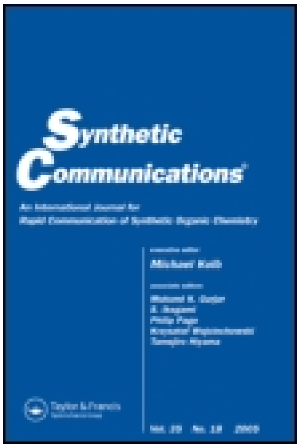

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Zirconium(IV) Chloride-Mediated Chemoselective Conjugate Addition of Aliphatic Amines to α,β-Ethylenic Compounds

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Zirconium(IV) Chloride–Mediated Chemoselective Conjugate Addition of Aliphatic Amines to α,β-Ethylenic Compounds

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Abstract: Zirconium chloride efficiently catalyzes the conjugate addition of a variety of aliphatic amines to *α*,*β*-unsaturated ester, nitriles, and ketones to give the corresponding *β*-amino derivatives in excellent yields under mild reaction conditions. Aromatic amines do not participate in this transformation.

Keywords: Amines, Michael addition, *α*,*β*-unsaturated compounds, zirconium(IV) chloride

INTRODUCTION

As a result of its vast range of applications,[1] the synthesis of *β*-amino carbonyl compounds and their derivatives have attracted much attention in organic synthesis.[2] The conjugate addition method is frequently utilized to prepare *β*-amino carbonyl derivatives. However, the conjugate addition requires basic or acid catalysts.[3] A Lewis acid–induced addition of amines to *α*,*β*-ethylenic compounds has been reported.[4] The metal-catalyzed reactions to prepare *β*-amino carbonyl compounds have been studied.[5] Many of these methods are fraught with difficulties.

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Recently, zirconium(IV) chloride has gained wide popularity as a mild and efficient Lewis acid catalyst for various organic transformations.[6–12] In continuation of our interest in zirconium chloride–catalyzed reaction, herein we report the chemoselective-conjugated addition of aliphatic amines to α,β-ethylenic compounds.

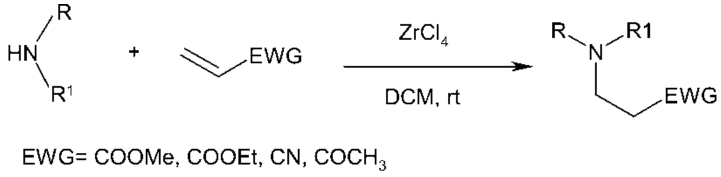
RESULTS AND DISCUSSION

Treatment of morpholine with methyl acrylate in the presence of zirconium chloride(IV) (10 mol%) in dichloromethane resulted in the formation of addition product in almost quantitative yield at ambient temperature (Scheme 1). A variety of aliphatic amines were reacted with α,β-unsaturated esters, nitrites, and ketones to produce the corresponding Michael adducts. In all the cases, the starting materials were consumed within 2–4 h at room temperature, giving rise to addition products in good yields. Although the reaction did proceed with 5 mol% of zirconium(IV) chloride, we reasoned that 10 mol% was optimum for completion of the reaction. The results are summarized in Table 1.

Secondary cyclic amines such as morpholine, piperidine, pyrrolidine, and piperizine showed higher reactivity than their acyclic counterparts. Piperazine gave the *bis*-addition product. Primary amines such as benzylamine and butylamine reacted smoothly, leading to the conjugated addition products.

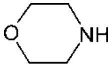
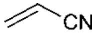
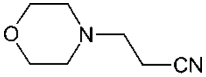
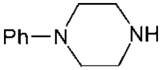
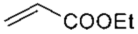
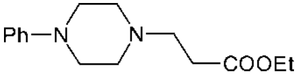
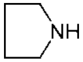
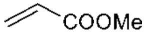
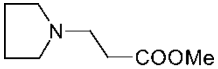
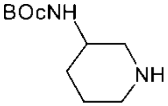
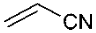
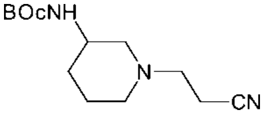
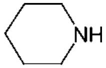
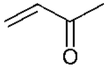
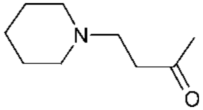
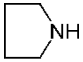
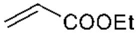
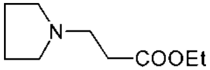
We also demonstrated the chemoselective addition of aliphatic amines to α,β-ethylenic compounds in the presence of aromatic amines (Scheme 2). When an equimolar mixture of aniline and pyrrolidine was exposed to methylacrylate in the presence of $ZrCl_4$ the pyrrolidine adduct was obtained as a single product. Several aromatic amines such as p-chloroaniline, p-hydroxyaniline, and p-nitroaniline were subjected to this reaction, and we found that in all cases Michael addition proceeded only at aliphatic amines. This result clearly shows that the Lewis acidity of zirconium(IV) chloride is suitable only for active aliphatic amines. This selectivity could be useful to distinguish the two types of amines in synthetic applications.

In summary, we have developed a simple and efficient method for the synthesis of β-amino derivatives using inexpensive zirconium(IV) chloride as a mild catalyst.



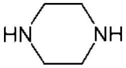
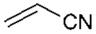
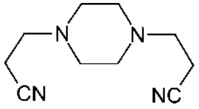
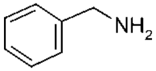
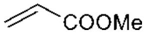
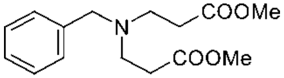
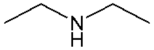
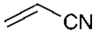
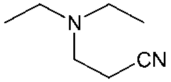
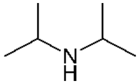
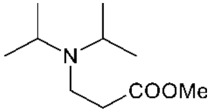
Scheme 1.

Table 1. Zirconium(IV) chloride–catalyzed Michael addition of aliphatic amines with α,β-ethylenic compounds

Entry	Amines	Unsaturated	Product[a]	Time (h)	Yield[b] (%)	Lit.[c]
1				1.0	Quant.	2a
2				2.5	92	—
3				0.75	Quant.	2b
4				2.0	86	—
5				1.5	78	—
6				2.0	94	—

(*continued*)

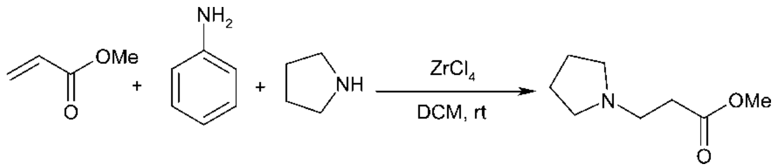
Table 1. Continued

Entry	Amines	Unsaturated	Product[a]	Time (h)	Yield[b] (%)	Lit.[c]
7				3.0	83	2a
8				2.0	79	—
9				3.0	80	2b
10	n-BuNH$_2$		n-BuN(CH$_2$CH$_2$COOMe)$_2$	2.5	82	—
11				0.75	84	2b

[a] All the products were characterized by ^{1}H NMR mass, and IR spectral data.

[b] Isolated yields.

[c] Physical and spectral data agree with those reported in the literature.



Scheme 2.

EXPERIMENTAL

Melting points were determined on Buchi R535 apparatus and are uncorrected. IR spectra were recorded on either a Perkin-Elmer spectrophotometer or the IR Nicole 740 FT-IR. ^{1}H NMR was recorded on a Gemini 200-MHz instrument using TMS as an internal standard. M/s were recorded on a Micromass 7070 h or a Finnigan Mat 1020 B mass spectrometer operating at 70 eV. Thin-layer chromatography was done on precoated silica-gel 60f 254 (0.5 mm) glass plates.

General Procedure

A mixture of morpholine (1 mmol), methyl acrylate (1.2 mmol), and zirconium(IV) chloride (10 mol%) in anhydrous dichloromethane (10 mL) was kept at ambient temperature under stirring for 1 h. It was quenched with water and the organic layer separated. The aqueous layer was extracted with dichloromthane. The combine organic layer was washed with water, dried over sodium sulphate, and concentrated to give the crude product, which was purified by silica-gel column chromatography using ethyl acetate–pet. ether (1 : 9).

SPECTRAL DATA FOR UNKNOWN COMPOUNDS

Ethyl 3-(4-phenylhexahydro-1-1pyrazinyl) propanoate (entry 2): ^{1}H NMR (200 MHz, CDCl$_3$) δ: 1.25 (t, $J = 7.2$ Hz, 3 H), 2.52 (t, $J = 7.5$ Hz, 2 H), 2.64 (t, $J = 4.9$ Hz, 4 H), 2.74 (t, $J = 7.5$ Hz, 2 H), 3.02 (t, $J = 4.9$ Hz, 4 H), 4.10 (q, $J = 7.2$ Hz, 2 H), 7.27–7.45 (m, 5 H); ^{13}C NMR: δ 13.8, 32.6, 49.4, 47.2, 53.4, 59.6, 116.4, 120.7, 127.1, 148.0, 171.2; mass (EI) m/z: 262 (M$^+$); anal. calcd for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.68; found: C, 68.80; H, 8.24; N, 10.47%.

3-[(tert-Butoxycarbonyl) amino] hexahydro-1-1pridinyl-ethyl cyanide (entry 4): ^{1}H NMR (200 MHz, CDCl$_3$) δ: 1.42 (s, 9 H), 2.22–2.70 (m, 12 H), 3.70(brs, 1 H), 4.95 (m, 1 H); ^{13}C NMR: (14.9, 20.2, 28.2, 29.4, 46.2, 53.0, 53.2, 60.1, 156.6; mass (EI) m/z: 253 (M$^+$); anal. calcd for $C_{13}H_{23}N_3O_2$: C, 61.63; H, 9.15; N, 16.59; found: C, 61.69; H, 9.33; N, 16.77%.

4-Hexahydro-1-pyridinyl-2-butanone (entry 5): ^{1}H NMR ($CDCl_3$, 200 MHz,) δ: 1.38–1.50 (m, 6 H), 2.25–2.36(m, 4 H), 2.52 (s, 3H), 2.61–2.86 (m, 4 H); ^{13}C NMR: δ 24.5, 26.2, 29.3, 39.8, 52.6, 55.4, 206.2; mass (EI) m/z: 155 (M^+); anal. calcd. for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.02; found: C, 69.52; H, 11.06; N, 9.04%.

Ethyl 3-tetrahydro-1H-1-pyrrolylpropanoate (entry 6): ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.22 (t, $J = 7.0$ Hz, 3 H), 1.62–1.83 (m, 4 H), 2.64–2.72 (m, 2 H), 2.79–2.90 (m, 4 H), 2.96–3.10 (m, 2 H), 4.08 (q, $J = 7.0$ Hz, 2 H); ^{13}C NMR: δ 14.2, 23.6, 32.7, 47.2, 52.4, 58.8, 169.2; mass (EI) m/z: 171 (M^+); anal. calcd. for $C_9H_{17}NO_2$: C, 63.13; H, 10.01; N, 8.18: Found: C, 63.26; H, 10.28; N, 8.24%.

Methyl 3-(2-methoxycarbonylethylanilino) propanoate (entry 8): ^{1}H NMR ($CDCl_3$, 200 MHz,) δ: 2.45 (t, $J = 6.8$ Hz, 4 H), 2.80 (t, $J = 6.8$ Hz, 4 H), 3.59 (s, 2 H), 3.62 (s, 6 H), 7.15–7.32 (m, 5 H); ^{13}C NMR: δ 32.6, 49.2, 51.4, 58.3, 63.6, 127.0, 128.2, 128.6, 172.8; mass (EI) m/z: 279 (M^+); anal. calcd. for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01: found: C, 64.25; H, 7.62; N, 5.11%.

Methyl 3-butyl (2-methyloxycarbonylethyl) aminopropanoate (entry 10): ^{1}H NMR ($CDCl_3$, 200 MHz,) δ: 0.88 (t, $J = 6.8$ Hz, 3 H), 1.23–1.45 (m, 4 H), 2.35–2.44 (m, 6 H), 2.75 (t, $J = 6.9$ Hz, 4 H), 3.65 (s, 6 H); ^{13}C NMR: δ 13.6, 20.1, 29.1, 32.3, 49.1, 53.3, 172.5; mass (EI) m/z: 245 (M^+); anal. calcd. for $C_{12}H_{23}NO_4$: C, 58.75; H, 9.45; N, 5.71; found: C, 58.60; H, 9.49; N, 5.75%.

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