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Cerium(IV) ammonium nitrate (CAN) catalyzed aza-Michael addition of amines to α,β-unsaturated electrophiles

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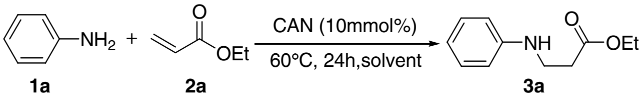
Abstract—Cerium(IV) ammonium nitrate (CAN) catalyzed facile and efficient aza-Michael addition of aromatic and aliphatic amines with α,β-unsaturated electrophiles in the absence of solvent under ultrasound irradiation.

The development of catalysts for the formation of carbon–nitrogen bonds by simple addition of amines to double bonds is a focus of increasing interest.[1] The aza-Michael reaction provides an easy and direct route to β-amino esters.[2] In general, this type of conjugated addition reaction of nucleophiles to unsaturated carbonyl compounds requires basic conditions or acidic catalysts.[3] In order to overcome some of these limitations, a number of alternative procedures have been reported over the past few years using a variety of reagents such as Pd compounds,[4] $InCl_3$,[5] $CeCl_3·7H_2O$–NaI,[6] $Yb(OTf)_3$,[7] $Bi(NO_3)_3$,[8] $Bi(OTf)_3$,[9] Cu salts,[10] $LiClO_4$,[11] clay,[12] silica gel,[13] boric acid,[14] KF/alumina[15] and SmI_2.[16] $FeCl_3·7H_2O$, $CrCl_3·6H_2O$ and $SnCl_4·4H_2O$ had been used to catalyze aza-Michael reactions under mild conditions in aqueous solution, both aliphatic and aromatic amines could be used as the nucleophiles.[17] Due to the inertness of aromatic amines relative to aliphatic ones, most of these procedures are not successful with arylamines. Very recently, Rao and co-workers reported β-cyclodextrin promoted aza-Michael addition of arylamines.[18] In these reactions, an equivalent amount of the recyclable catalyst was added. The development of less expensive, simpler, 'greener' metal catalysts for the aza-Michael addition with arylamines is still highly desirable.

The readily available, cheap, low toxicity, easy handling and profound reactivity combined with its solubility in organic solvents, have made CAN attractive in organic synthesis.[19] Very recently, CAN catalyzed Michael addition of indole to α,β-unsaturated ketones was reported.[20] Substitution took place at the 3-position, and *N*-alkylation products were not observed. To the best of our knowledge, CAN catalyzed aza-Michael addition of amines to α,β-unsaturated compounds are unknown. Herein we would like to report CAN as an efficient catalyst in the aza-Michael addition. The advantages of this protocol include high yield reactions that can be conducted under ambient temperature without solvent. CAN is suitable to activate aliphatic amines and even aromatic amines for the aza-Michael addition reactions.

At first, aniline and ethyl acrylate were chosen as model system. We found that this CAN catalyzed aza-Michael

Table 1. CAN catalyzed Michael addition of aniline to ethyl acrylate in various solvents



Entry	Solvent[a]	Yield[b](%)
1	H_2O	39
2	C_2H_5OH/H_2O[c]	38
3	C_2H_5OH	75
4	THF	78
5	Dioxane	8
6	CH_3CN	66

[a] 2 ml was added.
[b] Isolated yield.
[c] v/v = 1/1.

Keywords: CAN; Amines; Michael addition; Catalysis; Ultrasound.

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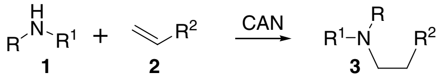
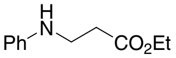
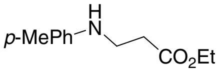
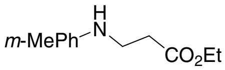
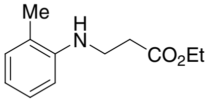
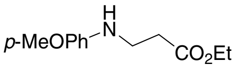
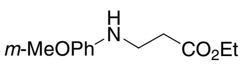
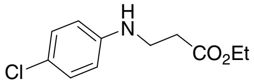
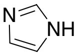
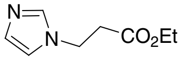
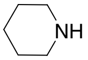
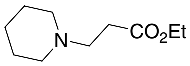
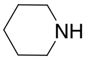
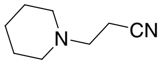
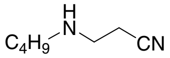
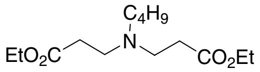
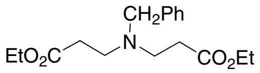
addition was strongly dependent on the solvent. Among the solvents tested, THF and EtOH gave fair yields (75–78%), as well as CH_3CN (66%). Low yields were obtained with the other solvents (Table 1).

In a typical procedure, to a THF solution of aniline (1.5 mmol) and ethyl acrylate (1 mmol) was added CAN (0.1 mmol). The reaction mixture was stirred at 60 °C for 24 h under air atmosphere. Then the crude reaction mixture was purified by thin layer chromatography (TLC). The results are summarized in Table 2. All the products were characterized by ^{1}H, ^{13}C NMR and mass spectrometry.

As can be seen from Table 2, primary aromatic amines with electron-donating group gave better results. When *p*-chloroaniline was used, Michael adduct product formed only in moderate yield (entry 7). No reaction was observed when *m*-nitroaniline (entry 8) was used.

Table 2. CAN catalyzed aza-Michael addition of amines



Entry	Amine		Reaction time (h)[a]	Product		Yield[b] (%)
1	$PhNH_2$	**1a**	24 (6)		**3a**	78 (80)[c]
2	p-$MePhNH_2$	**1b**	24 (4)		**3b**	78 (78)[c]
3	m-$MePhNH_2$	**1c**	24 (4)		**3c**	77 (71)[c]
4	o-$MePhNH_2$	**1d**	(6)		**3d**	(56)[c]
5	p-$MeOPhNH_2$	**1e**	24 (4)		**3e**	82 (80)[c]
6	m-$MeOPhNH_2$	**1f**	24 (6)		**3f**	74 (82)[c]
7	p-$ClPhNH_2$	**1g**	24 (6)		**3g**	64 (72)[c]
8	m-NO_2PhNH_2	**1k**		N/A		N/A
9		**1l**	(4)		**3l**	(60)[c]
10		**1m**	(20 min)		**3m**	(Quant.)[c]
11		**1m**	(20 min)		**3n**	(96)[c]
12	$C_4H_9NH_2$	**1n**	(20 min)		**3o**	(93)[c]
13	$C_4H_9NH_2$	**1n**	(40 min)		**3p**	(98)[d]
14	$Ph_2CH_2NH_2$	**1o**	(1)		**3q**	(90)[d]

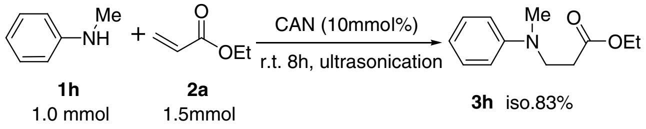
[a] Reaction times with ultrasonic irradiation are given in parentheses.

[b] Isolated yields. Yields for reactions with ultrasonic irradiation are given in parentheses.

[c] 1.5 equiv amine was added.

[d] 2.5 equiv ethyl acrylate was added.

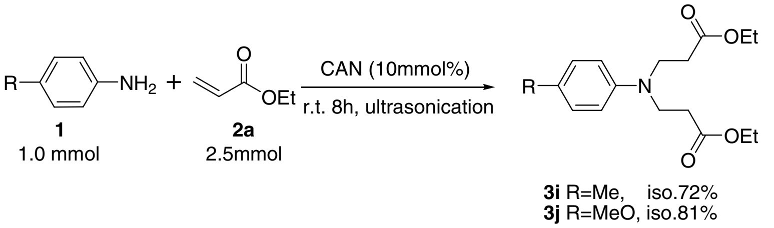
Under the same condition, the reaction of a secondary aromatic amine, *N*-methylaniline, with ethyl acrylate did not work very well. To our surprise, when a mixture of *N*-methylaniline, ethyl acrylate and a catalytic amount of CAN was sonicated[21] at room temperature in an ultrasonic cleaner, a faster reaction occurred to give the desired product in 83% isolated yield (Eq. 1).



(1)

This result promoted us to investigate the ultrasound-assisted aza-Michael addition. To our gratified, all the reactions proceeded with reduced reaction time (Table 2) and no solvent was needed. The electron poor arylamines showed no reactivity (entry 8). Due to the stereo-hindrance effect, *o*-toluidine showed lower reactivity (entry 4) than *p*-toluidine and *m*-toluidine (entries 2 and 3). Imidazole also could be used as the nucleophile and the addition product formed in moderate yield (entry 9). A control experiment (in the absence of CAN) showed no desired adduct of amine with ethyl acrylate.

With ultrasonic irradiation, primary arylamines could selectively react with one or two molecules of ethyl acrylate, gave the monoalkylation (entries 2 and 5) or dialkylation (Eq. 2) products.



(2)

We have utilized a variety of aliphatic amines successfully with different α,β-unsaturated compounds catalyzed by CAN under ultrasonic irradiation, rapid conversions were observed. When primary aliphatic amines were used, the di-substituted products formed exclusively (Table 2, entries 13 and 14).

In conclusion, we have developed a new methodology for an intermolecular aza-Michael addition of amines to α,β-unsaturated carbonyl compounds under solvent-free condition. Even aromatic amines could be used as nucleophiles. The advantages of this methodology are air and moisture stable, environmentally benign and less expensive processes, which will contribute to the progress of green chemistry.

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