cooled, and EtOAc (5 mL) was added to the mixture. The organic layer was then washed with water (2×20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The desired compound was purified by flash chromatography (petroleum ether/EtOAc, 95:5). All compounds reported in Table 2 were characterized by MS, ^1H and ^{13}C NMR.
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20. *Characterization of selected products: Entry 1*: ^1H NMR $CDCl_3$, 300 MHz) δ 2.89 (m, 2H); 3.15 (m, 2H); 5.24 (s, 1H); 6.89 (d, J = 7.7 Hz, 1H); 7.16 (m, 2H); 7.25 (m, 1H); 7.46 (t, J = 7.8 Hz, 1H); 7.55 (d, J = 7.8 Hz, 1H); 8.11 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.5; 30.6; 45.1; 122.0; 123.6; 126.4; 127.5; 128.6; 129.1; 130.1; 134.8; 135.1; 136.6; 145.6; 148.2. LRMS: (DCI/NH_3, m/z) calcd for $C_{15}H_{13}NO_2S$: 271.1, found 289.4 $(M+NH_4)^+$. *Entry 4*: (sulfone) ^1H NMR ($CDCl_3$, 300 MHz) δ 3.29 (m, 1H); 3.61 (m, 3H); 6.31 (s, 1H); 6.84 (d, J = 7.2 Hz, 1H); 7.16 (d, J = 6.0 Hz, 2H); 7.31 (d, J = 4.2 Hz, 2H); 7.42 (t, J = 7.6 Hz, 1H); 7.57 (m, 2H); 7.90 (t, J = 8.2 Hz, 2H); 8.27 (d, J = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 29.4; 45.2; 64.3; 123.8; 125.0; 126.2; 126.9; 127.4; 128.2; 128.9; 129.3; 129.8; 131.1; 132.7, 132.1; 133.8; 133.9. LRMS: (DCI/NH_3, m/z) calcd for $C_{19}H_{16}O_2S$: 308.1, found 326.4 $(M+NH_4)^+$. *Entry 8*: ^1H NMR $CDCl_3$, 300 MHz) δ 2.83 (m, 1H); 2.87 (m, 1H); 3.97 (m, 1H); 4.19 (m, 1H); 5.84 (s, 1H); 6.71 (d, J = 7.6 Hz, 1H); 7.11 (m, 1H); 7.21 (m, 2H); 7.53 (t, J = 7.7 Hz, 1H); 7.68 (d, J = 7.6 Hz, 1H); 8.2 (m, 1H+1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.6; 64.1; 78.6; 123.1; 123.7; 126.2; 126.5; 127.2; 129.1; 129.4; 133.8; 134.8; 135.8; 144.4; 148.3. LRMS: (DCI/NH_3, m/z) calcd for $C_{15}H_{13}NO_3$: 255.1, found 273.4 $(M+NH_4)^+$.
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