Tetrahedron 73 (2017) 2740–2746

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Copper-catalyzed methylation of 1,3-diketones with *tert*-butyl peroxybenzoate

Zhi-Hao Zhou, Cheng-Kun Li, Shao-Fang Zhou, Adedamola Shoberu, Jian-Ping Zou*

Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry and Chemical Engineering, Soochow University, 199 Renai Street, Suzhou, Jiangsu 215123, China

ARTICLE INFO

Article history:
Received 12 February 2017
Received in revised form
19 March 2017
Accepted 21 March 2017
Available online 24 March 2017

Keywords:
1,3-Diketone
Methylation
Copper catalyst
Radical reaction

ABSTRACT

Copper-catalyzed radical methylation of 1,3-diketones with *tert*-butyl peroxybenzoate in air is described, providing a general pathway to α-methyl 1,3-diketones in moderate to good yields. This protocol has been scaled up to 50 g, and one of the synthesized products can be used in the synthesis of medicine, Rosuvastatin.

1. Introduction

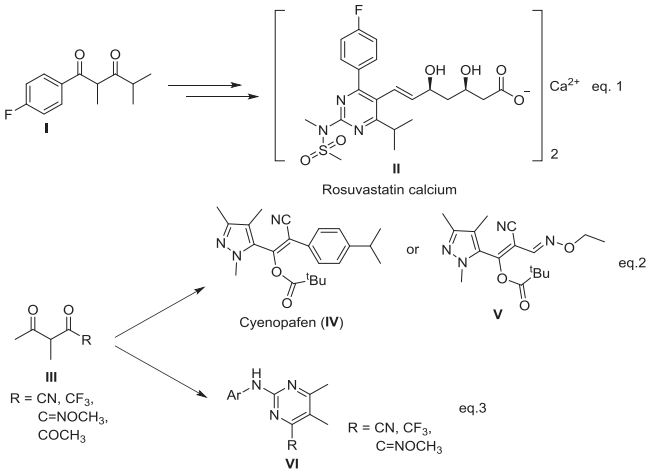
The introduction of methyl groups into organic molecules can improve the physical properties and bioactivities of biologically active molecules, hence, methylation reaction has aroused much interest in recent years.[1] α-Methyl-1,3-diketones are widely employed for the preparation of medicines and agrochemicals,[2] e.g. 1-(4-fluorophenyl)-2,4-dimethylpentane-1,3-dione (I) has been used for the preparation of Rosuvastatin calcium (II) (Scheme 1, eq 1) which could treat hyperchol-esterolemia, hyper-lipoproteinemia and atherosclerosis[3]; α-Methyl-1,3-diketones (III) have been employed in the synthesis of pesticides (IV, V)[4] and fungicides (VI)[5] (Scheme 1, eqs 2 and 3). One of the most important routes to α-methyl-1,3-diketones is through methylation reaction. The traditional process involves the use of a strong base and poisonous methyl iodide (Scheme 2, eq 1).[3b,6] Thus, the development of new routes and reagents for the methylation of 1,3-diketones is highly desirable. In 2008, the Li's group first reported that organic peroxides could be used as a methyl source for the methylation of arenes in the presence of palladium catalysts.[7] Thereafter, several groups have employed organic peroxides as the methylating reagent for N–, O– or C-methylation and oxidative methylation–cyclization of alkenes.[1c,1f,1g,1h,1k,1l] In continuation of our effort on the organic peroxides promoted methylation of organic molecules,[8] herein, we report a novel methylation protocol for the preparation of α-methyl-1,3-diketones (Scheme 2, eq 2), this protocol features selective monomethylation in air with *tert*-butyl peroxybenzoate (TBPB), short reaction time (0.5 h), thus avoiding the use of poisonous methyl iodide, scaling up to 50 g level, and applying the synthesized 1-(4-fluorophenyl)-2,4-dimethylpentane-1,3-dione (**I**) for synthesis of the medicine, Rosuvastatin.

2. Results and discussion

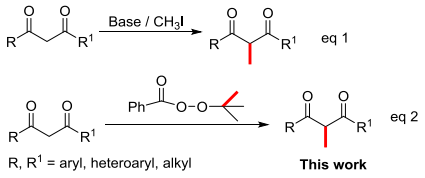
Initially, we began by investigating the reaction of 1,3-diphenylpropane-1,3-dione (**1a**) with di-*tert*-butyl peroxide (DTBP) (1.0 mmol)) using CuI catalyst (10 mol %) in 10 mL AcOH under air at 100 °C. To our delight, the desired product **2a** was obtained in a low yield of 33% (Table 1, entry 1). By increasing the amount of DTBP used, we found that an optimal use of 3 eq. of the oxidant resulted in an improved 71% yield of **2a** (Table 1, entries 2–4). No reaction was observed in the absence of CuI (Table 1, entry 5) which indicates that the Cu salt was essential for the formation of product. Also, we employed other Cu salts and found CuCl to be the most effective catalyst giving product **2a** in 87% yield (Table 1, entries 6–7). The choice of oxidant was also varied; when *tert*-butyl hydroperoxide (TBHP) was used in place of DTBP, the reaction

* Corresponding author.
E-mail address: jpzou@suda.edu.cn (J.-P. Zou).

http://dx.doi.org/10.1016/j.tet.2017.03.058
0040-4020/

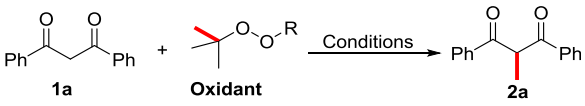


Scheme 1. Application of α-methyl-1,3-diketones in medicines, pesticides and fungicides synthesis.



Scheme 2. α-Methylation of 1,3-diketones.

Table 1
Optimization of the reaction conditions[a].



Entry	Catalyst	**1a**:Oxidant	Temp (°C)	Time (h)	Yield (%)[b]
1	CuI	1:1 (DTBP)	100	6	33
2	CuI	1:3 (DTBP)	100	6	71
3	CuI	1:6 (DTBP)	100	6	63
4	CuI	1:12 (DTBP)	100	6	60
5	None	1:3 (DTBP)	100	6	N.R.[c]
6	CuBr	1:3 (DTBP)	100	6	74
7	CuCl	1:3 (DTBP)	100	6	87
8	CuCl	1:3 (TBHP)	100	24	30
9	CuCl	1:3 (TBPB)	100	1.5	91
10	CuCl	1:3 (TBPB)	120	0.5	90
11	CuCl	1:3 (TBPB)	80	12	72
12	CuCl	1:3 (TBPB)	60	24	18
13	CuCl	1:3 (TBPB)	25	48	trace
14	$CuCl_2$	1:3 (TBPB)	120	0.5	53
15	$Cu(OTf)_2$	1:3 (TBPB)	120	0.5	50

[a] Reaction conditions: the mixture of 1a (1.0 mmol), catalyst (10 mol %), and oxidant (di-tert-butyl peroxide (DTBP), tert-butyl hydroperoxide (TBHP), tert-butyl peroxybenzoate (TBPB)) was heated in HOAc (10 mL) under air.
[b] Isolated yield.
[c] N. R. means no reaction.

became complex and only 30% yield of product **2a** could be obtained (Table 1, entry 8). However, the use of *tert*-butyl peroxybenzoate (TBPB) gave a very satisfactory yield of 91% (Table 1, entry 9). After screening the reaction temperature and time, the optimized reaction conditions were a combination of 1,3-diketone/TBPB/CuCl (1:3:0.1) in AcOH for 0.5 h under air at 120 °C (Table 1, entry 10).

With the optimal reaction conditions in hand, we explored the scope of 1,3-dicarbonyl derivatives (Table 2). A variety of substituted aromatic, aliphatic and cyclic 1,3-diketones reacted with TBPB to give methylated products in moderate to good yields (30–90%). Electronic effect was found to play a significant role during the methylation process. With diketones bearing electron-donating groups on the aromatic rings, the reaction took place smoothly resulting in good yields (**2b-2g**). It is noteworthy that halogens were also tolerated under our copper-catalyzed protocol (**2h-2j, 2q**). However, low yields of products were obtained when the phenyl rings contains an electron-withdrawing substituent (e.g. **2k**) or different substituent types (e.g. **2j**). In addition, the reactions of unsymmetrical diketones containing aromatic-ethyl, aromatic-cyclohexyl and aromatic-isopropyl 1,3-dicarbonyl derivatives all occurred smoothly to afford methylated products, **2l**, **2p** and **I** in 68%, 77% and 61% yield respectively. Also, an enol substrate underwent methylation to produce a good yield of product **2o**. Remarkably, the reaction involving aliphatic and cyclic 1,3-diketones also occurred giving products **2m** and **2n** respectively; the low yield of **2m** (41%) may be attributed to the steric hindrance caused by the tertiary butyl group. Finally, the benzoyl ethyl acetate was reacted with TBPB, no reaction was observed (**2r**), hence this protocol is selective.

Subsequently, we investigated the scope of mono- or bis-heteroaryl 1,3-diketones. As shown in Table 3, a wide range of substrates reacted readily including both electron-deficient and electron-rich heteroaryls, thereby producing the corresponding methylated products in varying yields. Notably, α-mono-methylation **4g** and bismethylation **4g′** were generated by substrate 1-(pyridin-2-yl)butane-1,3-dione (**3g**) under standard procedure, however only **4g** was produced when 1.2 equivalent TBPB was used. In addition, we found that the isolated product **4g** can be totally converted to **4g′** when reacted with 5 equivalents of TBPB; this result indicated that the bismethylation product was generated from the α-monomethylation compound. A reasonable explanation for this experimental result could be the chelation of the Cu salt with N-atom and methine carbon.[9] This metal-chelate function may activate the methine so that the bismethylation derivatives can also be generated. To verify this hypothesis, we carried out the reactions of substrates 1-(quinolin-2-yl)butane-1,3-dione (**3h**), 1-(1*H*-pyrrol-2-yl)butane-1,3-dione (**3i**) and 1-(1-methyl-1*H*-pyrrol-2-yl)butane-1,3-dione (**3i′**) under standard conditions. Fortunately, a similar result was observed with **3h** where the ratio of derivatives **4h**/**4h′** was 3:1; with **3i** however, the bismethylation product was not detected but rather the N-methylation compound **4i′** after 10 min (see **footnote e**). Meanwhile, only product **4i′** was obtained when **3i′** was employed (see **footnote g**), this is probably because the angle of chelation between Cu salt and N-atom was too wide. Another interesting result was the simultaneous formation of products **4j** and **4j′** even when TBPB was decreased to 0.99 equivalent. Thus, a competing reaction was taking place between α-monomethylation on 1,3-dicarbonyls and methylation on 2-furyl ring.

To further demonstrate the practicability of this methodology, 30 g-scale preparation of α-mono-methylated 1,3-dicarbonyl compounds was performed as illustrated in Scheme 3 (a). 1,3-Diphenylpropane-1,3-dione **1a** (50.0 g, 222.5 mmol) was converted to **2a** (31.8 g, 133.5 mmol) in 60% isolated yield. Besides, another utility is shown in Scheme 3 (b), where I can be employed as an important intermediate in the synthesis of Rosuvastatin. Compared with the traditional method of synthesizing **I** which involves the use of poisonous MeI and refluxing for 48 h, this copper-catalyst protocol offers a friendly and rapid method of carrying out the α-monomethylation of 1-(4-fluorophenyl)-2,4-