Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 47 (2006) 8351–8354
Tetrahedron Letters

Direct-type catalytic three-component Mannich reaction in aqueous media

Thierry Ollevier,* Etienne Nadeau and Andrée-Anne Guay-Bégin

Département de chimie, Université Laval, Québec (Québec), Canada G1K 7P4

Received 18 August 2006; revised 13 September 2006; accepted 15 September 2006
Available online 6 October 2006

Abstract—Bismuth triflate catalyzed direct-type Mannich reaction of cyclohexanone, aromatic aldehyde, and aromatic amine proceeded smoothly in water to afford the corresponding β-amino ketone with very good yield and moderate to good *anti* selectivity.

Organic reactions in aqueous media have attracted much attention recently not only because water is the most abundant, environmentally benign, and cheapest solvent but also because unique selectivity and reactivity can be expected from this solvent.

Recently, several laboratories disclosed significant advances regarding rare earth and lanthanide triflates as catalysts for Mannich-type reactions.[1] High catalytic activity, low toxicity, moisture and air tolerance make lanthanide triflates valuable catalysts. However, the high cost of these catalysts restricts their use. Bismuth compounds are of interest as lower toxicity and cheaper alternatives to the former.[2] Bismuth salts have been reported as catalysts for the opening of epoxides,[3] Mukaiyama-aldol reaction,[4] formation and deprotection of acetals,[5] Friedel–Crafts reactions,[6] Fries and Claisen rearrangements,[7] and Sakurai reactions.[8] $Bi(OTf)_3$ is particularly attractive because it is commercially available or can be easily prepared from commercially available starting materials.[9]

We recently reported the $Bi(OTf)_3$-catalyzed Mannich-type reaction of a variety of aldimines generated in situ using aldehydes, amines and silyl enolates in a three-component reaction.[10a,b] An alternate method was also reported by our group involving the Mannich-type reaction of *N*-alkoxycarbonylamino sulfones with silyl enolates.[10c] This method was shown to be very efficient to prepare Cbz-protected β-amino carbonyl compounds. These results encouraged us to pursue different approaches to the bismuth(III)-catalyzed Mannich-type reaction.

Most of the recent methods have focused on the use of preformed imines or iminium salts and preformed enolate equivalents such as silyl enol ethers or silyl ketene acetals, which are more reactive than their respective parent carbonyl compounds. Such methods, known as indirect-type Mannich reactions, suffer from the drawback of the necessity for the isolation and purification of these preformed imine and enolate equivalents. An improvement of the methodology was realized with metal catalyst systems[11] and organocatalysts[12] that promoted the direct-type catalytic Mannich reaction, which involves unmodified carbonyl compounds as nucleophiles. Recently, Brønsted acid-catalyzed Mannich-type reactions have been disclosed in aqueous media.[13] Similarly, Brønsted acid-catalyzed three-component Mannich-type reactions have been reported to proceed efficiently in water without organic solvent in the presence of a surfactant.[14]

As a part of our ongoing interest in bismuth triflate-catalyzed Mannich reactions, herein we report a general $[Bi(OTf)_3{\cdot}4H_2O]$-catalyzed direct-type Mannich reaction of cyclohexanone with imines derived from various benzaldehydes and anilines. β-Amino carbonyl compounds are obtained efficiently in the presence of 5 mol % of $Bi(OTf)_3{\cdot}4H_2O$ in water as the solvent.

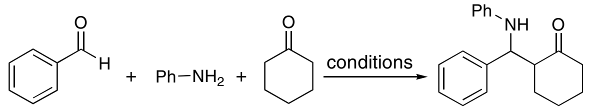
We first chose the reaction of benzaldehyde and aniline with cyclohexanone as a model reaction in water

---

Keywords: Mannich; Three-component reaction; Bismuth; Bismuth(III) triflate; Aqueous media.

* Corresponding author. Tel.: +1 418 656 5034; fax: +1 418 656 7916; e-mail: thierry.ollevier@chm.ulaval.ca

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.09.082



1a **2a** **3** **4a**

Scheme 1.

Table 1. Direct-type catalytic Mannich reaction of benzaldehyde, aniline, and cyclohexanone in water[a]

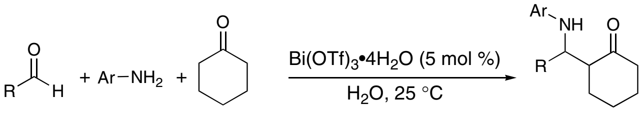
Entry	Conditions	*anti*:*syn*[b]	Yield[c] (%)
1	15% HOTf	77:23	92
2	5% $Bi(O_2CCF_3)_3$	77:23	77
3	1% $Bi(OTf)_3{\cdot}4H_2O$	72:28	94
4	5% $Bi(OTf)_3{\cdot}4H_2O$	86:14	84
5	10% $Bi(OTf)_3{\cdot}4H_2O$	83:17	97

[a] The reaction was conducted at 25 °C (reaction time: 7 h) in water.
[b] *anti*/*syn* Ratio was determined by ^1H NMR.
[c] Isolated yield.

Table 2. 5 mol % Bismuth(III) triflate direct-type catalytic Mannich reaction of benzaldehyde, aniline and cyclohexanone

Entry	Solvent	*T* (h)	*anti*:*syn*[a]	Yield[b] (%)
1	H_2O	7	86:14	84
2	CH_3CN	2	70:30	89
3	CH_2Cl_2	4	69:31	73
4	Et_2O	6	87:13	89
5	PhMe	5.5	82:18	89

[a] *anti*/*syn* Ratio was determined by ^1H NMR.
[b] Isolated yield.



1 **2** **3** **4**

Scheme 2.

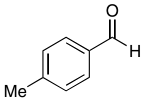
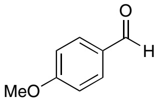
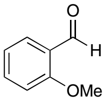
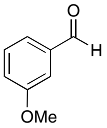
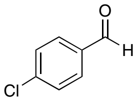
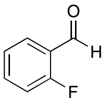
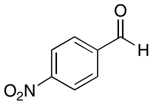
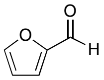
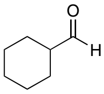
(Scheme 1). Increasing the catalyst loading of $Bi(OTf)_3{\cdot}4H_2O$ from 1% to 5% led to improved stereoselectivity (Table 1, entries 3 and 4). Increasing the catalyst loading to 10% did not lead to an improved ratio of diastereoisomers (Table 1, entry 5) and therefore 5% $Bi(OTf)_3{\cdot}4H_2O$ was kept as the standard condition for our studies. As demonstrated, an aqueous solution of $Bi(OTf)_3$ is acidic,[9a] so it may be possible that our true catalyst was TfOH released from the hydrolysis of $Bi(OTf)_3{\cdot}4H_2O$. The observation that the same reaction still occurs in the presence of hindered 2,6-di-*t*-butylpyridine (1 equiv of PhCHO **1a**, 1 equiv of $PhNH_2$ **2a**, 2 equiv of cyclohexanone **3**, 0.05 equiv of $Bi(OTf)_3{\cdot}4H_2O$, 0.15 equiv of 2,6-di-*t*-butylpyridine, 25 °C, 7 h, 83% of **4a**, *anti*/*syn* = 75:25) does not indicate unambiguously that a Lewis acid is involved in the process, because the pyridinium salt itself also mediates the reaction (1 equiv of PhCHO **1a**, 1 equiv of $PhNH_2$ **2a**, 2 equiv of cyclohexanone **3**, 0.15 equiv of 2,6-di-*t*-butylpyridinium triflate, 25 °C, 7 h, 76% of **4a**, *anti*/*syn* = 79:21). However, the same reaction in the presence of K_2CO_3 as a proton scavenger (1 equiv of PhCHO **1a**, 1 equiv of $PhNH_2$ **2a**, 2 equiv of cyclohexanone **3**, 0.05 equiv of $Bi(OTf)_3{\cdot}4H_2O$, 0.15 equiv of K_2CO_3, 25 °C, 7 h) affords the expected product only in a low conversion (44%, *anti*/*syn* = 70:30), indicating that a Brønsted acid is clearly involved in the process. However, the observation that the diastereoselectivity of the TfOH-catalyzed reaction is lower than with 5–10% $Bi(OTf)_3{\cdot}4H_2O$ (Table 1, compare entry 1 and entries 4 and 5) suggests that a bismuth(III) salt is likely to be involved to some extent as a Lewis acid as well. Also, the practical use of $Bi(OTf)_3{\cdot}4H_2O$ is highly valuable as TfOH is very corrosive and difficult to handle. Moreover, another Lewis acid like $Bi(O_2CCF_3)$ did not afford better diastereoselectivity (Table 1, entry 2).

The $Bi(OTf)_3{\cdot}4H_2O$-catalyzed Mannich reaction was examined in various solvents (Scheme 1, Table 2). Interestingly, the best *anti* stereoselectivity was observed in diethyl ether (Table 2, entry 4) and in water (Table 2, entry 1) whereas the reaction in acetonitrile, dichloromethane, or toluene showed decreased stereoselectivity (Table 2, entries 2, 3 and 5). Water was thus selected as the solvent of choice for the continuing study.

Encouraged by our results in the 5% $Bi(OTf)_3{\cdot}4H_2O$ catalyzed model reaction in water, we studied the scope and limitations of this reaction with respect to the aldehyde and aniline employed in the process (Scheme 2). The results are summarized in Table 3.[15] Various substituted benzaldehydes were reacted with aniline or *p*-chloroaniline and 2 equiv of cyclohexanone. Most of the aldehydes (**1**) reacted readily to produce **4** in very good yields and moderate to good diastereoselectivity. Substitution effects concerning aniline (**2**) were also briefly studied. This factor has a negative impact on the diastereoselectivity of the process (Table 3, compare entries 1–5). Moreover, *p*-methoxyaniline led to a decreased yield of the product (Table 3, entry 3). Benzaldehyde derivatives with electron-rich substituents such as *o*- and *p*-methoxybenzaldehydes led to an improved stereoselectivity (Table 3, entries 6 and 7). Electron-poor substituents were not as effective regarding the stereoselectivity (Table 3, entries 9–11). In addition, heteroaromatic aldehyde such as furfural can also serve as a substrate in this reaction, giving the corresponding β-amino carbonyl compound in a good yield (Table 3, entry 12). The direct-type Mannich reaction was also efficient with cyclohexylcarboxaldehyde as the aldehydic partner giving the corresponding β-amino carbonyl derivative **4m** in a moderate yield albeit with almost no selectivity (Table 3, entry 13).

In summary, we have found that moderate to good *anti* selectivity was observed in the $Bi(OTf)_3{\cdot}4H_2O$-catalyzed direct-type Mannich reaction of cyclohexanone and in situ generated aldimines in aqueous media. This method offers several advantages including mild reaction conditions, low catalyst loading (5 mol %), and no formation of by-products such as aldol or deamination products. To the best of our knowledge, this is the first report of a bismuth triflate-catalyzed direct-type cata-

Table 3. Bismuth(III) triflate direct-type catalytic three-component Mannich reaction of cyclohexanone

Entry	**1**	**2**	*anti*:*syn*[a] (**4**)	*T* (h)	Yield[b] (%)
1	**1a**	$PhNH_2$	86:14 (**4a**)	7	84
2		$4\text{-}ClC_6H_4NH_2$	65:35 (**4b**)	19	83
3		$4\text{-}MeOC_6H_4NH_2$	74:26 (**4c**)	16	35[c]
4		$PhNH_2$	72:28 (**4d**)	5	89
5		$4\text{-}ClC_6H_4NH_2$	67:33 (**4e**)	17	95[c]
6		$PhNH_2$	92:8 (**4f**)	18	85
7		$PhNH_2$	94:6 (**4g**)	16	94
8		$PhNH_2$	75:25 (**4h**)	15	87
9		$PhNH_2$	67:33 (**4i**)	19	71
10		$PhNH_2$	77:23 (**4j**)	17	74
11		$PhNH_2$	60:40 (**4k**)	16	84
12		$PhNH_2$	66:34 (**4l**)	16	79
13		$PhNH_2$	41:59 (**4m**)	16	67

[a] *anti*/*syn* Ratio was determined by ^1H NMR.

[b] Isolated yield.

[c] The reaction was performed using 1.2 equiv of aldehyde.

lytic Mannich reaction. Moreover, our process involves an environmentally benign, cheap, and easy to handle catalyst. The β-amino carbonyl compound is smoothly obtained in mild conditions. Because of its numerous benefits, the $Bi(OTf)_3{\cdot}4H_2O$ protocol should find utility in the synthesis of biologically active compounds. Research is under way to demonstrate significant other applications of this $Bi(OTf)_3{\cdot}4H_2O$-catalyzed Mannich reaction.

Acknowledgements

This work was financially supported by the Natural Sciences and Engineering Research Council of Canada (NSERC), the Fonds Québécois de la Recherche sur la Nature et les Technologies (FQRNT, Québec, Canada), the Canada Foundation for Innovation, and Université Laval. E.N. thanks NSERC for a postgraduate scholarship. We thank Rhodia (Lyon, France) for the generous gift of chemicals.

References and notes

1. (a) Kobayashi, S.; Araki, M.; Ishitani, H.; Nagayama, S.; Hachiya, I. *Synlett* **1995**, 233–234; (b) Kobayashi, S.; Araki, M.; Yasuda, M. *Tetrahedron Lett.* **1995**, *36*, 5773–5776; (c) Kobayashi, S.; Busujima, T.; Nagayama, S. *Synlett* **1999**, 545–546; (d) Kobayashi, S.; Moriwaki, M.; Akiyama, R.; Suzuki, S.; Hachiya, I. *Tetrahedron Lett.* **1996**, *37*, 7783–7786.
2. (a) *Organobismuth Chemistry*; Suzuki, H., Matano, Y., Eds.; Elsevier: Amsterdam, 2001; (b) Gaspard-Iloughmane, H.; Le Roux, C. *Eur. J. Org. Chem.* **2004**, 2517–2532; (c) Leonard, N. M.; Wieland, L. C.; Mohan, R. S. *Tetrahedron* **2002**, *58*, 8373–8397.

3. (a) Ogawa, C.; Azoulay, S.; Kobayashi, S. *Heterocycles* **2005**, *66*, 201–206; (b) Ollevier, T.; Lavie-Compin, G. *Tetrahedron Lett.* **2004**, *45*, 49–52; (c) Ollevier, T.; Lavie-Compin, G. *Tetrahedron Lett.* **2002**, *43*, 7891–7893.
4. (a) Ollevier, T.; Desyroy, V.; Debailleul, B.; Vaur, S. *Eur. J. Org. Chem.* **2005**, 4971–4973; (b) Kobayashi, S.; Ogino, T.; Shimizu, H.; Ishikawa, S.; Hamada, T.; Manabe, K. *Org. Lett.* **2005**, *7*, 4729–4731; (c) Ollevier, T.; Desyroy, V.; Nadeau, E. *ARKIVOC 2007* (Gainesville, FL, USA), in press; (d) Le Roux, C.; Ciliberti, L.; Laurent-Robert, H.; Laporterie, A.; Dubac, J. *Synlett* **1998**, 1249–1251.
5. Leonard, N. M.; Oswald, M. C.; Freiberg, D. A.; Nattier, B. A.; Smith, R. C.; Mohan, R. S. *J. Org. Chem.* **2002**, *67*, 5202–5207.
6. (a) Le Roux, C.; Dubac, J. *Synlett* **2002**, 181–200; (b) Répichet, S.; Le Roux, C.; Dubac, J.; Desmurs, J. R. *Eur. J. Org. Chem.* **1998**, 2743–2746.
7. (a) Ollevier, T.; Desyroy, V.; Asim, M.; Brochu, M.-C. *Synlett* **2004**, 2794–2796; (b) Ollevier, T.; Mwene-Mbeja, T. M. *Tetrahedron Lett.* **2006**, *47*, 4051–4055; (c) Ollevier, T.; Mwene-Mbeja, T. M. *Synthesis*, in press.
8. (a) Komatsu, N.; Uda, M.; Suzuki, H.; Takahashi, T.; Domae, T.; Wada, M. *Tetrahedron Lett.* **1997**, *38*, 7215–7218; (b) Wieland, L. C.; Zerth, H. M.; Mohan, R. S. *Tetrahedron Lett.* **2002**, *43*, 4597–4600; (c) Ollevier, T.; Ba, T. *Tetrahedron Lett.* **2003**, *44*, 9003–9005; (d) Leroy, B.; Markó, I. E. *Org. Lett.* **2002**, *4*, 47–50; (e) Sreekanth, P.; Park, J. K.; Kim, J. W.; Hyeon, T.; Kim, B. M. *Catal. Lett.* **2004**, *96*, 201–204; (f) Choudary, B. M.; Chidara, S.; Raja Sekhar, C. V. *Synlett* **2002**, 1694–1696.
9. (a) Répichet, S.; Zwick, A.; Vendier, L.; Le Roux, C.; Dubac, J. *Tetrahedron Lett.* **2002**, *43*, 993–995; (b) Labrouillère, M.; Le Roux, C.; Gaspard, H.; Laporterie, A.; Dubac, J.; Desmurs, J. R. *Tetrahedron Lett.* **1999**, *40*, 285–286; (c) $Bi(OTf)_3 \cdot 4H_2O$ has been prepared from Bi_2O_3 according to Ref. 9a.
10. (a) Ollevier, T.; Nadeau, E. *Synlett* **2006**, 219–222; (b) Ollevier, T.; Nadeau, E. *J. Org. Chem.* **2004**, *69*, 9292–9295; (c) Ollevier, T.; Nadeau, E.; Eguillon, J.-C. *Adv. Synth. Catal.* **2006**, *348*, 2080–2084.
11. (a) Salter, M. M.; Kobayashi, J.; Shimizu, Y.; Kobayashi, S. *Org. Lett.* **2006**, *8*, 3533–3536; (b) Shibasaki, M.; Matsunaga, S. *J. Organomet. Chem.* **2006**, *691*, 2089–2100; (c) Ranu, B. C.; Samata, S.; Guchhait, S. K. *Tetrahedron* **2002**, *58*, 983–988.
12. (a) Notz, W.; Sakthivel, K.; Bui, T.; Zhong, G.; Barbas, C. F., III. *Tetrahedron Lett.* **2001**, *42*, 199–201; (b) List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827–833.
13. (a) Akiyama, T.; Takaya, J.; Kagoshima, H. *Adv. Synth. Catal.* **2002**, *344*, 338–347; (b) Azizi, N.; Torkiyan, L.; Saidi, M. R. *Org. Lett.* **2006**, *8*, 2079–2082.
14. For direct-type Mannich reactions: (a) Akiyama, T.; Matsuda, K.; Fuchibe, K. *Synlett* **2005**, 322–324; For indirect-type Mannich reactions: (b) Shimizu, S.; Shimada, N.; Sasaki, Y. *Green Chem.* **2006**, *8*, 608–614; (c) Manabe, K.; Mori, Y.; Kobayashi, S. *Tetrahedron* **2001**, *57*, 2537–2544; (d) Manabe, K.; Kobayashi, S. *Org. Lett.* **1999**, *1*, 1965–1967.
15. A typical experimental procedure for the direct-type Mannich reaction: To a solution of $Bi(OTf)_3 \cdot 4H_2O$ (0.05 mmol) in 1 mL of water was added the aldehyde (1 mmol), aniline (1 mmol) and cyclohexanone (2 mmol). The reaction mixture was stirred vigorously with a magnetic stirrer during the mentioned time and then stopped by the addition of EtOAc. The aqueous phase was extracted with EtOAc (3 × 10 mL). The organic phases were combined and washed with water (2 mL) and brine (2 mL) consecutively, dried over $MgSO_4$, and filtered. The solvents were removed under reduced pressure (rotatory evaporator). The crude mixture was either purified by column chromatography (hexane/EtOAc 85:15–99:1) or by trituration in hexane giving the pure β-aminoketone **4** as a mixture of diastereoisomers. Spectral data for **4a**,[13a] **4b**,[14b] **4c**,[14c] **4i**,[11c] and **4l**[14c] agree with those reported previously in the literature.

    Spectral data for 2-((3-methoxyphenyl)-(phenylamino)-methyl)cyclohexanone (**4h**): Yield 87%, *anti*/*syn* = 75/25; brownish solid; mp 91–93 °C, R_f 0.49 (hexane/ethyl acetate 4:1); IR (KBr): 3354, 1704 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 7.19$ (*anti*, 1H, t, $J = 7.9$ Hz), 7.18 (*syn*, 1H, t, $J = 8.0$ Hz), 7.01–7.07 (2H, m), 6.89–6.94 (2H, m), 6.73 (1H, dd, $J = 7.9$, 2.6 Hz), 6.59–6.63 (1H, m), 6.50–6.54 (2H, m), 4.76 (*syn*, 1H, d, $J = 4.1$ Hz), 4.56 (*anti*, 1H, $J = 7.4$ Hz), 3.75 (3H, s), 2.69–2.74 (1H, m), 2.27–2.43 (2H, m), 1.59–1.90 (6H, m); ^{13}C NMR ($CDCl_3$): $\delta = 213.2$, 211.5, 160.0, 159.9, 147.7, 147.3, 143.7, 143.6, 129.7, 129.6, 129.3, 129.2, 120.1, 120.0, 118.0, 117.9, 114.3, 113.9, 113.6, 113.3, 112.5, 112.2, 58.3, 57.6, 57.4, 56.8, 55.4, 42.6, 41.9, 31.5, 28.7, 28.1, 27.2, 25.1, 23.8; HRMS calcd for $C_{20}H_{23}NO_2$ [M^+] 309.1729, found 309.1723.