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# Cesium fluoride catalyzed Aza-Michael addition reaction in aqueous media

Vilas B. Labade · Shivaji S. Pawar · Murlidhar S. Shingare

**Abstract** A green approach to the Aza-Michael addition reaction between an amine and $\alpha,\beta$-unsaturated compounds has been achieved by conventional as well as non-conventional methods. The reaction is catalyzed by cesium fluoride (CsF) in aqueous media at ambient temperature to afford the product in excellent yield. Ultrasound irradiation has been used as a non-conventional energy source, which reduces the reaction time with improved product yield.

**Keywords** Aza-Michael addition · Cesium fluoride · Aqueous media · Ultrasound irradiation

## Introduction

Conjugate addition (Michael addition) of nucleophiles to $\alpha,\beta$-unsaturated compounds is one of the most important new bond-forming strategies in synthetic organic chemistry [1, 2]. The versatility of the conjugate addition is due to the large variety of nucleophiles (organometallic reagents, other carbanions, heteroatoms, Michael donors) and acceptors ($\alpha,\beta$-unsaturated carbonyl compounds, esters, nitriles, and nitroalkenes) that can be used [3–6].

Among these varieties of synthetic transformations, development of new methods for an efficient conjugate addition reaction with a wide range of heteroatom nucleophiles has attracted special attention [7–9]. In particular, the conjugate addition of nitrogen nucleophiles to $\alpha,\beta$-enones (Aza-Michael reaction) is noteworthy as a widely used method for carbon-nitrogen bond formation. The products of Aza-Michael additions, $\beta$-amino carbonyl compounds and derivatives, can be used in peptide analogues or as precursors to optically active amino acids, amino alcohols, diamines, and lactams, many of which serve as powerful antibiotics or other drugs [10, 11]. Among the methods for generating $\beta$-amino carbonyl compounds, Lewis acid and base-catalyzed conjugate addition of N-containing nucleophiles to $\alpha,\beta$-unsaturated carbonyl compounds is one of the most simple and effective methods [12, 13].

A number of alternative procedures have been developed over the past few years for the Aza-Michael addition reaction. Various metal catalysts, such as $Yb(OTf)_3$, $InCl_3$, $CeCl_3 \cdot 7H_2O/NaI$, $Bi(NO)_3$, $Bi(OTf)_3$, $Cu(OTf)_2$, transition metal salts, $LiClO_4$, heterogeneous solid acids, ionic liquids, quaternary ammonium salts, and $Cu(acac)_2$ immobilized in ionic liquids efficiently catalyze the Aza-Michael reaction [14–28]. However, many of these procedures require a large excess of reagents, long reaction time, and drastic reaction conditions. Hence, the search continues to develop better synthetic protocols for the Aza-Michael reaction in terms of operational simplicity, economic viability, etc.

Organic synthesis in aqueous media is rapidly gaining importance in view of the fact that the use of many toxic and volatile organic solvents contributes to pollution. Since the pioneering studies by Breslow [29] on Diels-Alder reactions, there has been profound research activity in the development of organic reactions in aqueous media offering key advantages, such as rate enhancement and insolubility of the final products, which facilitate their

V. B. Labade · M. S. Shingare (✉)
Department of Chemistry, Dr. Babasaheb Ambedkar
Marathwada University, Aurangabad 431 004,
Maharashtra, India
e-mail: prof_msshingare@rediffmail.com

S. S. Pawar
Department of Chemistry, Vinayakrao Patil Mahavidyalaya,
Vaijapur 423 701, Aurangabad, India

isolation by simple filtration. Also, in the context of green chemistry, aqueous media is acting as a stepping stone in the greener synthesis of bioactive heterocyclic compounds. In this respect, the development of water-tolerant catalysts has rapidly become an area of intense research. However, there are few reports on the conjugate addition of nitrogen nucleophiles to $\alpha,\beta$-unsaturated carbonyl compounds in water [15, 19, 20, 24]. These findings promoted us to investigate the Aza-Michael reaction in aqueous media.

For many chemical processes, a major adverse effect on the environment is the consumption of energy for heating and cooling. To overcome such problems, it is highly desirable to develop efficient methods that utilize alternative energy sources such as ultrasound and microwave irradiation to facilitate chemical reaction. The ultrasound technique has increasingly been used in organic synthesis in recent years. Ultrasonic irradiation enhances the chemical reaction via the process of acoustic cavitation. The assistance of ultrasonic irradiation efficiently shortens the reaction time. The simple experimental procedure, very high yields, increased selectivity, and clean reaction of many ultrasound-induced organic transformations offer additional convenience in the field of synthetic organic chemistry [30–33]. The chemical effects resulting from the irradiation of aqueous solutions with ultrasound were first introduced by Loomis et al. [34].

Cesium fluoride (CsF) is a useful base in organic chemistry because the fluoride ion is largely unreactive as a nucleophile [35]. Removal of silicon groups (desilylation) is one of the major applications of CsF in the laboratory, as its anhydrous nature allows clean formation of water-sensitive intermediates [36]. It is exploited as an efficient catalyst for the synthesis of carboxylic esters [37], *trans-α*-trifluoromethyl allylic alcohols [38], $\gamma$-lactones [39], aromatic esters and ethers [40], thioesters and thioethers [41], and 3,4-dihydropyrimidine-2-(1H)-ones [42]. In addition, it has been used for N-alkylation of anilines, carboxamides, and nitrogen heterocyclic compounds [43], and regio- and chemoselective ring opening of epoxides with thiols [44].

## Results and discussion

As a part of our ongoing project [45–49], we wish to report that cesium fluoride catalyzed convenient synthesis of $\alpha$-amino carbonyl compounds via Aza-Michael addition reaction in aqueous medium at ambient temperature by the conventional and ultrasonication method (Scheme 1).

In search for the best experimental reaction conditions, the Aza-Michael addition reaction between piperidine and methyl acrylate in the presence of CsF (10 mol%) at ambient temperature was considered as a standard model reaction.
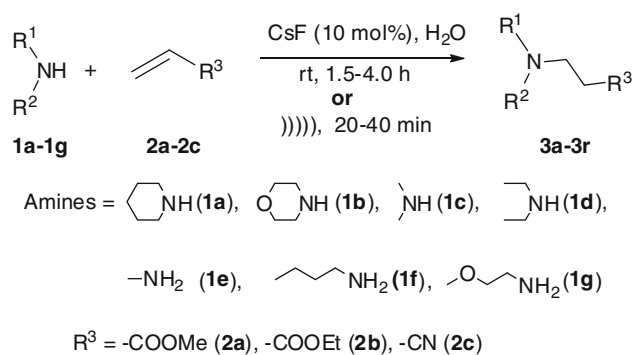


**Scheme 1**

The effect of various solvents, such as $CH_3CN$, THF, MeOH, EtOH, $CHCl_3$, DCM, $H_2O$ as well as mixtures of solvents, viz., $CH_3CN/H_2O$, $MeOH/H_2O$, and $EtOH/H_2O$, were evaluated and used for the model reaction (Table 1). The use of different solvents, such as $CH_3CN$, THF, MeOH, EtOH, $CHCl_3$, and DCM, afforded the desired product in very low yields (35–55%, Table 1, entries 1–6). However, the addition of water to $CH_3CN$, MeOH, and EtOH gave the product in slightly higher yields (66–75%, Table 1, entries 7–9), whereas water brought the reaction to completion efficiently to obtain the corresponding 3-(piperidin-1yl)-propionic acid methyl ester in excellent 92% yield. The reaction proceeds smoothly at ambient temperature with 10 mol% of CsF and is completed within 2.0 h (Table 1, entry 10). This is due to the fact that water has a profound effect on the basic behavior of the fluoride anion [50, 51].

The model reaction was further investigated under ultrasound irradiation in the presence of CsF with a view to explore whether (1) the reaction could be expedited and (2) the product yield could be enhanced. In this case, no significant improvement in the product yield (94%) was

**Table 1** Screening of solvents

| Entry | Solvent | Time/h | Yield[a]/% |
|-------|---------|--------|------------|
| 1 | $CH_3CN$ | 3 | 35 |
| 2 | THF | 3 | 40 |
| 3 | MeOH | 3 | 45 |
| 4 | EtOH | 3 | 50 |
| 5 | $CHCl_3$ | 3 | 52 |
| 6 | DCM | 3 | 55 |
| 7 | $CH_3CN/H_2O$ (1:1) | 3 | 66 |
| 8 | $MeOH/H_2O$ (1:1) | 3 | 70 |
| 9 | $EtOH/H_2O$ (1:1) | 3 | 75 |
| 10 | $H_2O$ | 2 | 92 |

Standard conditions: piperidine (1 mmol), methyl acrylate (1.1 mmol), CsF (10 mol%), solvent, rt

[a] Isolated yields

observed, but the reaction time enormously reduced to 20 min as compared to conventional method (2.0 h).

For assessing the generality of the optimized reaction conditions various primary and secondary amines such as piperidine, morpholine, dimethylamine, diethylamine, methylamine, 2-methoxyethanamine, *n*-butylamine and anilines with respect to acrylonitrile and α,β-unsaturated esters such as methyl acrylate and ethyl acrylate were subjected to the Aza-Michael addition reaction in the presence of CsF (Table 2). It was observed that secondary amines react faster than primary amines, providing excellent product yields (90–92%, Table 2, entries 1–12). In comparison with these results, primary aliphatic amines required longer reaction time and formed the corresponding monoadduct in 76–85% yields (Table 2, entries 13–16), whereas utilization of 2.2 equivalents of ethyl acrylate with respect to primary aliphatic amine resulted in the formation of bisadduct in good yields (78–81%, Table 2, entries 17–18). Unfortunately, when anilines were subjected to undergoing this addition reaction, starting materials were recovered even after prolonged reaction time by both conventional and non-conventional methods. Ultrasound irradiation technique was also established to be compatible

with all these substrates, and products were obtained in excellent yield (81–94%) within only 20–40 min (Table 2). This is an immense advantage of this method. Formation of the product was confirmed by IR, ^{1}H NMR, ^{13}C NMR, and mass spectroscopic data.

It is a well established fact that fluoride ion is capable of forming strong hydrogen bonding with a variety of hydrogen bond acceptor compounds [52]. On the basis of that, it is proposed that CsF forms a hydrogen bond between fluoride anion and amine (Fig. 1), which results in the transfer of electron density from the fluoride anion to amine, and ultimately enhances the nucleophilicity of amine, while at the same time it reduces the nucleophilicity of the fluoride [53]. This accelerates the rate of reaction enormously and affords the desired product in shorter reaction time.

## Conclusion

In conclusion, CsF has been proved to be an efficient catalyst for the synthesis of β-amino esters/nitriles via aza-Michael reaction in water at ambient temperature by conventional and ultrasonication methods. This method offers remarkable advantages such as the simple experimental procedure, mild reaction conditions, lower reaction time, and higher product yields, avoiding hazardous organic solvents.
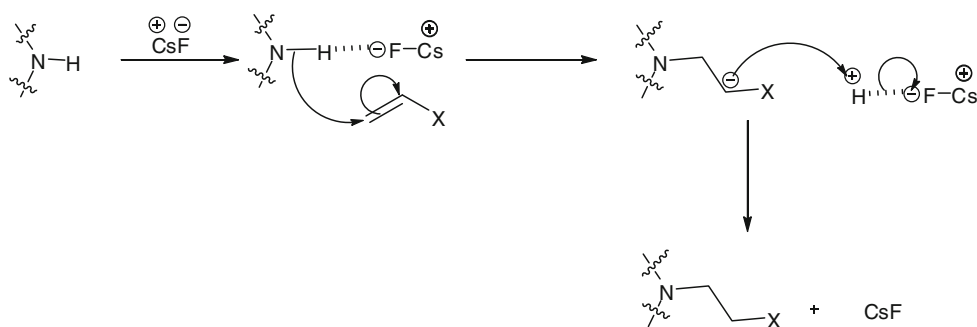
## Experimental

All chemicals and solvents were purchased from Merck (Darmstadt, Germany), Spectrochem (Mumbai, India), and S.D. Fine-chem (Mumbai, India). Solvents were commercially available materials of reagent grade. Bandelin Sonorex (with a frequency of 35 kHz and a nominal power 200 W) ultrasonic bath was used for ultrasonic irradiation with built-in heating, 30–80 °C thermostatically adjustable. IR spectra were recorded on JASCO FT-IR 4100 (Japan) using KBr discs. ^{1}H NMR spectra were recorded on a Varian Mercury Plus 400 MHz NMR spectrometer. Mass spectra were recorded on a Micromass-QUATTRO-II mass spectrometer. The progress of the reactions was monitored by TLC on Merck silica plates.

### General procedure

Conventional method
Corresponding amine 1 (1 mmol) and α,β-unsaturated compound 2 (1.1 mmol) were added to a 25-cm³ conical flask containing 10 cm³ water, and 10 mol% of CsF was added. The reaction mixture was stirred at room

**Table 2** CsF catalyzed Aza-Michael addition reaction

| Entry | Amine 1 | Olefin 2 | Product[a] 3 | Conventional | | Ultrasonication | |
|---|---|---|---|---|---|---|---|
| | | | | Time/h | Yield[b]/% | Time/min | Yield[b]/% |
| 1 | 1a | 2a | 3a | 2.0 | 92 | 20 | 94 |
| 2 | 1a | 2b | 3b | 1.5 | 90 | 20 | 93 |
| 3 | 1a | 2c | 3c | 2.0 | 90 | 25 | 91 |
| 4 | 1b | 2a | 3d | 2.0 | 92 | 24 | 92 |
| 5 | 1b | 2b | 3e | 2.0 | 91 | 28 | 93 |
| 6 | 1b | 2c | 3f | 2.5 | 90 | 30 | 92 |
| 7 | 1c | 2a | 3g | 2.0 | 92 | 24 | 92 |
| 8 | 1c | 2b | 3h | 2.0 | 90 | 30 | 91 |
| 9 | 1c | 2c | 3i | 2.0 | 91 | 24 | 94 |
| 10 | 1d | 2a | 3j | 2.5 | 90 | 26 | 93 |
| 11 | 1d | 2b | 3k | 2.5 | 90 | 27 | 92 |
| 12 | 1d | 2c | 3l | 2.5 | 90 | 26 | 93 |
| 13 | 1e | 2b | 3m | 3.5 | 76 | 35 | 81 |
| 14 | 1f | 2b | 3n | 2.5 | 80 | 28 | 84 |
| 15 | 1f | 2c | 3o | 2.0 | 85 | 25 | 88 |
| 16 | 1g | 2b | 3p | 3.2 | 79 | 33 | 83 |
| 17 | 1e | 2b | 3q | 4.0 | 81[c] | 40 | 86[c] |
| 18 | 1g | 2b | 3r | 4.0 | 78[c] | 40 | 83[c] |

Standard conditions: **1** (1 mmol), **2** (1.1 mmol), CsF (10 mol%), $H_2O$ (10 cm³), rt

[a] All compounds were oils at rt [26]

[b] Isolated yields

[c] 2.2 equiv ethyl acrylate was added

**Fig. 1** Proposed mechanism for CsF catalyzed Aza-Michael addition



temperature for the appropriate time (see Table 2). Progress of the reaction was monitored using TLC. Upon completion, the reaction mixture was extracted with ethyl acetate (10 cm$^3$ ×2), and the organic layer was dried over anhydrous sodium sulfate. Ethyl acetate was distilled under reduced pressure to afford the desired compound. Obtained materials were identical to the compounds described in [26].

Ultrasound method

Corresponding amine **1** (1 mmol) and α,β-unsaturated compound **2** (1.1 mmol) were added to a 25-cm$^3$ conical flask containing 10 cm$^3$ water, and to this 10 mol% of CsF was added. The reaction mixture was irradiated in an ultrasonicator for 20–40 min (Table 2). The progress of the reaction was monitored using TLC. Upon completion, the reaction mixture was extracted with ethyl acetate (10 cm$^3$ ×2) and the organic layer was dried over anhydrous sodium sulfate. Ethyl acetate was distilled under reduced pressure to afford the desired compounds. The obtained materials were identical to the compounds described in [26].

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