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Tetrahedron Letters 46 (2005) 7747–7750

Tetrahedron Letters

Environment friendly organic synthesis using bismuth compounds. An efficient method for carbonyl-ene reactions catalyzed by bismuth triflate

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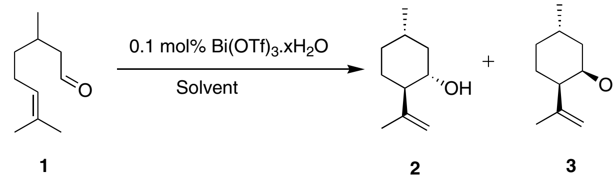
Received 26 July 2005; revised 5 September 2005; accepted 7 September 2005
Available online 23 September 2005

Abstract—Bismuth triflate (0.1 mol %) is a highly efficient catalyst for the cyclization of citronellal **1**, a reaction that yields a ratio of 80:20 of isopulegol **2** and neoisopulegol **3**. This methodology has also been extended to the synthesis of substituted piperidines. The bismuth triflate catalyzed ene reaction of aldehyde **4** gives a 70:30 mixture of piperidines **5** and **6**. The advantages of these methods include the use of a highly efficient catalyst that is relatively nontoxic, cheap and easy to handle.

The intramolecular carbonyl-ene reaction is a useful way to generate a C–C bond and has been well studied.[1] Of particular interest is the cyclization of citronellal to yield isopulegol, an important intermediate in an industrial synthesis of menthol. The selectivity of this cyclization depends on the Lewis acid, solvent, and reaction temperature. Some of the catalysts that have been used for this purpose include $ZnBr_2$,[2] $Sc(OTf)_3$,[3] Mo(II) complexes such as $BnEt_3N^+[Mo(CO)_4ClBr_2]^-$,[4] $SnCl_4$,[2] hydrous zirconia,[5] $InCl_3$,[6] $NbCl_5$,[6] $TaCl_5$,[6] and silica supported heteropoly acids such as $H_3PW_{12}O_{40}$.[7] However, many of these catalysts suffer from some drawbacks. They are either very expensive and moisture sensitive [$Sc(OTf)_3$], or are corrosive and toxic ($InCl_3$ and $SnCl_4$) while, others require elaborate preparation in the laboratory. Our continued interest in bismuth compounds, due largely to their remarkably low toxicity, low cost, ease of handling, and high catalytic efficiency prompted us to investigate the bismuth triflate, $Bi(OTf)_3{\cdot}xH_2O$, catalyzed cyclization of citronellal (Scheme 1).[8–10] The cyclization of citronellal catalyzed by $BiCl_3$ (2–5 mol %) has been previously reported.[11] We now report that $Bi(OTf)_3{\cdot}xH_2O$ (0.1 mol %) is a highly efficient catalyst for the cyclization of citronellal **1**, a reaction that yields isopulegol **2** and neoisopulegol **3** in a 80:20 ratio, respectively (Scheme 1).



Scheme 1.

An attempt to see if complexation of the carbonyl group in citronellal to bismuth triflate induces a shift in the NMR signal was unsuccessful due to fast reaction times. The cyclization of citronellal in $CDCl_3$ catalyzed by 0.1 mol % $Bi(OTf)_3{\cdot}xH_2O$ was complete in less than 5 min at rt. The best selectivity was obtained in CH_2Cl_2 (Table 1, entries 1 and 2) while the use of THF (Table 1, entry 3) gave a ca. 50:50 ratio of **2**:**3**. At −78 °C, the reaction in CH_2Cl_2 proceeded smoothly in the presence of 1.0 mol % $Bi(OTf)_3{\cdot}xH_2O$ (Table 1, entry 2). However, no change in the ratio of isopulegol to neoisopulegol was observed even at this low temperature. The cyclization also worked in DME and toluene but no reaction was observed in CH_3CN. In contrast to the high catalytic efficiency of $Bi(OTf)_3{\cdot}xH_2O$, ytterbium triflate (Table 1, entry 7) proved inefficient. A catalytic loading of 10.0 mol % and a reaction time of 1 h were required. Other reported catalysts for this cyclization are

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Keywords: Bismuth and compounds; Carbonyl-ene reaction; Cyclizations; Lewis acids.

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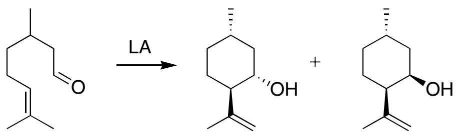
doi:10.1016/j.tetlet.2005.09.035

Table 1. Cyclization of citronellal catalyzed by $Bi(OTf)_3{\cdot}xH_2O$[13,14]



1 2 3

Entry	Catalyst	Mol %	Solvent, *T* (°C)[a]	*t* (min)[b]	**2**:**3**[c]
1	$Bi(OTf)_3{\cdot}xH_2O$	0.10	CH_2Cl_2	5	78:22
2	$Bi(OTf)_3{\cdot}xH_2O$	1.0	CH_2Cl_2 −78 °C	60	79:21
3	$Bi(OTf)_3{\cdot}xH_2O$	1.0	THF	10	52:48
4	$Bi(OTf)_3{\cdot}xH_2O$	1.0	DME	50	61:39[d]
5	$Bi(OTf)_3{\cdot}xH_2O$	1.0	CH_3CN	300	NR[e]
6	$Bi(OTf)_3{\cdot}xH_2O$	1.0	Toluene	10	68:32
7	$Yb(OTf)_3{\cdot}xH_2O$	10.0	CH_2Cl_2	60	78:22

[a] All reactions were carried out at rt using racemic citronellal unless otherwise mentioned. Citronellal was purified by distillation or flash chromatography prior to use.

[b] Reaction progress was followed by GC and TLC.

[c] Ratios were obtained by GC analysis of the crude reaction mixture. Products were separated and isolated by flash chromatography. Products were identified by comparison of their ^1H and ^{13}C NMR spectra with those reported in the literature. Typical isolated yields were 35–40% of **2** and 10–12% of **3**.

[d] Crude product contained 39% unreacted citronellal.

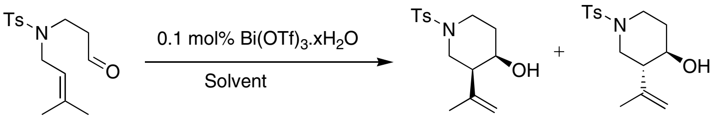
[e] Starting material was recovered unchanged.

also not nearly as efficient as bismuth triflate (equimolar amounts of $ZnBr_2$, 5.0 mol % $Sc(OTf)_3$, 10.0 mol % $NbCl_5$). While $ZnBr_2$ gave the best stereoselectivity (94% isopulegol),[2] $NbCl_5$ only afforded a 50:50 ratio of **2**:**3**.[6] Scandium triflate afforded a ratio of **2**:**3** that was similar to that obtained with bismuth triflate at room temperature.[3] However, in contrast to $Bi(OTf)_3{\cdot}xH_2O$, at −78 °C $Sc(OTf)_3$ gave a 94:6 mixture of **2**:**3**. The high catalytic efficiency of bismuth triflate coupled with its low cost, ease of handling (anhydrous solvents are not required), and low toxicity make this an attractive procedure for the large-scale synthesis of isopulegol from citronellal.

The typical isolated yields (of **2** and **3**) were around 40–50%. The low isolated yields were attributed to the formation of a complex mixture of fairly non-polar products that contained several peaks in the olefinic region. Similar low yields were reported in the $Sc(OTf)_3$ catalyzed (5 mol %) cyclization of citronellal and were attributed to the reaction of isopulegol with citronellal.[3] We found the ratio of isopulegol to neoisopeulegol to be quite reproducible and control experiments using authentic samples showed that both isopulegol **2** and neoisopulegol **3** were stable to the reaction conditions. Significantly improved yields were not obtained even when the reaction was carried out at −78 °C.

We have also extended this methodology to the intramolecular ene reaction of aldehyde **4** to synthesize substituted piperidines **5** and **6** (Table 2). These cyclizations have been previously carried out with several catalysts

Table 2. Synthesis of substituted piperidines catalyzed by $Bi(OTf)_3{\cdot}xH_2O$



4 5 6

Entry	Catalyst	Mol %	Solvent, *T* (°C)[a]	*t* (min)[b]	**8**:**9**[c]
1	$Bi(OTf)_3{\cdot}xH_2O$	0.1	CH_2Cl_2	10	70:30
2	$Bi(OTf)_3{\cdot}xH_2O$	5.0	CH_2Cl_2 −70 °C	120[d]	67:33
3	$Bi(OTf)_3{\cdot}xH_2O$	1.0	CH_2Cl_2	10	67:33
4	$Bi(OTf)_3{\cdot}xH_2O$	1.0	THF	25	72:28
5	$Yb(OTf)_3{\cdot}xH_2O$	20.0	CH_2Cl_2	360[e]	59:41
6	TMSOTf	1.0	[bmim][OTf] 230 °C	5	40:60

[a] All reactions were carried out at rt unless otherwise mentioned.

[b] Reaction progress was followed by TLC.

[c] Ratios were obtained by NMR analysis of the crude reaction product as described in Ref. 12. Products were separated and isolated by flash chromatography. Products were identified by comparison of their ^1H and ^{13}C NMR spectra with those reported in the literature.[12]

[d] Crude product contained 35% unreacted starting material.

[e] Crude product contained 43% unreacted starting material.

including $MeAlCl_2$, HCl, $AlCl_3$, $Sc(OTf)_3$, $SnCl_4$, and CF_3SO_3H.[12] In addition to being highly corrosive, most of these reagents were not very catalytic (10–50 mol % was required) while HCl was used in excess. We now report an efficient synthesis of 3,4-disubstituted piperidines catalyzed by as little as 0.1 mol % bismuth triflate. The intramolecular ene reaction of **4** afforded a 67:33 mixture of substituted piperidines **5** and **6**, respectively. It has been reported that the use of 30 mol % $MeAlCl_2$ at −78 °C afforded a 70:30 ratio of **5**:**6**, respectively, while the use of 50 mol % $Sc(OTf)_3$ gave a 50:50 mixture of **5**:**6**.[11] Thus bismuth triflate (0.1 mol %) has proven to be remarkably efficient for this type of ene cyclization. Interestingly, the major product of cyclization of **4** with bismuth triflate is the cis isomer **5**, unlike the cyclization of citronellal, which afforded isopulegol, the trans isomer as the major product. Both **5** and **6** were separable by flash chromatography.

The cyclization of **4** at −70 °C proceeded only in the presence of 5.0 mol % $Bi(OTf)_3{\cdot}xH_2O$ and even after 2 h, a considerable amount of starting material remained. Once again, in contrast to the high catalytic efficiency of $Bi(OTf)_3{\cdot}xH_2O$, $Yb(OTf)_3{\cdot}xH_2O$ proved quite inefficient for the cyclization of **7** (Table 2, entry 5). In order to determine if a greater amount of the thermodynamic product **6** was obtained at elevated temperatures, the cyclization was carried out in the ionic liquid [bmim][OTf], which allowed the reaction to be conveniently heated to 230 °C. Analysis of the crude product mixture showed that the cyclization at this temperature yielded a 40:60 mixture of **5** and **6**. It has been reported that the use of 30 mol % $MeAlCl_2$ affords a stereoselective reaction giving predominantly the trans isomer **6** at elevated temperatures (8:92 ratio of **5** and **6** at 61 °C in $CHCl_3$).[12]

In summary, a highly catalytic method for the carbonyl-ene reaction catalyzed by bismuth triflate has been developed. The advantages of this method include the use of as little as 0.1 mol % catalyst, which is relatively non-toxic and easy to handle.

Acknowledgments

We are grateful to the National Science Foundation for an RUI (Research at An Undergraduate Institution) grant. We also wish to acknowledge Research Corporation for a Cottrell College Science Award. R.M. wishes to thank The Camille and Henry Dreyfus Foundation for a Henry Dreyfus Teacher Scholar Award.

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13. Representative procedure for cyclization of citronellal catalyzed by $Bi(OTf)_3{\cdot}xH_2O$: A solution of citronellal **1** (2.00 g, 12.97 mmol) in CH_2Cl_2 (40 mL) was stirred at rt as $Bi(OTf)_3{\cdot}xH_2O$ (8.5 mg, 0.013 mmol, 0.1 mol %) was added. After 25 min, the reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with saturated aqueous $NaHCO_3$ (15 mL). The aqueous layer was extracted with CH_2Cl_2 (15 mL) and the combined organic layers were washed with saturated NaCl (15 mL), dried (Na_2SO_4), and concentrated on a rotary evaporator to yield 1.82 g of a crude product. The product was purified by flash chromatography on silica gel (75 g) using ethyl acetate/hexane (5:95, v/v) as the eluent to yield 0.69 g (35%) of isopulegol

2 and 0.21 g (11%) of neoisopulegol **3**. Both products were analyzed by ^{1}H and ^{13}C NMR spectroscopy and GC as well as by comparison of their spectra with those of authentic samples.

14. Representative procedure for the synthesis of substituted piperidines catalyzed by $Bi(OTf)_3{\cdot}xH_2O$: A solution of aldehyde **4** (1.51 g, 5.11 mmol) in anhydrous CH_2Cl_2 (20 mL) was stirred at rt as $Bi(OTf)_3{\cdot}xH_2O$ (3.3 mg, 0.00511 mmol, 0.1 mol %) was added. After 15 min, the reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with 10% aqueous Na_2CO_3 (15 mL) and saturated NaCl (15 mL). The organic layer was dried (Na_2SO_4) and concentrated on a rotary evaporator to give 1.55 g of an oil with a pale yellow tint. The crude product was purified by flash chromatography on silica gel (100 g) using ethyl acetate/hexane (30:70, v/v) as the eluent to yield 0.719 g (48%) of the cis diastereomer **5** as a colorless oil and 0.300 g of the trans diastereomer **6** as a white solid (20%). Mp of **6**: 154–156 °C (Lit.:[12] 149–151 °C). Both isomers have been previously reported.[12]