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Tetrahedron Letters
Tetrahedron Letters 45 (2004) 9369–9371

Environment-friendly organic synthesis using bismuth compounds. Bismuth triflate catalyzed synthesis of substituted 3,4-dihydro-2*H*-1-benzopyrans

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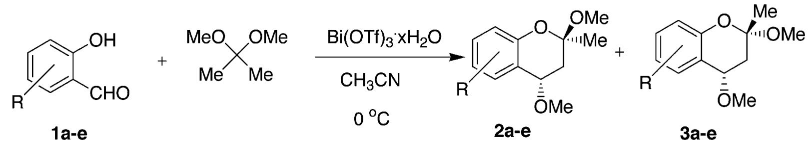
Received 20 September 2004; revised 20 October 2004; accepted 21 October 2004
Available online 6 November 2004

Abstract—A highly catalytic method for the synthesis of dihydrobenzopyrans from salicylaldehydes has been developed. An extension of this method to the synthesis of a pyrano[2,3,*b*]benzopyran has also been achieved. $Bi(OTf)_3{\cdot}xH_2O$ ($1 < x < 4$) (0.1 mol%) smoothly catalyzes the condensation of substituted salicylaldehydes with 2,2-dimethoxypropane to give the corresponding substituted 3,4-dihydro-2*H*-1-benzopyrans as a mixture of diastereomers (9:1) in moderate yields. The relative configuration of the methoxy groups in the two diastereomers was established by NOE experiments. The advantages of this method include the use of an easy to handle, inexpensive and relatively non-toxic catalyst.

The dihydro-2*H*-1-benzopyran skeleton is found in many biologically active compounds. Such moieties have also been used in the synthesis of other biologically active molecules.[1] Hence their synthesis has received attention. Some catalysts used for formation of dihydro-2*H*-1-benzopyran include $(Ph_3P)_2PdCl_2$,[2] I_2,[3] and $Sc(OTf)_3$.[4] Few of these methods are highly catalytic in nature or report the use of environment-friendly reagents. For example, I_2 vapor is extremely corrosive while scandium compounds are toxic and moisture sensitive besides being very expensive. In addition, these reactions are carried out in an environmentally unfriendly solvent, CH_2Cl_2. According to the principles of green chemistry, synthetic methods should be designed to use substances that exhibit little or no toxicity to human health and the environment.[5] Further, the principles of green chemistry state that catalytic processes are always superior to those that require a stoichiometric amount of the reagent. In this regard, bismuth compounds have attracted considerable attraction recently.[6] Bismuth compounds are remarkably non-toxic, and many bismuth reagents have proven to be versatile catalysts for a variety of organic transformations. Bismuth has been heralded as the green element, and the low toxicity of many bismuth compounds is evident from their LD_{50} values.[7,8] We now report a highly catalytic method for the synthesis of substituted dihydro-2*H*-1-benzopyrans. $Bi(OTf)_3{\cdot}xH_2O$ ($1 < x < 4$) (0.1 mol%) smoothly catalyzes the condensation of substituted salicylaldehydes with 2,2-dimethoxypropane to give the corresponding substituted 3,4-dihydro-2*H*-1-benzopyrans in moderate yields (Scheme 1, Table 1).[9]



Scheme 1.

Keywords: Bismuth and compounds; Green chemistry; Dihydrobenzopyrans; Bismuth triflate.
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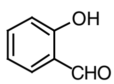
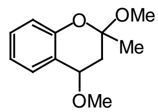
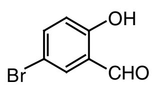
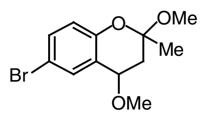
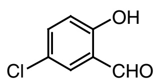
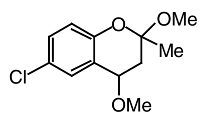
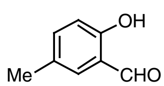
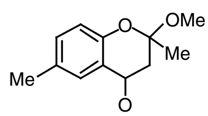
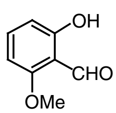
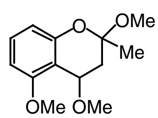
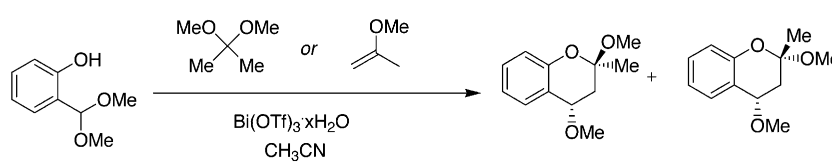
0040-4039/$ - see front matter
doi:10.1016/j.tetlet.2004.10.118

Table 1. Bismuth triflate catalyzed conversion of salicylaldehydes to dihydrobenzopyrans

Entry	Aldehyde	Product	Mol% $Bi(OTf)_3{\cdot}xH_2O$	Time (h)	Yield[a] of **2a–e** (%)	Yield of **3a–e** (%)
1a			0.1 2.0	24 2.5	72 70[c]	8[b] —
1b			0.1 2.0	15 1.75	56 57	7 —
1c			2.0	4	62[d]	—
1d			0.1 2.0	15.5 2.75	69 63[d]	5[e]
1e			0.1	18	60	4

[a] Refers to yield of isolated and purified product. All products were at least 98% pure as determined by ^1H and ^{13}C NMR spectroscopy and GC analysis unless otherwise mentioned.
[b] Product was determined to be 94% pure by GC analysis. Remainder was isomer **2a**.
[c] Product was isolated as a mixture of diastereomers (90:10 ratio of **2a**:**3a**).
[d] Only one diastereomer was isolated.
[e] Product was determined to be 95% pure by GC analysis. Remainder was isomer **2d**.

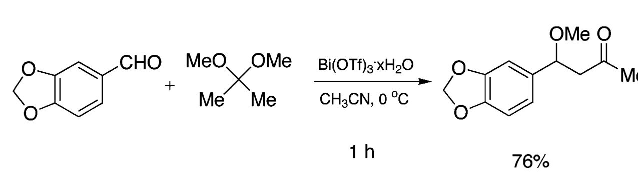


Scheme 2.

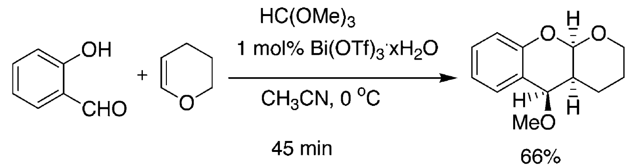
The condensation proceeded smoothly at 0 °C with as little as 0.1 mol% $Bi(OTf)_3{\cdot}xH_2O$. With the use of 2.0 mol% of $Bi(OTf)_3{\cdot}xH_2O$, the reaction proceeds at a much faster rate and was complete in about 1–4 h. Although one diastereomer was largely favored, the product was obtained as a mixture of diastereomers (ca. 90:10). This is in contrast to results previously reported in the literature.[4] However, because the two diastereomers have close R_f values, their separation required careful column chromatography with analysis of fractions by gas chromatography. The previously unreported minor diastereomer has been characterized by ^1H and ^{13}C NMR spectroscopy. The *trans*-configuration of the two methoxy groups in the major diastereomer and the *cis*-configuration in the minor diastereomer was established by NOE experiments. A plausible mechanism assumes the intermediacy of an acetal and its reaction with 2-methoxypropene generated from 2,2-dimethoxypropane.[4] In order to test this mechanism, the dimethyl acetal of salicylaldehyde was synthesized and reacted independently with both 2,2-dimethoxypropane and 2-methoxypropene. Indeed, both reactions gave the same products as those from the reaction of salicylaldehyde with 2,2-dimethoxypropane (Scheme 2). The condensation of salicylaldehyde and 2,2-dimethoxypropane was also carried out in CD_3CN and reaction progress was followed by ^1H NMR spectroscopy. This experiment also confirmed the formation of the acetal from salicylaldehyde (δ 5.52, singlet, C*H*$(OMe)_2$).

When the reaction of piperonal was carried out under the reaction conditions, the corresponding aldol condensation product was obtained (Scheme 3).

As expected from the mechanistic studies, when salicylaldehyde was treated with trimethylorthoformate and dihydropyran (an enol ether), the corresponding pyranobenzopyran was obtained in moderate yields



Scheme 3.



Scheme 4.

(Scheme 4).[10] The *cis*-relationship of the two six-membered rings in the product was confirmed by an NOE experiment. The NOE study also showed that all three methine hydrogens (CH) were on the same side of the six-membered ring.

In summary, a highly catalytic method for the synthesis of dihydrobenzopyrans from salicylaldehydes has been developed. An extension of this method to the synthesis of a pyrano[2,3,*b*]benzopyran has also been achieved. The advantages of the method include the use of an easy to handle, inexpensive, and relatively non-toxic catalyst. A representative procedure is given here. A solution of salicylaldehyde (0.5017 g, 4.108 mmol) and 2,2-dimethoxypropane (1.279 g, 12.28 mmol) in anhydrous CH_3CN (10 mL) was stirred under N_2 at 0 °C as $Bi(OTf)_3{\cdot}xH_2O$[11] (2.7 mg, 0.00411 mmol, 0.1 mol%) was added. The reaction progress was followed by GC. After 24 h, the reaction mixture was diluted with ether (20 mL) and extracted with 10% aqueous NaOH (20 mL). The organic layer was washed with saturated NaCl (20 mL), dried, and concentrated on a rotary evaporator to yield a crude product that was purified by flash chromatography on 50 g of silica gel (10% EtOAc/90% hexane) to yield 0.6178 g of the major diastereomer, **2a** (72%) and 0.0646 g of the minor diastereomer (8%), **2b**. ^{13}C NMR spectral data for both diastereomers are given here.

^{13}C NMR of **2a**: δ 23.2, 36.7, 48.9, 56.0, 71.2, 100.4, 116.5, 121.0, 123.9, 127.0, 128.7, 151.6.
^{13}C NMR of **3a**: δ 23.3, 36.4, 49.2, 56.8, 72.0, 99.1, 117.2, 121.0, 122.7, 129.2 (two peaks), 151.8.
^{13}C NMR of **2b**: δ 23.1, 36.4, 49.0, 56.3, 70.9, 100.7, 113.3, 118.4, 126.1, 129.8, 131.5, 150.7.
^{13}C NMR of **3b**: δ 23.1, 36.1, 49.3, 57.0, 71.6, 99.4, 113.2, 119.1, 125.0, 131.9, 132.1, 151.0.
^{13}C NMR of **2c**: δ 23.1, 36.5, 48.9, 56.2, 70.9, 100.7, 117.9, 125.6, 126.0, 126.9, 128.6, 150.2.
^{13}C NMR of **2d**: δ 20.5, 23.2, 36.8, 48.8, 56.0, 71.3, 100.2, 116.2, 123.4, 127.2, 129.3, 130.1, 149.3.
^{13}C NMR of **3d**: δ 20.5, 23.2, 36.4, 49.1, 56.9, 72.1, 98.9, 117.0, 122.4, 129.4, 130.0, 130.3, 149.6.
^{13}C NMR of **2e**: δ 23.2, 36.7, 48.8, 55.6, 55.9, 71.4, 100.3, 111.0, 115.3, 117.3, 124.3, 145.6, 154.0.
^{13}C NMR of **3e**: δ 23.2, 36.5, 49.1, 55.7, 56.8, 72.2, 98.9, 113.0, 116.0, 118.0, 123.4, 145.7, 153.9.

Acknowledgements

We gratefully acknowledge funding from the National Science Foundation (RUI grant # 0350216). R.S.M. is also indebted to The Camille Henry Dreyfus foundation for a Henry Dreyfus Teacher Scholar award.

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