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Bismuth(III) Chloride Catalyzed Cycloisomerization of Enynes

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Several simple bismuth(III) salts were screened for the suitability to catalyze the cycloisomerization of enynes. Among them, $BiCl_3$ gave the best results. Under the optimized reaction conditions, eight substrates were studied, and acceptable to excellent isolated yields were obtained. Consistent with data in the literature, electron-deficient alkynes were found to be better substrates for the reaction than electron-rich ones. Because $BiCl_3$ is readily available, inexpensive and environmentally benign, this soft Lewis acid catalyzed isomerization reaction is expected to be a good choice for organic chemists to prepare pyrrolidine derivatives.

Introduction

The transition-metal-catalyzed cyclization of 1,6-enynes to five-membered rings is one of the most studied reactions in the literature. The starting materials of the reaction are readily available, and the products are highly functionalized carbocycles or heterocycles, which are valuable intermediates in organic synthesis.[1] The reaction can proceed either with the participation of another reactant such as carbon monoxide or through an isomerization. Precious late transition metals such as gold,[2] palladium[3] and rhodium[4] are usually used as catalysts for the reaction. However, for industrial applications, the use of inexpensive and nontoxic metals as the catalyst is highly desired. To this end, several catalysts based on inexpensive metals were developed, which include titanocene catalysts,[5] low-valent iron complexes[6] and in-situ generated Ni^0.[7] Although readily available metals were used, these catalysts are not expected to be inexpensive when the costs associated with the preparation of the complexes are considered. Beside these complexes, mercuric triflate, which is toxic but simple to prepare, was also found suitable for catalyzing the reaction.[8]

Although a heavy metal, unlike its neighbors in the periodic table such as mercury, thallium and lead, bismuth is relatively nontoxic due to its low bioavailability.[9] In addition, despite a lone pair on the metal atom, bismuth(III) salts such as its chloride and triflate have been found capable of serving as Lewis acids to catalyze many transformations.[9,10] We recently became interested in the soft Lewis acid catalyzed isomerization reactions of alkynyl compounds. In this type of reactions, the soft Lewis acid coordinates a carbon–carbon triple bond and activates it toward nucleophile attack. Subsequent rearrangements usually give valuable highly functionalized carbocyclic and heterocyclic compounds. In this field, we have found that several alkynyl epoxides and an alkyl alcohol could be isomerized to dihydro-1,4-oxazine derivatives using $PtCl_2$ as the catalyst.[11] In searching less expensive catalysts for the reaction, bismuth(III) salts attracted our attention as ideal candidates. Unfortunately, these salts including triflate, bromide, chloride and fluoride were not active for the transformation. However, we found that $BiCl_3$ was capable of catalyzing the cycloisomerization of enynes, which were our precursors toward alkynyl epoxides.[11] In this communication, we report our results on this study.

Results and Discussion

As shown in Table 1, we first tested the isomerization of enyne **1**[12] in CH_2Cl_2 with $BiCl_3$ as the catalyst. At room temperature, no reaction was observed according to TLC even after 6 h with vigorous stirring. Heating of the reaction mixture to reflux did also not result in any conversion of the starting material (Entry 1). In order to increase the reaction temperature, benzene was next used as the solvent (Entry 2). At reflux temperature, we did see some conversion after 12 h. The product was identified to be the five-membered cycle **2**,[13] but the yield was only 20%. Further increase of the reaction temperature by changing the solvent to toluene did not increase the yield significantly (Entry 3). In addition, an increase of the catalyst loading from 10 mol-% to 20 mol-% still did not give satisfactory results (Entry 4). Change of the solvent to 1,2-dichloroethane and use of 10 mol-% of catalyst gave a slightly higher yield (32%; Entry 5). However, when the catalyst loading was increased to 20 mol-%, with 1,2-dichloroethane as the solvent, at only 60 °C, the starting material was completely consumed within 12 h, and the product **2** was obtained in

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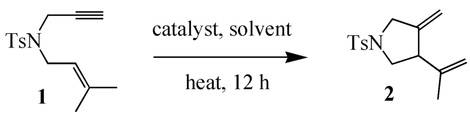
Table 1. Optimization of reaction conditions for the bismuth(III)-catalyzed isomerization of enynes.[a]



Entry	Catalyst	Catalyst loading	Solvent	Temperature[b]	Yield[c]
1	$BiCl_3$	10 mol-%	CH_2Cl_2	reflux	0%
2	$BiCl_3$	10 mol-%	PhH	reflux	20%
3	$BiCl_3$	10 mol-%	PhMe	reflux	25%
4	$BiCl_3$	20 mol-%	PhMe	reflux	30%
5	$BiCl_3$	10 mol-%	$ClCH_2CH_2Cl$	60 °C	32%
6	$BiCl_3$	20 mol-%	$ClCH_2CH_2Cl$	60 °C	66%
7	$Bi(OTf)_3$	20 mol-%	$ClCH_2CH_2Cl$	reflux	25%
8	BiF_3	20 mol-%	$ClCH_2CH_2Cl$	reflux	10%
9	BiI_3	20 mol-%	$ClCH_2CH_2Cl$	reflux	10%
10	$BiCl_3$	20 mol-%	$ClCH_2CH_2Cl$ (wet)	60 °C	50%
11	$BiCl_3/AgSbF_6$	20 mol-%/20 mol-%	$ClCH_2CH_2Cl$	room temp.	0%[d]

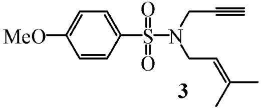
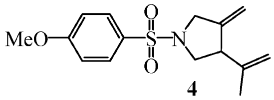
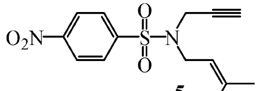
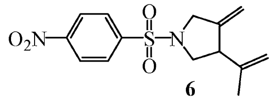
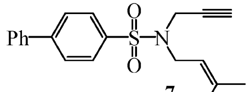
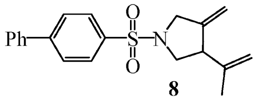
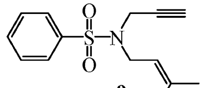
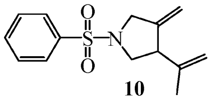
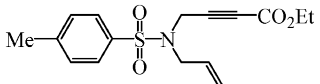
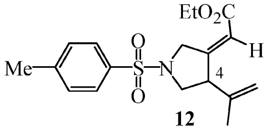
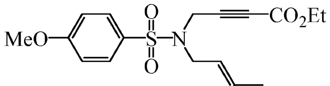
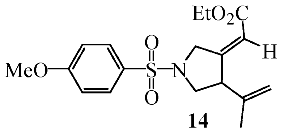
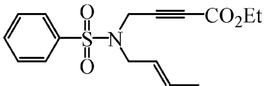
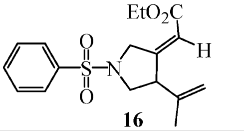
[a] Reaction conditions: **1**, catalyst, solvent, stirred under N_2 for 12 h. [b] The reactions were first tested at room temp., if no reaction occurred within 6 h, the temperature was raised to 60 °C; if still no reaction occurred or the reaction was slow, reflux temperature was used. Indicated temperatures are the highest ones. [c] Isolated yield. [d] Deprenylation product was obtained.

66% isolated yield (Entry 6). In order to see if other bismuth(III) salts could give better yields for the reaction under similar conditions, $Bi(OTf)_3$, BiF_3 and BiI_3 were screened, but all gave inferior results (Entries 7–9). In our earlier studies on the isomerization of alkynyl alcohols with $PtCl_2$ as catalyst, we found that a small amount of water could improve the yield of the desired product.[11] To see if the current reaction could also benefit from the presence of water, 1,2-dichloroethane saturated with water was used as the solvent. Under similar conditions with 20 mol-% $BiCl_3$ as catalyst, **1** was isomerized to **2** in 50% isolated yield (Entry 10). Although the yield was not as good as that under anhydrous conditions (compare Entries 10 and 6), this experiment showed that the reaction could tolerate a significant amount of moisture, which may be important for some applications. Finally, we hoped to see if $AgSbF_6$ could abstract a chloride ion from $BiCl_3$ and increase the yield of the reaction. However, in 1,2-dichloroethane, even at room temperature, the starting material was all converted into the deprenylation product 4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide; no desired product **2** was formed (Entry 11). After these studies, we decided to use the conditions shown in Entry 6 of Table 1 to explore the scope of the reaction.

As shown in Table 2, with an electron-donating group on the phenyl ring of the benzenesulfonyl group, substrate **3**[11] was isomerized to product **4** in 52% yield (Entry 1), which was lower than that for the isomerization of **1** to **2**. However, when substrate **5**[11] was used, which has an electron-withdrawing group, the yield was not improved as well (Entry 2). One hypothesis was that the electronic effect did not play an important role in these reactions; instead, the larger sizes of the methoxy and nitro groups compared to that of the methyl group might be more responsible for the lower yields in the isomerization of **3** and **5**. Indeed, when **7**[11] was used as the substrate, which has a phenyl group on the phenyl ring of the benzenesulfonyl group, the yield was further lowered to 19% (Entry 3). With no substitution group at this position, substrate **9**[14] was converted to **10**[14] in 71% yield (Entry 4).

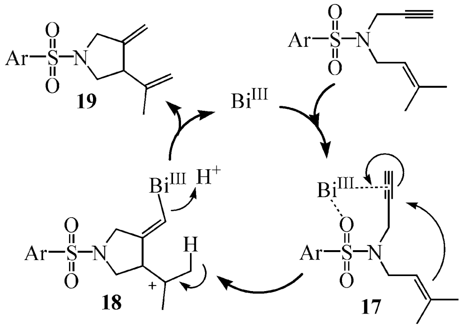
In our previous studies on the soft Lewis acid catalyzed isomerization of alkynyl epoxides, we observed that alkynes with an electron-withdrawing group were better substrates for the reaction.[11] Similar observations were also made previously by Fürstner and co-workers in their work.[15] In the present study, substrates with electron-deficient alkynes also gave higher yields of the desired isomerization products. As shown in Table 2, enyne **11**[11] was isomerized to **12** in 70% isolated yield under the optimized conditions for the isomerization of **1**. If recovered starting material was subtracted from the initial substrate quantity, the yield was as high as 94% (Entry 5). Significantly, only one stereoisomer (**12**) concerning the trisubstituted double bond was formed under these reaction conditions. The (*Z*) geometry of this double bond was established by NOE experiments, in which NOEs were observed between the vinyl proton of the trisubstituted alkene (δ = 5.62 ppm) and the proton on C-4 of the pyrrolidine ring (δ = 3.43 ppm), and between the vinyl proton (δ = 5.62 ppm) and the protons of the methyl group attached to the vinyl group (δ = 1.54 ppm). With substrates **13** and **15**, both of which also contain an electron-deficient alkyne, excellent isolated yields of five-membered cyclic isomerization products were achieved (Entries 6 and 7). Significantly, these yields were even higher than those of the isomerization of similar enynes with a palladium catalyst (70–80% vs. 60%).[16] Like the isomerization of **11**, the isomerization of **13** and **15** also gave only the (*Z*) stereoisomers concerning the trisubstituted double bond. In order to further probe the electronic effects of the substitution groups on the alkyne, substrates with a phenyl and a methyl group attached to the alkyne were prepared and subjected to the optimized isomerization conditions. Unfortunately, none of the trials gave any conversion, even after long reaction times. Heating of the reaction mixtures to reflux temperature for long times gave complex mixtures.

Table 2. Substrate scope study of $BiCl_3$-catalyzed isomerization of enynes.[a]

Entry	Enyne	Product	Yield[b]
1	 **3**	 **4**	52%
2	 **5**	 **6**	42%
3	 **7**	 **8**	19% (41%)[c]
4	 **9**	 **10**	71%
5	 **11**	 **12**	70% (94%)[c]
6	 **13**	 **14**	81% (94%)[c]
7	 **15**	 **16**	82% (91%)[c]

[a] Reaction conditions: **1**, $BiCl_3$ (20 mol-%), $ClCH_2CH_2Cl$, 60 °C, 12 h. [b] Isolated yield. [c] Isolated yield after subtraction of unreacted starting material.

Based on literature information on the soft Lewis acid catalyzed isomerization of alkynyl compounds[10,17] and our previous study on the isomerization of alkynyl epoxides and an alkynyl alcohol,[11] the following mechanism was proposed for the current $BiCl_3$-catalyzed isomerization of enynes (Scheme 1). The Bi^{III} salt coordinates to the π-electrons of the alkyne of an enyne to form intermediate **17**. The sulfonamide group may help to stabilize the complex. The alkene of the enyne serves as a nucleophile and attacks the activated alkyne intramolecularly to give intermediate **18**, which undergoes proton transfers to give the isomerization product **19**. According to this mechanism, when substrates **11**, **13** and **15** were used, products with an (*E*) trisubstituted double bond were expected. This was contrary to the observed results. A potential explanation is that (*E*) products were initially formed. However, due to the steric hindrance between the ethyl ester group and the 1-methylvinyl group, under the acidic reaction conditions, the (*E*) products were isomerized to the more stable (*Z*) products.



Scheme 1. Potential mechanism of the $BiCl_3$-catalyzed isomerization of enynes.

Conclusions

We have found that $BiCl_3$ could be used as soft Lewis acid to catalyze the isomerization of several enynes. The reaction can tolerate a significant amount of moisture. Acceptable to excellent isolated yields of isomerization product were obtained. We also found that electron-deficient alkynes were more suitable substrates for the reaction, and in the examples studied, only one stereoisomer was formed in all cases. Although the catalyst loading was quite high under the conditions we used, considering the low price of the catalyst, its environmental friendliness and low toxicity, we believe that $BiCl_3$ will be one of the choices of chemists in the pharmaceutical industry to catalyze the isomerization of enynes.

Experimental Section

General Procedure for the $BiCl_3$-Catalyzed Cycloisomerization of Enynes: A round-bottomed flask was charged with the enyne and $BiCl_3$, and 1,2-dichloroethane was added via syringe (for amounts of reagents and solvents, see Supporting Information). The mixture was heated to 60 °C under nitrogen for 12 h. After cooling to room temp., volatile components were removed under reduced pressure. The residue was partitioned between water and CH_2Cl_2, and the aqueous phase was further extracted with CH_2Cl_2 for at least three times. The combined organic phases were dried with anhydrous Na_2SO_4, filtered, and the solvent was removed under reduced pressure. Purification by flash column chromatography (SiO_2) gave pure cycloisomerization product.

Supporting Information (see footnote on the first page of this article): Experimental procedures and copies of the ^1H and ^{13}C NMR spectra of all new compounds.

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