General, Mild and Efficient Synthesis of β-Enaminones Catalyzed by Ceric Ammonium Nitrate

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Abstract: Ceric ammonium nitrate catalyzes the reaction between aromatic or aliphatic primary amines and a variety of β-dicarbonyl compounds, including β-ketoesters, β-ketothioesters and β-diketones. The reaction proceeds smoothly at room temperature in short reaction times and gives β-enaminones in good to excellent yields.

Key words: enaminones, ceric ammonium nitrate, lanthanides, Lewis acids, β-dicarbonyl compounds

The preparation of enamines from β-dicarbonyl derivatives is an important transformation due to the wide range of synthetic applications of β-enaminones[1] in the preparation of heterocycles,[2] including alkaloids,[3] α-[4] and β-amino acids,[5] peptides,[6] β,γ-unsaturated ketones,[7] γ-amino alcohols,[8] azo compounds[9] and azacarbasugars,[10] among other synthetically relevant compounds. Existing methods for the preparation of β-enaminones normally involve the reaction of β-dicarbonyl compounds with amines in the presence of catalysts such as protic acids,[11] K-10 montmorillonite and other clays,[12] silica gel,[13] alumina,[14] bismuth trifuoroacetate in water[15a] or molten TBAB,[15b] zinc perchlorate,[16] cerium trichloride,[17] indium tribromide,[18] trimethylsilyl triflate[19] or boron trifluoride.[20] Occasionally, these reactions can be performed in the absence of catalysts by use of ionic liquids[21a] or water[21b] as the reaction media, or under ultrasound irradiation,[22] but in these cases the scope of the method is limited by solubility issues. Alternative, less direct procedures include the acylation of imines via benzotriazole derivatives,[23] the ruthenium-catalyzed reaction between anilines and propargyl alcohols,[24] the addition of ester or amide enolates to a variety of electrophiles,[25] and the transformation of enaminoesters into enaminoketones by reaction with organolithium reagents.[26] In spite of this abundance of methods, they suffer from a number of limitations such as the use of toxic or expensive catalysts or reaction media, moderate yields and limited scopes, since many methods do not work well with aromatic amines, some require the use of the neat β-dicarbonyl compound as the reaction medium, and some of them are restricted to β-ketoesters. For this reason, the development of a general and efficient method for β-enaminone synthesis that uses a nontoxic and inexpensive catalyst is still important.

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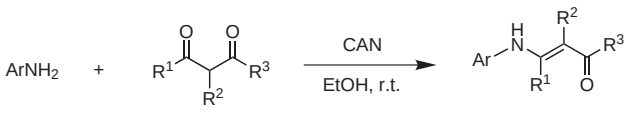
Lanthanide salts, and particularly their triflates, are considered as 'green' alternatives to traditional Lewis acids,[27] since they have low toxicities and are compatible with aqueous reaction media. Although cerium is the most common lanthanide, the use of its salts as Lewis acids has received relatively little attention and most work has focused on Ce(III) compounds.[28] However, Ce(IV) species have low toxicities and are the only tetravalent lanthanides that are stable in water. These qualities make them particularly attractive as environmentally benign reagents and, indeed, they are, to date, the only synthetically useful Ln(IV) reagents. Although Ce(IV) derivatives are normally employed as one-electron oxidants, the use of the commercially available, inexpensive and easily handled cerium(IV) ammonium nitrate (CAN) in C–C bond-forming reactions has recently attracted much attention,[29] although these studies are still in their early stages. As stated in a recent review on the subject,[29d] one of the main goals yet to be achieved in this area is the development of reactions that allow the use of catalytic amounts of CAN.[30] Within this context, we describe here our work on the use of cerium(IV) ammonium nitrate as a catalyst for β-enaminone synthesis.

Table 1 shows the results obtained in the CAN-catalyzed reaction between β-ketoesters and aromatic amines (Scheme 1), which were initially chosen as nucleophiles due to the unsatisfactory results that they give in many of the published β-enaminone syntheses.[31] We first set out to establish the optimal amount of CAN, finding that the reaction with a 10% catalyst loading gave a 81% yield after 1.5 hours (entry 1), which was lowered to 76% when the reaction time was extended to 4 hours (entry 2). However, the best result (91% yield) corresponded to the use of 5% catalyst and a reaction time of 1.5 hours (entry 3). The preference for a 5% catalyst loading was confirmed when *p*-toluidine was used as the nucleophile (compare the yields in entries 4 and 5). Other reactions involving cyclic β-ketoesters proceeded uneventfully, and gave yields higher than 90% in all cases (entries 6–11). In the case of open-chain β-ketoesters, an initial study of the reaction



1 2 3

Scheme 1

Table 1 CAN-Catalyzed Synthesis of Enaminones Derived from Aromatic Amines

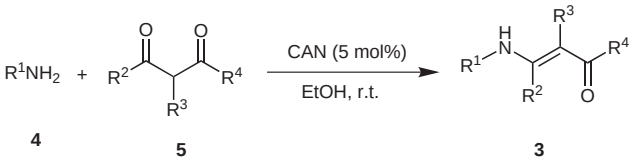
Entry	Product	Ar	R^1	R^2	R^3	CAN (mol%)	Time (h)	Yield (%)
1	**3a**	Ph	$(CH_2)_4$		OEt	10	1.5	81
2	**3a**	Ph	$(CH_2)_4$		OEt	10	4	76
3	**3a**	Ph	$(CH_2)_4$		OEt	5	1.5	91
4	**3b**	4-MeC_6H_4	$(CH_2)_4$		OEt	5	1.5	88
5	**3b**	4-MeC_6H_4	$(CH_2)_4$		OEt	10	1.5	79
6	**3c**	4-$MeOC_6H_4$	$(CH_2)_4$		OEt	5	1.5	93
7	**3d**	Ph	$(CH_2)_3$		OEt	5	1.5	99
8	**3e**	4-MeC_6H_4	$(CH_2)_3$		OEt	5	1.5	99
9	**3f**	4-$MeOC_6H_4$	$(CH_2)_3$		OEt	5	1.5	99
10	**3g**	4-ClC_6H_4	$(CH_2)_3$		OEt	5	1.5	98
11	**3h**	4-FC_6H_4	$(CH_2)_3$		OEt	5	1.5	99
12	**3i**	Ph	Me	Et	OEt	5	1.5	83
13	**3i**	Ph	Me	Et	OEt	5	3	87
14	**3i**	Ph	Me	Et	OEt	10	1.5	66
15	**3j**	4-$MeOC_6H_4$	Me	Et	OEt	5	1.5	89
16	**3k**	4-FC_6H_4	Me	Et	OEt	5	3	73
17	**3l**	3-MeC_6H_4	Me	Et	OEt	5	1.5	83
18	**3m**	3,5-$Me_2C_6H_4$	Me	Et	OEt	5	3	71
19	**3n**	Ph	Me	H	*t*-BuO	5	2	74
20	**3o**	Ph	Me	H	*t*-BuS	5	2	98
21	**3p**	4-$MeOC_6H_4$	Me	H	*t*-BuS	5	1.5	99
22	**3q**	4-ClC_6H_4	Me	H	*t*-BuS	5	1.5	93
23	**3r**	Ph	Me	H	Me	5	1	88
24	**3s**	4-MeC_6H_4	Me	H	Me	5	1	93
25	**3t**	4-$MeOC_6H_4$	Me	H	Me	5	1	98
26	**3u**	4-ClC_6H_4	Me	H	Me	5	2	76
27	**3u**	4-ClC_6H_4	Me	H	Me	5	4	68
28	**3v**	Ph	Me	H	Ph	5	1	99
29	**3w**	Ph	Me	H	Ph	5	1	99
30	**3x**	4-MeC_6H_4	Me	H	Ph	5	1	99
31	**3e**	Ph	$(CH_2)_3$		OEt	0	1.5	7

between aniline and ethyl acetoacetate (entries 12–14) confirmed the preference for a 5% catalyst loading (compare the yields in entries 13 and 14). Other reactions with ethyl acetoacetate (entries 15–18) and *tert*-butyl acetoacetate (entry 19) gave yields between 71% and 89%.

We next examined the reaction between aromatic amines and other types of β-dicarbonyl compounds. In the case of β-ketothioesters the yields were excellent, irrespectively of the presence of electron-releasing or electron-withdrawing substituents in the aniline derivative (entries 20–22). Several experiments involving β-diketones were also carried out (entries 23–30), normally in excellent yields.

The reaction between 4-chloroaniline and 2,4-pentanedione (entries 26 and 27) showed again that long reaction times are detrimental to yield. The reactions starting from 1-phenyl-1,3-butanedione (entries 28–30) can in principle give two different enaminones, but they proceeded with complete regiocontrol and afforded exclusively the product with a double bond adjacent to the methyl group, in quantitative yield in all cases studied. Finally, a control experiment (entry 31) showed that the reaction between aniline and ethyl 2-oxocyclopentanecarboxylate proceeded in a very low conversion in the absence of catalyst.

Finally, in order to extend the scope of this method and to include also the more favorable cases, some CAN-catalyzed reactions between aliphatic amines and β-dicarbonyl compounds were also performed. As shown in Scheme 2 and Table 2, all β-ketoesters, β-ketothioesters and β-diketones assayed gave yields normally above 90% in their reactions with benzylamine and butylamine, the only exception being the reaction between benzylamine and ethyl 2-oxocyclopentane-1-carboxylate that proceeded in a slightly lower 80% yield.



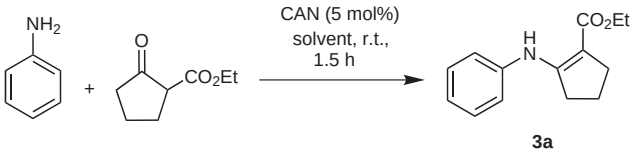
Scheme 2

Table 2 CAN-Catalyzed Synthesis of Enaminones Derived from Aliphatic Amines

Entry	Product	R^1	R^2	R^3	R^4	Time (h)	Yield (%)
1	**3y**	Bn	$(CH_2)_3$		OEt	2	80
2	**3z**	Bn	Me	H	OEt	2	91
3	**3aa**	Bn	Me	H	*t*-BuS	1	97
4	**3ab**	*n*-Bu	Me	H	OEt	0.5	98[a]
5	**3ac**	*n*-Bu	Me	H	*t*-BuS	0.5	94[a]
6	**3ad**	Bn	Me	H	Me	1	90

[a] In these cases, 1.5 equiv of amine were used.

As a final check of the flexibility of the CAN-catalyzed synthesis of β-enaminones, we investigated its scope in terms of the range solvents that it is able to tolerate. Using the reaction between aniline and ethyl 2-oxocyclopentane-1-carboxylate as a reference system, we were able to ascertain that the method proceeds in excellent yields in nine different solvents, which ranged in polarity from water to benzene (Scheme 3, Table 3). We expect that this unusual broad solvent tolerance of the reaction will facilitate its synthetic application, and more specifically the development of one-pot multicomponent procedures based on the well-known[1] reactivity of enaminones.



Scheme 3

Table 3 Solvent Effects in the Reaction Between Aniline and Ethyl 2-Oxocyclopentanecarboxylate

Entry	Solvent	Yield (%)
1	H_2O	88
2	MeOH	98
3	EtOH	99
4	MeCN	92
5	1,4-Dioxane	99
6	THF	93
7	$CHCl_3$	81
8	CH_2Cl_2	98
9	Benzene	85

In an effort to clarify whether CAN exerts its role in our enaminone synthesis through a one-electron oxidative pathway, we have performed the reaction between ethyl 2-oxocyclohexanecarboxylate and aniline (entry 3 in Table 1) in the presence of a large amount of a radical trap, namely 1,1-diphenylethylene. In this experiment we found no noticeable loss in yield, which indicates that a radical mechanism is not in operation under our conditions. In this regard, it is relevant to note that some literature results can be interpreted by assuming that CAN may behave as a Lewis acid, although this role has not been systematically studied. The clearest example can be found in a study about the use of CAN as a catalyst for acetal and ketal deprotection, where it has been proved by cyclic voltammetry that cerium remains in the Ce(IV) oxidation state, strongly suggesting that it acts as a Lewis acid.[32]

In conclusion, we have shown that CAN is an inexpensive, eco-friendly catalyst that allows the general and efficient construction of β-enaminone derivatives from primary amines under mild conditions and using an experimentally simple protocol. Furthermore, most reactions were extremely clean, as shown by the NMR spectra of the crude reaction mixtures. We expect that the very high efficiency of our method, coupled with the unusually broad solvent tolerance of the reaction, will allow the development of one-pot multicomponent procedures involving the in situ generation of β-enaminones, followed by the addition of further reactants. Work along these lines is in progress in our laboratory.

Acknowledgment

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(31) **General Experimental Procedure for β-Enaminone Synthesis**
To a stirred solution of 3 mmol of amine **1** and 3 mmol of β-dicarbonyl compound **2** in 3 mL of EtOH was added 5 mol% of CAN. The mixture was stirred at r.t. for the time periods specified in Tables 1 and 2. After completion of the reaction the mixture was dissolved in CH_2Cl_2, washed with H_2O, dried, and evaporated. Analytically pure compounds **3** were obtained by a rapid column chromatography on Et_3N-pretreated silica gel, eluting with PE–EtOAc mixtures. Characterization data for two representative, previously unknown enamines follow.
Ethyl 2-(4-methylphenylamino)cyclohex-1-enecarboxylate (**3b**): viscous liquid. IR (neat): 3228.5, 2935.4, 2858.6, 1650.6, 1603.4, 1515.9, 1236.9, 1175.8, 1077.8 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 1.33 (t, *J* = 7.1 Hz, 3 H), 1.61–1.63 (m, 4 H), 2.26–2.40 (m, 7 H), 4.21 (q, *J* = 7.1 Hz, 2 H), 6.98 (d, *J* = 8.2 Hz, 2 H), 7.13 (d, *J* = 8.2 Hz, 2 H), 10.69 (br s, 1 H). ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT-135): δ = 15.1 (CH_3), 21.3 (CH_3), 22.7 (CH_2), 23.1 (CH_2), 24.3 (CH_2), 28.5 (CH_2), 59.5 (CH_2), 92.7 (CH), 125.7 (CH), 129.8 (CH), 134.6 (C), 137.5 (C), 157.5 (C), 171.3 (C). Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.06; H, 8.32; N, 5.71.
tert-Butyl 3-(butylamino)but-2-enethioate (**3ac**): viscous liquid. IR (neat): 3253.3, 2960.1, 2928.2, 1606.0, 1582.8, 1499.8, 1360.6, 1266.3, 1084.5 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 0.94 (t, *J* = 7.3 Hz, 3 H), 1.37–1.56 (m, 4 H), 1.50 (s, 9 H), 1.87 (s, 3 H), 3.20 (q, *J* = 7.3 Hz, 2 H), 4.86 (s, 1 H), 9.34 (br s, 1 H). ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT-135): δ = 14.2 (CH_3), 19.2 (CH_3), 20.4 (CH_2), 31.0 (CH_3), 32.8 (CH_2), 43.3 (CH_2), 46.8 (C), 94.2 (CH), 160.1 (C), 188.9 (C). Anal. Calcd for $C_{12}H_{23}NOS$: C, 62.83; H, 10.11; N, 6.11; S, 13.98. Found: C, 62.76; H, 9.96; N, 5.86; S, 13.74.
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