Silicon Tetrachloride Catalyzed Aza-Michael Addition of Amines to Conjugated Alkenes under Solvent-Free Conditions

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Abstract: The efficient and very simple conjugate addition of aromatic and aliphatic amines to α , β -unsaturated carbonyl compounds under solvent-free conditions in the presence of catalytic amount of silicon tetrachloride is reported. The reaction of aryl and alkyl amines with different Michael acceptors gave the corresponding Michael adducts with simple catalyst and good to excellent yields.

Key words: aromatic amine, conjugate addition, silicon tetrachloride, β-aminocarbonyl compounds

The aza-Michael addition reaction is one of the most important methodologies in synthetic organic chemistry for preparation of β -aminocarbonyl compounds, which not only constitute components of biologically important natural products but also serve as key intermediates for the synthesis of β -amino alcohols, antibiotics, β -amino acids, chiral auxiliaries, and other nitrogen-containing compounds.^{1,2}

The Mannich reaction is a classical method for the synthesis of β -amino carbonyl compounds. However, the reaction has disadvantages such as harsh reaction conditions, long reaction times, and a relatively narrow scope of substrates.³ The aza-Michael addition of nitrogen nucleophiles including amides, carbamates, sulfonamides, and amines to electron-deficient alkenes in the presence of strong base or acid catalyst has attracted considerable attention as an alternative route for the synthesis of β -amino carbonyl compounds.⁴ Since some functional groups may be susceptible to strong acid or base, a variety of catalysts⁵ and promoters for aliphatic amines⁶ have been introduced over the past few years.

However, there are still some limitations with the existing methods; for example, the range of amine nucleophiles and Michael acceptors well suited to both catalytic and stoichiometric methodologies is generally restricted to simple aliphatic amines and Michael acceptors and there have been few reports involving simple catalysts or reagents to effect these transformations.⁷ Thus, development of an efficient catalytic protocol that could overcome the above-mentioned disadvantages and facilitate the addition of both aromatic/aliphatic amines to α , β -unsaturated compounds remains a challenge.

As a part of our research aimed at developing green chemistry by using water as the reaction medium or by performing organic transformations under solvent-free conditions,⁸ we describe herein a simple, highly efficient, and eco-friendly method for the synthesis of β -amino carbonyl compounds from aromatic and aliphatic amines and α , β -unsaturated Michael acceptors under solvent-free conditions.

In order to find the best reaction conditions, we first studied the reaction of aniline and methyl acrylate with different loadings of starting materials and catalyst. It was found that the reaction of methyl acrylate (1.04 equiv) and aniline (1 equiv) in the presence of commercially available silicon tetrachloride (2 mol%) under solvent-free conditions proceeded smoothly within four hours to afford the conjugate addition product exclusively and in quantitative yield. Furthermore, in organic solvents, such as CH_2Cl_2 , MeCN, toluene, ethanol, water, and tetrahydrofuran the Michael addition reaction proceeded over longer reaction times to give the desired product in lower yields (Scheme 1).



Scheme 1

To explore the scope of the protocol, a number of electron-deficient olefins and aromatic and aliphatic amines was examined under the optimized conditions (Table 1). Several primary and secondary amines underwent smooth addition with α , β -unsaturated ketones, nitriles, and amides under catalyst-free conditions. In all cases, reactions proceeded smoothly and gave the corresponding products in good to excellent yield. Both aliphatic and aromatic amines react with a variety of conjugated alkenes by this procedure to produce the corresponding adducts in high yields. As evident from the results, anilines bearing either electron-donating or electron-withdrawing groups give the Michael addition products in good yields. Simi-

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larly, the corresponding products from the reaction of aliphatic amines with α , β -unsaturated alkenes were also obtained with excellent yields. In general the reaction rates are faster with aliphatic amines compared to those of aromatic amines and very electron-withdrawn amines, such as 4-nitroaniline, did not react. Addition to α , β -unsaturated aldehydes was also unsuccessful. Primary amines give only monoaddition products in most cases and no bisaddition product was isolated. Similarly, various α , β -unsaturated compounds such as methyl acrylate, acrylonitrile, acrylamide, benzylidenacetone, methyl vinyl ketone, methyl methacrylate, methyl crotonate, and crotonitrile underwent 1,4-addition with a variety of amines to furnish the corresponding addition products. The reactive Michael acceptor methyl vinyl ketone (MVK) underwent Michael addition at room temperature and short reaction time to give the mono-Michael adduct when one equivalent of MVK was used (Table 1), but when three equivalents of MVK were used, bisadduct was formed over a longer reaction time.



	$R^1R^2NH + R^3$	SiCl ₄ (2 mol%)	
	1 2	60 °C, 1–4 h R ¹ R ² N X	
	X = CN, COOMe, C	CONH ₂ , COR 3	
	$\begin{array}{c c} H \\ H $	$ \overset{NH_2}{\longmapsto} \overset{NH_2}{\underset{OMe}{\overset{NH_2}}{\overset{NH_2}{\overset{NH_2}{\overset{NH_2}}{\overset{NH_2}{\overset{NH_2}{\overset{NH_2}{\overset{NH_2}{\overset{NH_2}}{\overset{NH_2}{\overset{NH_2}}{\overset{NH_2}{\overset{NH_2}}{\overset{NH_2}{\overset{NH_2}}{\overset{NH_2}{\overset{NH_2}}{\overset{NH_2}{\overset{NH_2}}{\overset{NH_2}{\overset{NH_2}}{\overset{NH_2}}{\overset{NH_2}}{\overset{NH_2}}{\overset{NH_2}}{\overset{NH_2}}{\overset{NH_2}}{\overset{NH_2}}{\overset{NH_2}}{\overset{NH_2}}{\overset{NH_2}}{\overset{NH_2}}{\overset{NH_2}}{\overset{NH_2}}{\overset{NH_2}}}{\overset{NH_2}}{\overset{NH_2}}{\overset{NH_2}}{\overset{NH_2}}}}}}}}}}}}}}}}}}}}}}$	MH ₂ Me
	NHMe H 1f 1g	1h 1i 1j 1k 1l	1m
Entry	Michael acceptor	Amine (R ¹ R ² NH)	Yields (%) ^a
1		1a	94
2		1b	90
3		1c	84
4		1d	88
5		1e	80
6		10 1f	82
7	O II	1σ	72
8		15 1h	95
9	~ Ome	1	92
10		1	78
10		лј 11/	78
11		1K 1l	82
12		11 1m	82
15		1111	00
14		1a	94
15		1b	90
16		1c	84
17		1d	88
18		1e	80
19		1f	82
20	S CN	1g	72
21		1h	95
22		1i	92
23		1j	78
24		1k	75
25		11	82
26		1m	80
27		1a	80
28		 1b	72
29	0	 1c	74
30	, Ĭ	 1d	60
31	OMe	1f	64
32		 1h	50
33		11	56
55		11	50

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Entry	Michael acceptor	Amine (R ¹ R ² NH)	Yields (%) ^a	
34		1a	90	
35		1b	90	
36		1c	84	
37	Q	1f	76	
38	\sim	1h	82	
39	OMe	1i	80	
40		1k	60	
41		1m	68	
42		1a	82	
43	Q	1b	78	
44		1c	70	
45	₩ NH ₂	1d	75	
46	0	1a ^b	88	
47	Ph	1b	84	
48		1a	88	
49	CN CN	1b	90	
50	Ph' 🗡	1c	80	
51		1a	82	
52	CN	1b	80	
53		1c	85	
54		1a ^c	90	
55		1b	90	
56	0	1c	84	
57	↓	1f	78	
58	\sim	1h	94	
59		11	88	

^a NMR and GC yields.

^b Conditions: 5 mmol benzylidenacetone and 8 mmol amines were used.

^c In the case of methyl vinyl ketone, bis-substitution products were observed with aromatic amines.

In summary, we have developed an efficient and very simple procedure for the aza-conjugate addition of α , β -unsaturated carbonyl compounds with aromatic and aliphatic amines in the presence of a catalytic amount of silicone tetrachloride that provides access to useful and synthetically challenging β -amino ketones. The use of inexpensive and readily available reagents, chemical efficiency, operational simplicity, and simple workup make this process particularly attractive.⁹

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- (9) To the mixture of amine (5 mmol) and Michael acceptor (5.2 mmol) under argon, SiCl₄ (2 mol%) was added at 0 °C, and the mixture was warmed to 60 °C and stirred for 1–4 h until the disappearance of the starting amine as indicated by TLC or GC. When the reaction was complete, EtOAc (10 mL) and H₂O (10 mL) was added, the organic phase was separated, and dried over Na₂SO₄. The solvent was removed under reduced pressure, and in most cases, pure product was obtained. If needed, the residue was purified by silica gel column chromatography (hexane–EtOAc). All materials had analytical data in good agreement with data in the literature.

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