An efficient conversion of β-diketones into β-keto enol ethers with P_2O_5/SiO_2 under solvent-free conditions

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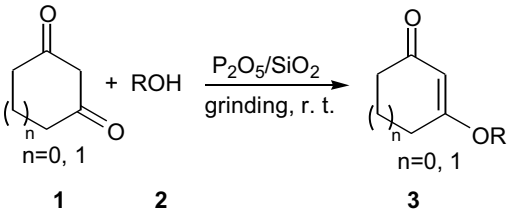
P_2O_5/SiO_2 was found to be an efficient reagent for converting cyclic-β-diketones into their corresponding β-keto enol ethers at room temperature under solvent-free conditions.

Keywords: β-keto enol ethers, cyclic-β-diketones, etherification, phosphorus pentoxide, silica gel, solvent-free conditions

β-Keto enol ethers are versatile intermediates in the synthesis of a vast variety of biologically active natural and synthetic prducts.[1] For example, they are useful precursors for the synthesis of both enantiomers of the pharmacologically interesting 4-hydroxycyclohex-2-en-1-one,[2] tetrahydropyrido[1,2-*b*]-indazole,[3] spirobenzazepines,[4] bicyclo[2.2.2]octane derivatives,[5] optically active 3-alkoxy-6-hydroxymethyl-6-methyl-2-cyclohexenone,[6] the alkaloid aspidospermidine[7] and the asymmetric synthesis of protected C(1)–C(6) and C(7)–C(15) fragments of epothilone A.[8] Due to the importance of these compounds in organic synthesis, a variety of methods for the synthesis of β-keto enol ethers have been developed.[9] One of the most practical and widely used routes for the synthesis of these compounds is the direct etherification of cyclic β-diketones.[10] A variety of catalysts such as *p*-toluenesulfonic acid (*p*-TSA),[11] $TiCl_4$,[12a] cerium (IV) ammonium nitrate,[12b] $B(C_6F_5)_3$,[13] iodine[14] and indium(III) chloride/silica gel[15] have been used to effect this transformation. Nevertheless, the reported methodologies suffer from one or more of the following disadvantages such as high temperature and the use of toxic solvents,[11] expensive as reagents,[13] or the requirement of a special apparatus.[15] Thus, there is need to develop a simple, efficient and practical method for the synthesis of β-keto enol ethers under mild conditions.

In recent years, phosphorus pentoxide has been widely used to promote various organic transformations.[16] The advantages are that it is an inexpensive and selective reagent, which gives high yields in simple operations under solvent-free conditions and in short reaction times.[17] P_2O_5/silica gel is stable and can be kept at room temperature for months without losing its activity.[18] It has been reported as an efficient medium for the oxidation of sulfides to the corresponding sulfoxides,[18] the esterification of phenols,[19] Beckmann-type rearrangement,[20] the Fries rearrangement,[21] the sulfonylation of aromatic rings,[22] the conversion of aldehydes into their corresponding acylals,[23] the acylation of alcohols, phenols and amines,[24] the acetalisaton of carbonyl compounds,[25] the synthesis of nitriles,[26] the preparation of *Z*-aldoximes,[27] the formation[28] and selective deprotection[29] of 1,1-diacetates, and the nitration of aromatic compounds.[30] As part of our ongoing interest in the use of cheap and eco-friendly materials as catalysts for various transformations,[31] we wish to report herein a mild and highly efficient method for the preparation of β-keto enol ethers using P_2O_5/silica gel under solvent-free conditions (Scheme 1).

In a typical experiment, a mixture of cyclic β-diketone, alcohol and P_2O_5/SiO_2 was ground with a pestle and mortar at room temperature until completion of the reaction, monitored by TLC. Consequently, it was diluted with 5% aqueous hydrochloric acid and extracted with ethyl acetate. The combined organic layers were then evaporated and the residue was purified by column chromatography on silica gel



Scheme 1

to afford pure β-keto enol ethers. The products were identified based on their spectroscopic properties (IR and ^{1}H NMR) and TLC relative to authentic samples.

The general reaction is illustrated in Scheme 1 and the results are reported in Table 1. As shown in the Table 1, various cyclic β-diketones such as cyclohexana-1,3-dione, dimethylcyclohexane-5,5-dione (dimedone) and cyclopentane-1,3-dione reacted efficiently with alcohols to produce the corresponding β-keto enol ethers in high to excellent yields. The reaction was also found to be effective for allyl and propargyl alcohols (entries **f** and **g**). The control reaction performed in the presence of silica gel alone failed to yield the desired product; this confirmed the efficiency of P_2O_5 as a catalyst for the etherification of cyclic β-diketones. The method is clean and free from side reactions. No acetals or bis-enol ethers were observed.

In summary, the reported procedure is an easy and versatile method for the synthesis of β-keto enol ethers from cyclic β-diketones and alcohols at room temperature under solvent-free conditions. The present method has many obvious advantages compared to those reported in the previous literature, including its generality, the simplicity of the methodology, the cheapness and the availability of the reagents and the high yields of products.

Experimental

IR spectra were recorded on a Bio-Rad FTS 135 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker AVANCE 300 spectrometer with TMS as internal standard. The P_2O_5/SiO_2 was prepared according to the literature.[18]

General procedure for the preparation of β*-keto enol ethers*: A mixture of cyclic β-diketone (**1**, 2 mmol), alcohol (3 mmol) and P_2O_5/SiO_2 (0.5 g) was ground thoroughly in a mortar at room temperature. After completion of reaction (monitored by TLC), 10 ml of 5% aqueous HCl was added to the mixture. The resulting solution was extracted with ethyl acetate (3 × 10 ml). The combined organic layers were dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc-hexane, 2:8) to afford the pure β-keto enol ether **3**.[12a,13,14,32]

Selective spectroscopic data:
3-Ethoxycyclohex-2-enone **(3b)**[14]: Liquid. IR (film): 3071, 2982, 2945, 2895, 1650, 1601, 1476, 1457, 1379, 1223, 1184, 1136, 1030 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ ppm: 1.05 (t, *J*=6.9 Hz, 3H), 1.66 (quint, *J*=6.3 Hz, 2H), 2.02 (t, *J*=6.3 Hz, 2H), 2.09 (t, *J*=6.3 Hz, 2H), 3.59 (q, *J*=6.9 Hz, 2H), 5.03 (s, 1H).

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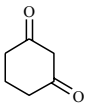
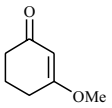
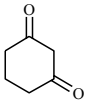
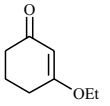
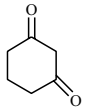
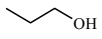
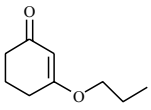
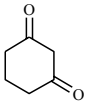
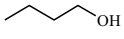
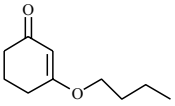
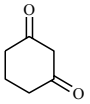
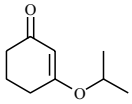
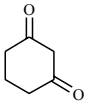
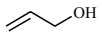
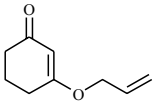
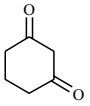
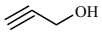
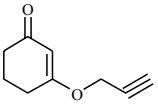
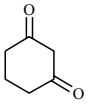
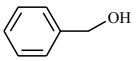
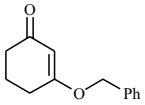
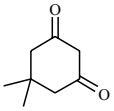
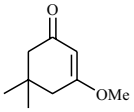
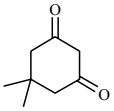
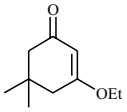
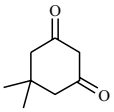
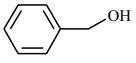
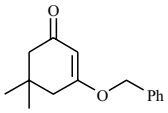
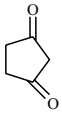
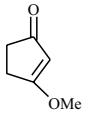
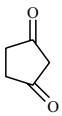
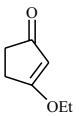
Table 1 Conversion of β-diketones to β-keto enol ethers in the presence of P_2O_5/SiO_2

Entry	β-Diketone	Alcohol	Product	Time/min	Yield/%[a]	Ref.
a		MeOH		15	92	14
b		EtOH		15	94	14
c				20	93	14
d				20	91	14
e				25	90	14
f				40	89	13
g				45	88	13
h				20	94	14
i		MeOH		20	87	14
j		EtOH		20	91	12a
k				25	90	32
l		MeOH		20	90	14
m		EtOH		20	95	13

[a]Isolated yield.

3-Allyloxycyclohex-2-enone (**3f**)[13]: Liquid. IR (film): 3082, 2948, 1652, 1604, 1386, 1221, 1183, 1136, 1058, 990, 961 cm^{-1}. ^1H NMR ($CDCl_3$) δ ppm: 1.99 (quint, *J*=6.3 Hz, 2H), 2.35 (t, *J*=6.3 Hz, 2H), 2.44 (t, *J*=6.3 Hz, 2H), 4.38 (d, *J*=5.4 Hz, 2H), 5.29-5.35 (m, 2H), 5.37 (s, 1H), 5.09-6.03 (m, 1H).

3-Benzyloxycyclohex-2-enone (**3h**)[14]: Liquid. IR (film): 3064, 3033, 2948, 1651, 1602, 1498, 1455, 1224, 1180, 1136, 1057, 960, 698 cm^{-1}. ^1H NMR ($CDCl_3$) δ ppm: 2.00 (quint, *J*=6.3 Hz, 2H), 2.36 (t, *J*=6.3 Hz, 2H), 2.47 (t, *J*=6.3 Hz, 2H), 4.89 (s, 2H), 5.48 (s, 1H), 7.36 (s, 5H).

3-Methoxy-5,5-dimethylcyclohex-2-enone (**3i**)[14]: Liquid. IR (film): 2959, 2872, 1724, 1653, 1607, 1465, 1376, 1227, 1147, 1014 cm^{-1}. ^1H NMR ($CDCl_3$) δ ppm: 0.91 (s, 6H), 2.06 (s, 2H), 2.13 (s, 2H), 3.56 (s, 3H), 5.25 (s, 1H). ^{13}C NMR ($CDCl_3$) δ ppm: 28.32, 32.64, 42.73, 50.58, 55.95, 101.10, 177.79, 200.32.

3-Ethoxy-5,5-dimethylcyclohex-2-enone (**3j**)[12a]: Liquid. IR (film): 2955, 2892, 1658, 1608, 1471, 1376, 1357, 1220, 1163, 1145, 1034 cm^{-1}. ^1H NMR ($CDCl_3$) δ ppm: 1.01 (s, 6H), 1.31 (t, J = 6.9 Hz, 3H), 2.15 (s, 2H), 2.22 (s, 2H), 3.85 (q, J = 6.9 Hz, 2H), 5.30 (s, 1H). ^{13}C NMR ($CDCl_3$) δ ppm: 14.31, 28.47, 32.67, 43.13, 50.88, 64.44, 101.65, 176.51, 199.85.

3-(Benzyloxy)-5,5-dimethylcyclohex-2-enone (**3k**)[32]: Liquid. IR (film): 3064, 2958, 1654, 1603, 1498, 1361, 1224, 1206, 1145 cm^{-1}. ^1H NMR ($CDCl_3$) δ ppm: 1.06 (s, 6H), 2.04 (s, 2H), 2.32 (s, 2H), 4.86 (s, 2H), 5.45 (s, 1H), 7.32–7.38 (m, 5H). ^{13}C NMR ($CDCl_3$) δ ppm: 28.47, 32.75, 43.09, 50.88, 70.71, 102.39, 127.16, 128.00, 128.64, 128.77, 128.95, 135.28, 176.29, 200.00.

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