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Aza-Michael reaction promoted by aqueous sodium carbonate solution

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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 ($\leqslant$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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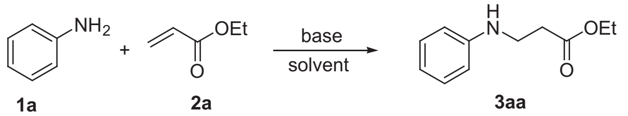
Table 1
Optimization of reaction conditions[a]



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.

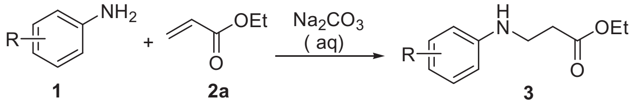
[c] The conversion was 72%.

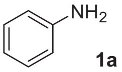
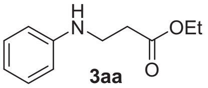
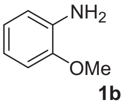
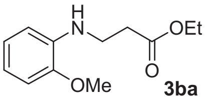
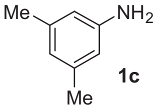
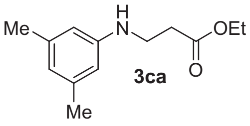
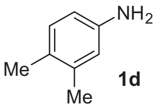
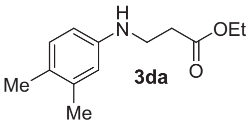
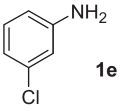
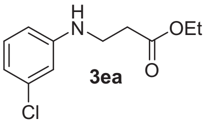
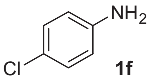
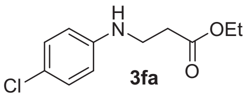
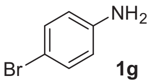
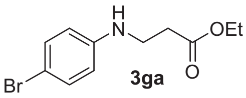
[d] Solvents: CH_2Cl_2, CH_3CN, EtOAc, acetone, DMSO, toluene, Et_2O, THF.

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]



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.