Direct Addition of Glycine Derivatives to Enamines

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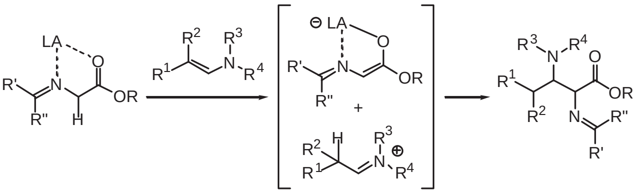
Direct addition of glycine derivatives to enamines proceeded smoothly in the presence of a catalytic amount of a Lewis acid to afford the corresponding α,β-diamino acid derivatives in excellent yields. In this reaction, enamines would initially act as a base and subsequently as a C=N electrophile. This is the first example of Mannich-type reactions using enamines as imine equivalents.

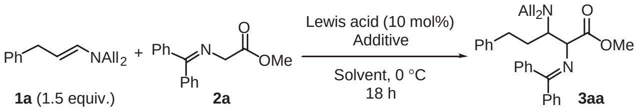
Enamines are useful and important intermediates in synthetic organic chemistry.[1] Because of their strong nucleophilic character, they have been widely used as enolate equivalents for α-alkylation and α-acylation of carbonyl compounds.[2] In these reactions, enamines are coupled with electrophiles to provide iminium ions, which are subsequently hydrolyzed to give α-alkylated or α-acylated carbonyl compounds. Although iminium ion intermediates are a reactive C=N double bond species and are expected to react with various nucleophiles smoothly,[3,4] those derived from enamines have been seldom used in this manner.[5] We thought that hydrogen-active compounds such as imines of glycine ester derivatives[6] might react with enamines in the presence of a Lewis acid to afford glycine enolates and iminium salts, which could couple together giving Mannich-type adducts (Scheme 1). Recently, some groups have reported Mannich-type reactions using glycine units and imines by combination of Lewis acids and tertiary amines[7] or under phase-transfer conditions.[8] Our new scheme using enamines is expected to realize a more direct process because external bases would not be needed. Herein, we report the first Lewis acid-catalyzed addition reaction of glycine derivatives to enamines leading to α,β-diamino acid derivatives.[9]

First, various Lewis acids (20 mol %) were tested in the reaction of enamine **1a** derived from 3-phenylpropanal and diallylamine with the benzophenone imine of glycine methyl ester (**2a**). Typical metal triflates such as $Sc(OTf)_3$, $Cu(OTf)_2$, CuOTf, AgOTf, $Zn(OTf)_2$, and $In(OTf)_3$ were found to catalyze the reaction smoothly under mild conditions (toluene, 0 °C) to afford the corresponding α,β-diamino ester derivative **3aa** as a mixture of two diastereomers in good yields (72–92%). We then investigated the reaction using 10 mol % of these effective Lewis acids, and the results are summarized in Table 1. In the cases of $In(OTf)_3$ and $Sc(OTf)_3$, yields were significantly lowered (Entries 1 and 2), while Ag(I), Cu(I), Cu(II), and Zn(II) triflates still afforded the desired adducts in good yields (>70%, Entries 3–6). After optimization of the reaction conditions, addition of molecular sieves 4A (MS 4A) was found to be effective in improving yields. When the reaction was carried out using 10 mol % of $Zn(OTf)_2$ in the presence of MS 4A, the desired product was obtained in excellent yield (96%, Entry 7). At this stage, the effect of solvents was investigated. The reaction also proceeded cleanly to afford good yields of the products when more polar solvents such as THF, CH_2Cl_2, CH_3CN, and DMF were used, although each reaction yield was slightly inferior to that in toluene (Entries 8–11). These results indicated that this reaction course was considerably tolerant to various types of solvents used.



Scheme 1. Lewis acid-catalyzed direct addition of glycine derivatives to enamines.

Table 1. Lewis acid-catalyzed addition of glycine derivative **2a** to enamine **1a**

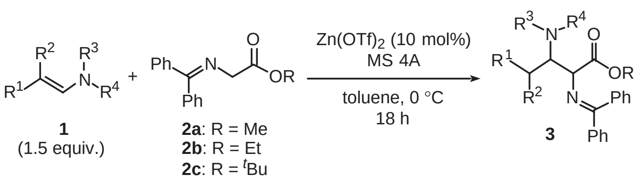


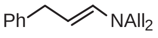
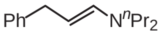
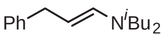
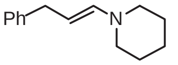
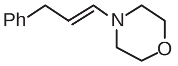
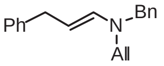
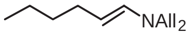
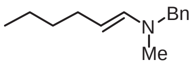
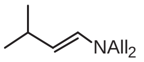
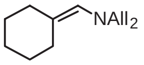
Entry	Lewis acid	Solvent	Additive	Yield[a,b]/%
1	$In(OTf)_3$	toluene	—	28
2	$Sc(OTf)_3$	toluene	—	36
3	AgOTf	toluene	—	70
4	$Cu(OTf)_2$	toluene	—	73
5	CuOTf	toluene	—	73
6	$Zn(OTf)_2$	toluene	—	75
7	$Zn(OTf)_2$	toluene	MS 4A	96
8	$Zn(OTf)_2$	THF	MS 4A	79
9	$Zn(OTf)_2$	CH_2Cl_2	MS 4A	85
10	$Zn(OTf)_2$	CH_3CN	MS 4A	81
11	$Zn(OTf)_2$	DMF	MS 4A	75

[a]Isolated yield. [b]Diastereomer ratio is 43/57–63/37 determined by ^1H NMR. Relative configuration assignment was not made.

Various substrates were next subjected to this reaction (Table 2). The diastereomeric ratio was moderate even in the case of using N-(diphenylmethylene)glycine ethyl or *tert*-butyl ester, which were expected to have a larger steric effect (Entries 1–3). Enamines derived from various secondary amines were also tested. It appeared that dialkyl moieties on enamine nitrogens had a significant effect on yields. While di-*n*-propyl enamine **1c** also gave a high yield (98%, Entry 5), it was revealed that yields were significantly decreased when the size of the dialkyl group was either larger or smaller than that of the di-*n*-propyl group; diethyl and diisobutyl enamines resulted in lower yields (Entries 4 and 6). A drastic effect on the yield was also observed when cyclic secondary amine-derived enamines were used. Piperidine-derived enamine **1e** was found to be a very good substrate affording the corresponding product quantitatively

Table 2. $Zn(OTf)_2$-catalyzed addition of glycine derivatives to various enamines



Entry	Enamine		Glycine deriv.	Yield^{a,b}/%
1		**1a**	**2a**	96
2			**2b**	96
3			**2c**	94
4		**1b**	**2a**	31
5		**1c**	**2a**	98
6		**1d**	**2a**	26
7		**1e**	**2a**	quant
8		**1f**	**2a**	nr
9		**1g**	**2a**	95
10		**1h**	**2a**	93
11		**1i**	**2a**	98
12		**1j**	**2a**	93
13^c		**1k**	**2a**	92

^{a}Isolated yield. nr = no reaction. ^{b}Diastereomer ratio is 51/49–69/31 determined by ^{1}H NMR. Relative configuration assignment was not made. ^{c}Reaction time was 36 h.

(Entry 7), whereas the reaction did not proceed at all when the enamine **1f** derived from morpholine was used (Entry 8). In the latter reaction, the basicity of morpholine might be insufficient for the deprotonation step. The reactions using asymmetrical secondary amine-derived enamines or other aldehyde-derived enamines were then performed. Allyl-benzyl enamine **1g**, diallyl enamine of hexanal **1h**, and benzyl-methyl enamine **1i** also reacted with **2a** to provide the corresponding α,β-diamino ester derivatives in excellent yields (Entries 9–11). Furthermore, it is noteworthy that the reaction of γ-branched enamine **1j** and β-branched enamine **1k** also proceeded smoothly to give the desired adducts in high yields (Entries 12 and 13).

A typical experimental procedure is described for the reaction of enamine **1a** with N-(diphenylmethylene)glycine methyl ester **2a**. To a suspension of $Zn(OTf)_2$ (0.04 mmol) and MS 4A (150 mg) in toluene (0.4 mL) were successively added **2a** (0.4 mmol) in toluene (0.8 mL) and **1a** (0.6 mmol) in toluene (0.8 mL) at 0 °C. The reaction mixture was stirred at the same temperature for 18 h, and quenched with saturated aqueous $NaHCO_3$. The mixture was filtered through a pad of celite and the aqueous layer was extracted with dichloromethane. The combined organic extracts were washed with brine and dried over Na_2SO_4. After filtration and concentration under reduced pressure, the crude product was purified by alumina column chromatography to give α,β-diamino ester derivative **3aa**.

In summary, we have developed direct addition of glycine derivatives to enamines, that is a new type of addition reaction. A Lewis acid was found to accelerate this reaction. This highly atom-economical process is based on both the basic and electrophilic characters of tertiary enamines. Moreover, the reaction can be performed with a simple operation under mild conditions to afford various α,β-diamino ester derivatives in excellent yields. It is noted that, in the overall process of this reaction, enamines act as C=N electrophiles, namely, aliphatic imine equivalents, whose reactions are generally known to be difficult to control. In addition, this is the first example of Mannich-type reactions using tertiary enamines as imine surrogates. Further investigation to improve diastereoselectivity and to develop a catalytic asymmetric process as well as to clarify the reaction mechanism is now in progress.

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