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The First Catalytic Mannich-Type Reaction of *N*-Alkoxycarbonylamino Sulfones with Silyl Enolates

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Abstract: Bismuth triflate was found to be an efficient catalyst in the Mannich-type reaction of silyl enolates with *N*-alkoxycarbonylamino sulfones. The reaction proceeded smoothly with a low catalyst loading of bismuth triflate (0.5–1.0 mol%) to afford the corresponding protected β-aminocarbonyl compound in very good yields (up to 96%).

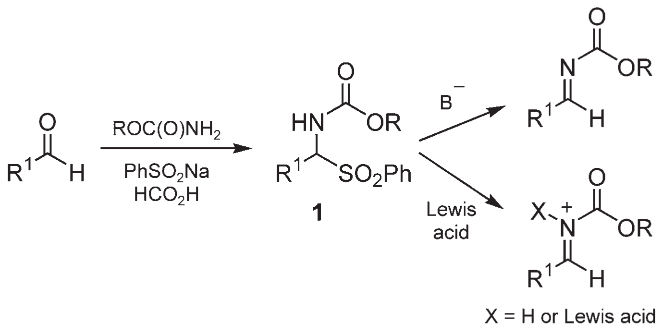
Keywords: *N*-alkoxycarbonylamino sulfones; bismuth; green chemistry; Mannich bases; Mannich reaction; silyl enolates

The development of new methods for the synthesis of β-aminocarbonyl derivatives is an important area of synthetic efforts. β-Aminocarbonyl compounds are extremely important as biologically active molecules. Among the variety of synthetic methods reported so far, Lewis acid-catalyzed reactions of imines with silyl enolates provide an efficient route for the synthesis of β-amino ketones and esters. 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-aminocarbonyl compounds.[1] However, many imines tend to be unstable during the purification process, such as distillation, chromatography, or prolonged storage. Thus, methods involving the *in situ* generation of the imine are highly attractive, among which is the one-pot preparation of imines formed *in situ* from aldehydes and amines, have been proposed.[2] Nevertheless, most Lewis acids cannot be used in this reaction because they deactivate or decompose in the presence of the amine and water produced during imine formation. Very reactive *N*-acyliminium species, which can easily be prepared from stable precursors, provide an attractive alternative.

Recently, several laboratories have disclosed significant advances regarding rare-earth and lanthanide triflates as catalysts for Mannich-type reactions.[3] 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 less toxic and cheaper alternatives to the latter.[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] Fries and Claisen rearrangements,[9] and Sakurai reactions.[10] $Bi(OTf)_3$ is particularly attractive because it is commercially available or can be easily prepared from commercially available starting materials.[11] 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.[12] This method was very efficient with anilines but using Cbz carbamate instead of an aniline gave only a moderate yield of the Cbz-protected β-aminocarbonyl compound.[12b] These results encouraged us to pursue a different approach to the bismuth(III)-catalyzed Mannich-type reaction.

As a part of our ongoing interest in bismuth(III)-catalyzed reactions involving silyl nucleophiles, we report herein a general bismuth triflate hydrate [$Bi(OTf)_3 \cdot 4H_2O$] catalyzed method for the addition of silyl enolates to *N*-alkoxycarbonylamino sulfones.[13] Scheme 1 illustrates the preparation of the *N*-acylimine or -iminium precursor from the corresponding aldehydes.[14] *N*-Alkoxycarbonyl imines have been prepared from the basic treatment of the *N*-alkoxycarbonylamino sulfones **1**;[15] the corresponding *N*-alkoxycarbonyliminium derivatives have been prepared by the use of a Lewis acid with **1** (Scheme 1).

We report the first catalytic Mannich-type reaction of *N*-alkoxycarbonylamino sulfones with silyl enolates. Alkoxycarbonyl protected β-aminocarbonyl derivatives are obtained efficiently in the presence of



Scheme 1. Alkoxycarbonylamino sulfones as precursors of *N*-alkoxycarbonylimine derivatives.

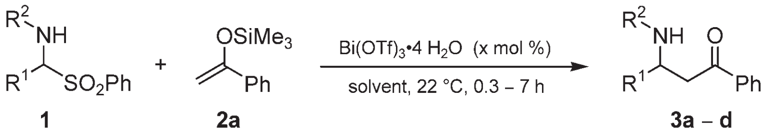
0.5–1.0 mol% of $Bi(OTf)_3{\cdot}4H_2O$. To the best of our knowledge, a catalytic version of this reaction has never been reported. The only published Mannich-type reactions from *N*-alkoxycarbonylamino sulfones involve a Lewis acid-like $TiCl_4$ or $SnCl_4$ used in a stoichiometric amount or in large excess.[16]

Initially, we screened various solvents for the Mannich-type reaction of *N*-alkoxycarbonylamino sulfones **1** with trimethyl(1-phenylvinyloxy)silane **2a** in the presence of $Bi(OTf)_3{\cdot}4H_2O$. Interestingly, when the latter was treated with 0.5 mol% $Bi(OTf)_3{\cdot}4H_2O$ in THF for 7 h at 22 °C, the corresponding Cbz-protected β-amino ketone was isolated in moderate yield (51%) (Table 1, entry 1). Among various polar solvents tested, acetonitrile and dichloromethane gave the best yields of the expected product (Table 1, entries 2 and 3). The catalyst loading had to be increased to 1 mol% for some substrates (Table 1, entry 4). Because of the poor solubility in acetonitrile of many *N*-alkoxycarbonylamino sulfones **1** presented here, dichloromethane was selected as the solvent of choice. Other carbamate protecting groups on **1** led to very good yields of the desired products **3** (Table 1, entries 5 and 6). *N*-Benzyloxycarbonylamino phenyl sulfones were chosen as model substrates for the following studies.

Several examples of $Bi(OTf)_3$-catalyzed Mannich-type reactions of various *N*-benzyloxycarbonylamino sulfones **1** with silyl enol ethers are summarized in Table 2. *N*-Benzyloxycarbonylamino sulfones **1** derived from differently substituted benzaldehydes were reacted with trimethyl(1-phenylvinyloxy)silane in dichloromethane at room temperature. The corresponding β-amino ketones **3** were obtained in very good to excellent yields (Table 2, entries 1–6). The reaction was efficient using electron-deficient benzaldehyde-derived sulfones and the corresponding β-amino ketones **3** were obtained with very good yields (Table 2, entries 1 and 2). Sulfones derived from several electron-rich aromatic aldehydes led to the desired products in good yields (Table 2, entries 3–6). For selected substrates, a slightly better yield was obtained when using a catalyst loading of 1 mol% instead of 0.5 mol% (Table 2, compare entries 5 and 6). *N*-Benzyloxycarbonylamino sulfones derived from aliphatic aldehydes afforded products **3** in very good to excellent yields (Table 2, entries 7–9). Trimethyl(prop-1-en-2-yloxy)silane afforded β-amino ketone **3m** in good yield (Table 2, entry 10). Silyl enol ethers derived from 3-pentanone, cyclopentanone, or 2,4-dimethyl-3-pentanone afforded smoothly β-amino ketones **3n**, **3o**, and **3p**, respectively (Table 2, entries 11–13).[17]

A further investigation with various silyl ketene acetals is summarized in Table 3. Silyl ketene acetals **4** derived from various esters were reacted with *N*-benzyloxycarbonylamino sulfones **1** in the presence of 0.5–1 mol% $Bi(OTf)_3{\cdot}4H_2O$. The corresponding β-

Table 1. $Bi(OTf)_3$-catalyzed Mannich-type reactions involving *N*-alkoxycarbonylamino phenylsulfones and trimethyl(1-phenylvinyloxy)silane.[a]



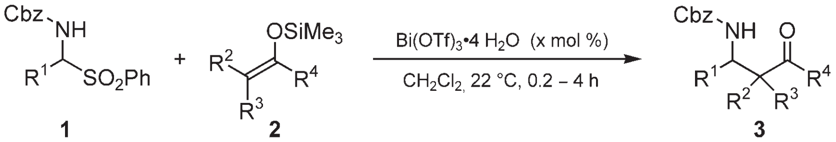
Entry	R^1	R^2	x (mol%)	Solvent	**3**	Yield of **3** [%][b]
1	Et	Cbz	0.5	THF	**3a**	51
2	Et	Cbz	0.5	MeCN	**3a**	90
3	Et	Cbz	0.5	CH_2Cl_2	**3a**	94
4	Ph	Cbz	1	CH_2Cl_2	**3b**	85
5	Ph	Boc	1	CH_2Cl_2	**3c**	80[c]
6	Ph	CO_2Et	0.5	CH_2Cl_2	**3d**	85

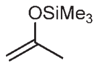
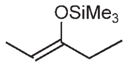
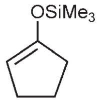
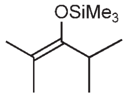
[a] *Conditions:* *N*-alkoxycarbonylamino phenylsulfone (1.0 equiv.), trimethyl(1-phenylvinyloxy)silane **2a** (1.3 equivs.), $Bi(OTf)_3{\cdot}4H_2O$ (0.005–0.01 equivs.).

[b] Isolated yield.

[c] Product **3c** slightly decomposed on silica gel chromatography and was contaminated by small quantities of deprotected β-aminoketone.

Table 2. $Bi(OTf)_3$-catalyzed Mannich-type reactions with various *N*-benzyloxycarbonylamino phenyl sulfones and silyl enol ethers.[a]



Entry	R^1	Silyl enol ether **2**	x (mol %)	**3**	Yield of **3** [%][b]
1	4-ClC_6H_4	**2a**	0.5	**3e**	84
2	4-FC_6H_4		0.5	**3f**	92
3	4-MeC_6H_4		0.5	**3g**	89
4	2-MeC_6H_4		0.5	**3h**	88
5	4-$MeOC_6H_4$		0.5	**3i**	83
6	4-$MeOC_6H_4$		1	**3i**	87
7	$CH_3(CH_2)_2$		1	**3j**	87
8	$(CH_3)_2CH$		1	**3k**	96
9	*c*-C_6H_{11}		0.5	**3l**	85
10	$CH_3(CH_2)_2$		0.5	**3m**	80
11	$C_6H_5CH_2$		1	**3n**	77[c]
12	$CH_3(CH_2)_2$		0.5	**3o**	81[d]
13	4-MeC_6H_4		0.5	**3p**	86

[a] *Conditions: N*-benzyloxycarbonylamino phenyl sulfone (1.0 equiv.), silyl enol ether (1.3 equivs.), $Bi(OTf)_3 \cdot 4H_2O$ (0.005–0.01 equivs.).

[b] Isolated yield.

[c] Silyl enol ether was used as a mixture of stereoisomers ($Z/E = 87{:}13$). Product **3n** was isolated as a mixture of stereoisomers (*syn/anti* = 72:28) (ratio determined by ^1H NMR).

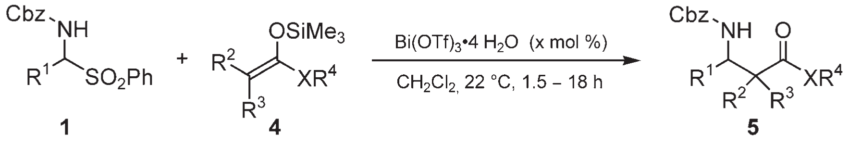
[d] Product **3o** was isolated as a 57/43 mixture of diastereosisomers as determined by ^1H NMR.

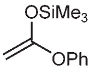
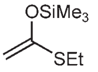
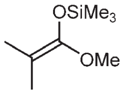
amino esters **5** were obtained in moderate to good yields (Table 3). Silyl enolates derived from esters as well as thioesters reacted smoothly to give the adducts. The *N*-benzyloxycarbonylamino sulfone derived from *n*-butyraldehyde **1** led to moderate yields of β-amino esters when reacted with acetate derived silyl ketene acetals (Table 3, entries 1 and 2). A very good yield was obtained when the same sulfone was subjected to a tetrasubstituted silyl ketene acetal (Table 3, entry 3). The latter afforded moderate to good yields of β-amino esters **5d**, **5e**, and **5f** with phenylacetaldehyde, *p*-tolualdehyde, and *o*-tolualdehyde derived sulfones respectively (Table 3, entries 4–6).

The potential of this catalytic approach is further demonstrated by the synthesis of a substituted 1,3-oxazinan-2-one *via* a reduction-cyclization strategy (Scheme 2).[18] Optimization of the previously reported Mannich-type reaction of trimethyl(pent-2-en-3-yloxy)silane with the sulfone derived from phenylacetaldehyde (Table 2, entry 11) led to the corresponding β-amino ketone in a good yield with moderate diastereoselectivity [2 mol% $Bi(OTf)_3 \cdot 4H_2O$, yield = 84%, **3n**/**3n'** (*syn*/*anti*) = 72:28] (Scheme 2). Reduction of the major diastereoisomer **3n** with lithium tri-*tert*-butoxyaluminohydride afforded **6** as the only diastereoisomer. Further cyclization of the latter with NaH afforded 4-benzyl-6-ethyl-5-methyl-1,3-oxazinan-2-one **7**. The relative configuration of the six-membered carbamate was established as *cis-cis via* NMR analysis.

In summary, we have found that the Mannich-type reaction of *N*-benzyloxycarbonylamino sulfones **1** proceeds smoothly with silyl enolates and a catalytic amount of $Bi(OTf)_3 \cdot 4H_2O$. This method offers several advantages including mild reaction conditions, very low catalyst loading (0.5–1 mol%), and no formation of by-products such as deamination products. To the best of our knowledge, this is the first report of a catalytic Mannich-type reaction of *N*-alkoxycarbonylamino sulfones with silyl enolates. Moreover, our process involves an environmentally benign, cheap, and easy to handle catalyst. The β-aminocarbonyl compound, already protected as a Cbz derivative, is smoothly ob-

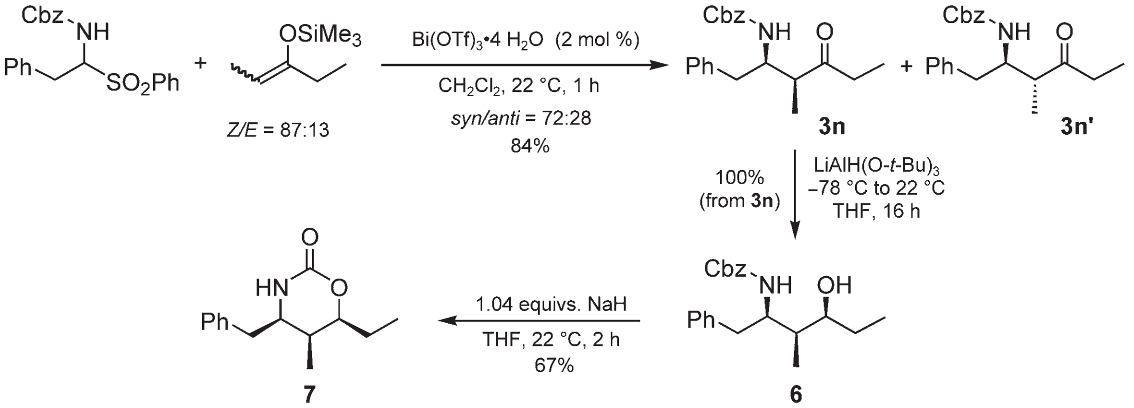
Table 3. $Bi(OTf)_3$-catalyzed Mannich-type reactions with various *N*-benzyloxycarbonylamino phenyl sulfones and silyl ketene acetals.[a]



Entry	R^1	Silyl ketene acetal **4**	x (mol%)	**5**	Yield of **5** [%][b]
1	$CH_3(CH_2)_2$		0.5	**5a**	66
2	$CH_3(CH_2)_2$		0.5	**5b**	61
3	$CH_3(CH_2)_2$		1	**5c**	86
4	$C_6H_5CH_2$		1	**5d**	67
5	$4\text{-}MeC_6H_4$		1	**5e**	78
6	$2\text{-}MeC_6H_4$		1	**5f**	73

[a] *Conditions: N*-benzyloxycarbonylamino phenyl sulfone (1.0 equiv.), silyl ketene acetal (1.3 equivs.), $Bi(OTf)_3 \cdot 4H_2O$ (0.005–0.01 equivs.).

[b] Isolated yield.



Scheme 2. Synthesis of 1,3-oxazinan-2-ones *via* the *N*-alkoxycarbonylamino phenyl sulfone pathway.

tained under 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 other significant applications of this $Bi(OTf)_3 \cdot 4H_2O$-catalyzed Mannich-type reaction.

Experimental Section

General Remarks

Infrared spectra were recorded on an FT infrared spectrometer and are reported in reciprocal centimeters (cm^{-1}). ^1H, ^{13}C, and ^{19}F NMR spectra were recorded on a 400 MHz nuclear magnetic resonance spectrometer in $CDCl_3$. For ^1H NMR, tetramethylsilane (TMS) served as internal standard ($\delta = 0$). For ^{13}C NMR, $CDCl_3$ was used as internal standard ($\delta = 77.0$) and spectra were obtained with complete proton decoupling. For ^{19}F NMR, $CFCl_3$ was used as internal standard ($\delta = 0$). Column chromatography was performed on silica gel (230–400 mesh) and analytical thin-layer chromatography was carried out using 250 μm commercial silica gel plates. Acetonitrile and dichloromethane were distilled from calcium hydride (CaH_2). Tetrahydrofuran was distilled from sodium/benzophenone.

General Procedure for the Bismuth-Catalyzed Mannich-type Reaction

Under an inert atmosphere of argon, the silyl enolate (0.65 mmol) in 0.5 mL of dry dichloromethane was added dropwise to a solution of $Bi(OTf)_3 \cdot 4H_2O$ (0.0025 mmol, 1.8 mg or 0.0050 mmol, 3.6 mg) and the *N*-alkoxycarbonylamino sulfone (0.5 mmol) in 1 mL of dry dichloromethane. The mixture was stirred at room temperature until the reaction was complete as indicated by TLC. The reaction was quenched with water (2 mL) and the mixture extracted with ethyl acetate (3×10 mL). The organic phase was washed with water (2 mL) and saturated aqueous sodium chloride (2 mL), dried over magnesium sulfate, and concentrated under vacuum (rotary evaporator). The crude product was purified by silica gel chromatography (hexane/ethyl acetate/triethylamine 75/24/1–96/3/1).

Acknowledgements

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