

Tandem bis-aza-Michael addition reaction of amines in aqueous medium promoted by polystyrenesulfonic acid

Vivek Polshettiwar and Rajender S. Varma*

Sustainable Technology Division, National Risk Management Research Laboratory,
US Environmental Protection Agency, 26 W. Martin Luther King Dr., MS 443, Cincinnati, OH 45268, USA

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Abstract—An efficient and environmentally benign tandem bis-aza-Michael addition of amines catalyzed by polystyrenesulfonic acid (PSSA) is described. This operationally simple high yielding microwave assisted synthetic protocol proceeded in water in the absence of any organic solvent.

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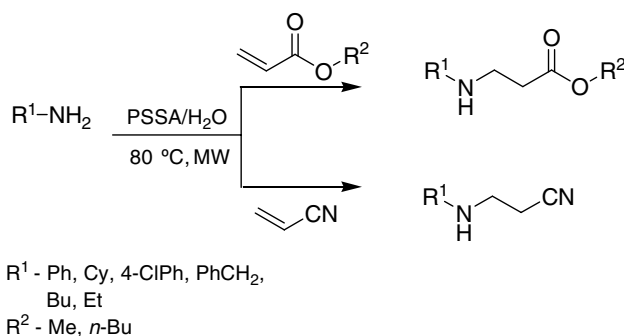
1. Introduction

The development of new methodologies aimed at improving synthetic efficiency is an important goal in contemporary organic synthesis. A domino process, which involves several bond-forming reactions in a single manipulation, represents an attractive strategy in the facile assembly of molecular architecture. These operationally simple processes are atom economic, and minimize the generation of chemical waste and the use of energy.¹ In this context, aza-Michael addition is an important class of carbon–nitrogen bond-forming reactions, and has been intensively explored and demonstrated to be a powerful tool in organic synthesis. Several methods have been developed for Michael addition using a variety of reagents such as various Lewis acids, Cu(acac)₂/ionic liquid, and boric acid.² While most of the aza-Michael additions are performed in organic solvents, increasingly the focus is shifting to reactions in aqueous medium wherein β-cyclodextrin,³ ytterbium triflate,⁴ 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU),⁵ pyrrolidine–thiourea,⁶ and surfactant-type asymmetric organocatalyst (STAO) type catalyst⁷ have been used. Although today's environmental concerns encourage the development of such greener synthetic methodology in an aqueous medium,⁸ many of these methods suffer from limitations such as the use of expen-

sive and toxic catalyst, and harsh reaction conditions. Recently, Ranu and Banerjee have developed an aqueous protocol for the aza-Michael reaction without using any catalyst.⁹ However, the protocol was restricted to only aliphatic amines as aromatic amines do not undergo reaction under those conditions.

2. Results and discussion

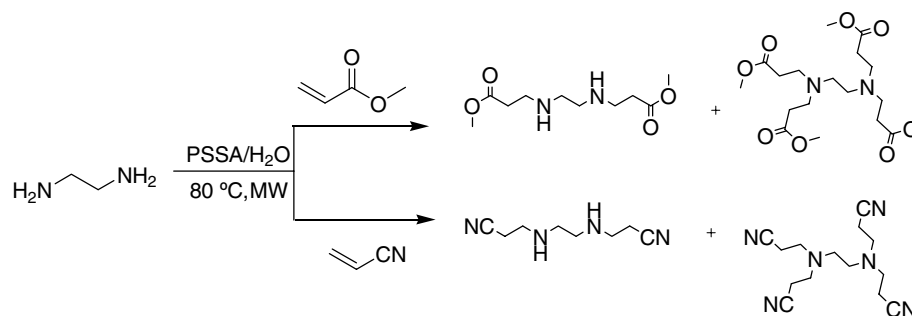
In view of the emerging application of microwave (MW) chemistry in aqueous reaction medium,¹⁰ and in keeping with our ongoing program on the development of cleaner pathways,¹¹ we tried to develop greener conditions for these reactions. Our recent success in the application of polystyrenesulfonic acid (PSSA) for various synthetic protocols in aqueous medium using microwaves^{11a–c} prompted us to explore the aza-Michael (Scheme 1)



Scheme 1. PSSA-catalyzed aza-Michael addition reaction of amines.

Keywords: Aza-Michael reaction; Polystyrenesulfonic acid (PSSA); Aqueous medium; Microwave irradiation.

* Corresponding author. Tel.: +1 513 487 2701; fax: +1 513 569 7677; e-mail: varma.rajender@epa.gov



Scheme 2. PSSA-catalyzed tandem bis-aza-Michael addition reaction of alkyl diamines.

Table 1. PSSA-catalyzed aqueous aza-Michael addition of amines with alkyl acrylate using microwaves

Entry	R ¹	R ²	Product	Yield ^a (%)
1	Ph	Me		95
2	Ph	Bu		92
3	Cy	Me		93
4	Cy	Bu		92
5	4-ClPh	Me		92
6	4-ClPh	Bu		92
7	PhCH ₂	Me		88
8	PhCH ₂	Bu		89
9	Bu	Me		90
10	Bu	Bu		90
11	Et	Me		92
12	Et	Bu		90

^a GC yields.

and tandem bis-aza-Michael (Scheme 2) addition reactions of amines with alkyl acrylate and acrylonitrile.

During initial exploratory reactions, aqueous aza-Michael addition of aniline with methyl acrylate under MW irradiation condition was studied. We found that PSSA was the most efficient catalyst for this protocol in water at 80 °C. Using these optimized reaction conditions, the scope and efficiency of this aqueous approach were explored for a wide variety of amines with Michael acceptors, methyl- and butyl acrylate (Table 1), and with acrylonitrile (Table 2).

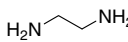
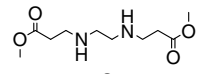
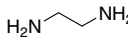
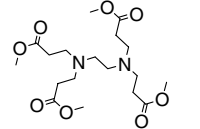
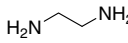
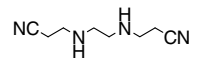
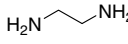
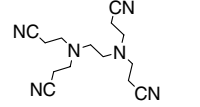
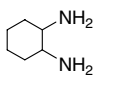
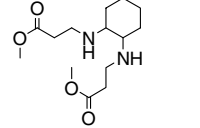
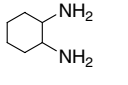
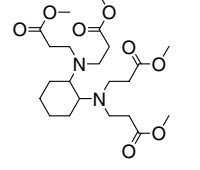
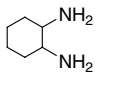
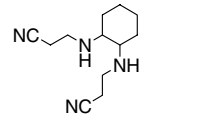
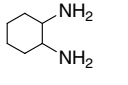
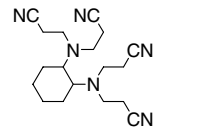
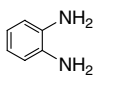
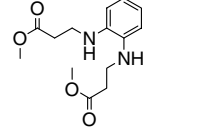
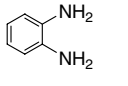
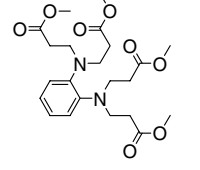
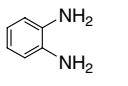
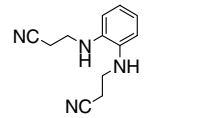
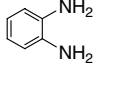
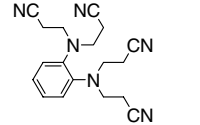
Aromatic amines bearing various functional groups gave excellent results in terms of yield and purity. These reactions also get completed under conventional heating conditions in an oil bath at 100 °C with comparable yields but requires extended periods of time, 2–3 h. In order to study the versatility of this protocol, few examples of aliphatic amines were also examined using similar reaction conditions as applied to aromatic amines and excellent yields of Michael products were obtained.

Table 2. PSSA-catalyzed aqueous aza-Michael addition of amines with acrylonitrile using microwaves

Entry	R ¹	Product	Yield ^a (%)
1	Ph		90
2	Cy		88
3	4-ClPh		90
4	PhCH ₂		85
5	Bu		88
6	Et		86

^a GC yields.

Table 3. PSSA-catalyzed aqueous tandem bis-aza-Michael addition of alkyl diamine with methyl acrylate (**A**) and acrylonitrile (**B**) using microwaves

Entry	Diamine	Moles of		Product	Yield (%)
		(A)	(B)		
1		2	—		95
2		4	—		90
3		—	2		92
4		—	4		89
5		2	—		94
6		4	—		90
7		—	2		92
8		—	4		90
9		2	—		96
10		4	—		90
11		—	2		93
12		—	4		90

It is noteworthy to mention that these reactions are working well in an aqueous medium without using any phase-transfer catalyst (PTC). This may be due to selective absorption of microwaves by diamines, alkyl acrylates, and a polar aqueous medium,¹² which accelerate the reaction even in the absence of PTC. Also, we observed that the catalyst PSSA can be reused without any change in the reactivity (not shown).

Substituted diamines are an important class of compounds extensively used for preparation of hybrid materials¹³ and functional nano-structured materials.¹⁴ To further explore the feasibility of this catalytic system, we studied the tandem bis-aza-Michael addition reaction of alkyl diamine with methyl acrylate (**A**) and acrylonitrile (**B**) (Scheme 2) and the results are summarised in Table 3.

A variety of bis-aza-Michael addition products of diamine were obtained readily depending upon the relative mole ratio of the reactants. One mole equivalent of diamine with two mole equivalents of Michael acceptor afforded disubstituted diamines (entries 1, 3, 5, 7, 9 and 11), without any tri or tetrasubstituted products, whereas using four equivalents of Michael acceptor gave exclusively the tetrasubstituted diamine product (entries 2, 4, 6, 8, 10 and 12).

In conclusion, we have demonstrated a sustainable and operationally simple aza-Michael MW-assisted protocol using PSSA, which proceeds efficiently in an aqueous medium without the use of an organic solvent. Also the use of polymer supported, relatively low toxic, and inexpensive PSSA as a catalyst renders this method greener and eco-friendly.

3. Experimental

All starting materials were used as obtained. TLC (silica gel; 20% EtOAc/hexane) and GC were used to monitor the reactions. The crude products were identified by GC–MS qualitative analysis using a GC system with a mass selective detector. The identities were further confirmed by ¹H and ¹³C NMR spectra that were recorded in chloroform-*d* (CDCl₃) with TMS as internal reference using a 300 MHz NMR spectrometer.

Typical experimental procedure using MW heating: The amines (1 mmol) and alkyl acrylate, or acrylonitrile (1.2 mmol) were placed in a 10 mL crimp-sealed thick-walled glass tube equipped with a pressure sensor and a magnetic stirrer. The contents were dissolved in 20% PSSA solution in water (one time the weight of amines) and the reaction tube was placed inside the cavity of a CEM Discover focused microwave synthesis system, 80 ± 5 °C (temperature monitored by a built-in infrared sensor), power range 40–140 W and pressure 40–70 psi for 10–15 min. After completion of the reaction, products were extracted with ethyl acetate and washed with sodium bicarbonate solution. After concentration in vacuum, the crude product was subjected to flash column chromatography for further purification.

For bis-aza-Michael reaction of diamines, a similar procedure was followed with the following mole ratios: for disubstituted diamine, diamine (1 mmol), alkyl acrylate or acrylonitrile (2 mmol), 10–15 min reaction time; for tetrasubstituted diamine, diamine (1 mmol), alkyl acrylate or acrylonitrile (4 mmol), 30 min reaction time.

Typical experimental procedure under conventional heating: The amines (1 mmol) and alkyl acrylate or acrylonitrile (1.2 mmol) were placed in a 10 mL glass tube, followed by addition of catalyst PSSA (20%) (one time the weight of amines). The capped tube was then heated at 100 °C for 2–3 h. After completion of the reaction, products were extracted with ethyl acetate and washed with sodium bicarbonate solution. After concentration in vacuum, the crude product was subjected to flash column chromatography for further purification.

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