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β-Cyclodextrin promoted aza-Michael addition of amines to conjugated alkenes in water☆

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Abstract—Highly efficient and environmentally benign aza-Michael additions of amines to α,β-unsaturated compounds catalyzed by β-cyclodextrin in water to produce the corresponding β-amino compounds in excellent yields under mild conditions are described. β-Cyclodextrin can be recovered and reused in subsequent reactions without loss of activity.

1. Introduction

The aza-Michael reaction is an important reaction in organic chemistry especially for the synthesis of heterocycles containing a β-amino carbonyl unit.[1] β-Amino carbonyl compounds are versatile synthetic intermediates for the synthesis of a variety of biologically important natural products, antibiotics, β-amino alcohols, chiral auxiliaries, and other nitrogen-containing compounds.[2] These compounds also find wide applications in fine chemicals and pharmaceuticals.[3] This has led to the development of novel synthetic methodologies for β-amino carbonyl compounds. The Mannich reaction is one of the classical methods for the construction of this functionality,[4] however, this reaction can suffer from drawbacks such as long reaction times, low yields, and harsh conditions which limit its use in the synthesis of complex molecules.[5]

An alternative approach for the synthesis of β-amino carbonyl compounds is the widely used conjugate addition of amines to α,β-unsaturated compounds (aza-Michael reaction) due to its simplicity and atom economy. The conjugate addition of amines to electron-deficient alkenes is usually promoted by either acidic or basic catalysts.[6] A variety of reagents such as $SnCl_4$, $TiCl_4$, $InCl_3$, $CeCl_3{\cdot}7H_2O$, $Yb(OTf)_2$, phosphine/TMSCl, $Cu(OTf)_2$, $Bi(NO)_3$, $Bi(OTf)_2$, $LiClO_4$, KF/alumina, etc. have been reported as promoters for this reaction.[7] Heterogeneous solid acids have also been utilized to promote the reaction.[8] Recently, there was also a report of this reaction conducted in ionic liquids,[9] $Cu(acac)_2$/ionic liquid,[10] ionic liquid/quaternary ammonium salt in water,[11] and boric acid in water.[12] These reactions were unsuccessful in water alone, without using acid or base catalyst.[13,6a,11] Furthermore, acid or base induced conjugate addition frequently suffers from polymerization of the starting olefin. However, despite their remarkable success, the use of heavy metal salts coupled with hazardous solvents is not desirable from the 'green chemistry' point of view. Ranu[14] and Basu[15] disclosed solvent-free and catalyst-free conjugate additions, but even these reactions have the drawback of elevated temperatures. Most of these procedures are not successful with arylamines. Thus, the aza-Michael addition of arylamines needs a more generalized and environmentally friendly approach.

With 'green chemistry' becoming an important issue in the 21st century,[16] developing the aza-Michael addition in water with a recyclable catalyst and without the use of any harmful organic solvents is desirable. Water is a safe, economical and environmentally benign solvent.[17] To achieve this we chose to study supramolecular catalysis involving cyclodextrins. However, there is a report of aza-Michael addition using water-soluble N-donor ligands with sodium vinylsulfonates in water.[18a] Michael additions of nitroalkanes to methyl vinyl ketone are also known in the presence of sugars.[18b]

Keywords: Aza-Michael addition; β-Amino carbonyl compounds; Amines; Conjugated alkenes; β-Cyclodextrin; Water.
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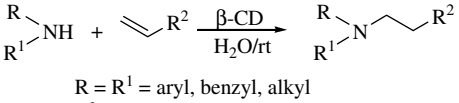
Cyclodextrins (CDs) are cyclic oligosaccharides possessing hydrophobic cavities, which bind substrates selectively and catalyze chemical reactions with high selectivity by involving reversible formation of host–guest complexes with noncovalent bonding as seen in enzymes. Complexation depends on the size, shape, and hydrophobicity of the guest molecule. Thus, by mimicking biochemical selectivity, which is due to orientation of the substrate by complex formation thus positioning the substrate for favorable attack, could be superior to random attack based on the intrinsic reactivity of the substrate. Our earlier expertise in the field of biomimetic modeling of organic chemical reactions involving cyclodextrins[19] prompted us to attempt the aza-Michael addition of various amines to conjugated alkenes under biomimetic conditions using cyclodextrins with water as a solvent at room temperature (Scheme 1).

The reaction was carried out by the in situ formation of the β-CD complex of the amine in water followed by the addition of olefin and stirring for 12 h at room temperature to give the corresponding β-amino carbonyl compounds in impressive yields (Table 1). This is the first practically feasible aza-Michael addition reaction of amines with a variety of conjugated alkenes in water. All the products were characterized by ^{1}H NMR, IR, and mass spectrometry. The reaction proceeded efficiently at room temperature without the need of any acid or base catalyst. This methodology is compatible with various α,β-unsaturated ketones, esters, and nitriles and different aliphatic primary and secondary amines, fluoro-, chloro-, methyl-, and methoxy-, aromatic amines, and benzyl amines. In the case of conventional aza-Michael addition, for example, in a report by Xia et al.[11] the yields with primary amines were in the ratio 60:36 corresponding to the product monomer and dimer, thereby reducing the selectivity, whereas in our case only the monomer is formed with high selectivity. In the case of aliphatic amines only 0.1 mmol of β-CD was used. These reactions do take place with α-CD, however, β-CD was chosen as the catalyst since it is inexpensive and easily accessible.

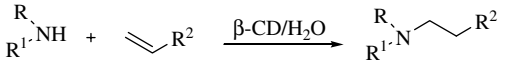
The catalytic activity of cyclodextrins for these aza-Michael additions was established by the fact that no reaction was observed in the absence of cyclodextrin. We suggest that the mechanism of addition of amines as β-cyclodextrin complexes to conjugated alkenes is as follows. Hydrogen bonding of amines with the CD hydroxyl makes the N–H bond weaker enhancing the nucleophilicity of nitrogen for addition to electron-deficient alkenes.

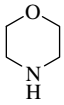
These CD-mediated aqueous reactions are very useful from both economical and environmental points of view. β-Cyclodextrin, apart from being nontoxic, is also considered as metabolically safe.[20] We have demonstrated the successful use of β-cyclodextrin in water as a solvent for the aza-Michael addition of amines to electron-deficient olefins to produce β-amino compounds in good yields. The experimental conditions are simple with ease of recovery and reuse of the catalyst. This method precludes the use of acid or base catalysts.



Scheme 1.

Table 1. Aza-Michael addition of amines to conjugated alkenes in the presence β-CD in water



Entry	Amine	R^2	Time (h)	Yield[a,b] (%)
1	$C_6H_5NH_2$	COMe	6	90[c]
2	$C_6H_5NH_2$	CN	8	88
3	$C_6H_5NH_2$	CO_2Me	8	88
4	*p*-$FC_6H_4NH_2$	COMe	6	92
5	*p*-$FC_6H_4NH_2$	CN	6	90
6	*p*-F-$C_6H_4NH_2$	CO_2Me	6	88
7	*o*-$ClC_6H_4NH_2$	CN	8	85
8	*o*-$MeC_6H_4NH_2$	CN	8	86
9	*p*-$MeC_6H_4NH_2$	CN	8	88
10	*p*-$MeC_6H_4NH_2$	CO_2Me	8	86
11	*o*-$MeOC_6H_4NH_2$	CO_2Me	8	85
12	$C_6H_5CH_2NH_2$	CN	8	82
13	$C_6H_5CH_2NH_2$	CO_2Me	8	80
14		CN	6	85
15	$C_6H_5NHCH_3$	COMe	8	84
16	*n*-Bu_2NH	CN	6	82
17		CN	6	86
18		CN	6	84

[a] All the products were characterized by ^{1}H NMR, IR, and mass spectrometry.
[b] Isolated yields.
[c] Catalyst was recovered and reused for three consecutive runs in this reaction without change in the yield and purity.

2. General procedure for the aza-Michael addition

β-CD (1 mmol) was dissolved in water (15 ml) by warming up to 60 °C until a clear solution was formed, then the amine (1 mmol) dissolved in acetone (1 ml) was added dropwise and the mixture allowed to cool to room temperature. The alkene (1.5 mmol) was then added and the mixture stirred at room temperature until the reaction was complete (Table 1). The organic material was extracted with ethyl acetate. The organic phase was separated, filtered, and washed with brine. β-CD was recovered by filtration and reused. The organic phase was then dried (Na_2SO_4), filtered, and the solvent was removed under vacuum. The crude product was purified by passing through a column of silica gel using ethyl acetate–*n*-hexane (2:8) as the eluent.

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