

## Ytterbium triflate catalyzed synthesis of $\beta$ -keto enol ethers

Massimo Curini,<sup>a,\*</sup> Francesco Epifano<sup>b</sup> and Salvatore Genovese<sup>a</sup>

<sup>a</sup>*Dipartimento di Chimica e Tecnologia del Farmaco, Sezione di Chimica Organica, Universit  di Perugia, Via del Liceo, 06123 Perugia, Italy*

<sup>b</sup>*Dipartimento di Scienze del Farmaco, Via dei Vestini 31, 66013 Chieti Scalo, Italy*

Received 18 February 2006; revised 14 April 2006; accepted 26 April 2006

Available online 19 May 2006

**Abstract**— $\beta$ -Keto enol ethers have been synthesized in very good yield in solvent-free conditions from differently substituted alcohols and  $\beta$ -diketones in the presence of  $\text{Yb}(\text{OTf})_3$  as catalyst. The method is applicable to both cyclic and acyclic  $\beta$ -diketones with only slight differences in the experimental procedure.

  2006 Elsevier Ltd. All rights reserved.

$\beta$ -Keto enol ethers have been extensively used as key intermediates in organic synthesis.<sup>1–5</sup> In particular, they have been employed as synthons of natural products incorporating a cyclohexenone skeleton (i.e., 4-(2'-*p*-methoxyphenyl)-cyclohexen-2-one isolated from gametophytic tissues of *Plagiochila longispina* Lindenb. & Gottsche).<sup>6</sup>

$\beta$ -Keto enol ethers have been usually prepared starting from  $\beta$ -diketones by treatment with diazomethane,<sup>1</sup> with alcohols and *p*-toluenesulfonic acid at reflux,<sup>2</sup> from 3-chloro-cycloalk-2-enones with methoxide,<sup>3,4</sup> from  $\beta$ -diketones by reaction with alcohols catalyzed by  $\text{TiCl}_4$ ,<sup>7</sup> iodine,<sup>8</sup>  $\text{InCl}_3$  supported on silica,<sup>9</sup>  $\text{B}(\text{C}_6\text{F}_5)_3$ ,<sup>10</sup> or finally promoted by microwaves and *p*-toluenesulfonic acid.<sup>11</sup> Unfortunately, many of these processes suffer major or minor limitations, such as drastic reaction conditions, low yields, tedious work-up procedures and co-occurrence of several side reactions. Moreover, in the case of Lewis acid catalyzed reactions, no recycling of the catalyst renders these methods environmentally unsound, especially with regard to a potential application to large-scale synthesis. So, although different methods are available for the synthesis of the above cited compounds, development of another facile, high-yielding, nonpolluting preparation is still of great importance.

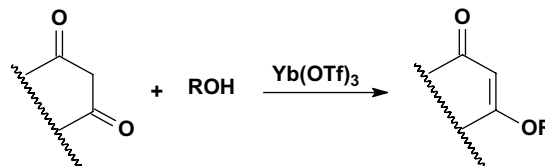
During the last decade, rare earth metal triflates have been found as unique Lewis acids in that they are water

tolerant reusable catalysts and they can effectively promote several carbon–carbon bond and carbon–heteroatom formation reactions in good yield.<sup>12</sup>

As a part of our ongoing studies to explore the utility of lanthanide triflates catalyzed reactions in solvent-free conditions,<sup>13</sup> we decided to investigate the use of  $\text{Yb}(\text{OTf})_3$  as a catalyst for the preparation of  $\beta$ -keto enol ethers (Scheme 1).

Initially, we tested this type of reaction using cyclic  $\beta$ -diketones as starting materials because these compounds have a more predictable reactivity toward this kind of reaction.<sup>7</sup>

The reaction was carried out in neat at room temperature for 12 h using commercially available 1,3-cyclohexanedione (2.0 mmol) and MeOH (2.0 mmol) in the presence of  $\text{Yb}(\text{OTf})_3$  hydrate (0.01 mmol) as catalyst. After addition of NaOH 1 N to precipitate Yb(III) as the corresponding hydroxide and extraction with  $\text{Et}_2\text{O}$ , the desired product (**1**) was obtained in 93% yield. This protocol was then applied to all other reactions carried out employing structurally different alcohols. Results



Scheme 1.

\* Corresponding author. Fax: +39 0755855116; e-mail: [curmax@unipg.it](mailto:curmax@unipg.it)

are summarized in Table 1 and show that methyl, primary, secondary, and benzylic alcohols react without any significant difference to give the corresponding  $\beta$ -keto enol ether in nearly quantitative yield. Loading of the catalyst upper than 0.01 mmol did not increase reaction times significantly.

Employing linear  $\beta$ -diketones as substrates, such commercially available acetylacetone, using the same reac-

tion conditions reported above, the corresponding  $\beta$ -keto enol ethers were obtained in very low yield (<10%). An hypothesis to explain this difference in reactivity with respect to cyclic  $\beta$ -diketones could be the one suggested by Yogeve and Mazur:<sup>16</sup> linear  $\beta$ -diketones in fact exist predominantly in the *cis*-enol form and so are capable to act as bidentate ligands to chelate the metal center yielding a stable ( $\beta$ -diketonato)<sub>3</sub>-Yb(III) complex in which the coordinative sites of the lanthanide are

**Table 1.** Yb(OTf)<sub>3</sub> catalyzed formation of  $\beta$ -keto enol ethers

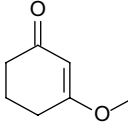
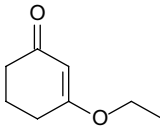
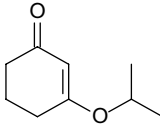
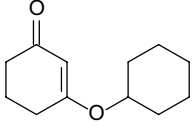
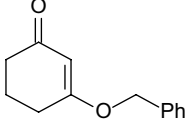
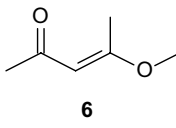
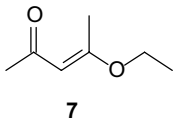
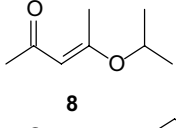
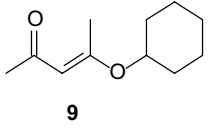
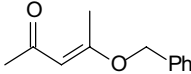
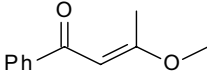
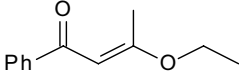
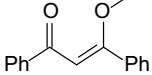
Reactant	Alcohol	Product	Yield <sup>a</sup> (%)
1,3-Cyclohexanedione	Methanol	 <b>1</b>	93
1,3-Cyclohexanedione	Ethanol	 <b>2</b>	95
1,3-Cyclohexanedione	Isopropanol	 <b>3</b>	99
1,3-Cyclohexanedione	Cyclohexanol	 <b>4</b>	99
1,3-Cyclohexanedione	Benzyl alcohol	 <b>5</b>	99
Acetylacetone	Methanol	 <b>6</b>	95
Acetylacetone	Ethanol	 <b>7</b>	99
Acetylacetone	Isopropanol	 <b>8</b>	76
Acetylacetone	Cyclohexanol	 <b>9</b>	60

Table 1 (continued)

Reactant	Alcohol	Product	Yield <sup>a</sup> (%)
Acetylacetone	Benzyl alcohol	 <b>10</b>	74
Benzoylacetone	Methanol	 <b>11</b>	89
Benzoylacetone	Ethanol	 <b>12</b>	84
Dibenzoylacetone	Methanol	 <b>13</b>	76

<sup>a</sup> Yields of pure isolated products, characterized by IR, GC-MS, <sup>1</sup>H NMR and <sup>13</sup>C NMR.

saturated.<sup>17</sup> Consequently neither coordination of alcohols to the metal, nor regeneration of the catalyst would occur, thus preventing the implementation of an efficient catalytic cycle. On the other hand, cyclic  $\beta$ -diketones exist in a *trans*-enol form and so coordination to a metal is sterically impossible. Increasing the temperature under reaction conditions may decrease the stability of ( $\beta$ -diketonato)<sub>3</sub>-lanthanide complex getting the catalyst more active as Lewis acid.

The reaction conditions for the synthesis of linear  $\beta$ -keto enol ethers had to be modified and were optimized increasing the catalyst quantity to 0.1 mmol and raising the temperature up to 50 °C. After 12 h the desired products were obtained in good to nearly quantitative yield as reported in Table 1.

From linear  $\beta$ -diketones we always obtained the corresponding  $\beta$ -keto enol ether having a (*E*) configuration of the carbon–carbon double bond, as put in evidence by <sup>1</sup>H NMR analysis and NOE experiments, following the procedure reported by Porta and co-workers,<sup>7</sup> except in the case of using dibenzoylacetone as starting material where a (*Z*) geometry of the double bond was obtained. Its interesting to note that in both kind of reactions no acetal adducts were detected, even in the case of linear  $\beta$ -diketones for which it has been reported that conversion into  $\beta$ -keto enol ether is strongly time-dependent and the reaction catalyzed by Lewis acid or other promoters often yields mixture of enol ether and acetal.<sup>7</sup>

In all cases the catalyst have been recovered by precipitation as Yb(OH)<sub>3</sub>, filtration, and transformation into triflate salt as already reported.<sup>13</sup> Recycled in this way, the catalyst could be reused several times without any loss of activity.<sup>18</sup>

In conclusion, we disclosed an easy and environmentally sound method for the synthesis of  $\beta$ -keto enol ether from ketones and differently substituted alcohols under the catalysis of Yb(OTf)<sub>3</sub>. The simple work-up procedure, mild reaction conditions, and high yields make our methodology a valid contribution to the existing processes in the field of  $\beta$ -keto enol ether synthesis. Further investigations into the scope and other application of Yb(OTf)<sub>3</sub> promoted reactions of  $\beta$ -diketones derivative synthesis (e.g.,  $\beta$ -enaminones) are now in progress in our laboratories and will be reported in due course.

## Experimental

### Synthesis of cyclic $\beta$ -keto enol ethers. Typical procedure

A mixture of  $\beta$ -diketone (2.0 mmol) and alcohol (2.0 mmol) was stirred well with Yb(OTf)<sub>3</sub> (0.01 mmol) at room temperature for 12 h. NaOH 1 N (2 mL) was added, the white precipitate filtered and the resulting solution extracted with Et<sub>2</sub>O (3 × 2 mL). Collected organic phases were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and the solvent evaporated to dryness to give the desired product.

3-Methoxycyclohex-2-en-1-one (**1**): pale yellow oil; <sup>1</sup>H NMR;<sup>8</sup> <sup>13</sup>C NMR;<sup>8</sup> GC/MS: M<sup>+</sup> = 126.

3-Ethoxycyclohex-2-en-1-one (**2**): pale yellow oil; <sup>1</sup>H NMR;<sup>8</sup> <sup>13</sup>C NMR;<sup>8</sup> GC/MS: M<sup>+</sup> = 140.

3-Isopropoxycyclohex-2-en-1-one (**3**): pale yellow oil; <sup>1</sup>H NMR;<sup>8</sup> <sup>13</sup>C NMR;<sup>8</sup> GC/MS: M<sup>+</sup> = 154.

3-(Cyclohexyloxy)cyclohex-2-en-1-one (**4**): pale yellow oil; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>)  $\delta$  1.24–2.39 (m,

16H), 3.45–4.82 (m, 1H), 5.39 (s, 1H);  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ )  $\delta$  199.2, 161.0, 108.4, 80.2, 36.0, 35.3, 28.2, 25.1, 23.8, 20.6; GC/MS:  $M^+$  = 194.

3-(Benzyloxy)cyclohex-2-en-1-one (**5**): pale yellow oil;  $^1\text{H}$  NMR; $^8$   $^{13}\text{C}$  NMR; $^8$  GC/MS:  $M^+$  = 202.

#### Synthesis of acyclic $\beta$ -keto enol ethers. Typical procedure

A mixture of  $\beta$ -diketone (2.0 mmol) and alcohol (2.0 mmol) was stirred well with  $\text{Yb}(\text{OTf})_3$  (0.1 mmol) at 50 °C for 12 h. Following which  $\text{NaOH}$  1 N (2 mL) was added, the white precipitate filtered and the resulting solution extracted with  $\text{Et}_2\text{O}$  ( $3 \times 2$  mL). Collected organic phases were dried over anhydrous  $\text{Na}_2\text{SO}_4$  and the solvent evaporated to dryness to give the desired product.

(3E)-4-Methoxypent-3-en-2-one (**6**): pale yellow oil;  $^1\text{H}$  NMR; $^{14}$   $^{13}\text{C}$  NMR; $^{14}$  GC/MS:  $M^+$  = 114.

(3E)-4-Ethoxypent-3-en-2-one (**7**): pale yellow oil;  $^1\text{H}$  NMR; $^8$   $^{13}\text{C}$  NMR; $^{14}$  GC/MS:  $M^+$  = 128.

(3E)-4-Isopropoxypent-3-en-2-one (**8**): pale yellow oil;  $^1\text{H}$  NMR; $^{15}$   $^{13}\text{C}$  NMR; $^{15}$  GC/MS:  $M^+$  = 142.

(3E)-4-(Cyclohexyloxy)pent-3-en-2-one (**9**): pale yellow oil;  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  1.20–1.85 (m, 10H), 1.99 (s, 3H), 2.04 (s, 3H), 3.55–3.72 (m, 1H), 4.68 (s, 1H);  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ )  $\delta$  196.4, 161.2, 108.4, 80.2, 35.1, 25.0, 23.7, 23.4, 21.5; GC/MS:  $M^+$  = 182.

(3E)-4-(Benzyloxy)pent-3-en-2-one (**10**): pale yellow oil;  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  2.05 (s, 3H), 2.08 (s, 3H), 4.75 (s, 2H), 5.24 (s, 1H), 7.26–7.49 (m, 5H);  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ )  $\delta$  193.1, 165.2, 153.6, 143.5, 142.9, 142.7, 104.9, 86.7, 22.3, 18.1; GC/MS:  $M^+$  = 190.

(2E)-3-Methoxy-1-phenylbut-2-en-1-one (**11**): pale yellow oil.  $^1\text{H}$  NMR; $^{19}$   $^{13}\text{C}$  NMR; $^{19}$  GC/MS:  $M^+$  = 176.

(2E)-3-Ethoxy-1-phenylbut-2-en-1-one (**12**): pale yellow oil.  $^1\text{H}$  NMR; $^{19}$   $^{13}\text{C}$  NMR; $^{19}$  GC/MS:  $M^+$  = 190.

(2Z)-3-Methoxy-1,3-diphenylprop-2-en-1-one (**13**): pale yellow oil.  $^1\text{H}$  NMR; $^{19}$   $^{13}\text{C}$  NMR; $^{19}$  GC/MS:  $M^+$  = 238.

#### Recovery of the catalyst. Typical procedure

The precipitate filtered after work-up of the reaction was suspended in  $\text{H}_2\text{O}$  (2 mL), the mixture was acidified with  $\text{CF}_3\text{SO}_3\text{H}$  and the resulting solution stored at 0 °C for 24 h; the white precipitate formed was filtered, dried at 70 °C for 5 h and used for further reactions.

#### Acknowledgments

Financial support from MIUR National Project ‘Sviluppo di processi sintetici ecocompatibili nella sintesi organica’, COFIN 2004 is gratefully acknowledged. F.E. also wishes to thank Consorzio Cresci, Perugia, Italy. Authors also wish to thank Paola Pisani and Maria Grazia Lamagna for their helpful and friendly collaboration.

#### Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.tetlet.2006.04.121](https://doi.org/10.1016/j.tetlet.2006.04.121).

#### References and notes

- (a) Marshall, D. R.; Roberts, T. R. *J. Chem. Soc.* **1971**, 797–800; (b) House, H. O.; Rasmusson, G. H. *J. Org. Chem.* **1963**, *28*, 27–30; (c) Takahashi, K.; Tanaka, T.; Suzuki, T.; Hirama, M. *Tetrahedron* **1994**, *50*, 1327–1340.
- Zimmerman, H. E.; Wang, P. A. *J. Am. Chem. Soc.* **1993**, *115*, 2205–2216.
- Mphahlele, M. J.; Modro, T. A. *J. Org. Chem.* **1995**, *60*, 8236–8240.
- Nelson, P. H.; Nelson, J. T. *Synthesis* **1992**, 1287–1291.
- Chen, B. C.; Weismiller, M. C.; Davis, F. A. *Tetrahedron* **1991**, *47*, 173–182.
- Liu, H. J.; Tran, D. D. P. *Nat. Prod. Lett.* **1998**, *11*, 251–253.
- Clerici, A.; Pastori, N.; Porta, O. *Tetrahedron* **2001**, *57*, 217–225, and reference cited herein.
- Bhosale, R. S.; Bhosale, S. V.; Wang, T.; Zubaidha, P. K. *Tetrahedron Lett.* **2004**, *45*, 7187–7188.
- Murugan, R.; Kamakshi, R.; Reddy, B. S. R. *Aust. J. Chem.* **2005**, *58*, 228–230.
- Chandrasekhar, S.; Rao, Y. S.; Reddy, N. R. *Synlett* **2005**, *9*, 1471–1473.
- Murugan, R.; Reddy, B. S. R. *Ind. J. Chem. Sect. B.* **2005**, *44*, 1512–1515.
- Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W. L. *Chem. Rev.* **2003**, *6*, 2227–2302.
- Curini, M.; Epifano, F.; Genovese, S.; Marcotullio, M. C.; Rosati, O. *Org. Lett.* **2005**, 1331–1334, and references cited herein.
- Kraus, M. E.; Sy, J. *Org. Synth.* **1989**, *67*, 202.
- Shono, T.; Kashimura, S.; Sawamura, M.; Soejima, T. *J. Org. Chem.* **1988**, *53*, 907–910.
- Yogev, A.; Mazur, Y. *J. Org. Chem.* **1967**, *32*, 2162.
- For the formation of lanthanide- $\beta$ -diketonato complexes see Zhao, Z. X.; Liu, G. F. *Synth. React. Inorg. Met.-Org. Chem.* **2002**, *32*, 465–473.
- After having recovered and recycled the catalyst by the procedure described herein, the reaction to yield compound **1** has been repeated three more times with the following yields: 96%, 97%, 96%.
- Nishino, T. *Synthesis* **1980**, *12*, 1013–1015.