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Bismuth Triflate-Catalyzed Three-Component Mannich-Type Reaction

Thierry Ollevier* and Etienne Nadeau

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

thierry.ollevier@chm.ulaval.ca

Abstract: Bismuth triflate catalyzes the Mannich-type reaction of a variety of in situ generated aldimines using aldehydes, anilines, and silyl enol ethers in a three-component reaction. The reaction proceeds rapidly and affords the corresponding protected β-amino ketones in high yields (up to 94%).

β-Amino carbonyl compounds are extremely important compounds as biologically active molecules.[1] Therefore, the development of new catalytic methods for their preparation is of prime importance in organic synthesis. Catalytic Mannich-type reactions have been reported by several groups as an efficient method to prepare β-amino carbonyl compounds.[2] Lately, synthetic methods involving lanthanide triflates as catalysts for Mannich-type reactions have been reported.[3] High catalytic activity, low toxicity, and moisture and air tolerance make lanthanide triflates attractive catalysts. However, the high cost of these catalysts limits their use.

Bismuth compounds too have attracted recent attention due to their low toxicity, low cost, and good stability.[4] Bismuth salts have been reported as catalysts for opening of epoxides,[5] Mukaiyama-aldol reactions,[6] formation and deprotection of acetals,[7] Friedel−Crafts reactions,[8] Diels−Alder reactions,[9] and intramolecular Sakurai cycliza-

tions.[10] $Bi(OTf)_3$ is particularly attractive because it is commercially available or can be easily prepared from commercially available starting materials.[11]

We have recently reported the $Bi(OTf)_3$-catalyzed allylation of a variety of protected aldimines generated in situ using aldehydes, primary carbamates, and allyltrimethylsilane in a three-component reaction.[5c,12] The results encouraged us to use a similar three-component protocol in the bismuth(III)-catalyzed Mannich-type reaction. A major merit of the three-component reaction is indeed that the reaction can be done without a separate step for imine preparation prior to the Mannich-type reaction.[13]

Herein, we report a general $Bi(OTf)_3$-catalyzed method for addition of silyl enol ethers to aryl imines in a three-component process. β-Amino ketones are obtained efficiently in the presence of 1 mol % of $Bi(OTf)_3 \cdot 4H_2O$.

The bismuth-catalyzed Mannich-type reaction was first studied with preformed imines. Interestingly, when equimolar amounts of *N*-benzylideneaniline and (1-phenylvinyloxy)trimethylsilane were treated with 1 mol % $Bi(OTf)_3 \cdot 4H_2O$ in acetonitrile for 2 h at 25 °C, the corresponding β-amino ketone was isolated in low yield (26%) because of low conversion.[14] Consequently, a one-pot sequence involving the formation of the imine and its in situ Mannich-type reaction was investigated.

Initially, we screened various solvents for the one-pot Mannich-type reaction of imine derived from benzaldehyde **1a** and aniline **2a** with silyl enol ether **3a** in the presence of 1 mol % of $Bi(OTf)_3 \cdot 4H_2O$. Among various polar solvents tested, diethyl ether, dichloromethane, and nitromethane gave moderate yields of the expected product (Table 1, entries 1, 2, and 5). The best solvent was found to be acetonitrile. In such solvent, 1,3-diphenyl-3-(*N*-phenylamino)propan-1-one **4a** was obtained with the best yield (Table 1, entry 4). With further optimization of the reaction conditions, we found that a lower catalyst loading gave decreased yields.

A possible explanation for the low yield obtained in the $Bi(OTf)_3$-catalyzed reaction of preformed imines would be that the mechanism of the one-pot process is different. Products other than imines could be the true substrates in this process. For exemple, aminals have already been

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TABLE 1. Three-Component Bi(OTf)₃-Catalyzed Mannich-Type Reactions Involving Benzaldehyde and Aniline[a]
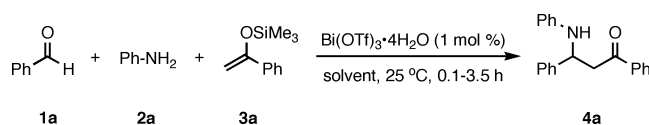
entry	solvent	yield **4a**[b] (%)
1	Et₂O	72
2	CH₂Cl₂	60
3	PhMe	54
4	MeCN	82
5	MeNO₂	71

[a] Conditions: benzaldehyde (1.0 equiv), aniline (1.0 equiv), (1-phenylvinyloxy)trimethylsilane **3a** (1.0 equiv), Bi(OTf)₃·4H₂O (0.01 equiv). [b] Isolated yield.

TABLE 2. Three-Component Bi(OTf)₃-Catalyzed Mannich-Type Reactions with Various Silyl Enol Ethers[a]
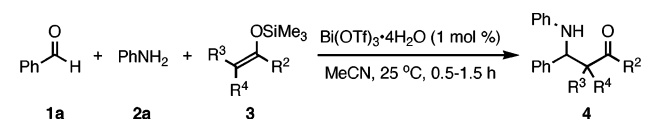
entry	silyl enol ether **3**	product	yield **4** (%)[b]
1		**4a**	82 (94)[c]
2		**4b**	73[d]
3		**4c**	82
4		**4d**	42[e]
5		**4e**	80[f]
6		**4f**	81[g]

[a] Conditions: benzaldehyde (1.0 equiv), aniline (1.0 equiv), silyl enol ether (1.0 equiv), Bi(OTf)₃·4H₂O (0.01 equiv). [b] Isolated yield. [c] Silyl enol ether (1.5 equiv). [d] Syn/anti = 50/50. [e] Crude yield of **4d** was 81%. After column chromatography, **4d** was obtained with a decreased yield (42%) and a double-Mannich adduct was also isolated as a mixture of diastereoisomers (dr = 52/48) in a 24% yield. [f] Syn/anti = 68/32. [g] Syn/anti = 39/61.

characterized as intermediates in similar three-component reactions.[15]

Several examples of Bi(OTf)₃-catalyzed Mannich-type reactions with various silyl enol ethers are summarized in Table 2. Silyl enol ethers derived from aromatic ketones and from aliphatic ketones were reacted with an equimolar mixture of benzaldehyde **1a** and aniline **2a**.

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TABLE 3. Three-Component Bi(OTf)₃-Catalyzed Mannich-Type Reactions with Various Aldehydes[a]
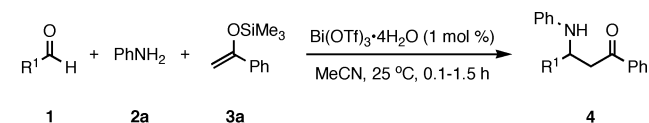
entry	aldehyde **1**	product	yield (%)[b]
1		**4a**	89
2		**4g**	82
3		**4h**	88
4		**4i**	87
5		**4j**	86
6		**4k**	76
7		**4l**	81
8		**4m**	72
9		**4n**	77

[a] Conditions: aldehyde (1.0 equiv), aniline (1.0 equiv), (1-phenylvinyloxy)trimethylsilane (1.2 equiv), Bi(OTf)₃·4H₂O (0.01 equiv). [b] Isolated yield.

The corresponding β-amino ketones **4** were obtained in good yields (Table 2, entries 1−3). Trimethyl(prop-1-en-2-yloxy)silane **3d** afforded β-amino ketone **4d** in poor yield (Table 2, entry 4). Silyl enol ethers derived from cyclopentanone or cyclohexanone afforded β-amino ketones **4e** and **4f** with good yields (Table 2, entries 5 and 6).

In this one-pot protocol, the reaction involving benzaldehyde was further optimized using 1.2 equiv of silyl enol ether (Table 3, entry 1). Other aldehydes were tested and the results are summarized in Table 3. Generally, excellent yields of β-amino ketone were obtained with 1.2 equiv of (1-phenylvinyloxy)trimethylsilane **3a** and 0.01 equiv of Bi(OTf)₃·4H₂O at 25 °C in acetonitrile. Aromatic aldehydes as well as heterocyclic and α,β-unsaturated aldehydes reacted smoothly to give the corresponding β-amino ketone derivatives **4** in high yield (Table 3, entries 1−8). The reaction worked well with a variety of aldehydes including those bearing an electron-withdrawing group, and the corresponding β-amino ketones **4** were obtained with very good yields (Table 3, entries 2−4). Several electron-rich aromatic aldehydes led to the desired products in good yields (Table 3, entries 5 and

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TABLE 4. Three-Component Bi(OTf)$_3$-Catalyzed Mannich-Type Reactions Involving Benzaldehyde and Various Amines[a]

entry	amine 2	product	yield 4 (%)[b]
1	(2-OMe aniline)	**4o**	65
2	(MeO–C6H4–NH2)	**4p**	79
3	(2-OMe, 4-NO2 aniline)	**4q**	85 [c]
4	(2-NO2, 4-MeO aniline)	**4r**	88 [c]
5	(PhCH2O–C(O)–NH2)	**4s**	49 [c]

[a] Conditions: benzaldehyde (1.0 equiv), amine (1.0 equiv), (1-phenylvinyloxy)trimethylsilane **3a** (1.2 equiv), Bi(OTf)$_3$·4H$_2$O (0.01 equiv). [b] Isolated yield. [c] Reaction performed at 0 °C.

7). Conjugated aldehydes were good substrates as well (Table 3, entry 8). Aliphatic aldehydes do not react under such conditions probably due to enamine formation, except cyclohexane carboxaldehyde, which afforded product **4n** in good yield (Table 3, entry 9). Interestingly, we never observed side reaction products such as aldol and deamination products.

The scope of our method could be extended to other amines. *o*- and *p*-Anisidines gave moderate to good yield of the corresponding β-amino carbonyl compounds (Table 4, entries 1 and 2), which are known to be easily cleavable under oxidative conditions.[16] 2-Methoxy-4-nitro- and 4-methoxy-2-nitroanilines afforded the β-amino carbonyl compounds in high yield (Table 4, entries 3 and 4). Using Cbz-carbamate instead of an aniline gave only a moderate yield of the Cbz-protected β-amino carbonyl compound (Table 4, entry 5).

Although the precise mechanism has not been elucidated, we have investigated the nature of the catalyst as the true catalyst might be TfOH released from hydrolysis of Bi(OTf)$_3$·4H$_2$O. TfOH is indeed as effective as Bi(OTf)$_3$·4H$_2$O to catalyze the Mannich-type reaction (1 equiv of PhCHO **1a**, 1 equiv of PhNH$_2$ **2a**, 1 equiv of (1-phenylvinyloxy)trimethylsilane **3a**, 0.03 equiv of TfOH, 25 °C, 0.3 h, 80% of **4a**). However, the observation that the same reaction in the presence of hindered 2,6-di-*tert*-butylpyridine still occurs (1 equiv of PhCHO **1a**, 1 equiv of PhNH$_2$ **2a**, 1 equiv of (1-phenylvinyloxy)trimethylsilane **3a**, 0.01 equiv of Bi(OTf)$_3$·4H$_2$O, 0.03 equiv of 2,6-di-*tert*-butylpyridine, 25 °C, 0.3 h, 80% of **4a**) does not indicate unambiguously that a Lewis acid is involved in the process because the pyridinium salt itself also medi-

ates the reaction (1 equiv of PhCHO **1a**, 1 equiv of PhNH$_2$ **2a**, 1 equiv of (1-phenylvinyloxy)trimethylsilane **3a**, 0.03 equiv of 2,6-di-*tert*-butylpyridinium triflate, 25 °C, 0.3 h, 80% of **4a**). Other bismuth(III) salts such as BiCl$_3$ catalyze the Mannich-type reaction albeit with a lower yield (1 equiv of PhCHO **1a**, 1 equiv of PhNH$_2$ **2a**, 1 equiv of (1-phenylvinyloxy)trimethylsilane **3a**, 0.01 equiv of BiCl$_3$, 25 °C, 1.5 h, 59% of **4a**). Competition studies involving an excess of the aldehyde (2 equiv of PhCHO **1a**, 1 equiv of PhNH$_2$ **2a**, 1 equiv of (1-phenylvinyloxy)-trimethylsilane **3a**, 0.01 equiv of Bi(OTf)$_3$·4H$_2$O show complete chemoselectivity for the Mannich-type reaction vs Mukaiyama-aldol (25 °C, MeCN, 89% of 1,3-diphenyl-3-(*N*-phenylamino)propan-1-one **4a**). The Mukaiyama-aldol product is indeed formed in the absence of amines (1 equiv of PhCHO **1a**, 1.2 equiv of (1-phenylvinyloxy)-trimethylsilane **3a**, 0.01 equiv of Bi(OTf)$_3$·4H$_2$O, 25 °C, 0.8 h, 93% of 3-hydroxy-1,3-diphenylpropan-1-one). This clearly indicates coordination of the aldimine or aminal by Bi(OTf)$_3$ prior to the silyl enol ether attack. Moreover, our studies clearly suggest that Bi(OTf)$_3$ would behave as an aldimine-selective Lewis acid.[14] However, a contribution of Me$_3$SiOTf in a silicon-catalyzed mechanism cannot be ruled out,[6,17] and further mechanistic investigations of the nature of the catalyst are in progress.

In summary, we have found that the Mannich-type reaction of in situ prepared imines proceeds smoothly with silyl enol ethers and a catalytic amount of Bi(OTf)$_3$·4H$_2$O. This method offers several advantages including mild reaction conditions, a highly catalytic (1%) process, and no formation of byproducts. To the best of our knowledge, such a low catalyst loading (1%) for a metal-catalyzed Mannich-type reaction has not been previously reported using silyl enol ethers.[18] Moreover, our protocol does not require prior isolation of the imine. The β-amino ketone is directly obtained, usually as a crystalline product, in a one-pot process. Because of its numerous benefits, the Bi(OTf)$_3$·4H$_2$O protocol should find utility in the synthesis of biologically active compounds. Development of other Bi(OTf)$_3$·4H$_2$O-catalyzed Mannich-type reactions and related mechanistic studies will be reported in due course.

Experimental Section

General Procedures. Infrared spectra were recorded on an FT infrared spectrometer and are reported in reciprocal centimeters (cm^{-1}). ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a 400 MHz magnetic resonance spectrometer in CDCl$_3$. For ^{1}H NMR, tetramethylsilane (TMS) served as internal standard (δ = 0). For ^{13}C NMR, CDCl$_3$ was used as internal standard (δ = 77.0), and spectra were obtained with complete proton decoupling. For ^{19}F NMR, CFCl$_3$ was used as internal standard (δ = 0). Acetonitrile was distilled from calcium hydride (CaH$_2$).

Typical Procedure for the Bismuth-Catalyzed Three-Component Reaction. Under an inert atmosphere of argon, the silyl enol ether (2.4 mmol) in 2 mL of dry acetonitrile was added in one portion to a solution of Bi(OTf)$_3$·4H$_2$O (0.02 mmol),

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the aldehyde (2 mmol), and the aniline (2 mmol) in 2 mL of dry acetonitrile. The mixture was stirred at room temperature until the reaction was completed as indicated by TLC. The reaction was quenched with water and extracted with diethyl ether. The organic phase was washed with water and saturated aqueous sodium chloride, dried over magnesium sulfate, and concentrated under vacuum (rotary evaporator). The crude product was filtered under a glass frit and washed with hexane except for **4d,o−r**, which has been purified by silica gel chromatography (hexane/ethyl acetate). β-Amino ketones **4a−g,i−p,s** accord exactly with those that have been previously reported in the literature.

1,3-Diphenyl-3-(*N*-phenylamino)propan-1-one (4a):[19,20] 89% yield.

2-Methyl-1,3-diphenyl-3-(*N*-phenylamino)propan-1-one (4b):[19,21] 73% yield.

1-(4-Chlorophenyl)-3-phenyl-3-(*N*-phenylamino)propan-1-one (4c):[22] 82% yield.

4-Phenyl-4-(*N*-phenylamino)butan-2-one (4d):[22,23] 42% yield.

2-(Phenyl-*N*-phenylaminomethyl)cyclopentanone (4e):[20] 80% yield.

2-(Phenyl-*N*-phenylaminomethyl)cyclohexanone (4f):[19,21] 81% yield.

3-(4-Chlorophenyl)-1-phenyl-3-(*N*-phenylamino)propan-1-one (4 g):[19] 82% yield.

3-[4-(Trifluoromethyl)phenyl]-1-phenyl-3-(*N*-phenylamino)propan-1-one (4h). Reagents: 4-(trifluoromethyl)benzaldehyde (273 µL, 348 mg, 2.0 mmol), **2** (182 µL, 186 mg, 2.0 mmol), **3a** (462 mg, 2.4 mmol), and Bi(OTf)₃·4H₂O (14 mg, 0.02 mmol). The reaction was stirred for 0.5 h and quenched according to the typical procedure. The crude product was washed with hexane to afford 654 mg (88%) of **4h** as a white solid: mp 144−145 °C; R_f 0.39 (hexane/ethyl acetate = 4:1); IR (KBr) ν 3403, 1671; ¹H NMR (CDCl₃) δ 7.89 (2H, d, J = 7.4 Hz), 7.55−7.59 (5H, m), 7.44 (2H, t, J = 7.7 Hz), 7.11 (2H, t, J = 7.9 Hz), 6.71 (1H, t, J = 7.3 Hz), 6.56 (2H, d, J = 7.8 Hz), 5.06 (1H, t, J = 6.3 Hz), 3.52 (1H, d, J = 2.5 Hz), 3.50 (1H, d, J = 3.7 Hz); ¹³C NMR (CDCl₃) δ 197.9, 147.3, 146.7, 136.7, 133.9, 129.8 (q, J = 32.2 Hz), 129.5, 129.0, 128.6, 128.4, 127.1, 126.0 (q, J = 3.8 Hz), 124.3 (q, J = 270 Hz), 118.5, 114.2, 54.6, 46.2; ¹⁹F NMR (CDCl₃) δ −62.94; HRMS calcd for C₂₂H₁₈F₃NO (M⁺) 369.1340, found 369.1336.

3-(4-Nitrophenyl)-1-phenyl-3-(*N*-phenylamino)propan-1-one (4i):[19] 87% yield.

3-(4-Methoxyphenyl)-1-phenyl-3-(*N*-phenylamino)propan-1-one (4j):[24] 86% yield.

3-(Furan-2-yl)-1-phenyl-3-(*N*-phenylamino)propan-1-one (4k):[19,22] 76% yield.

1-Phenyl-3-(*N*-phenylamino)-3-*p*-tolylpropan-1-one (4l):[19] 82% yield.

(*E*)-1,5-Diphenyl-3-(*N*-phenylamino)pent-4-en-1-one (4m):[19] 72% yield.

3-Cyclohexyl-1-phenyl-3-(*N*-phenylamino)propan-1-one (4n):[19] 77% yield.

3-[*N*-(2-Methoxyphenylamino)]-1,3-diphenylpropan-1-one (4o):[25] 65% yield.

3-[*N*-(4-Methoxyphenylamino)]-1,3-diphenylpropan-1-one (4p):[19,20] 79% yield.

3-[*N*-(2-Methoxy-4-nitrophenylamino)]-1,3-diphenylpropan-1-one (4q). Reagents: benzaldehyde (203 µL, 212 mg, 2.0 mmol), 2-methoxy-4-nitroaniline (336 mg, 2.0 mmol), **3a** (462 mg, 2.4 mmol), and Bi(OTf)₃·4H₂O (14 mg, 0.02 mmol). The reaction was carried out at 0 °C, stirred for 0.5 h, and quenched according to the typical procedure. The crude product was purified by silica gel chromatography (hexane/ethyl acetate = 80:20) to afford 642 mg (85%) of **4q** as a yellow solid: mp 138−140 °C; R_f 0.18 (hexane/ethyl acetate = 4:1); IR (KBr) ν 3393, 1683; ¹H NMR (CDCl₃) δ 7.90−7.92 (2H, m), 7.74 (1H, dd, J = 8.9, 2.4 Hz), 7.61 (1H, d, J = 2.3 Hz), 7.58 (1H, t, J = 7.5 Hz), 7.46 (2H, t, J = 7.7 Hz), 7.32−7.40 (4H, m), 7.25−7.28 (1H, m), 6.37 (1H, d, J = 9.0 Hz), 5.17 (1H, t, J = 6.3 Hz), 3.95 (3H, s), 3.57 (1H, d, J = 3.3 Hz), 3.55 (1H, d, J = 2.0 Hz); ¹³C NMR (CDCl₃) δ 197.5, 145.7, 143.1, 141.6, 137.8, 136.7, 133.9, 129.3, 129.0, 128.4, 128.1, 126.4, 119.7, 108.5, 104.9, 56.2, 53.9, 46.2. HRMS calcd for C₂₂H₂₀N₂O₄ (M⁺) 376.1423, found 376.1419.

3-[*N*-(4-Methoxy-2-nitrophenylamino)]-1,3-diphenylpropan-1-one (4r). Reagents: benzaldehyde (203 µL, 212 mg, 2.0 mmol), 4-methoxy-2-nitroaniline (336 mg, 2.0 mmol), **3a** (462 mg, 2.4 mmol), and Bi(OTf)₃·4H₂O (14 mg, 0.02 mmol). The reaction was carried out at 0 °C, stirred for 0.5 h, and quenched according to the typical procedure. The crude product was purified by silica gel chromatography (hexane/ethyl acetate = 85:15) to afford 659 mg (88%) of **4r** as an orange solid: mp 106−108 °C; R_f 0.31 (hexane/ethyl acetate = 4:1); IR (KBr) ν 3352, 1683; ¹H NMR (CDCl₃) δ 8.53 (1H, br s), 7.91−7.93 (2H, m), 7.56−7.61 (2H, m), 7.41−7.47 (4H, m), 7.34 (2H, t, J = 7.5 Hz), 7.24−7.28 (1H, m), 7.01 (1H, dd, J = 9.4, 3.1 Hz), 6.77 (1H, d, J = 9.4 Hz), 5.34 (1H, t, J = 6.1 Hz), 3.75 (3H, s), 3.64 (1H, dd, J = 16.9, 7.5 Hz), 3.50 (1H, dd, J = 16.9, 5.4 Hz); ¹³C NMR (CDCl₃) δ 196.9, 150.2, 142.0, 140.3, 136.7, 133.8, 131.9, 129.3, 129.0, 128.4, 128.0, 127.1, 126.5, 116.7, 107.4, 56.0, 54.0, 47.1; HRMS calcd for C₂₂H₂₀N₂O₄ (M⁺) 376.1423, found 376.1419.

Benzyl 3-oxo-1,3-diphenylpropylcarbamate (4s):[26] 49% yield.

Supporting Information Available: Experimental details, characterization data, and NMR spectra for compounds **4a−s**. This material is available free of charge via the Internet at http://pubs.acs.org.

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