

Note

Ceric(IV) ammonium nitrate catalyzed synthesis of β -enaminones

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β -Enaminones have been synthesized in good yield from 1,3-dicarbonyl compounds and activated amines in the presence of ceric ammonium nitrate as catalyst.

Keywords: β -Enaminones, ceric ammonium nitrate, 1,3-dicarbonyl compounds, catalysis

β -Enaminones have received significant attention in the modern synthetic organic chemistry¹ due to their important role as valuable precursors for the synthesis of bioactive molecules such as oxytocin antagonists², dopamine auto-receptor agonists³, acetylcholinesterase inhibitor⁴ and anticonvulsants⁵. The most common method for the synthesis of β -enaminones is the reaction between β -diketone and amine in the presence of benzene by azeotropic removal of water⁶. Moreover, synthesis of β -enaminones were demonstrated subsequently by using $\text{BF}_3\text{-Et}_2\text{O}$ (Ref 7), alumina^{8a}, montmorillonite K-10 (Ref 8), microwave irradiation⁹, NaAuCl_4 (Ref 10), bismuth(III) trifluoroacetate¹¹, erbium triflate¹², zirconium(IV) chloride¹³, reductive cleavage of silyloxazoles¹⁴, ionic liquid¹⁵, $\text{Yb}(\text{OTf})_3$ (Ref 16), and direct condensation of amines with diketones in water¹⁷. Many of the reported procedures suffer from certain drawbacks such as drastic reaction conditions, low yields and the use of costly or sensitive reagents. Ceric(IV) ammonium nitrate (CAN) has been widely used¹⁸ in the carbon-carbon and carbon-heteroatom bond forming reactions and also as a powerful one electron oxidant¹⁹ in organic synthesis for several years. In continuation to the efforts²⁰ to develop novel

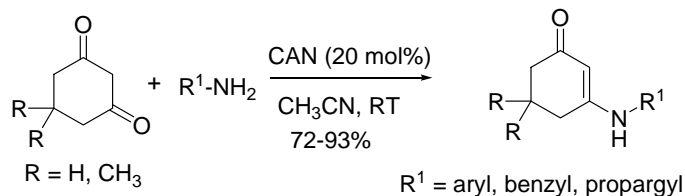
synthetic methodologies by using cheap and commercially available CAN as a catalyst, herein is reported a mild and efficient method for the synthesis of β -enaminones from 1,3-dicarbonyl compounds and activated primary amines such as aryl, benzyl, allyl and propargyl amines catalyzed by ceric ammonium nitrate.

Results and Discussion

In a typical experiment, a solution of 1,3-dicarbonyl compound (2 mmole) and activated amine (2 mmole) in acetonitrile was stirred at RT in the presence of a catalytic amount of CAN (0.4 mmole, 20 mol%) to afford β -enaminones in good to excellent yields (**Scheme I**). The crude product was pure enough to characterize without further purification by chromatography.

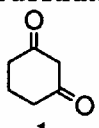
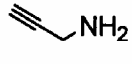
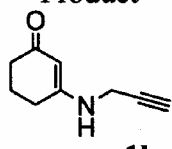
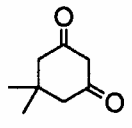
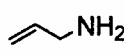
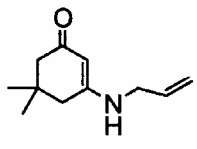
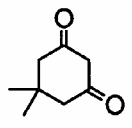
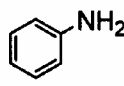
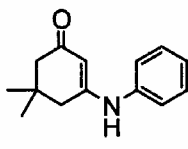
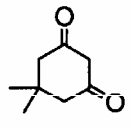
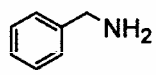
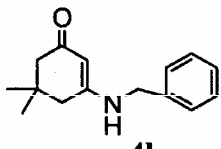
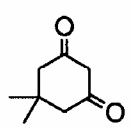
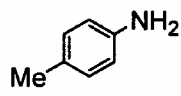
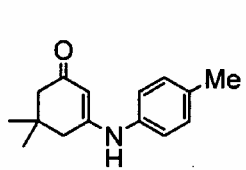
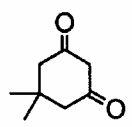
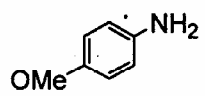
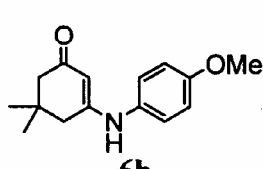
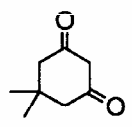
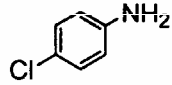
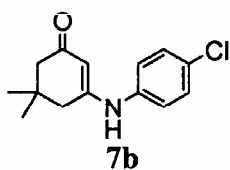
Thus, cyclohexane-1,3-dione, 5,5-dimethylcyclohexane-1,3-dione (dimedone), acetylacetone and ethyl acetoacetate were subjected to the amination reaction at RT with various primary amines in the presence of a catalytic amount of CAN (20 mol%) to furnish β -enaminones and the results are summarized in **Table I**. The reaction proceeded in a clean fashion at RT without the formation of any other products. It was observed that aromatic and benzylic primary amines reacted much faster compared to the propargyl amine (Entries 1 and 2). It is noteworthy that the amination reaction did not proceed at all with aliphatic and secondary or tertiary amines even after prolonged stirring. It is interesting to observe here that there is a report²¹ wherein the acyclic 1,3-diketones on treatment with excess of CAN in acetonitrile at RT yielded carboxylic acids as the sole product. But the present amination reaction with a catalytic amount of CAN (20 mol%) furnished only the β -enaminones in satisfactory yields (Entries 11-14) without the isolation of any carboxylic acids.

In conclusion, a mild and efficient method has been developed for the synthesis of β -enaminones from



Scheme I

Table I—CAN catalyzed amination of β -dicarbonyl compounds

Entry	Substrate	Amine	Product	Time (min)	Yield ^a
1	 1a		 1b	30	79
2	 2a		 2b	28	81
3	 2a		 3b	4	84
4	 2a		 4b	8	88
5	 2a		 5b	12	86
6	 2a		 6b	5	93
7	 2a		 7b	10	72

—Contd

Table I—CAN catalyzed amination of β -dicarbonyl compounds—*Contd*

Entry	Substrate	Amine	Product	Time (min)	Yield ^a
8				3	92
9				15	79
10				18	89
11				8	90
12				7	86
13				10	70
14				9	75

^aYields refer to pure isolated products.

β -diketones and various activated amines catalyzed by ceric ammonium nitrate at RT in good to excellent yield.

Experimental Section

Typical procedure: A solution of 5,5-dimethylcyclohexane-1,3-dione **2a** (280 mg, 2.0 mmol) and *p*-anisidine (248 mg, 2.0 mmol) in dry acetonitrile (20 mL) was stirred with CAN (219 mg, 0.4 mmol) at

RT under N₂ for 5 min. Then the volatiles were removed under reduced pressure and the residue obtained was extracted with ethyl acetate (2 × 50 mL). The combined organic layer was washed successively with water (20 mL) and brine (20 mL) and finally dried over anhyd. Na₂SO₄. The solvent was removed under reduced pressure and the residue obtained was purified by column chromatography over silica gel (50% ethyl acetate in petroleum ether)

to furnish the pure β -enaminone **6b** (228 mg, 93%) as a viscous oil. IR (neat): 3257, 2958, 1716, 1510, 1242 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz): δ 1.09 (s, 4H), 2.22 (s, 3H), 2.33 (s, 3H), 3.80 (s, 3H), 5.41 (s, 1H), 6.86 (d, $J = 8.7$ Hz, 2H), 7.08 (d, $J = 8.7$ Hz, 2H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 198.3, 175.7, 164.9, 157.7, 130.6, 126.1, 114.4, 96.5, 55.5, 49.3, 46.1, 42.8, 32.8, 28.3, 21.1; HRMS: Calcd. for $\text{C}_{15}\text{H}_{20}\text{O}_2\text{N}$: m/z $[\text{M}+\text{H}]^+$ 246.1488. Found 246.1480.

All the products were characterized by IR, NMR and HRMS analysis and by comparing the data with authentic samples⁶⁻¹⁷.

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References

- 1 *The Chemistry of Enamines*, edited by Rappoport Z, Part 1 (John Wiley and Sons, New York), **1994**.
- 2 Bell I M, Erb J M, Freidinger R M, Gallicchio R A, Hobbs D W, Hominck C F, Kuo M S, Lis E V, Mathse D J, Michelson S R, Pawluczak J M, Pettibone D J, Reiss D R, Michelson S R, Pawluczak J M, Pettibone D J, Reiss D R, Vickers S, Williams P D & Woyden C J, *J Med Chem*, **41**, **1998**, 2146.
- 3 Caprathe B W, Jaen J C, Wise L D, Heffner T G, Pudsley T A, Melther L T & Parvez M, *J Med Chem*, **34**, **1991**, 3726.
- 4 Gatta F, Del Giudice M R, Pomponi M & Marta M, *Heterocycles*, **34**, **1992**, 991.
- 5 Scott K R, Edafiogho I O, Richardson E C, Farrar V A, Moore J A, Tietz E I, Hinko C N, Chang H, El-Assadi A & Nicholson J M, *J Med Chem*, **36**, **1993**, 1947.
- 6 Martin D F, Janusonis G A & Martin B B, *J Am Chem Soc*, **83**, **1961**, 73.
- 7 Azzaro M, Geribaldi S & Videan B, *Synthesis*, **1981**, 880.
- 8 (a) Texier-Boullet F, Kelin B & Hamelin J, *Synthesis*, **1986**, 409; (b) Braibante M E F, Braibante H S, Missio L & Andricoputo A, *Synthesis*, **1994**, 898; (c) Valduga C J, Squizani A, Braibante H S & Braibante M E F, *Synthesis*, **1998**, 1019.
- 9 Rechsteiner B, Texier-Boullet F & Hamelin J, *Tetrahedron Lett*, **34**, **1993**, 5071.
- 10 Arcadi A, Bianchi G, Di Giuseppe S & Marinelli F, *Green Chemistry*, **2003**, 64.
- 11 Khosropour A R, Khodaei M M & Kookhazadeh M, *Tetrahedron Lett*, **45**, **2004**, 1725.
- 12 Dal Pozzo R, De Nino A, Nardi M, Russo B & Procopio A, *Synthesis*, **2006**, 1127.
- 13 Lin J & Zhang L F, *Monatsh Chem*, **138**, **2007**, 77 and references cited therein.
- 14 Calle M, Calvo L A, Gonzales-Ortega A & Gonzales-Nogal A, *Tetrahedron*, **62**, **2006**, 611.
- 15 Bhosale R S, Suryawanshi P A, Ingle S A, Lokhande M N, More S P, Mane S B, Bhosale S V & Pawar R P, *Synlett*, **2006**, 933.
- 16 Epifano F, Genovese S & Curini M, *Tetrahedron Lett*, **48**, **2007**, 2717.
- 17 Stefani H A, Costa I M & Silva D G, *Synthesis*, **2000**, 1526.
- 18 (a) Imamoto T in *Lanthanide Reagents in Organic Synthesis* (Academic Press, London), **1994**, p. 119; (b) Moreno-Dorado F J, Guerra F M, Manzano F L, Aladro F J, Jorge Z D & Massanet G M, *Tetrahedron Lett*, **44**, **2003**, 6691; (c) Zhan Z-P & Lang K, *Org Biomol Chem*, **3**, **2005**, 727; (d) Adinolfi M, Iadonisi A, Ravida A & Schiattarella M, *J Org Chem*, **70**, **2005**, 5316; (e) Nair V, Panicker S B, Nair L G, George T G & Augustine A, *Synlett*, **2003**, 156.
- 19 (a) Nair V, Mathew J & Prabhakaran J, *Chem Soc Rev*, **1997**, 127; (b) Molander G A, *Chem Rev*, **92**, **1992**, 29; (c) Pan W-B, Chang F-R, Wei L-M, Wu M-J & Wu Y-C, *Tetrahedron Lett*, **44**, **2003**, 331 and references cited therein.
- 20 (a) Roy S C, Rana K K, Guin C & Banerjee B, *Synlett*, **2003**, 221; (b) Roy S C, Rana K K, Guin C & Banerjee B, *ARKIVOC*, **IX**, **2003**, 34; (c) Banerjee B, Mandal S K & Roy S C, *Chemistry Letters*, **35**, **2006**, 16 and references cited therein.
- 21 Zhang Y, Jiao L & Flowers R B II, *J Org Chem*, **71**, **2006**, 4516.