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Novel and efficient aqueous phase synthesis of N-substituted azepines via tandem Michael addition and cyclization in the presence of β-cyclodextrin

K. Ramesh, S. Narayana Murthy, Y. V. D. Nageswar *

Organic Chemistry Division-I, Indian Institute of Chemical Technology, Hyderabad 500607, India

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ABSTRACT

N-substituted azepines were synthesized for the first time in water under neutral conditions by the reaction of aromatic amines, dimethyl/diethyl acetylene dicarboxylate, 2,5-dimethoxytetrahydrofuran mediated by β-cyclodextrin in high yields. β-Cyclodextrin can be recovered and reused with just a small loss of catalytic activity.

Azepine and its analogues exhibit varied biological activities, such as antihistaminic, spasmolytic, serotonin antagonistic, anticonvulsive, antiemetic, anti-inflammatory, and fungicidal activities.[1] These derivatives are also used in antimalarial drug therapy,[2a–c] anti-HIV,[2d] stomach disorders,[3] antiarrhythmic,[4] hypertension (glaucoma),[5] and other pharmaceutical applications.[6] There are numerous drugs, such as Imipramine (**1**), Carbamazepine (**2**), Oxcarbazepine (**3**), containing the azepine skeleton as shown in Figure 1.

A number of synthetic routes have been developed for azepines, because of their interesting biological activities. In general these can be synthesized by the insertion of nitrenes derived by the thermolysis of azides, cyclization of diene conjugated nitrile ylides prepared by the base catalyzed dehalogenation of the corresponding imidoyl chlorides, and [4+2] cycloaddition reactions.[7] Intramolecular aza-Wittig reaction has been one of the convenient methods for the synthesis of azepines. Tietze and Schimpf reported an interesting synthetic protocol for azepines by the intramolecular Heck reaction.[8] Toste and co-worker, developed Au(III)-catalyzed synthesis of *N*-arylazepines via inter molecular annulation between propargyl ester and *N*-phenylimine.[9] Wender et al. reported the preparation of N-substituted azepines by transition metal-catalyzed aza [5+2] cycloaddition strategy, involving various imines.[10] However, the existing methods have a number of drawbacks, such as the use of transition metal catalysts, anhydrous organic solvents, low yields, and moisture sensitive reagents. Thus, in view of these shortcomings, there is a need to develop a mild and eco-friendly synthetic protocol for the synthesis of substituted azepines by replacing flammable toxic or carcinogenic organic solvents with water using a recyclable activator/catalyst in the context of green chemical methodologies.

Presently organic reactions in aqueous phase have attracted the attention of researchers because of the added advantages of water as an environmentally benign and economically affordable solvent. However, the fundamental problem in performing the reactions in water is that many organic substrates are hydrophobic and insoluble in water. Cyclodextrins, possessing hydrophobic cavities, are well known supramolecular catalysts, which by reversible formation of host–guest complexes, activate the organic molecules and catalyze the reactions. As part of our ongoing program toward the development of greener chemical approaches for the synthesis of novel reaction intermediates and heterocyclic moieties,[11] herein

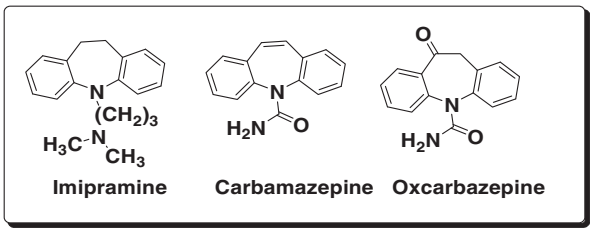

Figure 1. Some marketed drugs with azepine skeleton.

* Corresponding author. Tel.: +91 40 27191654; fax: +91 40 27160512.
E-mail address: dryvdnageswar@gmail.com (Y.V.D. Nageswar).

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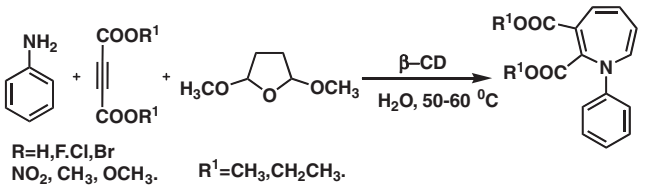


Scheme 1. Synthesis of N-substituted azepines.

Table 1
Optimization of reaction conditions using different catalysts[a]

Entry	Catalyst	Yield[b] (%)
1	γ-Cyclodextrin	78
2	α-Cyclodextrin	38
3	β-Cyclodextrin	92
4	(2-Hydroxy propyl)-β-cyclodextrin	42
5	Methyl-β-cyclodextrin	40
6	Water	36

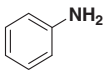
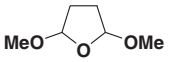
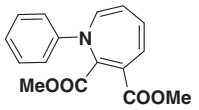
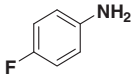
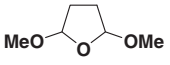
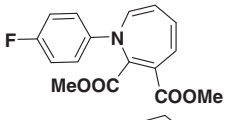
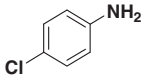
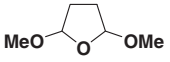
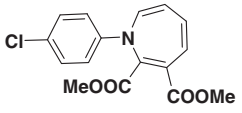
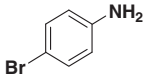
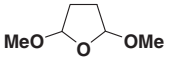
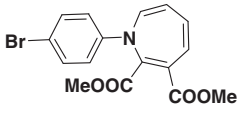
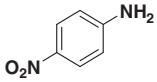
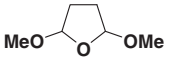
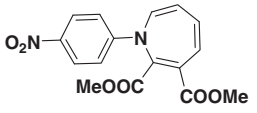
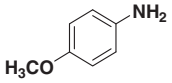
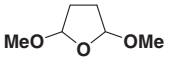
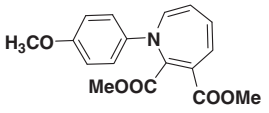
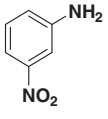
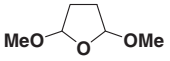
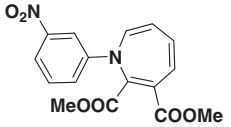
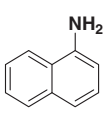
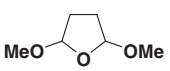
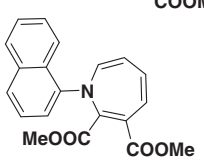
[a] All reactions were carried out using aniline (1.0 mmol), DMAD (1.0 mmol), and 2,5-dimethoxytetrahydrofuran (1.0 mmol), β-CD (1.0 mmol).
[b] Yield obtained after column chromatography.

we report the synthesis of N-substituted azepines by the reaction of aromatic amines, DMAD/DEAD with 2,5-dimethoxytetrahydrofuran, using β-cyclodextrin[12] as a reusable catalyst under supramolecular catalysis, for the first time in water.

In this study, a model reaction was conducted by reacting aniline, DMAD/DEAD with 2,5-dimethoxytetrahydrofuran in water at room temperature to obtain the corresponding N-substituted azepine in low yields (36%). The poor solubility of aniline in water at elevated temperature resulted in the formation of undesired products. When the same reaction was conducted using β-CD at room temperature the product was obtained in moderate yield (65%). However by a controlled experiment using β-CD, as a supramolecular catalyst, at 50–60 °C the product was obtained in excellent yield (92%)[13] (Scheme 1). In due course of methodology development, for the first time various cyclodextrins, such as α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin, 2-hydroxy propyl-β-cyclodextrin, and methyl-β-cyclodextrin were examined for their efficiency as promoters in carrying out the reaction under supramolecular catalysis.

Of these cyclodextrins (Table 1), β-CD and γ-CD were found to be superior mediators and both gave moderate to excellent yields of the desired substituted azepine. As β-cyclodextrin was inexpensive and readily available when compared to γ-cyclodextrin, β-cyclodextrin was selected as a better choice to carry out the

Table 2
Synthesis of N-substituted azepines[a]

Entry	Aniline	DMAD/DEAD	2,5-Dimethoxy tetrahydro furan	Product	Yield[b] (%)
1					92
2					91
3					92
4					90
5					86
6					94
7					80
8					91

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