Polyethylene Glycol (PEG-400) as an Efficient and Recyclable Reaction Medium for the One-Pot Synthesis of N-Substituted Azepines under Catalyst-Free Conditions

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Abstract: Polyethylene glycol (PEG) was found to be an inexpensive nontoxic and effective medium for the one-pot synthesis of N-substituted azepines under catalyst-free conditions in excellent yields. Environmental acceptability, low cost, high yields, and recyclability of the PEG are the important features of this protocol.

Key words: anilines, dialkylacetylene dicarboxylates, 2,5-dimethoxytetrahydrofuran, N-substituted azepines, polyethylene glycol, catalyst-free conditions

N-Substituted azepines and their derivatives are an important class of organic compounds found in many biologically active molecules. These compounds exhibit properties such as antihistaminic, spasmolytic, serotonin antagonistic, anticonvulsive, antiemetic, anti-inflammatory, and fungicidal activity.[1] They have also been widely used in antimalarial[2a–2c] and anti-HIV drug therapy,[2d] and in treatments for stomach disorders,[3] arrhythmia,[4] and hypertension (glaucoma).[5,6]

Although several protocols have been developed for the synthesis of azepine derivatives,[7] many of the methods possess drawbacks such as harsh reaction conditions, tedious experimental procedures, unsatisfactory yields, long reaction times or use of expensive and moisture-sensitive catalysts. Hence, there is a need for a rapid and efficient method for the synthesis of N-substituted azepine derivatives under catalyst-free conditions.

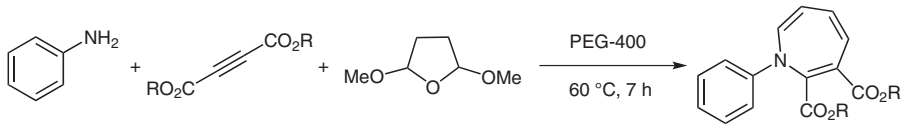
In recent years, polyethylene glycol (PEG) has emerged as a powerful phase-transfer catalyst and performs many useful organic transformations under mild reaction conditions. Moreover, PEG is inexpensive, easy to handle, thermally stable, nontoxic, and recyclable in various organic transformations.[8] In continuation of our interest in the field of the PEG-catalyzed synthesis of heterocyclic compounds under catalyst-free conditions,[9] we report herein the first synthesis of N-substituted azepine derivatives via tandem Michael addition–cyclization using PEG-400 as a recyclable medium without additional organic solvent and catalyst (Scheme 1).

To the best of our knowledge there are no previous reports for the synthesis of azepine derivatives by using PEG-400 as a reaction medium under catalyst-free conditions.

The generality of this reaction was investigated for the synthesis of various N-substituted azepine derivatives by using a variety of anilines and dialkylacetylene dicarboxylates with 2,5-dimethoxytetrahydrofuran (Table 1).[10]

In general, all the reactions were very clean, and the N-substituted azepine derivatives were obtained in high yields. Anilines bearing electron-donating groups (Me, OMe) reacted efficiently; whereas in the presence of electron-withdrawing groups (NO_2) a slight decrease in the yield of the N-substituted azepines was observed (Table 1 entries 6, 7, 15, and 16). Aliphatic amines gave the desired products in low yields (Table 1, entries 9 and 18). The structures of all the products were determined from their analytical and spectroscopic (IR, ^{1}H NMR, and ^{13}C NMR) data and by direct comparison with authentic samples.

In conclusion, we have developed an efficient and facile method for the synthesis of N-substituted azepine derivatives by treatment of aniline, dialkylacetylene dicarboxylate, and 2,5-dimethoxytetrahydrofuran using PEG as a recyclable medium without the addition of any additive or organic co-solvent. Mild reaction conditions, inexpensive reaction medium, operational simplicity, and high yields are the advantages of the protocol.



Scheme 1

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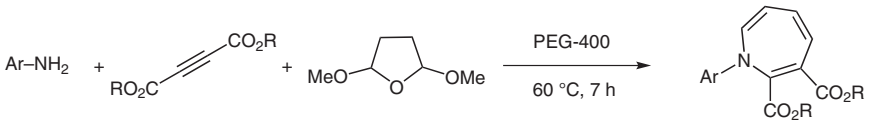
Table 1 Synthesis of N-Substituted Azepine Derivatives in PEG[a]



Entry	Ar	R	Yield (%)
1	Ph	Me	94
2	4-MeC_6H_4	Me	89
3	4-$MeOC_6H_4$	Me	91
4	4-ClC_6H_4	Me	88
5	4-BrC_6H_4	Me	89
6	4-$O_2NC_6H_4$	Me	81
7	3-$O_2NC_6H_4$	Me	76
8	4-HOC_6H_4	Me	85
9	Bn	Me	35
10	Ph	Et	92
11	4-MeC_6H_4	Et	88
12	4-$MeOC_6H_4$	Et	90
13	4-ClC_6H_4	Et	86
14	4-BrC_6H_4	Et	87
15	4-$O_2NC_6H_4$	Et	79
16	3-$O_2NC_6H_4$	Et	74
17	4-HOC_6H_4	Et	81
18	Bn	Et	31

[a] Reaction conditions: amine (1.0 mmol), diethyl acetylenedicarboxylate (DEAD, 1.0 mmol) or dimethyl acetylenedicarboxylate (DMAD, 1.0 mmol), 2,5-dimethoxytetrahydrofuran (1.0 mmol), PEG (5 mL), 60 °C.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(10) **General Procedure for the Synthesis of N-Substituted Azapins by Using PEG as a Reaction Medium**

A mixture of the requisite aniline (1.0 mmol), dialkyl-acetylene dicarboxylate (1.0 mmol), and 2,5-dimethoxy-tetrahydrofuran (1.0 mmol) was taken in PEG (5 mL) and stirred at 60 °C for the appropriate time. After completion of the reaction, as monitored by TLC, the reaction mixture was poured into H_2O and extracted with EtOAc. The organic layer was removed under reduced pressure, and the crude product was purified by column chromatography. The recovered PEG could be reused for a number of cycles without significant loss of activity.