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# Friedel–Crafts cyclization of tertiary alcohols using bismuth(III) triflate

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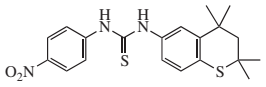
ABSTRACT

Bismuth(III) triflate [$Bi(OTf)_3$] has been developed as an efficient and mild catalyst for intramolecular Friedel–Crafts cyclizations of tertiary alcohols to prepare disubstituted tetrahydronapthalenes, chromans, thiochromans, tetrahydroquinolines, and tetrahydroiso-quinolines. The method represents a unified strategy to synthesize a variety of ring systems from tertiary alcohols using a common Lewis acid.

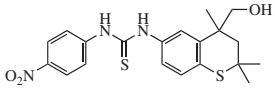


Several recent publications have described methods for the preparation of 1,1-disubstituted tetrahydronaphthalenes and 4,4-disubstituted chromans, thiochromans, tetrahydroquinolines, and tetrahydroisoquinolines, which are known to have biological activity.[1] To date, several synthetic approaches have been used to access these systems.[2] The most common strategies involve acid-catalyzed ring closure of an alkene on an electron-rich arene,[3] radical cyclization,[4] olefin metathesis ring closure,[5] and metal-catalyzed cyclization.[6] The use of Lewis or Bronsted acids, such as $AlCl_3$,[7] $FeCl_3{\cdot}6H_2O$,[8] Amberlyst-15® (A-15),[9] $H_2SO_4$,[10] and polyphosphoric acid (PPA)[11] to promote Friedel–Crafts cyclization of tertiary alcohols on aromatic rings has also been attempted, but with varied success. These reactions gave inconsistent yields largely due to the harsh nature of these reagents. Therefore, the development of a general, high-yield, mild, and convenient method to synthesize carbocyclic and heterocyclic structures using a common catalyst would be a worthwhile endeavor.

Our investigation began with the goal of developing a more efficient strategy to synthesize the drug SHetA2 (**1**) and its prodrug **2**. Currently, **1** is being evaluated for clinical studies to treat renal and ovarian cancer.[12] The reported synthesis of this compound[7a] involved cyclization of tertiary alcohol **3** by a Friedel–Crafts reaction, using stoichiometric $AlCl_3$ in PhCl, and gave the core heterocycle **4** of the target molecules in 58% yield (entry 1, Table 1). The present study sought to further evaluate a series of Lewis and Bronsted acids for this process under different solvent and temperature regimes. Problems were encountered with this transformation, however, due to substrate insolubility, unwanted side reactions, toxic and corrosive reagents, elaborate work-up procedures, and irreproducible yields. Overcoming these challenges in the cyclization was a critical concern.



SHetA2 (**1**)



SHetA2 Prodrug (**2**)

During the past decade, $Bi(OTf)_3$ has been employed as a Lewis acid in a wide range of reactions.[13] To determine the suitability of this catalyst for the current Friedel–Crafts ring closure, a $CHCl_3$ solution of alcohol **3** was heated in the presence of 20 mol % of $Bi(OTf)_3$, and was found to give clean conversion to **4** in 90% yield. To the best of our knowledge, only one prior study has utilized $Bi(OTf)_3$ for the ring closure of a tertiary alcohol.[14] In the current work, this catalyst gave a significant improvement over previously reported reagents.

Optimization of the Friedel–Crafts ring closure of **3** to **4** was chosen as the model system to evaluate the efficiency of $Bi(OTf)_3$ compared to previously reported acid catalysts (Table 1). Catalysts, such as $AlCl_3$, $FeCl_3{\cdot}6H_2O$, *p*-TsOH, $CH_3SO_2H$, and A-15, all required prolonged heating at $\geqslant 75\ ^\circ C$, which led to fragmentation of the substrate, numerous side reactions, and only modest yields of the desired product. $Bi(OTf)_3$, however, efficiently promoted the reaction under mild heating to afford **4** in good to excellent yields. Further investigation of catalyst loadings indicated that 15 mol % of $Bi(OTf)_3$ provided consistently superior results.

The solvent was also varied to ascertain the most favorable medium for the reaction. These experiments revealed that the sol-

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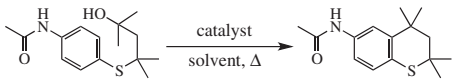
**Table 1**
Synthesis of an SHetA2 precursor




**3** **4**

| Entry | Catalyst | mol % | Solvent | *T* (°C) | *t* (min) | Yield (%) |
|---|---|---|---|---|---|---|
| 1 | $AlCl_3$ | 100 | PhCl | 70–75 | 30 | 58 |
| 2 | $AlCl_3$ | 100 | PhH | 80 | 90 | 70 |
| 3 | $FeCl_3{\cdot}6H_2O$ | 20 | PhH | 80 | 90 | 58 |
| 4 | $FeCl_3{\cdot}6H_2O$ | 10 | $CHCl_3$ | 61 | 60 | 32 |
| 5 | *p*-TsOH | 100 | PhH | 80 | 240 | 0 |
| 6 | $CH_3SO_3H$ | 30 | PhH | 80 | 90 | 30 |
| 7 | Dry A-15 | 100 | PhH | 80 | 180 | 40 |
| 8 | $Bi(OTf)_3$ | 50 | PhH | 80 | 20 | 75 |
| 9 | $Bi(OTf)_3$ | 20 | $CHCl_3$ | 61 | 20 | 90 |
| **10** | **$Bi(OTf)_3$** | **15** | **$CHCl_3$** | **61** | **35** | **92** |
| 11 | $Bi(OTf)_3$ | 15 | PhH | 80 | 45 | 78 |
| 12 | $Bi(OTf)_3$ | 15 | THF | 66 | 45 | 80 |

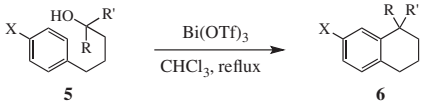
vent had a significant effect on the product yields. In $CHCl_3$, substrate **3** gave the desired product in 92% yield, while other solvents, such as PhCl, PhH, and THF, generally afforded lower returns.

Variation of the temperature was also examined. At room temperature, no product was formed, even after an extended reaction period (24 h). At 90 °C, the solution darkened, and the yields decreased as more impurities were produced. Under moderate heating at 60–65 °C, however, excellent yields were achieved with a minimum of side reactions. These results further validated $CHCl_3$ (bp 61 °C) as the best solvent for the reaction. An additional advantage to using this solvent was that the catalyst could be easily recycled and reused. Due to the relatively low solubility of $Bi(OTf)_3$ in $CHCl_3$ at 20 °C, the catalyst could be readily reclaimed and reused at the end of the reaction. However, since the recovered catalyst trapped small quantities of product, the recycled $Bi(OTf)_3$ was always employed for same transformation.

With the optimized protocol established, the methodology was extended to other substrates. Cyclizations of 1,1-disubstituted-1,2,3,4-tetrahydronaphthalenes were initially evaluated (Table 2) using substrates prepared by literature methods.[9] Employing our standard conditions, reactants **5a–f** were cleanly converted to targets **6a–f**. Remarkably, even the deactivated substrate **5c** underwent ring closure in excellent yield. Treatment of this substrate with A-15 in refluxing benzene had previously given only dehydration products.[9] Additionally, hindered substrates incorporating *gem*-diphenyl substitution (e.g. **5d** and **5e**) were also successfully cyclized using $Bi(OTf)_3$, although the yields were slightly lower than those observed for the dimethyl cases.

Our method also permitted cyclizations of chroman **8a** and thiochroman **8b** in yields comparable to or better than those previously recorded (Table 3).[15] Ring closures to prepare tetrahydroquinolines **10a–e** and tetrahydroisoquinolines **12a–e** were also

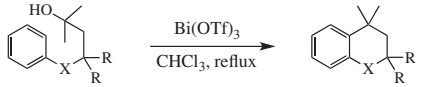
**Table 2**
Tetrahydronaphthalene Cyclizations using $Bi(OTf)_3$




**5** **6**

| | X | R | R′ | Cat (mol %) | *t* (min) | Yield (%) |
|---|---|---|---|---|---|---|
| **a** | H | Me | Me | 15 | 30 | 96 |
| **b** | OMe | Me | Me | 15 | 30 | 92 |
| **c** | $CF_3$ | Me | Me | 20 | 60 | 81 |
| **d** | H | Ph | Ph | 20 | 90 | 76 |
| **e** | Cl | Ph | Ph | 20 | 90 | 74 |
| **f** | H | Me | $CH_2CO_2Me$ | 25 | 90 | 90 |

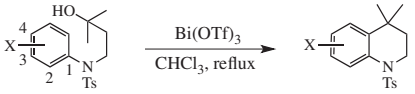
**Table 3**
Chroman and thiochroman cyclizations using $Bi(OTf)_3$




**7** **8**

| | X | R | Cat (mol %) | *t* (min) | Yield (%) |
|---|---|---|---|---|---|
| **a** | O | H | 15 | 20 | 95 |
| **b** | S | Me | 10 | 15 | 88 |

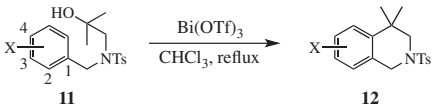
**Table 4**
Tetrahydroquinoline cyclizations using $Bi(OTf)_3$




**9** **10**

| | X | Cat (mol %) | *t* (min) | Yield (%) |
|---|---|---|---|---|
| **a** | H | 15 | 30 | 78 |
| **b** | 4-OMe | 15 | 30 | 82 |
| **c** | 4-Cl | 15 | 30 | 72 |
| **d** | 2-Me | 15 | 30 | 72 |
| **e** | 2,3-$(CH_2)_4$– | 15 | 30 | 75 |

**Table 5**
Tetrahydroisoquinoline cyclizations using $Bi(OTf)_3$




**11** **12**

| | X | Cat (mol %) | *t* (min) | Yield (%) |
|---|---|---|---|---|
| **a** | H | 15 | 30 | 92 |
| **b** | 4-Cl | 15 | 30 | 94 |
| **c** | 4-F | 15 | 30 | 89 |
| **d** | 3-OMe | 15 | 30 | 78 |
| **e** | 2,3-Benzo | 15 | 30 | 94 |

possible (Tables 4 and 5, respectively). In these cases, $Bi(OTf)_3$ generally provided higher conversions than Al- and Fe-based catalysts.[7b,8c] Additionally, fragmentation, which typically occurred in 10–35% during the closure of nitrogen heterocycles, never exceeded 5% for reactions promoted by $Bi(OTf)_3$. Finally, in our earlier work, several substrates produced alkene by-products, which were not cyclized by conventional catalysts. In the current study, alkenes, intercepted from several of the reactions after short reaction times, were observed to undergo cyclization upon prolonged heating. Indeed, $Bi(OTf)_3$ has previously demonstrated utility as a catalyst for Friedel–Crafts reactions of alkenes.[16]

Finally, it was observed that substrates incorporating a free amine, such as the *N*-benzyl alcohol **13** and the *N*-methyl alkene **14**, failed to cyclize with catalytic $Bi(OTf)_3$. Presumably, the basic nitrogen in these substrates coordinated with the catalyst and deactivated it for the cyclization. Due to the expense of $Bi(OTf)_3$, however, no attempt was made to perform the reaction on **13** or **14** using stoichiometric or excess catalyst.

**13** **14**

A possible mechanism for the ring closure is given in Figure 1. In the intial step, the alcohol hydroxyl group would displace triflate from the catalyst to give 15. This could then be followed by direct

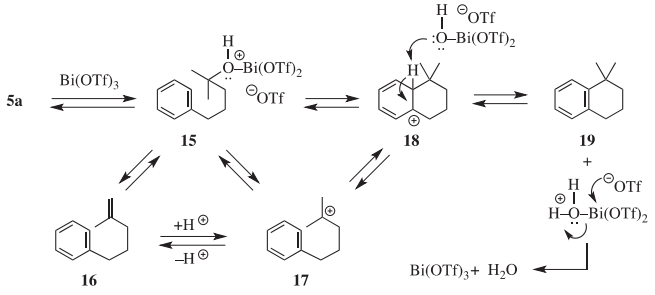



**Figure 1.** A possible mechanism for the cyclization.

cyclization to the arenium ion 18, or loss of the leaving group to give alkene 16 or carbocation 17 prior to cyclization. The bismuth(III) hydroxy ditriflate leaving group would subsequently promote rearomatization to give the final product 19. Finally, displacement of water from the protonated bismuth species by triflate would regenerate the catalyst.

In conclusion, we have developed an efficient synthetic strategy for the Friedel–Crafts ring closure of tertiary alcohols using $Bi(OTf)_3$ as catalyst. The procedure provides a unified protocol for the cyclization of both carbocyclic and heterocyclic ring systems using a common Lewis acid catalyst. The catalyst is very mild and furnishes cyclized products in yields comparable or superior to previously reported methods. Side reactions, such as fragmentation, are minimized due to lower reaction temperatures. Additionally, alkene intermediates formed by competitive dehydration of the substrates are further converted to the desired products. Finally, the catalyst can be recycled up to three times for the same reaction.

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## Supplementary data

Supplementary data (experimental details, $^1H$ and $^{13}C$ NMR spectra, and analytical data for all of the cyclized products) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.06.026.

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