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Mannich-Type Reaction with Trifluoromethylated *N*,*O*-Hemiacetal: Facile Preparation of *β*-Amino-*β*-trifluoromethyl Carbonyl Compounds

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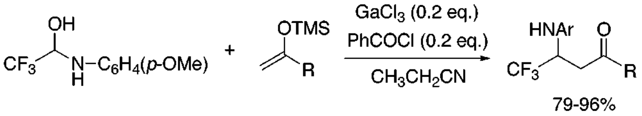
ABSTRACT



On treatment of silyl enolates and an *N*,*O*-hemiacetal, derived from trifluoroacetaldehyde ethyl hemiacetal and *p*-anisidine, with $GaCl_3$ (0.2 equiv) and C_6H_5COCl (0.2 equiv) in propionitrile, Mannich-type reaction took place smoothly to afford *β*-amino-*β*-trifluoromethyl carbonyl compounds in high yields.

There is currently widespread interest in organofluorine compounds not only because of their usefulness in the field of material science but also for their diverse biological activities and potential for clinical and other applications. Development of efficient methods for the preparation of organofluorine compounds thus continues to be an important goal of synthetic organic chemistry.[1] The synthesis of amino compounds bearing a trifluoromethyl moiety is a significant aspect of organofluorine chemistry. Nucleophilic addition of organometallics toward imines derived from trifluoroacetaldehyde should provide easy access to the *N*-2,2,2-trifluoroethylamines. However, this is hampered for the following reasons: (1) trifluoromethylated imines are labile due to the exceptionally high electrophilicity; (2) trifluoroacetaldehyde itself, being volatile gas, is not easy to handle. To overcome the former difficulty, *N*,*O*-acetal[2] and *N*,*N*-acetal[3] were employed. With respect to the latter issue, commercially available trifluoroacetaldehyde ethyl hemiacetal[4] has been employed as a starting material.

As part of our continued interest in the development of the activation of the C═N bond and subsequent addition of organometallics such as silyl enolates[5] and allylic organometallics,[6] we focused on the Mannich-type reaction of silyl

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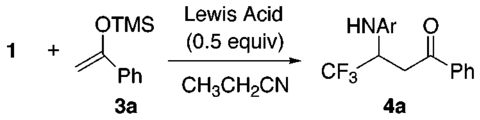
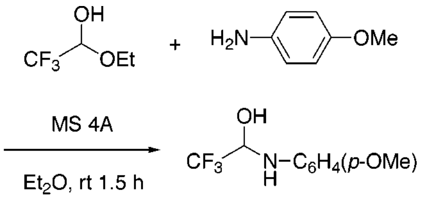
Table 1. Effect of Lewis Acid



Entry	Lewis Acid	Reaction time	Yield/%
1	$GaCl_3$	1 h	quant
2	$InCl_3$	1 h	72
3	$BF_3{\cdot}OEt_2$	2 h	61
4	$TiCl_4$	1 h	15
5	ZnI_2	1 h	5

enolate with an aldimine derived from trifluoroacetaldehyde.[7] We have found that an *N*,*O*-hemiacetal (**1**) is readily available by simply mixing trifluoroacetaldehyde ethyl hemiacetal and an amine followed by removal of the solvent. It is noted that **1** can be stored without significant decomposition in a refrigerator.[8] Furthermore, Mannich-type reaction with the *N*,*O*-hemiacetal proceeded smoothly under the influence of $GaCl_3$ to afford β-amino-β-trifluoromethyl carbonyl compounds in excellent yields.

At the outset, trifluoroacetaldehyde ethyl hemiacetal was treated with *p*-anisidine (1.0 equiv) in diethyl ether in the presence of MS 4A at room temperature for 1.5 h. Removal of the sieves by filtration and subsequent evaporation of the solvent afforded **1** in 97% yield. The *N*,*O*-hemiacetal was used without further purification. While preparation of an aldimine (**2**), derived from trifluoroacetaldehyde and *p*-anisidine, requires high temperature, acid catalyst, and careful distillation,[9] **1** is much superior to **2** in terms of its ease of preparation and higher stability.



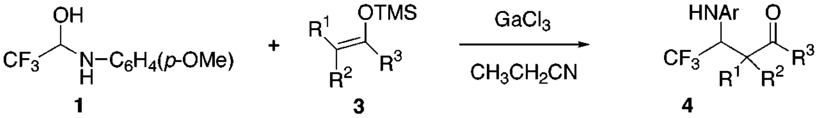
1

Next, Mannich-type reaction of a silyl enol ether (**3a**) with **1** was studied under the influence of 0.5 equiv of Lewis acid in propionitrile and the results are shown in Table 1. Although conventional Lewis acids such as $TiCl_4$ and ZnI_2 were not effective, use of either $BF_3{\cdot}OEt_2$ or $InCl_3$ afforded an adduct (**4a**) in a good yield. $GaCl_3$ exhibited the highest activity and afforded **3a** quantitatively.[10]

Mannich-type reactions with other silyl enolates were studied and the results are shown in Table 2. Although 0.5 equiv of $GaCl_3$ sufficed for **3a**, the yields dropped significantly with another silyl enol ether (**3b**) (entry 2). Gratifyingly, use of 1.0 equiv of $GaCl_3$ resulted in the formation of the adducts in excellent yields with various kinds of silyl enol ethers as well as ketene silyl acetals though the stereoselectivity was modest.

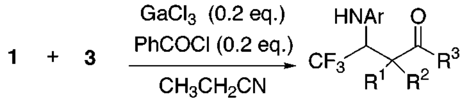
Although present Mannich-type reaction provides easy access to β-amino-β-trifluoromethyl carbonyl compounds in excellent yields, use of equimolar amount of promoter is not advantageous. For example, Mannich-type reaction of **1** with **3a** under the influence of 0.2 equiv of $GaCl_3$ afforded **4a** in 18% yield. To decrease the amount of $GaCl_3$, we screened several additives and found that the combined use of $GaCl_3$ (0.2 equiv) and PhCOCl (0.2 equiv) efficiently promoted the Mannich-type reaction to afford **4** in high yields. The results of the Mannich-type reaction under the influence of the $GaCl_3-C_6H_5COCl$ system are shown in Table 3. Mannich-type reaction took place smoothly to afford the corresponding adducts in high yields in all of the cases examined, exhibiting stereoselectivity comparable to those with 1.0 equiv of $GaCl_3$.

Table 2. Results of the Mannich-Type Reaction by Means of $GaCl_3$



Entry	Starting material	R^1	R^2	R^3	Eq of $GaCl_3$	Temp /°C	Time /h	Product	Yield/%	Major : Minor
1	**3a**	H	H	Ph	0.5	rt	1	**4a**	quant	-
2	**3b**	Me	H	Ph	0.5	rt	2	**4b**	25	70:30
3	**3b**	Me	H	Ph	1.0	rt	4.5	**4b**	quant	70:30
4	**3c**	H	$-(CH_2)_4-$		1.0	rt	1	**4c**	quant	68:32
5	**3d**	Me	Me	OMe	1.0	0	1	**4d**	quant	-
6	**3e**	H	Ph	OMe	1.0	–20	2	**4e**	quant	54:46
7	**3f**	H	Me	OEt	1.0	–20	1.5	**4f**	97	54:46

Table 3. Results of the Mannich-Type Reaction Employing $GaCl_3$−PhCOCl

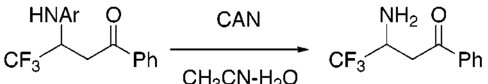


4

Entry	Starting material	Temp /°C	Time /h	Product	Yield/%[a]
1	**3a**	rt	1	**4a**	80
2	**3b**	rt	2	**4b**	79
3	**3c**	rt	1	**4c**	96
4	**3d**	0	2	**4d**	86
5	**3e**	–50	1.5	**4e**	86
6	**3f**	–20	2	**4f**	82

a) Diasteremer ratio. **4b** (70:30), **4c** (75:25), **4e** (55:45), **4f** (55:45).

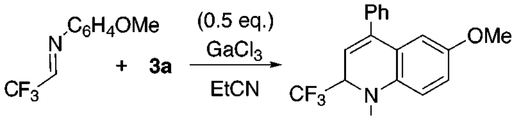
The *N*-aryl substituent was readily removed to give free β-amino carbonyl compounds. Treatment of **4a** with cerium ammonium nitrate (CAN) in acetonitrile−water (9:1) at 0 °C for 1 h led to the smooth deprotection of the *p*-methoxyphenyl group to afford a β-amino-β-trifluoromethyl ketone (**5**) in a good yield.[11]



4a

5: 78%

The present addition reaction is considered to proceed by in situ generation of an aldimine (**2**) and subsequent nucleophilic addition of silyl enolates. Interestingly, treatment of **3a** and **2** with $GaCl_3$ (0.5 equiv) in propionitrile at room temperature for 1.0 h led to the preferential formation of **6** in 75% yield[7] and **4a** was not obtained at all. Use of $GaCl_3$ (0.2 equiv) and PhCOOH (1.0 equiv) furnished **4a** in 79% yield. It is considered that present Mannich-type reaction of **1** with $GaCl_3$ proceeded by way of **2** and the actual activator would be a strong protic acid such as $H^+GaCl_3X^-$ ($X = OH$ or C_6H_5COO). In the case of the $GaCl_3$−PhCOCl protocol, PhCOCl facilitated the generation of **2** by way of *O*-benzoylation and thus liberated HX (X = PhCOO or Cl) would form $H^+GaCl_3X^-$ to afford **4**.



2

6: 75%

In summary, we have reported Mannich-type reaction of silyl enolates with *N*,*O*-hemiacetal derived from trifluoroacetaldehyde ethyl hemiacetal. Salient features of the present protocol are (1) the facile synthesis and high stability of the *N*,*O*-hemiacetal as a synthetic equivalent of trifluoromethylated aldimine and (2) the ability to obtain Mannich adducts exclusively without concomitant formation of the cyclization product.

Supporting Information Available: Experimental procedures and spectra data for the Mannich adducts. Complete analytical data of 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) Lewis acid mediated Mannich-type reaction of a silyl enol ether with an *N*,*O*-acetal ($CF_3CH(OCH_3)NEtPh$), prepared by means of electrochemical method, was reported, wherein a cyclization product was obtained preferentially accompanied by a Mannich adduct.[2b]

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