Tetrahedron Letters 50 (2009) 5578–5581

Contents lists available at ScienceDirect

Tetrahedron Letters

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

The reaction of terminal alkynes with $PhI(OAc)_2$: a convenient procedure for the preparation of α-acyloxy ketones

Dong-Liang Mo, Li-Xin Dai, Xue-Long Hou *

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, PR China

ARTICLE INFO

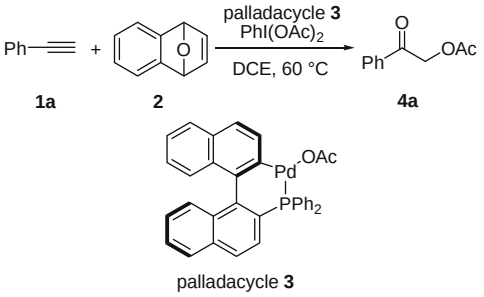
Article history:
Received 23 June 2009
Revised 13 July 2009
Accepted 14 July 2009
Available online 19 July 2009

ABSTRACT

Treatment of terminal alkynes with $PhI(OAc)_2$ in different acids at 70 °C provided the corresponding α-acyloxy ketones in good to excellent yields. A plausible mechanism has been proposed based on the experimental results.

α-Acetoxy ketones are one class of important intermediates in organic synthesis. They are easily transformed into α-hydroxy ketones, which are found in a variety of biologically interesting natural products.[1] To date many procedures have been developed to prepare α-acetoxy ketones, such as the acetolysis of α-bromo ketones,[2] the anodic oxidation of enol acetates in acetic acid,[3] the Cu-catalyzed insertion reaction of α-diazo ketones with carboxylic acids,[4] the oxidation of ketones with lead tetraacetate,[5] the oxidation of ketones with manganese(III) acetate in acetic acid,[6] and lead tetraacetate oxidation of trimethylsilyl enol ethers.[7] However they suffered from the low yields and environmental problem. Some other oxidants were also used in the transformation of ketones into α-acetoxy ketones.[8,9] On the other hand, hypervalent iodine reagents have attracted much attention of synthetic chemists in recent years because of their interesting activity, ready availability, and easy handling.[10,11] Oxidation of terminal alkynes to ketones in the presence of hypervalent iodine compounds has been documented,[12] However, few reports were given on the direct transformation of alkynes to α-acetoxy ketones.[13,14a] During our studies on the reaction using palladacycles as catalyst,[15] we found that α-acetoxy ketones were produced when the terminal alkynes reacted with iodosobenzene diacetate. Herein, we would like to report this convenient procedure for preparing α-acetoxy ketones by the reaction of terminal alkynes with hypervalent iodine compounds as oxidant.

Initially we studied the reaction of phenylacetylene **1a** with oxabicyclic alkene **2** using palladacycle **3** as catalyst in the presence of $PhI(OAc)_2$ in dichloroethane (DCE) at 60 °C under argon. It is surprising that α-acetoxy acetophenone **4a** was obtained in 40% yield (Eq. 1). Controlled experiment revealed that palladacycle was not essential for the reaction. Indeed, when $PhI(OAc)_2$ was used as the only oxidant, α-acetoxy ketone was also produced in 65% yield. Almost the same yield was obtained when the reaction proceeded under aerobic conditions.



(1)

Based on the above results, the influence of the reaction parameters on the reaction was investigated (Table 1). Screening of solvents showed that α-acetoxy ketone **4a** was obtained in 65%, 53%, or 66% yield, respectively, when the reaction proceeded in dichloroethane (DCE), MeCN, or MeOH (entries 1, 6, and 8) while lower yields of desired product were isolated if $CHCl_3$, toluene, THF, DME and DMF were used as solvent (entries 2–5 and 7). When acetic acid was the solvent the yield of product **4a** increased to 87% (entry 9), while it decreased to 78% and 80%, respectively, when 2 equiv of water or AcOK was added (entries 14 and 15). No desired product **4a** was separated if KI and I_2 were used as additives (not shown in Table 1). We also studied the influence of the temperature on the reaction. Poor yield of **4a** was obtained when the reaction was carried out at room temperature (entry 10) while the yields were 85% and 76% if the reaction ran at 100 °C and 120 °C, respectively (entries 12 and 13).

Under the optimized conditions, the scope of the substrates was examined (Table 2).[16] It can be seen that both aryl acetylenes and aliphatic terminal alkynes are suitable substrates in the reaction, affording the corresponding α-acetoxy ketones in moderate to excellent yields. Aryl acetylenes with methyl or trifluoromethyl group at the 4-position of benzene ring gave excellent yields of

* Corresponding author.
E-mail address: xlhou@mail.sioc.ac.cn (X.-L. Hou).

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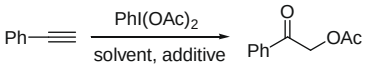
doi:10.1016/j.tetlet.2009.07.081

Table 1
Optimization of the reaction conditions[a]

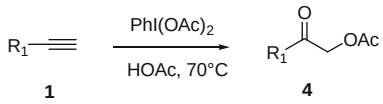


1a **4a**

Entry	Solvent	Temperature (°C)	Yield[b] (%)
1	DCE	60	65
2	$CHCl_3$	60	26
3	Toluene	60	26
4	THF	60	16
5	DME	60	29
6	CH_3CN	60	53
7	DMF	60	19
8	MeOH	60	66[c]
9	AcOH	60	87
10	AcOH	25	9
11	AcOH	70	89
12	AcOH	100	85
13	AcOH	120	76
14	AcOH	60	78[d]
15	AcOH	60	80[e]

[a] Reaction conditions: phenylacetylene **1a** (0.6 mmol), $PhI(OAc)_2$ (1.0 mmol), solvent (1.5 mL). Reaction time: 12 h.
[b] Isolated yields.
[c] 13% of α-methoxy ketone **6** as well as 6% of **7** was also separated.
[d] H_2O (2.0 equiv) was added.
[e] AcOK (2.0 equiv) was added.

Table 2
The scope of the terminal alkynes in the reaction[a,16]



1 **4**

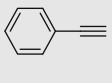
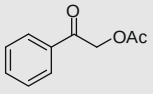
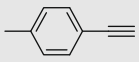
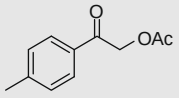
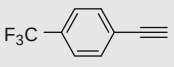
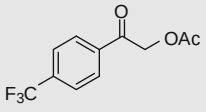
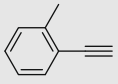
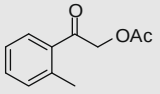
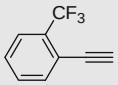
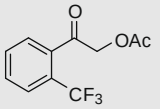
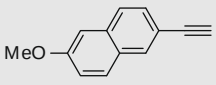
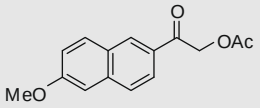
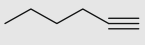
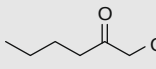
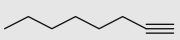
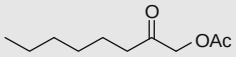
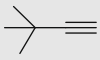
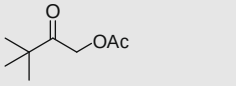
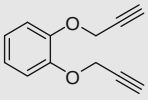
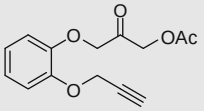
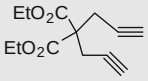
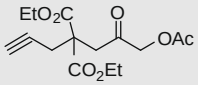
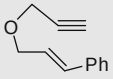
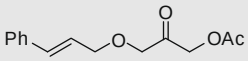
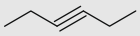
Entry	Substrate, **1**	Product	**4**	Yield[b] (%)
1			**a**	89
2			**b**	90
3			**c**	94
4			**d**	81
5			**e**	64
6			**f**	85
7			**g**	95

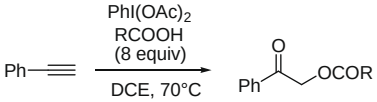
Table 2 (*continued*)

Entry	Substrate, **1**	Product	**4**	Yield[b] (%)
8			**h**	93
9			**i**	77
10			**j**	51[c]
11			**k**	41[c]
12			**l**	45[c]
13		–	**m**	–

[a] Reaction conditions: acetylene **1** (0.6 mmol), $PhI(OAc)_2$ (1.0 mmol), solvent (1.5 mL). Reaction time: 12 h.
[b] Isolated yields.
[c] $PhI(OAc)_2$ (2.0 mmol), reaction time: 24 h.

products (entries 2 and 3) while those with substituent at the 2-position of benzene ring afforded acetoxy ketones in lower yield maybe due to the steric hindrance (entries 4 and 5). Substituted naphthyl acetylene **1f** also provided product **4f** in high yield (entry 6). Reaction of aliphatic terminal alkynes furnished products in excellent yields (entries 7 and 8), except *tert*-butyl acetylene **1i**, which gave a little bit lower yield of acetoxy ketone **4i** (entry 9) which may also be due to the steric hindrance. However, alkyne **1m** with internal triple bond failed to afford oxidized product (entry 13). Interestingly, **1j** and **1k** with two terminal acetylenic bonds are also suitable substrates, $PhI(OAc)_2$ reacted with one triple bond specifically, providing α-acetoxy ketones with one triple bond intact (entries 10 and 11). Moreover, the reaction showed tolerance toward the carbon–carbon double bond. Reaction of 1,6-enyne **1l** furnished allyl ether **4l** in 45% yield (entry 12).

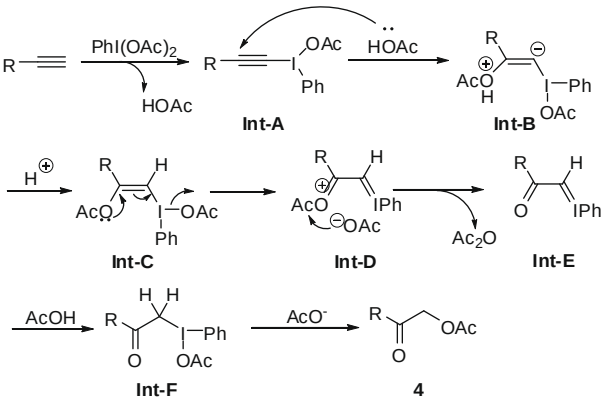
The reaction also proceeded if other carboxylic acids were used. When we used the above optimized conditions for the reaction of the phenylacetylene **1a** (1.0 equiv), $PhI(OAc)_2$ (2.0 equiv), and different acids (8.0 equiv) in DCE, the corresponding α-acyloxy ketones were obtained in good yields (Eq. 2).



1a **5a-d** (2)

R	**5a-d**
H	**51%**
Et	**82%**
Bu	**56%**
Ph	**69%**

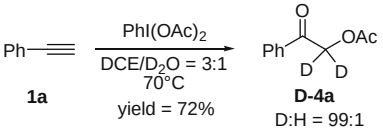
Based on the observations made by us and the others,[14a] a plausible mechanism could be proposed (Scheme 1). Reaction of the terminal alkyne with $PhI(OAc)_2$ forms the alkynyliodonium salts



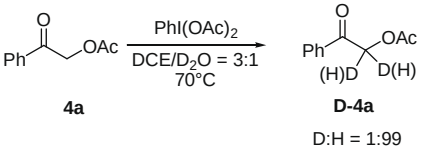
Scheme 1. A possible mechanism.

Int-A. Then a Michael-type addition of AcOH to the alkynyliodonium salt provides **Int-B**. Proton-transfer of **Int-B** affords (β-acetoxyalkeny1) phenyliodonium acetate **Int-C**, which is converted to **Int-D**. Attack of AcO^- on **Int-D** provided **Int-E**. Acidolysis of **Int-E** yields alkyliodonium salts **Int-F**. Substitution of the phenyliodonium group by AcO^- gives α-acetoxy ketones **4**.[14a]

To have a better understanding of the mechanism, the reaction was carried out in DCE/D_2O (3:1) instead of in AcOH (Eq. 3). α-Acetoxy ketone D-**4a** was obtained in 72% yield with D/H ratio of 99:1 at α-position of carbonyl group. Controlled experiment showed that no D/H exchange took place if α-acetoxy ketone **4a** was exposed to the reaction conditions (Eq. 4). These results provided the experimental support for the formation of the intermediate **Int-A** and the intermolecular trapping of **Int-E** by the proton of solvent.

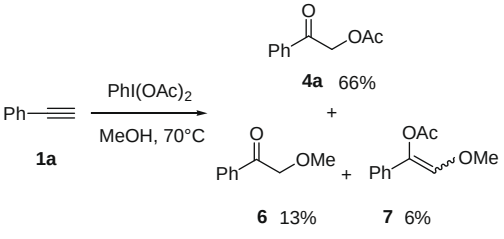


(3)



(4)

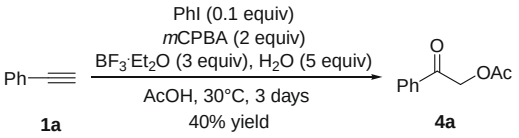
When the reaction was carried out in MeOH, α-methoxy ketone **6** and methoxy enolate **7** were afforded in 13% and 6% yields, respectively, in addition to the formation of α-acetoxy ketone **4a** in 66% yield (Eq. 5). These results gave the evidence to support the presence of the intermediate **Int-F**.



(5)

When the reaction proceeded in AcOH by using the oxidant PhI = NTs instead of $PhI(OAc)_2$, product **4a** was obtained in 76% yield. However, when the reaction was performed in MeOH or CH_3CN, no desired products were detected by ^1H NMR. Evidently, PhI = NTs could first be converted $PhI(OAc)_2$ in acetic acid which then reacted with the substrates to form α-acetoxy ketones.[17]

The reaction also proceeded by using catalytic amount of iodobenzene in the presence of 3-chloroperoxybenzoic acid and $BF_3{\cdot}Et_2O$ and water in acetic acid at 30 °C, affording **4a** in 40% yield after 3 days (Eq. 6).[18]



(6)

In summary, we have developed an efficient protocol for the preparation of α-acyloxy ketones by the reaction of terminal alkynes with PhI(OAc)2. The yields are good to excellent. A plausible mechanism was proposed. Further investigations on the reaction and its applications in organic synthesis are in progress.

Acknowledgments

This work was financially supported by the Major Basic Research Development Program (2006CB806100), National Natural Science Foundation of China (20532050, 20672130, and 20821002), Chinese Academy of Sciences, and Science and Technology Commission of Shanghai Municipality.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.07.081.

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16. *Representative procedure for the preparation of α-acetoxy ketones by phenylacetylene* **1a** *and PhI(OAc)$_2$*: In a Schlenk tube, phenylacetylene **1a** (66 μL, 0.6 mmol) was added to a stirring mixture of PhI(OAc)$_2$ (322 mg, 1.0 mmol), and acetic acid (1.5 mL) under atmosphere of air. The mixture was stirred at 70 °C for 12 h for the completion of the reaction (monitored by TLC). The solution was diluted with dichloromethane (5 mL) and water (5 mL) was added. The aqueous solution was extracted with dichloromethane (5 mL × 3) and the combined organic layers were washed with $NaHCO_3$ solution (5 mL × 2), and dried with anhydrous Na_2SO_4. Then, the solvent was removed and the residue was purified by flash chromatography on silica gel using PE/EtOAc (5:1) as eluent to give product **4a**. Oil, 95 mg (89% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.22 (s, 3H), 5.34 (s, 2H), 7.45–7.49 (m, 2H), 7.57–7.61 (m, 1H), 7.89 (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 20.42, 65.91, 127.61, 128.73, 133.77, 134.03, 170.30, 192.06; MS (EI) m/z (rel): 178 (1, M^+), 161 (3), 136 (1), 105 (100), 91 (3), 77 (37), 51 (12), 43 (19).
17. When PhI = NTs was stirred at 70 °C in acetic acid for 5 h, PhI(OAc)$_2$ and $TsNH_2$ were obtained in 88% yield.
18. If the reaction was performed at 70 °C, no desired product was detected in the crude reaction mixture by ^{1}H NMR.