Tetrahedron Letters 49 (2008) 4296–4301

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: http://www.elsevier.com/locate/tetlet

# Heteropoly acid-catalyzed highly efficient alkylation of 1,3-dicarbonyl compounds with benzylic and propargylic alcohols

J. S. Yadav *, B. V. Subba Reddy, T. Pandurangam, K. V. Raghavendra Rao, K. Praneeth, G. G. K. S. Narayana Kumar, C. Madavi, A. C. Kunwar

*Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad 500 007, India*

ARTICLE INFO

*Article history:*
Received 16 August 2007
Revised 12 April 2008
Accepted 23 April 2008
Available online 27 April 2008

*Keywords:*
Heteropoly acids
Benzylic/propargylic alcohols
1,3-Dicarbonyls
Nucleophilic substitution

ABSTRACT

Various 1,3-dicarbonyl compounds reacted readily with benzylic and propargylic alcohols in the presence of 10 mol % of phosphomolybdic acid supported on silica gel (PMA/$SiO_2$) under mild reaction conditions to produce 2-benzylic- and 2-propargylic-1,3-dicarbonyl compounds in excellent yields and with high selectivity.



The alkylation of 1,3-dicarbonyl compounds is a useful transformation involving C–C bond formation. In principle, direct nucleophilic substitution of the hydroxy group in alcohols with nucleophiles generally requires preactivation of the alcohol because of its poor leaving ability.[1] Consequently, hydroxyl groups are generally transformed into the corresponding halides, carboxylates, carbonates, phosphonates or related compounds.[2] However, such processes inevitably produce stoichiometric amounts of salt waste, and also substitution with halides requires a stoichiometric amount of base which limits their use in scale-up. In most cases, either a high reaction temperature or a promoter is required to enhance the leaving ability of the hydroxyl group. Subsequently, transition-metal based reagents such as palladium in the presence of a base or acid and stoichiometric amounts of cobalt salts have been reported for the direct nucleophilic substitution of unmodified alcohols.[3] Most of these methods worked well only with allylic alcohols but not with benzylic alcohols. Recently, acid catalysts such as $BF_3{\cdot}OEt_2$, $InCl_3$, $Bi(OTf)_3$, $Yb(OTf)_3$, $FeCl_3$ and H-montmorillonite have been employed to perform nucleophilic substitution of benzylic alcohols with active methylene compounds.[4,5] However, the use of high temperatures, extended reaction times and harsh conditions in many of the above-mentioned methods limit their practical utility in large scale synthesis. Moreover, little has been explored on nucleophilic substitution of propargylic alcohols with 1,3-dicarbonyls.[6] Therefore, the direct catalytic substitution of alcohols with 1,3-dicarbonyls using an efficient, cost-effective and recyclable catalyst is highly desirable.

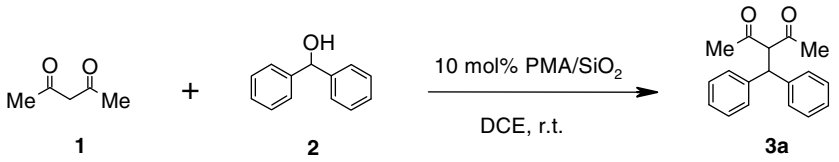
Recently, the use of heteropoly acids, HPAs, as environmentally friendly and economically viable solid acids, has gained increasing attention owing to their ease of handling and high catalytic activities and reactivities.[7] These compounds possess unique properties, such as well-defined structure, Bronsted acidity, the possibility to modify their acid–base and redox properties by changing their chemical composition (substituted HPAs), ability to accept and release electrons, high proton mobility, etc.[8] In view of green chemistry, the substitution of harmful liquid acids by reusable solid HPAs as catalysts in organic synthesis is a promising application of these acids.[9] Among them, phosphomolybdic acid (PMA, $H_3PMo_{12}O_{40}$) is one of the less expensive and commercially available catalysts.[10] However, there have been no reports on the use of phosphomolybdic acid for the direct alkylation of 1,3-dicarbonyl compounds with benzylic and propargylic alcohols.

In continuation of our efforts to explore the synthetic utility of phosphomolybdic acid supported on silica gel (PMA/$SiO_2$),[11] we herein report a direct and efficient protocol for the alkylation of 1,3-dicarbonyl compounds with benzylic and propargylic alcohols. Initially, we attempted the alkylation of acetyl acetone (**1**) with diphenylmethanol (**2**) in the presence of 10 mol% of PMA/$SiO_2$. The reaction went to completion at room temperature within 2.0 h to give product **3a** in 92% yield (Scheme 1).

This interesting catalytic activity of PMA/$SiO_2$ provided the incentive for further study of reactions with other active methylene compounds. Interestingly, 1,3-dicarbonyl compounds such

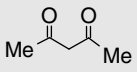
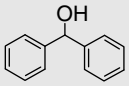
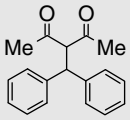
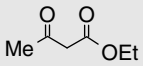
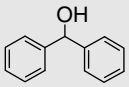
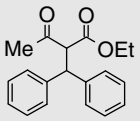
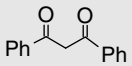
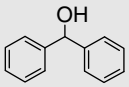
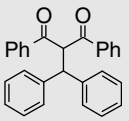
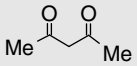
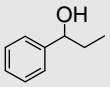
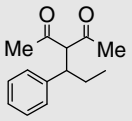
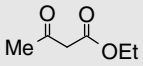
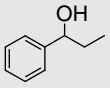
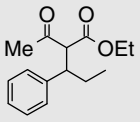
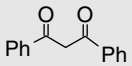
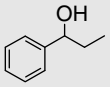
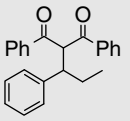
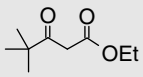
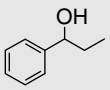
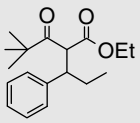
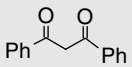
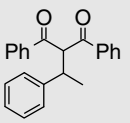
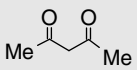
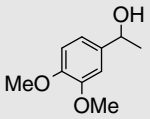
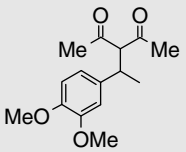
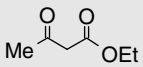
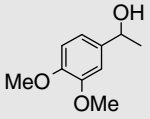
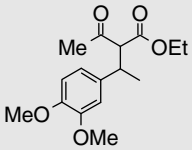
* Corresponding author. Tel.: +91 40 27193030; fax: +91 40 27160512.
*E-mail address:* yadavpub@iict.res.in (J. S. Yadav).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.04.126



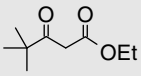
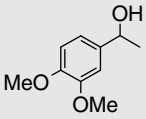
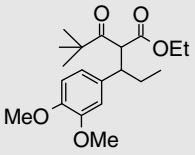
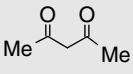
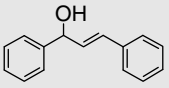
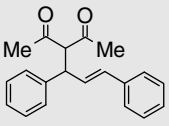
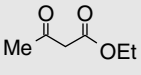
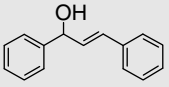
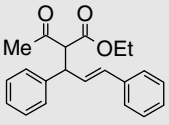
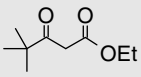
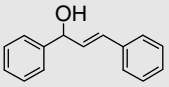
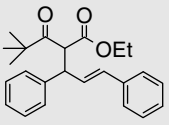

**Scheme 1.**

**Table 1**
PMA/$SiO_2$-catalyzed alkylation of 1,3-diketones with benzylic alcohols

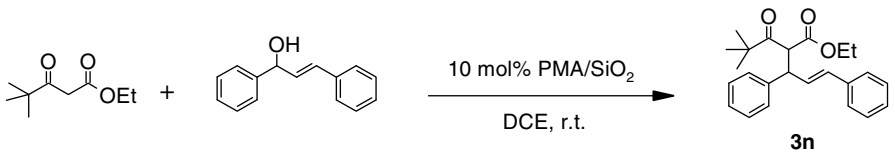
| Entry | 1,3-Diketone **1** | Alcohol **2** | Product **3**[a] | Time (h) | Yield[b] (%) |
|---|---|---|---|---|---|
| **a** |  |  |  | 2.0 | 92 |
| **b** |  |  |  | 2.5 | 90 |
| **c** |  |  |  | 2.0 | 90 |
| **d** |  |  |  | 1.5 | 88 |
| **e** |  |  |  | 3.0 | 65 |
| **f** |  |  |  | 2.5 | 88 |
| **g** |  |  |  | 2.0 | 75 |
| **h** |  |  |  | 2.5 | 88 |
| **i** |  |  |  | 2.0 | 93 |
| **j** |  |  |  | 2.5 | 82 |

(*continued on next page*)

**Table 1** (*continued*)

| Entry | 1,3-Diketone **1** | Alcohol **2** | Product **3**[a] | Time (h) | Yield[b] (%) |
|---|---|---|---|---|---|
| **k** |  |  |  | 3.0 | 88 |
| **l** |  |  |  | 1.5 | 90 |
| **m** |  |  |  | 2.0 | 75 |
| **n** |  |  |  | 3.0 | 90 |

[a] All products were characterized by $^{1}H$, $^{13}C$ NMR, IR and mass spectroscopy.
[b] Yield refers to pure products after chromatography.




**Scheme 2.**

**Table 2**
PMA/$SiO_2$-catalyzed alkylation of 1,3-diketones with propargylic alcohols

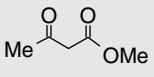
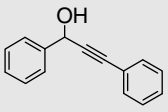
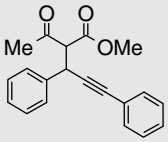
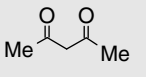
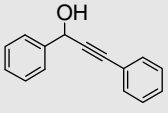
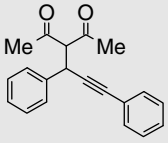
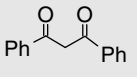
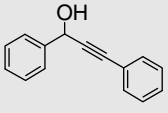
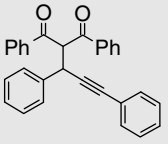
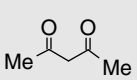
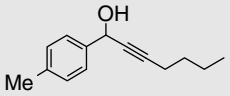
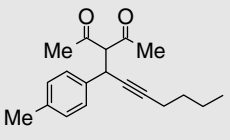
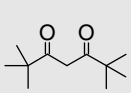
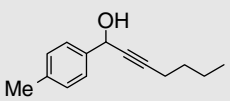
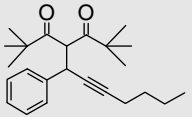
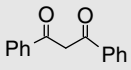
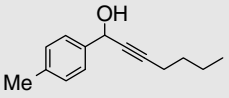
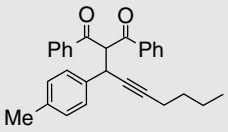
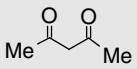
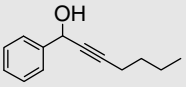
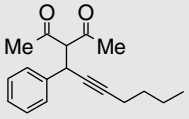
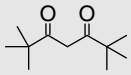
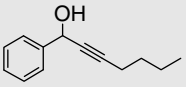
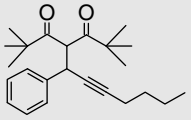
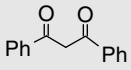
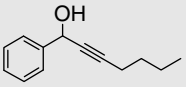
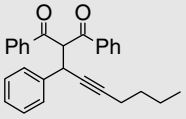
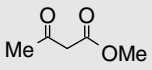
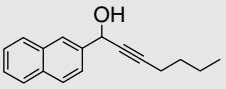
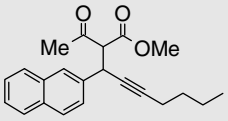
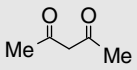
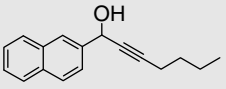
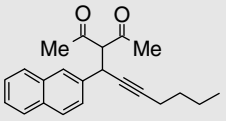
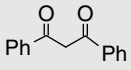
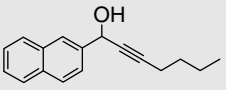
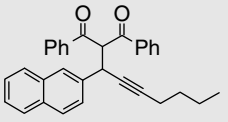
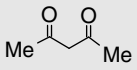
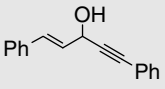
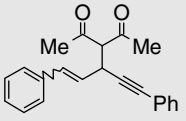
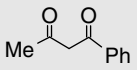
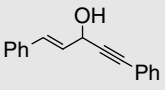
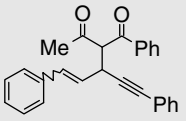
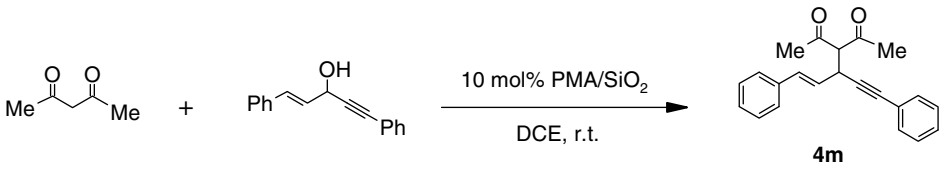
| Entry | 1,3-Diketone **1** | Alcohol **2** | Product **4**[a] | Time (h) | Yield[b] (%) |
|---|---|---|---|---|---|
| **a** |  |  |  | 3.5 | 90 |
| **b** |  |  |  | 3.0 | 86 |
| **c** |  |  |  | 2.5 | 88 |
| **d** |  |  |  | 3.0 | 88 |
| **e** |  |  |  | 3.0 | 85 |

**Table 2** (*continued*)

| Entry | 1,3-Diketone **1** | Alcohol **2** | Product **4**[a] | Time (h) | Yield[b] (%) |
|---|---|---|---|---|---|
| **f** |  |  |  | 2.5 | 90 |
| **g** |  |  |  | 3.0 | 86 |
| **h** |  |  |  | 3.5 | 80 |
| **i** |  |  |  | 2.5 | 85 |
| **j** |  |  |  | 2.5 | 88 |
| **k** |  |  |  | 3.0 | 85 |
| **l** |  |  |  | 3.0 | 86 |
| **m** |  |  |  | 2.0 | 90[c] |
| **n** |  |  |  | 2.0 | 92[c] |

[a] All products were characterized by $^{1}H$, $^{13}C$ NMR, IR and mass spectroscopy.
[b] Isolated and unoptimized yield.
[c] *E*/*Z* ratio 9:1.

as ethyl 3-oxobutanoate and 1,3-diphenyl-1,3-propanedione reacted smoothly with diphenylmethanol to give the corresponding 2-benzylic-1,3-dicarbonyl compounds in excellent yields (Table 1, entries **b** and **c**). Other benzylic alcohols such as, 1-phenyl-1-propanol, 1-phenylethanol and 1-(3,4-dimethoxyphenyl)-1-ethanol also reacted efficiently with 1,3-dicarbonyl compounds at room temperature to furnish benzyl substituted 1,3-dicarbonyl compounds (Table 1, entries **d**–**k**). Interestingly,




**Scheme 3.**

doubly activated benzylic alcohols reacted rapidly with 1,3-dicarbonyl compounds at room temperature to afford the corresponding C-2 benzylated 1,3-dicarbonyl compounds (Scheme 2, Table 1, entries **l**–**n**).

Like benzylic alcohols, various propargylic alcohols including 1,3-diphenyl-2-propyn-1-ol, 1-(4-methylphenyl)-2-heptyn-1-ol, 1-phenyl-2-heptyn-1-ol and 2-naphthyl-2-heptyn-1-ol also reacted readily with various 1,3-dicarbonyl compounds to furnish the respective 2-propargylic-1,3-dicarbonyl compounds (Table 2, entries **a**–**l**). In addition, doubly activated (*E*)-1,5-diphenyl-1-penten-4-yn-3-ol also participated well in this reaction (Scheme 3, Table 2, entries **m** and **n**).

The structure of **4m** was established by various NMR experiments. The product could have two possible structures depicted as **A** and **B**. HSQC and HMBC experiments were carried out to distinguish between the two possibilities. The HMBC correlation between H10–C3 is very distinct (Fig. 1), which can only arise in structure **A**. Further support for structure **A** came from the HMBC correlation between the acetylenic carbon C2 attached to the phenyl ring and the aliphatic proton at C4. Both these HMBC correlations in **B** would not be observed, being between nuclei five bonds apart. HMBC correlations between H4–C11, H4–C9, H5–C10 and H10–C5 provide additional evidence for the structure **A** for **4m**. The absence of a correlation between C7–H10 further supports structure **A**.

In all the cases, the reactions proceeded efficiently with high selectivity and were complete within 1.5–3.5 h. In the absence of $PMA/SiO_2$, no reaction was observed. No addition or rearranged products were observed in the cases of allylic and propargylic alcohols (Table 2, entries **m** and **n**). The nucleophilic substitution of the chiral secondary propargyl alcohol, (*R*)-1-(naphthalen-2-yl)-3-phenylprop-2-yn-1-ol with acetylacetone gave the racemic product. This clearly indicates that the reaction follows an $S_N1$ mechanism. This method is compatible with alkene, alkyne, ester and aryl alkyl ether functional groups. As solvent, dichloroethane gave the best results. All the products were characterized by $^1H$, $^{13}C$ NMR, IR

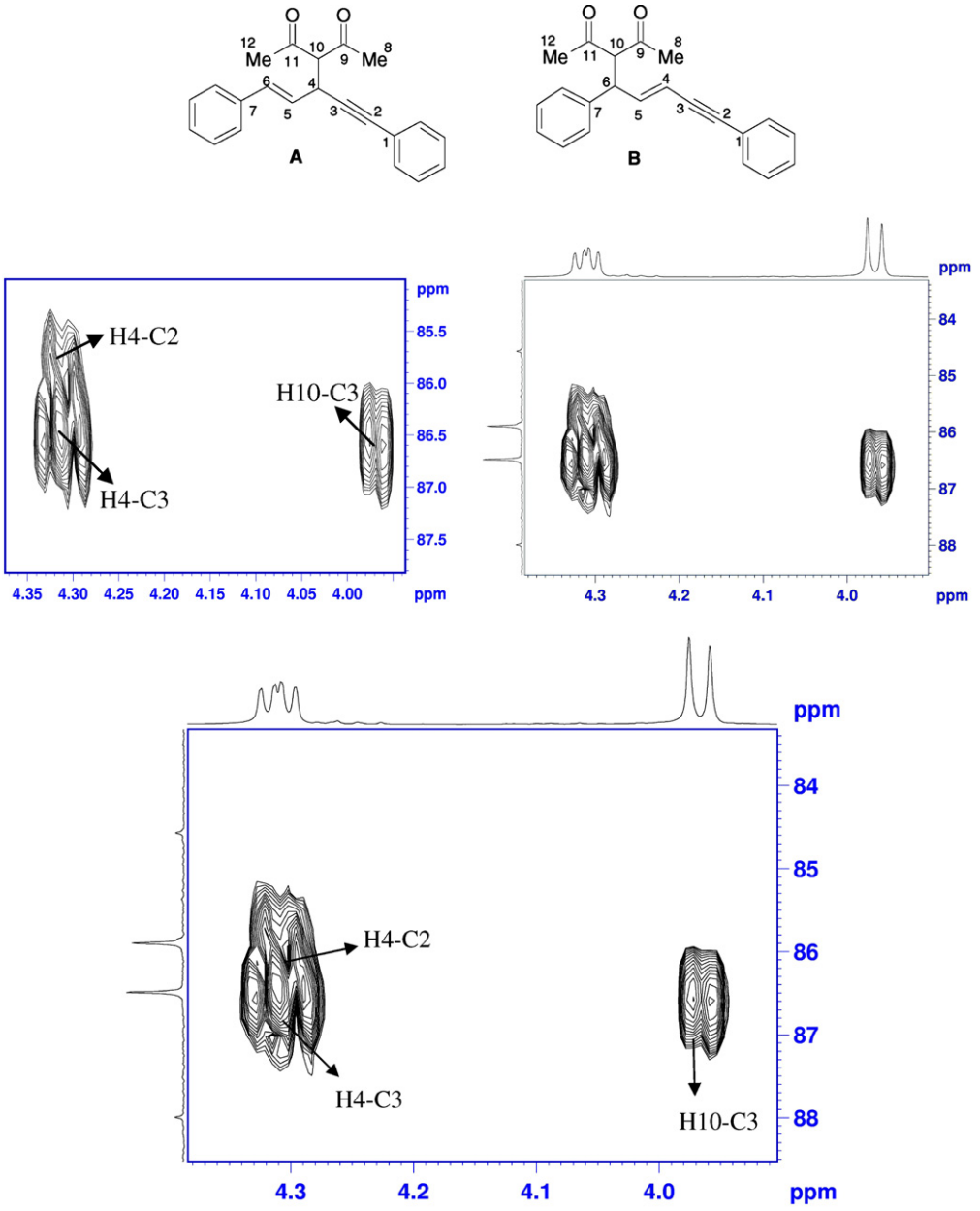



**Figure 1.** Characteristic HMBC and HSQC correlations of **4m**.

and mass spectroscopy. The effects of various silica-supported acid catalysts such as $HClO_4/SiO_2$, $H_2SO_4/SiO_2$ and $NaHSO_4/SiO_2$ were screened for this reaction. Of these catalysts, $PMA/SiO_2$ was found to give the best results in terms of conversion and reaction time. The scope and generality of this process was illustrated with respect to various 1,3-dicarbonyl compounds and benzylic as well as propargylic alcohols, and the results are presented in Tables 1 and 2.[12] The advantages of this method are the ready availability of alcohols, high atom efficiency, no salt formation and water as the only by-product.

In summary, we have described a simple, convenient and efficient protocol for the benzylation and propargylation of 1,3-dicarbonyl compounds with benzylic and propargylic alcohols using recyclable $PMA/SiO_2$ as the catalytic system. In addition to its efficiency, simplicity and mild reaction conditions, this method provides high yields of 2-benzyl- and 2-propargyl-1,3-dicarbonyl compounds in short reaction times with high selectivity.

## Acknowledgement

T.P., K.V.R.R., K.P. and G.G.K.S.N.K. thank CSIR, New Delhi for the award of fellowships.

## References and notes

1. (a) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921–2944; (b) Ma, S.; Yu, S.; Peng, Z.; Guo, H. *J. Org. Chem.* **2006**, *71*, 9865–9868.
2. (a) Westermaier, M.; Mayr, H. *Org. Lett.* **2006**, *8*, 4791–4794; (b) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Org. Lett.* **2004**, *6*, 3199–3202; (c) De la Herrán, G.; Segura, A.; Csáky, A. G. *Org. Lett.* **2007**, *9*, 961–964.
3. (a) Manabe, K.; Kobayashi, S. *Org. Lett.* **2003**, *5*, 3241–3244; (b) Mukhopadhyay, M.; Iqbal, J. *Tetrahedron Lett.* **1995**, *36*, 6761–6764.
4. (a) Bisaro, F.; Pretat, G.; Vitale, M.; Poli, G. *Synlett* **2002**, 1823–1826; (b) Yasuda, M.; Somyo, T.; Baba, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 793–796; (c) Rueping, M.; Nachtsheim, B. J.; Kuenkel, A. *Org. Lett.* **2007**, *9*, 825–828.
5. (a) Huang, W.; Wang, J.; Shen, Q.; Zhou, X. *Tetrahedron Lett.* **2007**, *48*, 3969–3973; (b) Jana, U.; Biswas, S.; Maiti, S. *Tetrahedron Lett.* **2007**, *48*, 4065–4069; (c) Motokura, K.; Fujita, N.; Mori, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 2605–2609.
6. Sanz, R.; Miguel, D.; Martinez, A.; Alvarez-Gutierrez, J. M.; Rodriguez, F. *Org. Lett.* **2007**, *9*, 727–730.
7. Misono, M.; Ono, I.; Koyano, G.; Aoshima, A. *Pure Appl. Chem.* **2000**, *72*, 1305.
8. Kozhevnikov, I. V. *Chem. Rev.* **1998**, *98*, 171–198.
9. (a) Saidi, M. R.; Torkiyan, L.; Azizi, N. *Org. Lett.* **2006**, *8*, 2079–2082; (b) Baskaran, S.; Kumar, G. D. K. *Chem. Commun.* **2004**, 1026–1027; (c) Kita, Y.; Tohma, H.; Kumar, G. A.; Hamamoto, H. *Chem. Eur. J.* **2002**, *8*, 5377–5383; (d) Rafiee, E.; Jafari, H. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2463–2466; (e) Okumura, K.; Yamashita, K.; Hirano, M.; Niva, M. *Chem. Lett.* **2005**, *34*, 716–717.
10. (a) Kishore Kumar, G. D.; Baskaran, S. *Synlett* **2004**, 1719–1722; (b) Kishore Kumar, G. D.; Baskaran, S. *J. Org. Chem.* **2005**, *70*, 4520–4523; (c) Kozhevnikova, E. F.; Derouane, E. G.; Kozhevnikov, I. V. *Chem. Commun.* **2002**, 1178–1179; (d) Firouzabadi, H.; Iranpoor, N.; Amani, K. *Synthesis* **2003**, 408–412.
11. (a) Yadav, J. S.; Raghavendra, S.; Satyanarayana, M.; Balanarsaiah, E. *Synlett* **2005**, 2461–2464; (b) Yadav, J. S.; Satyanarayana, M.; Balanarsaiah, E.; Raghavendra, S. *Tetrahedron Lett.* **2006**, *47*, 6095–6098.
12. *Experimental procedure*: A mixture of 1,3-dicarbonyl compound (1.0 mmol), alcohol (1.0 mmol) and $PMA/SiO_2$ (10 mol %) in dichloroethane (5 mL) was stirred at room temperature for the appropriate time (Tables 1 and 2). After completion of the reaction as indicated by TLC, the reaction mixture was filtered and diluted with water and extracted with dichloromethane ($2 \times 15$ mL). The combined organic layers were dried over anhydrous $Na_2SO_4$, concentrated in vacuo and purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate/hexane, 1:9) to afford pure 2-substituted 1,3-dicarbonyl compounds. The spectroscopic data of the products were identical with the data reported in the literature.
Spectral data for selected products:Compound **3b**: Ethyl 2-benzhydryl-3-oxobutanoate: Colourless solid, mp 89–91 °C; IR (KBr): 3084, 2993, 2955, 1736, 1600, 1456, 1363, 1320, 1246, 1143, 1013, 914, 840, 753, 700, 631, 542 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 0.98 (t, 3H, $J$ = 6.7 Hz), 2.06 (s, 3H), 3.95 (q, 2H, $J$ = 6.7 Hz), 4.42 (d, 1H, $J$ = 12.0 Hz), 4.72 (d, 1H, $J$ = 12.0 Hz), 7.10–7.27 (m, 10H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 13.7, 29.8, 50.8, 61.3, 65.1, 126.7, 126.8, 127.6, 127.7, 128.4, 128.7, 141.1, 141.5, 167.5; EIMS (M+Na): $m/z$: 319; HRMS calcd for $C_{19}H_{20}O_3Na$: 319.1310. Found: 319.1296.
Compound **3f**: 1,3-Diphenyl-2-(1-phenylpropyl)propane-1,3-dione: Colourless solid, mp 154–156 °C; IR (KBr): 3061, 2959, 2870, 1684, 1593, 1447, 1270, 1190, 1021, 962, 840, 760, 684, 598 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 0.71 (t, 3H, $J$ = 6.7 Hz), 1.55–1.83 (m, 2H), 3.75–3.85 (m, 1H), 5.49 (d, 1H, $J$ = 10.5 Hz), 7.05–7.57 (m, 11H), 7.67–7.74 (m, 2H), 8.02–8.08 (m, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 11.9, 27.0, 29.7, 48.7, 64.6, 126.6, 128.2, 128.3, 128.4, 128.6, 128.8, 132.8, 133.5, 137.0, 137.4, 141.2, 194.3, 195.1; EIMS (M+Na): $m/z$: 365; HRMS calcd for $C_{24}H_{22}O_2Na$: 365.1517. Found: 365.1507.
Compound **3h**: 1,3-Diphenyl-2-(1-phenylethyl)propane-1,3-dione: Colourless solid, mp 126–128 °C; IR (KBr): 3061, 3028, 2963, 1692, 1594, 1446, 1324, 1271, 1197, 972, 754, 697, 602, 539 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 1.33 (d, 3H, $J$ = 7.5 Hz), 4.02–4.12 (m, 1H), 5.44 (d, 1H, $J$ = 9.8 Hz), 7.01–7.56 (m, 11H), 7.70–7.77 (m, 2H), 7.99–8.07 (m, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 20.5, 41.3, 65.2, 125.0, 126.6, 127.7, 128.3, 128.4, 128.5, 128.8, 132.9, 133.5, 135.1, 136.1, 137.2, 194.6, 195.0; EIMS (M+Na): $m/z$: 351. HRMS calcd for $C_{23}H_{20}O_2Na$: 351.1360. Found: 351.1352.
Compound **4a**: Methyl 2-acetyl-3,5-diphenyl-4-pentynoate: Liquid, IR (KBr): $\nu$ 3028, 2921, 2851, 1739, 1598, 1490, 1439, 1354, 1280, 1249, 1149, 755 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 2.42 (s, 3H), 3.81 (s, 3H), 3.97 (d, 1H, $J$ = 10.1 Hz), 4.60 (d, 1H, $J$ = 10.1 Hz), 7.25–7.45 (m, 10H). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 24.0, 35.1, 75.5, 84.8, 85.4, 126.6, 127.7, 128.2, 128.3, 128.6, 128.8, 131.6, 138.1, 201.5; LCMS: $m/z$: (M+Na) 329. HRMS calcd for $C_{20}H_{18}O_3Na$: 329.1153. Found: 329.1155.
Compound **4m**: 3-[3-Phenyl-1-(2-phenyl-1-ethynyl)-(*E*)-2-propenyl]-2,4-pentanedione: Liquid, IR (KBr): $\nu$ 3027, 2923, 2853, 1702, 1597, 1490, 1444, 1418, 1356, 1262, 1151, 967, 755 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.45–7.21 (m, 10H, Ar), 6.75 (dd, 1H, dd, 1H, $J$ = 1.0, 15.7, Hz, H6), 6.06 (dd, 1H, $J$ = 6.7, 15.7 Hz, H5), 4.31 (ddd, 1H, $J$ = 1.0, 6.7, 10.3 Hz, H4), 3.96 (d, 1H, $J$ = 10.3 Hz, H10), 2.34 (s, 3H, Me), 2.23 (s, 3H, Me). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 28.8, 34.7, 73.6, 85.8, 86.4, 122.5, 124.6, 126.4, 127.9, 128.2, 128.5, 128.6, 131.6, 133.1, 136.1, 201.2. LCMS: $m/z$: (M+Na) 339. HRMS calcd for $C_{22}H_{20}O_2Na$: 339.1360. Found: 339.1366.