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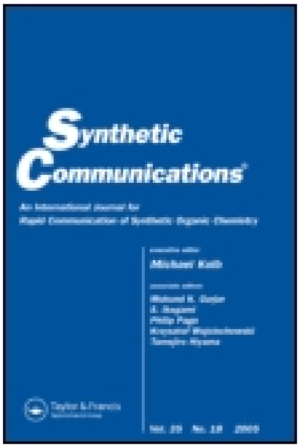

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Synthesis of Sterically Hindered 1,3-Diketones

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Synthesis of Sterically Hindered 1,3-Diketones

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Abstract: An efficient and practical method for the synthesis of sterically hindered aliphatic/aromatic 1,3-diketones via coupling of ketones with esters using potassium tert-butoxide is described. The protocol requires milder operating conditions, and the products are obained in good to excellent yields.

Keywords: claisen condensation, 1,3-diketone, ester, potassium tert-butoxide

INTRODUCTION

The traditional route for the synthesis of 1,3-diketones is generally carried out by Claisen condensation[1] using reagents such as SmI_3,[2] LiHMDS,[3] NaH/dibenzo 18-crown-6,[4] sodium hydride,[5] lithium amide,[2,6] and sodamide.[7,8] Recently, the use of potassium tert butoxide has been

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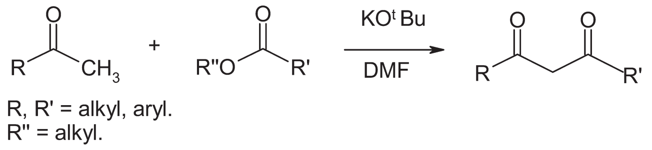
reported for the Michael reaction followed by intramolecular Claisen cyclizations to give cyclohexane-1,3-dione framework.[9]

RESULTS AND DISCUSSION

The present study reports a convenient, cost-effective, high-yielding protocol for the synthesis of higher aliphatic and aromatic 1,3-diketones involving sterically hindered substrates via coupling of ketones with esters using potassium tert-butoxide (Scheme 1). The mechanism of the reaction is outlined in Scheme 2.

A series of aliphatic/aromatic 1,3-diketones with different steric and electronic properties were synthesized as shown in Table 1. Initially, various aliphatic ketones with bulky groups were condensed with sterically hindered aliphatic esters (entries 1–4) to give the corresponding 1,3-diketone in good to excellent yields. The protocol was also applicable for the synthesis of industrially important 2,2,6,6-tetramethyl-3,5-heptanedione (dipivaloylmethane, entry 2). In addition to its simplicity and milder reaction conditions, the system also permits the condensation of ketones and esters with branching at the alpha position, which difficult to synthesize because the complexity of the substrates (entries 5–7). Successful condensation of acetyl ferrocene with ethyl acetate was also carried out, providing 80% yield of the desired product within 0.45 h. The protocol was also applicable for the condensation of deactivated aromatic ketones such as 4-Cl-acetophenone, affording excellent yield. The reaction of aromatic ketone with aliphatic ester and vice



Scheme 1.

(1) $CH_3COR + {}^{-}O^tBu \longrightarrow (CH_2COR)^{-} + Bu^tOH$

(2) $RCO_2C_2H_5 + (CH_2COR)^{-} \longrightarrow RCOCH_2COR + {}^{-}OC_2H_5$

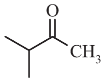
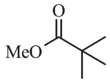
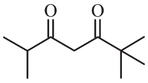
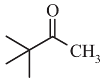
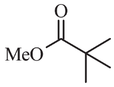
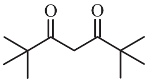
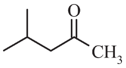
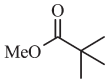
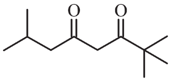
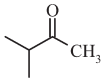
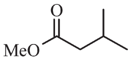
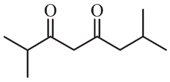
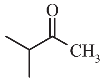
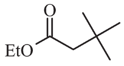
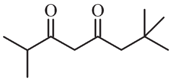
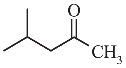
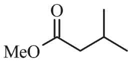
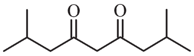
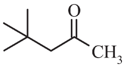
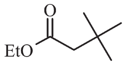
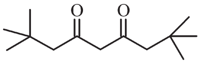
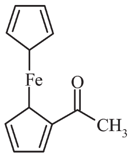
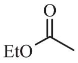
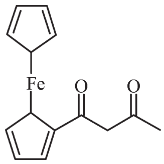
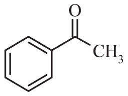
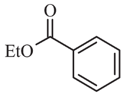
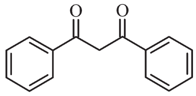
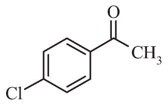
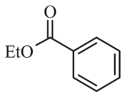
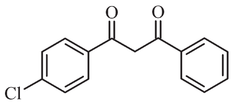
(3a) $RCOCH_2COR + (CH_2COR)^{-} \longrightarrow (RCOCHCOR)^{-} + CH_3COR$

or

(3b) $RCOCH_2COR + {}^{-}O^tBu \longrightarrow R(COCHCOR)^{-} + Bu^tOH$

Scheme 2.

Table 1. Synthesis of aliphatic and aromatic 1,3-diketones

Entry	Ketone	Ester	Time (h)	Product	Yield[b] (%)
1			5		70
2			5		64 (60)
3			5		65
4			5		66
5			5		46
6			6		34
7			6		40
8[a]			0.45		82
9[a]			0.45		80
10[a]			1		75

(*continued*)

Table 1. Continued

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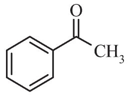
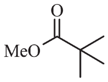
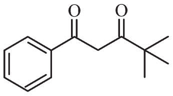
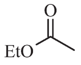
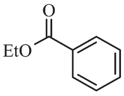
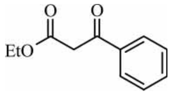
11[a]			1		70
12[a]			0.45		75

Notes. Reaction conditions: ketone (20 mmol), ester (30 mmol), KO^tBu (50 mmol), and DMF 27.5 ml at 50°C.

[a] KO^tBu (40 mmol).

[b] Isolated yield. Yields in parentheses represent purification by copper chelation.

versa was also studied (entries 11 and 12), and good yields were obtained within 0.45–1 h, indicating the generality of the procedure.

The influence of various parameters such as temperature, solvent, base, ketone–ester ratio, and ketone–base ratio on the reaction system was studied. Table 1 describes conditions with optimal yields.

EXPERIMENTAL

General

All chemicals were obtained from commercial sources and used as received. Optimization yields were based on gas chromographic (GC) analysis (Chemito 8610). The isolated products were characterized by spectral analysis such as FT-IR (Perkin-Elmer 100 spectrochem series) using KBr and ^1H NMR (Varian 400 MHz).

Typical Experimental Procedure (Table 1, Entry 2)

N,*N*-dimethylformamide (DMF) (25 ml) and potassium tert-butoxic (KO^tBu) (5.6 g, 50 mmol) were heated to 50°C under nitrogen. Methyl pivalate (3.5 g, 30 mmol) was added dropwise, followed by a solution of pinacolone (2 g, 20 mmol) in DMF (2.5 ml). The progress of the reaction was monitored by GC. After the completion of the reaction, the reaction mixture was allowed to cool and slowly neutralized with 20% H_2SO_4 solution. Water (25 ml) was further added to separate two layers. The layer containing the crude diketone 2,2,6,6-tetramethyl-3,5-heptanedione(thd) was purified using column chromatography (silica gel, 60–120 mesh) with petroleum ether (60/80) as an eluent (2.35 g, 64%).

Purification of 1,3-Diketone

A solution of $Cu(OAc)_2$ (1.4 g) in methanol (7 ml), H_2O (10 ml), and 2,2,6,6-Tetramethyl-3,5-heptanedione (THD) (2.5 g) was stirred. The solid was filtered and recrystallized from methanol. Pure THD was obtained after shaking the diethylether solution of chelate with 10% HCl, followed by evaporation of the solvent and distillation at 96–98°C/20 mm. IR (KBr): 3180 cm^{-1} (OH), 1608 cm^{-1} (C═O, C═C). ^1H NMR ($CDCl_3$), δ (ppm): 1.18 (18H, s, Bu^t), 5.73 (1H, s, CH), 16.18 (1H, s, OH).

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