An Efficient Method for the Enamination of 1,3-Dicarbonyl Compounds with Ceric Ammonium Nitrate (CAN)

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An efficient method for the enamination of 1,3-dicarbonyl compounds by employing ceric ammonium nitrate (CAN) as the catalyst has been described. A variety of β-amino-α,β-unsaturated ketones and esters have been synthesized in excellent yield within a short reaction time under solvent-free conditions.

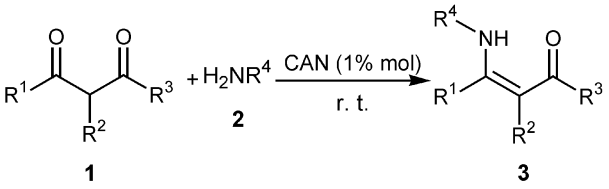
Keywords: Ceric ammonium nitrate; Enamination; 1,3-Dicarbonyl compounds; Solvent free.

INTRODUCTION

The enamination of 1,3-dicarbonyl compounds to yield β-amino-α,β-unsaturated ketones or esters is a useful transformation in organic synthesis and consequently has received considerable attention in recent years. A variety of catalysts such as HCl,[1] H_2SO_4,[2] *p*-TSA,[3] HAc,[4] trimethylsilyl trifluoromethanesulfonate (TMSTf),[5] montmorillonite K10,[6] $BF_3{\cdot}OEt_2$,[7] silica gel,[8] $CoCl_2{\cdot}6H_2O$,[9] $Zn(ClO_4)_2{\cdot}6H_2O$,[10] $CeCl_3{\cdot}7H_2O$,[11] $NaAuCl_4$,[12] $Bi(OTf)_3$,[13] sulfated zirconia[14] and natural clays[15] have been used to promote this transformation. However, these methodologies suffer from some drawbacks such as long reaction times, the use of large amounts of costly catalysts, the low yields of the desired products and the requirement of high temperatures. Therefore, introduction of a new and efficient method for the enamination of 1,3-dicarbonyl compounds is desirable.

In the past few years, ceric ammonium nitrate (CAN) has been exploited extensively as an inexpensive and easily available catalyst for various organic reactions such as oxidation, oxidative free-radical reactions, nitration, carbon-carbon bond formation, etc.[16] Last year, it was used as an efficient reagent for the synthesis of unsymmetrical bis-(indolyl)alkanes,[17] dihydrofuran-fused [60] fullerene derivatives[18] and conjugated nitro-olefins,[19] esterification-nitration of *ortho*-hydroxyphenyl carboxylic acids and benzoic acids,[20] oxidation of phenols,[21] the addition of azide to cinnamic ester,[22] the protection and deprotection of 4-oxo-4H-1-benzopyran-3-carbaldehydes,[23] oxidative deprotection of benzylic tetrahydropyranyl ethers,[24] direct thiocyanation of enolisable ketones,[25] and nitration of phenol, cresol, and anisole.[26] The unique catalytic feature of CAN is very different from a conventional acidic catalyst. Recently, it has also been utilized to catalyze the synthesis of β-keto enol ethers,[27] 3,3-di(heteroaryl)indolin-2-one[28] and 1,5-benzodiazepine derivatives.[29] This prompted us to explore further applications of CAN as a Lewis acid catalyst in organic synthesis. Herein, we wish to describe the enamination of 1,3-dicarbonyl compounds to prepare β-amino-α,β-unsaturated ketones and esters under solvent-free conditions using a catalytic amount of CAN (Scheme I).

Scheme I



1 3

RESULTS AND DISCUSSION

The reactions were first carried out using a 1:1 mole ratio of 4-bromoaniline and ethyl acetoacetate in a round-bottom flask with stirring under ambient conditions for 8 h without adding any catalyst under solvent-free conditions. The result showed more than 90% of 4-bromoaniline was

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recovered. It was observed that the reaction proceeded efficiently in the presence of CAN (1 mol%), giving ethyl 3-(4-bromophenylamino) but-2-enoate in 82% yield (Table 1, entry 16) under the same reaction conditions. Lower catalyst loading can also be used with only a slight drop in reaction rate.

Encouraged by this success, we extended the reaction of 1,3-dicarbonyl compounds **1** with a wide range of amines under similar conditions. A variety of primary, benzylic and aromatic amines reacted with acetylacetone effectively to afford the corresponding β-enaminone in good to excellent yields (Table 1). It has been observed that the substituent properties of the aniline have an effect toward the dicarbonyls on the rate and yield. Anilines containing electron-withdrawing groups, such as 4-chloroaniline afforded the corresponding β-enamino ketone in 80% yield after 3 h (Table 1, entry 6), which showed an obvious electronic effect. It should be pointed out that in the reaction of 1-benzoylacetone with amines the regioselective amination of the aliphatic carbonyl group (Table 1, entries 7 and 8) was observed.

Also, this protocol can be extended for the preparation of β-amino-α,β-unsaturated esters. Linear (Table 1, entries 9-17) and cyclic (Table 1, entries 18-20) β-ketoesters were treated with a wide range of amines such as aliphatic, cyclic and aromatic amines under the same reaction conditions. In all cases, the reactions proceeded rapidly and smoothly at room temperature in comparison with other methods; the products were obtained in excellent yields and chemoselectivity to afford *Z*-β-enaminones, confirmed by ^{1}H NMR spectrum of the products. It is noteworthy that in the case of 1,3-diaminopropane, 2 equiv of ethyl acetoacetate was used giving products with two enamino ester groups (Table 1, entry 17). Moreover, the optically active amine was converted into the corresponding β-ketoesters without any racemization or inversion by measuring its optical rotation and comparing with the literature values (Table 1, entry 20).

In conclusion, we have developed a facile and efficient procedure for the enamination of 1,3-dicarbonyl compounds using a catalytic amount of CAN at room temperature. The present method has the following advantages compared to those reported in the previous literature: (1) it is fast and efficient, employs a cheap, non-toxic CAN as catalyst; (2) has a simple workup procedure and high yield of products; (3) takes place under solvent-free conditions; and (4) has good substrate generality.

EXPERIMENTAL SECTION

Melting points were recorded on an X-4 apparatus and are uncorrected. IR spectra were recorded using a Bio-Rad FTS 135 spectrophotometer. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker spectrometer using TMS as internal standard. Mass spectra were performed on a ThermoFinnigan LCQ Advantage instrument with an ESI source. The elemental analyses were carried out in an Elemental Vario EL analyzer.

A Typical Procedure for the Enamination of 1,3-Dicarbonyl Compounds

In a 25 mL round-bottom flask, equimolar amounts of amine (5 mmol) and 1,3-dicarbonyl compounds along with the catalyst (0.05 mmol) were placed. The mixture was stirred at room temperature for the specified time (Table 1). After completion of the reaction, the product was extracted with ethyl acetate (3 × 10 mL) and washed with brine solution. The combined organic phases were dried over anhydrous sodium sulfate and concentrated under vacuum. The crude product thus was purified by column chromatography on silica gel using ethyl acetate-*n*-hexane (2:8 v/v).

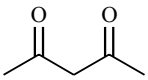
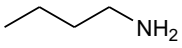
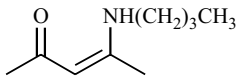
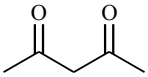
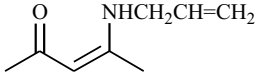
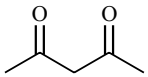
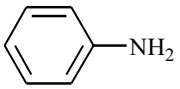
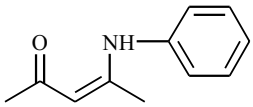
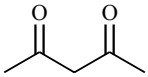
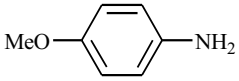
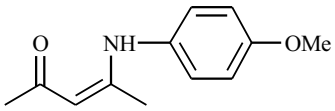
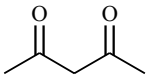
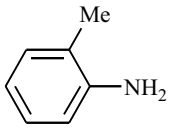
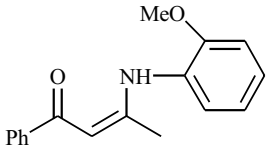
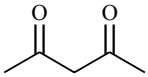
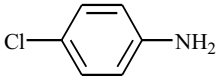
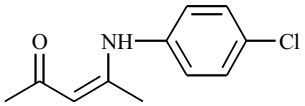
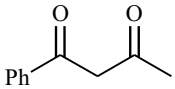
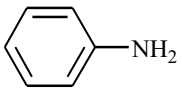
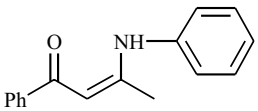
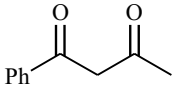
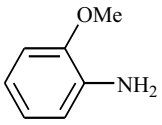
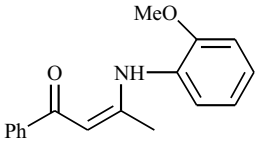
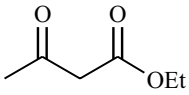
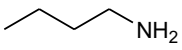
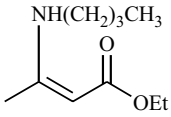
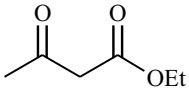
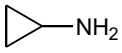
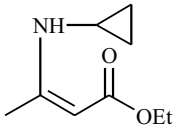
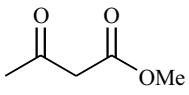
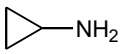
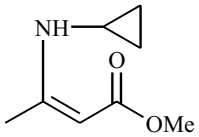
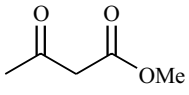
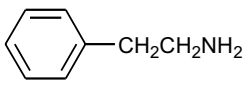
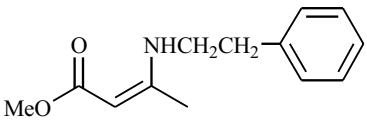
(*Z*)-Ethyl 3-(cyclopropylamino)but-2-enoate (entry 10)

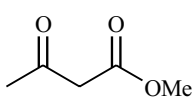
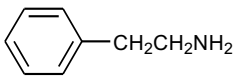
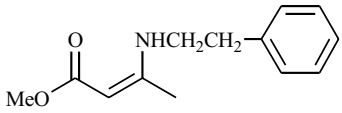
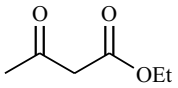
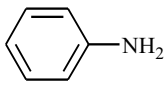
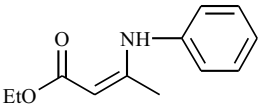
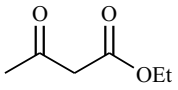
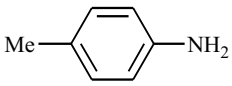
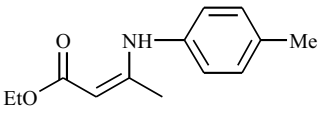
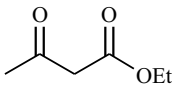
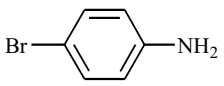
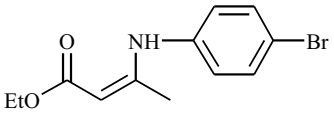
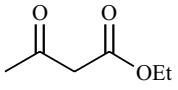
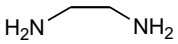
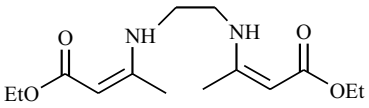
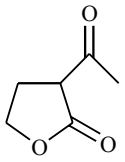
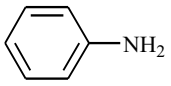
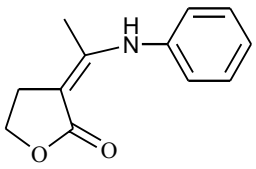
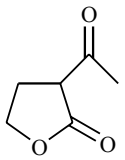
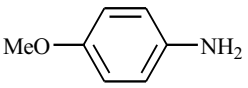
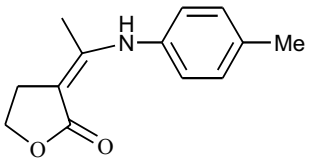
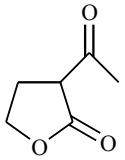
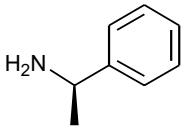
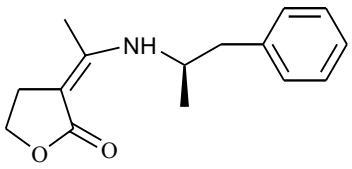
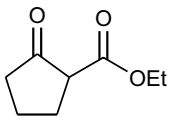
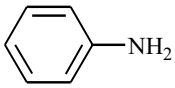
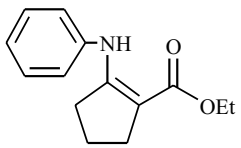
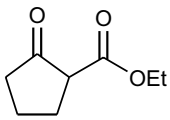
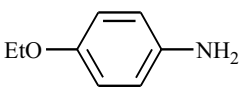
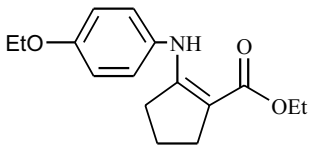
Yellowish oil. IR (neat) ν_{max} 3291, 3089, 2980, 2901, 1687, 1654, 1609, 1491, 1439, 1339, 1267, 1160, 1062, 1027, 902, 785 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.55-0.61 (m, 2H), 0.70-0.77 (m, 2H), 1.23 (t, J = 7.2 Hz, 3H), 2.05 (s, 3H), 2.52-2.60 (m, 1H), 4.07 (q, J = 7.2 Hz, 2H), 4.48 (s, 1H), 8.54 (br s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 7.6, 14.5, 19.7, 24.6, 58.2, 82.6, 163.5, 170.3; ESI-MS: 170 $(M+1)^+$; Anal. Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.93; N, 8.28; Found: C, 64.06; H, 8.82; N, 8.50.

(*Z*)-Methyl 3-(cyclopropylamino)but-2-enoate (entry 11)

Yellowish oil. IR (neat) ν_{max} 3521, 3294, 3006, 2948, 1691, 1655, 1608, 1493, 1339, 1269, 1163, 1062, 930, 785 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.56-0.61 (m, 2H), 0.71-0.77 (m, 2H), 2.05 (s, 3H), 2.52-2.60 (m, 1H), 3.60 (s, 3H), 4.48 (s, 1H), 8.53 (br s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 7.5, 19.7, 24.5, 49.7, 82.2, 163.6, 170.6; ESI-MS: 156 $(M+1)^+$;

Table 1. CAN mediated the enamination of 1,3-dicarbonyl compounds

Entry	1,3-Dicarbonyl Compounds	Amines	Products	Time (min)	Yield (%)[a]
1				15	94
2				20	95
3				15	94
4				12	95
5				15	93
6				360	80
7				60	83
8				100	88
9				18	96
10				10	95
11				10	93
12				15	93

13				15	94
14				60	92
15				50	94
16				360	82
17				25	92[b]
18				80	93
19				70	95
20				45	92
21				90	91
22				100	95

[a] Isolated yield. [b] 2 Equiv of ethyl acetoacetate (with respect to ethane-1,2-diamine) was used.

Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03; Found: C, 61.71; H, 8.20; N, 9.25.

(*Z*)-Methyl 3-(phenethylamino)but-2-enoate (entry 12)

Yellowish oil. IR (neat) ν_{max} 3289, 3021, 2945, 2864, 1652, 1603, 1498, 1441, 1287, 1265, 1170, 1114, 932, 751 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.82 (s, 3H), 2.84 (t, J = 7.2 Hz, 2H), 3.45 (q, J = 7.2 Hz, 2H), 3.61 (s, 3H), 4.42 (s, 1H), 7.28-7.33 (m, 5H), 8.65 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.7, 37.7, 45.2, 50.5, 82.3, 127.0, 129.1, 129.2, 139.0, 162.2, 171.2; Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39; Found: C, 71.48; H, 8.02; N, 6.18.

(*Z*)-Ethyl 3-(4-bromophenylamino)but-2-enoate (entry 16)

Pale yellow solid; mp 50-51 ºC. IR (KBr) ν_{max} 3275, 2977, 1646, 1609, 1579, 1479, 1384, 1260, 1168, 1063, 853, 789, 546 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (t, J = 7.2 Hz, 3H), 1.98 (s, 3H), 4.15 (q, J = 7.2 Hz, 2H), 4.71 (s, 1H), 6.95 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 10.35 (br s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.5, 20.2, 58.9, 117.9, 125.7, 132.1, 138.6, 162.3, 170.3; ESI-MS (negative mode): 382 $(M-1)^-$; Anal. Calcd for $C_{12}H_{14}BrNO_2$: C, 50.72; H, 4.97; N, 4.93; Found: C, 50.45; H, 5.10; N, 5.05.

3-(1-((*R*)-1-Phenylethylamino)ethylidene)-dihydrofuran-2(3*H*)-one (entry 20)

Pale yellow solid, mp 72-74 ºC (Lit.[30] mp 71-73 ºC); $[\alpha]_D^{20}$: -508 (*c* 1.05, EtOH) (Lit.[30] $[\alpha]_D^{20}$: -506); IR (KBr): ν = 3436, 3055, 2958, 1687, 1608, 1479, 1444, 1408, 1371, 1223, 1099, 1021, 768 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.51 (d, J = 6.6 Hz, 3H), 1.78 (s, 3H), 2.80 (t, J = 6.6 Hz, 2H), 4.27 (t, J = 6.6 Hz, 2H), 4.57-4.67 (m, 1H), 7.22-7.36 (m, 5H), 8.63 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 6.8, 24.7, 26.4, 52.9, 65.2, 86.2, 125.5, 127.2, 128.8, 145.1, 156.4, 174.0; ESI-MS: 232 $(M+1)^+$; Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06; Found: C, 72.90; H, 7.58; N, 5.88.

Ethyl 2-(phenylamino)cyclopent-1-enecarboxylate (entry 21)

Yellowish oil. IR (neat) ν_{max} 3284, 2956, 1655, 1623, 1503, 1479, 1263, 1171, 1048, 753 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31 (t, J = 7.2 Hz, 3H), 1.83-1.92 (m, 2H), 2.57 (t, J = 7.2 Hz, 2H), 2.80 (t, J = 7.2 Hz, 2H), 4.22 (q, J = 7.2 Hz, 2H), 7.03-7.30 (m, 5H), 9.60 (br s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.5, 21.6, 28.6, 33.5, 59.0, 97.6, 120.5, 123.0, 129.1, 140.6, 160.2, 168.5; ESI-MS: 232 $(M+1)^+$; Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06; Found: C, 72.52; H, 7.18; N, 6.30.

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