Cerium(IV) Ammonium Nitrate-catalyzed Synthesis of β-Keto Enol Ethers from Cyclic β-Diketones and Their Deprotection

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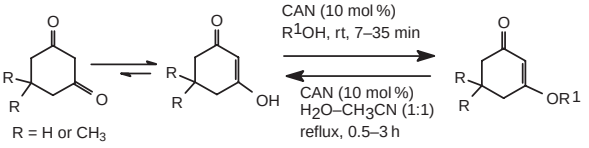
A mild and efficient method for etherification of cyclic β-diketones with alcohols has been developed using a catalytic amount of cerium(IV) ammonium nitrate at room temperature to afford the corresponding β-keto enol ethers in good to excellent yields. The deprotections of enol ethers in water–acetonitrile (1:1) using a catalytic amount (10 mol %) of cerium(IV) ammonium nitrate have also been achieved.

β-Keto enol ethers are versatile intermediates in synthetic organic chemistry.[1] For example, they have been widely used as precursors for the synthesis of different optically active compounds.[2] Usually, ethers are prepared by coupling reactions of alkoxide or alcohols with different alkyl halides in basic conditions.[3] Although several methods have been demonstrated for the synthesis of β-keto enol ethers from cyclic β-diketones such as *p*-toluene sulfonic acid catalyzed etherification,[4] methyl ether from 3-chlorocycloalk-2-enones,[5] methylation using diazomethane,[1] and catalytic etherification by $TiCl_4$,[6] iodine,[7] and $B(C_6F_5)_3$,[8] the use of lanthanides as reagents in this field is not much explored. In recent years, several lanthanide complexes have proven to be extraordinarily effective catalysts for various organic transformations.[9] We wish to report here a mild and efficient synthesis of β-keto enol ethers from cyclic β-diketones in good to excellent yields using a catalytic amount of CAN (10 mol %) at room temperature.

Cerium(IV) ammonium nitrate (CAN) has been widely used in carbon–carbon[9] as well as carbon–heteroatom[10] bond forming reactions and also as a powerful one electron oxidant[11] in organic synthesis for several years. In continuation to our efforts[12] to develop novel methodologies in organic synthesis using commercially available CAN as a catalyst, we treated cyclic β-diketones with an excess of alcohols (also act as solvents) at room temperature to afford the corresponding β-keto enol ethers in good to excellent yields (Scheme 1).

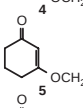
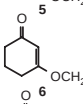
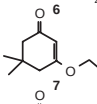
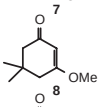
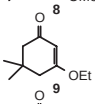
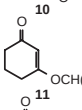
Thus, cyclohexan-1,3-dione and 5,5-dimethylcyclohexan-1,3-dione (dimedone) were subjected to the etherification reaction[13] at room temperature with various alcohols in the presence of a catalytic amount of CAN (10 mol %) to furnish β-keto enol ethers **1**–**12** and the results are summarized in Table 1.

Although primary (Entries 1–10) as well as secondary alcohols (Entries 11 and 12) underwent smoothly at room temperature, the reaction with secondary alcohols took place with an increased reaction time and with a lower yield of products compared to the reaction with primary alcohols. The etherification did not undergo at all with sterically crowded *tert*-butanol under the reaction conditions. It is noteworthy that the reaction of propargyl alcohol (Entry 7) and allyl alcohol (Entry 10) underwent smoothly with dimedone giving excellent yields of the β-keto enol ethers **7** and **10**, respectively.



Scheme 1.

Table 1. CAN-catalyzed etherification of cyclic β-diketones and their deprotection

Entry	Substrate	Alcohol	Product[a]	Yield (%) of enol ether (reaction time)	Yield (%) of deprotection (reaction time)
1		MeOH	 **1**	93 (8 min)	91 (0.5 h)
2		EtOH	 **2**	91 (7 min)	92 (0.5 h)
3		$CH_3(CH_2)_2CH_2OH$	 **3**	88 (12 min)	90 (0.75 h)
4		$CH_3(CH_2)_4CH_2OH$	 **4**	86 (22 min)	84 (1 h)
5		$PhCH_2OH$	 **5**	90 (15 min)	88 (0.75 h)
6		$PhCH_2CH_2OH$	 **6**	89 (14 min)	83 (1 h)
7			 **7**	89 (18 min)	84 (2 h)
8		MeOH	 **8**	92 (9 min)	90 (0.5 h)
9		EtOH	 **9**	90 (10 min)	89 (0.5 h)
10			 **10**	90 (16 min)	87 (1.5 h)
11		$(CH_3)_2CHOH$	 **11**	70 (25 min)	80 (2.5 h)
12			 **12**	62 (35 min)	75 (3 h)

[a]Products were characterized by NMR, IR, and HRMS analysis and also by comparing the spectral data with those of authentic samples.

We have also successfully deprotected[14] the β-keto enol ethers (**1**–**12**) to the corresponding cyclic β-diketones in good

to excellent yields by treatment with CAN (10 mol %) in water–acetonitrile (1:1) under reflux condition as depicted in Table 1. However, open chain β-diketones such as acetylacetone and benzoylacetone when treated with MeOH in the presence of a catalytic amount of CAN remained unchanged even after prolonged stirring. These open chain β-diketones preferably exist in *cis*-enol form in the solution and serve as bidentate ligands which may form a stable cerium complex.[6] In contract, enolization of cyclic β-diketones forms fixed *trans*-enols where no such complex formation is sterically possible.

In summary, we have developed a mild and efficient CAN-catalyzed method for the synthesis of β-keto enol ethers from β-diketones at room temperature in good to excellent yields. We have also developed a method for deprotection of β-keto enol ethers to the corresponding cyclic β-diketones in water–acetonitrile under reflux condition catalyzed by CAN (10 mol %).

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13 Typical procedure for etherification: A solution of 5,5-dimethylcyclohexan-1,3-dione (dimedone) (140 mg, 1 mmol) in 3-methylcycloxehanol (3 mL) was stirred with CAN (55 mg, 0.1 mmol) at room temperature under N_2 for 35 min. Then excess alcohol was removed under reduced pressure and the residue obtained was extracted with ether (2×50 mL). The combined ether layer was washed successively with water (20 mL) and brine (20 mL) and finally dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue obtained was purified by column chromatography over silica gel (30% ethyl acetate in petroleum ether) to obtain the pure β-keto enol ether **12** (147 mg, 62%) as a crystalline solid, mp 50–52 °C; IR (KBr): 2933, 2866, 1654, 1602, 1367, 1220 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.92 (d, $J = 6.5$ Hz, 3H), 1.05 (s, 6H), 1.12–1.46 (m, 4H), 1.61–2.06 (m, 5H), 2.19 (s, 2H), 2.22 (s, 2H), 4.03–4.13 (m, 1H), 5.36 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.0, 23.6, 28.0, 28.1, 31.0, 31.1, 32.2, 33.8, 39.7, 43.2, 50.4, 76.8, 101.6, 175.0, 199.5; HRMS Calcd for $C_{15}H_{24}O_2$: $[M + H]^+$ 237.1855. Found 237.1829.
14 Typical procedure for deprotection of enol ethers: A mixture of the β-keto enol ether **12** (354 mg, 1.5 mmol) and CAN (82 mg, 0.15 mmol) in water (3 mL) in acetonitrile (3 mL) was refluxed for 3 h under N_2. Then the mixture was diluted with saturated brine (20 mL) and extracted with ether (2×50 mL). The combined ether extract was washed with brine (20 mL) and finally dried (Na_2SO_4). Solvent was removed under reduced pressure and the residue obtained was purified by column chromatography on silica gel (40% ethyl acetate in petroleum ether) to obtain 5,5-dimethylcyclohexan-1,3-dione (dimedone) (158 mg, 75%).

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