Tetrahedron Letters 54 (2013) 2669–2673

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Aza-Michael reaction promoted by aqueous sodium carbonate solution

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ARTICLE INFO

Article history:
Received 12 January 2013
Revised 25 February 2013
Accepted 8 March 2013
Available online 17 March 2013

Keywords:
Aza-Michael reaction
Aqueous sodium carbonate solution
β-Amino carbonyl compounds
Mono-alkylation

ABSTRACT

A general and efficient aza-Michael reaction promoted by aqueous sodium carbonate solution has been developed. The reaction has complete mono-alkylation selectivity and proceeds with complete chirality retention for chiral amino esters. With a broad substrate scope, a well-common catalyst and simple operation, the catalytic approach provides a facile, practicable, economical, and environmentally benign method for the synthesis of β-amino carbonyl compounds.

β-Amino carbonyl structural motifs are embedded in a wide range of natural products and biologically active compounds.[1] β-Amino carbonyl compounds also represent versatile building blocks for the synthesis of β-amino acid derivatives, amino alcohols, diamines, many of which serve as important antibiotics or other drugs.[2] Classical synthetic approach to β-amino carbonyl unit is the Mannich-type reaction.[3] Alternatively, aza-Michael reaction provides a promising method due to its simplicity and atom economy. Despite considerable efforts made for aza-Michael reaction in the past decades,[4–7] to date, the substrate scope is still limited as follows: (1) Because of weak nucleophilicity compared with aliphatic amines, anilines especially bearing electron-withdrawing substituent on the arene ring, such as 4-haloaniline, reacted with methyl acrylate to give low conversions (⩽20%).[4e,4m,8] In 2006, Rao reported an aza-Michael reaction promoted by β-cyclodextrin (1 equiv),[9] then Leadbeater and Varma separately presented microwave assisted aza-Michael additions.[10] Although the three methods were efficient for the conjugate addition of anilines onto methyl acrylate, they are obviously hard to apply into mass production. In 2008, Bhanage reported a $Y(NO_3)_3{\cdot}6H_2O$ (10 mol %) catalyzed aza-Michael addition of aromatic amines in the absence of solvents, but more hindered β-substituted Michael acceptors were not suitable for the protocol (only 2–5% yields).[11] (2) Amino acids, as the largest amine sources, were less involved in the intermolecular aza-Michael reaction as nucleophiles.[12] Herein, we disclose a general, efficient, and environmentally friendly aza-Michael reaction promoted by aqueous sodium carbonate solution. This reaction has complete mono-alkylation selectivity and a broad substrate scope, especially including poor nucleophilic anilines and amino ester. Moreover, the aza-Michael reactions of chiral amino esters as Michael donors are with complete chirality retention.

Initially, we investigated the aza-Michael reaction with aniline (**1a**) and ethyl acrylate (**2a**) as model substrates. Considering unique reactivity of organic compounds in aqueous suspension and Maryr's findings that anilines react two times faster in water than in acetonitrile for the reaction of anilines with benzhydrylium ion [$(dma)_2CH^+$], as well as the 'on water' effect in rate acceleration which has been evidently observed by Sharpless et al.,[13] we chose water as solvent. The reaction was found to proceed in low conversion (<10%) in neat water at room temperature for 3 days (Table 1, entry 1). When alkali hydroxides (0.1 equiv) as catalysts were introduced, the conversion rose slightly (10–30% yields, Table 1, entries 2–4). To our delight, sodium carbonate could markedly promote the aza-Michael reaction of aniline and ethyl acrylate and the yield improved to 65%, while sodium bicarbonate was not effective (Table 1, entries 5–6). According to the solvent screening experiments, water did play an important role in the aza-Michael reaction (Table 1, entry 7). In order to enhance the rate of the reaction, we increased the reaction temperature to 50 °C. The yield improved remarkably to 90%, furthermore, no double alkylation product was observed (Table 1, entry 8). Nevertheless, higher temperature led to a significant drop in the yield due to the decomposition of product (Table 1, entries 9–10).

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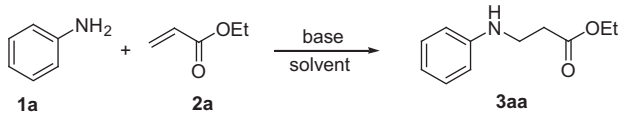
http://dx.doi.org/10.1016/j.tetlet.2013.03.043

Table 1
Optimization of reaction conditions[a]



1a 2a 3aa

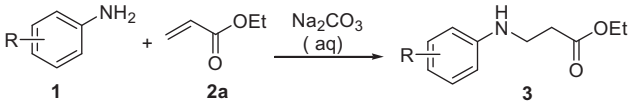
Entry	Base	Solvent	Temp (°C)	Yield[b] (%)
1	—	H_2O	rt	<10
2	LiOH	H_2O	rt	10
3	NaOH	H_2O	rt	30
4	KOH	H_2O	rt	25
5	Na_2CO_3	H_2O	rt	65[c]
6	$NaHCO_3$	H_2O	rt	20
7[d]	Na_2CO_3	Solvents	rt	⩽10
8	Na_2CO_3	H_2O	50	90
9	Na_2CO_3	H_2O	80	82
10	Na_2CO_3	H_2O	100	80

[a] Reaction conditions: aniline (1.0 mmol), ethyl acylate (1.2 mmol), and base (0.1 mmol) in solvent (1 mL) at rt for 72 h.
[b] Isolated yield.
[c] The conversion was 72%.
[d] Solvents: CH_2Cl_2, CH_3CN, EtOAc, acetone, DMSO, toluene, Et_2O, THF.

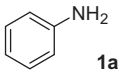
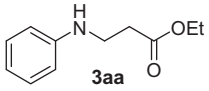
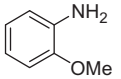
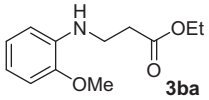
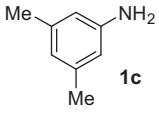
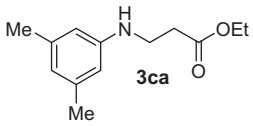
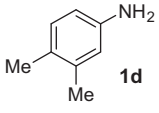
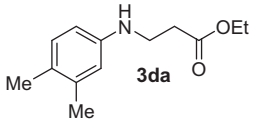
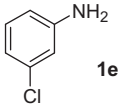
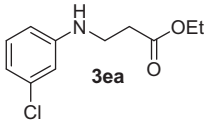
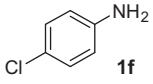
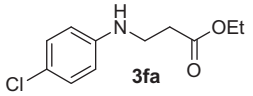
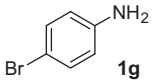
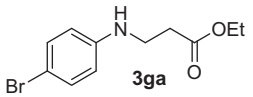
With the optimal reaction conditions in hand, we moved on to explore the scope of the aza-Michael reaction promoted by aqueous sodium carbonate solution. Firstly, a variety of substituted anilines were examined, and the results were summarized in Table 2. Electron-rich anilines underwent conjugate addition to ethyl acrylate giving the desired products in good yields (Table 2, entries 2–4). For the more challenging electron-poor anilines, such as 4-chloroaniline and 4-bromoaniline, in previous work, they gave poor conversion (20%) and low yield (10%), respectively.[8] Pleasingly, they provided useful yields in this catalytic reaction system, albeit the reactions required more reagents and higher reaction temperature (Table 2, entries 5–7).

Then we turned our attention to aza-Michael reaction of various amines with phenyl vinyl ketone under the catalytic reaction system. The aza-Michael addition was found to be general with a wide range of amines, and the reaction was fast at room temperature without diaddition products being observed. Both electron-withdrawing and electron-donating groups on the aromatic ring of anilines were tolerated, yielding the desired products in excellent yields (85–98%, Table 3, entries 1–9). 1-Naphthalenamine, aliphatic primary and secondary amine were suitable substrates for this process (Table 3, entries 10–12). Particularly remarkable was the participation of chiral amino esters in the aza-Michael reaction.

Table 2
Aza-Michael reaction of amines with ethyl acylate[a]

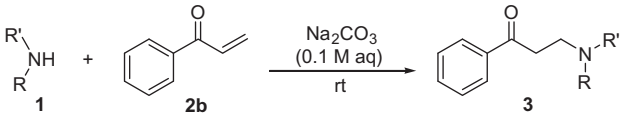


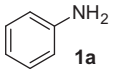
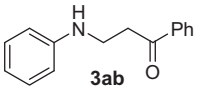
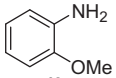
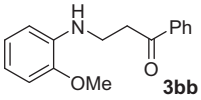
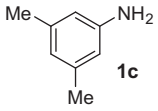
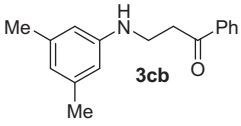
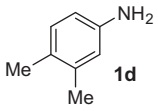
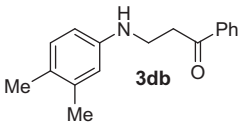
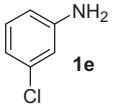
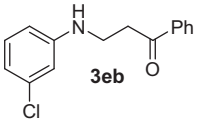
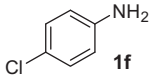
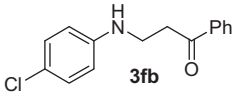
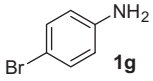
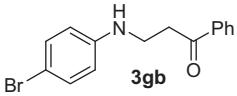
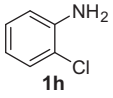
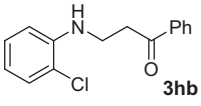
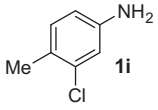
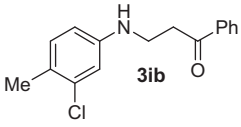
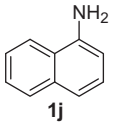
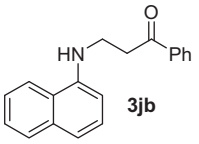
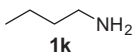
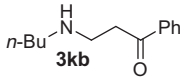
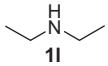
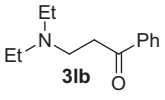
1 2a 3

Entry	Amine	Time (h)	Product	Yield[b] (%)
1	 1a	72	 3aa	90
2	 1b	72	 3ba	82
3	 1c	72	 3ca	85
4	 1d	72	 3da	80
5[c]	 1e	72	 3ea	75 (93)[d]
6[c]	 1f	72	 3fa	62 (95)[d]
7[c]	 1g	72	 3ga	65 (92)[d]

[a] Reaction conditions: ethyl acylate (1.2 mmol), amine (1 mmol), and Na_2CO_3 (0.1 M aq, 1 mL) at 50 °C.
[b] Isolated yield.
[c] Ethyl acylate (3 mmol), amine (1 mmol), and Na_2CO_3 (0.2 M aq, 1 mL) at 80 °C.
[d] Yield in parentheses based on recovered starting material.

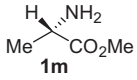
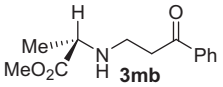
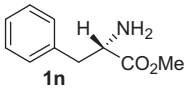
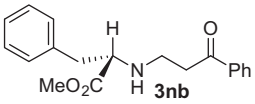
Table 3
Aza-Michael reaction of amines with phenyl vinyl ketone[a]



Entry	Amine	Time (h)	Product	Yield[b] (%)
1	 **1a**	0.5	 **3ab**	98
2	 **1b**	0.5	 **3bb**	94
3	 **1c**	0.5	 **3cb**	92
4	 **1d**	0.5	 **3db**	94
5	 **1e**	1	 **3eb**	92
6	 **1f**	1	 **3fb**	94
7	 **1g**	1	 **3gb**	85
8	 **1h**	1	 **3hb**	90
9	 **1i**	1	 **3ib**	90
10	 **1j**	2	 **3jb**	86
11	 **1k**	2	 **3kb**	78
12	 **1l**	3	 **3lb**	85

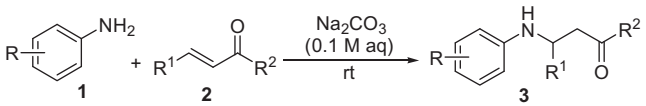
(*continued on next page*)

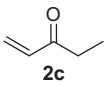
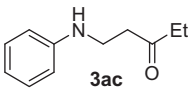
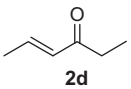
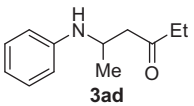
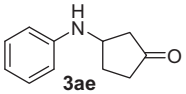
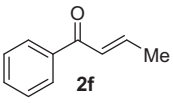
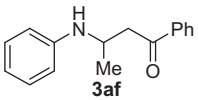
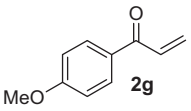
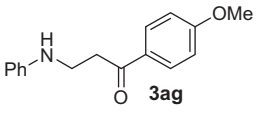
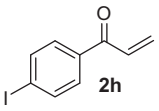
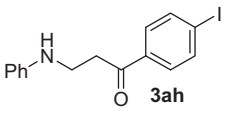
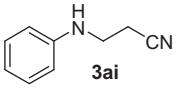
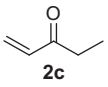
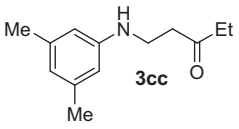
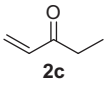
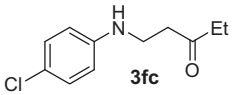
Table 3 (*continued*)

Entry	Amine	Time (h)	Product	Yield[b] (%)
13	 **1m**	2	 **3mb**	83 (>99% ee)
14	 **1n**	3	 **3nb**	87 (>99% ee)

[a] Reaction conditions: phenyl vinyl ketone (1 mmol), amine (1.2 mmol), and Na_2CO_3 (0.1 M aq, 1 mL) at rt.
[b] Isolated yield.

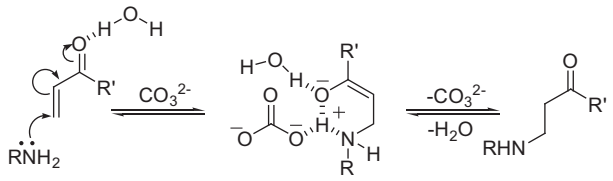
Table 4
Aza-Michael reaction of anilines with enone[a]



Entry	Acceptor	Time (h)	Product	Yield[b] (%)
1	 **2c**	2	 **3ac**	94
2	 **2d**	4	 **3ad**	86
3	 **2e**	6	 **3ae**	88
4	 **2f**	4	 **3af**	80
5	 **2g**	3	 **3ag**	87
6	 **2h**	3	 **3ah**	86
7	 **2i**	20	 **3ai**	72
8	 **2c**	2	 **3cc**	91[c]
9	 **2c**	3	 **3fc**	93[d]

[a] Reaction conditions: amine (1 mmol), Michael acceptors (1.2 mmol), and Na_2CO_3 (0.1 M aq, 1 mL) at rt.
[b] Isolated yield.
[c] Reacted with **1c**.
[d] Reacted with **1f**.

To our knowledge, amino esters were scarcely involved in the intermolecular aza-Michael reaction as nucleophiles, though they, as masked amino acids, are the largest amine sources. Under the standard reaction conditions, L-alanine and L-phenylalanine under-



Scheme 1. Plausible mechanism for the aza-Michael addition.

went successful reactions with 2b to provide the corresponding products in 83% and 87% yields, respectively, with the chirality of amino ester moiety intact (both products ee >99%, see Supplementary data) (Table 3, entries 13 and 14).

Finally, we studied the effect of electronic and structural variations to the enone by using aniline as Michael donor (Table 4). Gratifyingly, enones with various electronic properties and structural formations (cyclic or linear, terminal or internal) could proceed efficiently to produce the corresponding aza-Michael addition products at room temperature in good to excellent yields (80–94%) (Table 4, entries 1–6). Acrylonitrile also participated in the conjugate addition (Table 4, entry 7). Anilines substituted by electron-withdrawing group or electron-donating group reacted smoothly with EVK (**2c**) to give the corresponding addition products in 91% and 93% yields, respectively (Table 4, entries 8 and 9).

Our current understanding of the catalytic aza-Michael reaction is illustrated in Scheme 1. Initially, the amine adds to the Michael acceptor and carbonate ion in the transformation acts as a proton shuttle, using hydrogen bonding to facilitate transfer of the proton from nitrogen to oxygen.[5b] Water plays an important role here by pre-associating with the carbonyl group, and consequently accelerates the addition step.

In summary, we have developed an effective aza-Michael reaction promoted by aqueous sodium carbonate solution. The reaction shows complete mono-alkylation selectivity and complete chirality retention for chiral amino esters. With a broad substrate scope, a well-common catalyst and simple operation, the catalytic approach provides a facile, practicable, economical, and environmentally benign method for the synthesis of β-amino carbonyl compounds which are ubiquitous in nature. The method should have many applications in organic and medical chemistry. Detailed mechanistic investigations and applications to the synthesis of biologically active molecular complexes are currently underway.

Acknowledgments

This research was supported by the National Natural Science Foundation of China (NSFC-20872183, 20972126, 21272185), the Program for New Century Excellent Talents in University of the Ministry of Education China (NCET-10-0937), and the Education Department of Shaanxi Provincial Government (09JK776).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.03.043.

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