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An Efficient *α*-Phosphoryloxylation of Ketones

Ye Pu, Jie Yan*
College of Chemical Engineering and Materials Sciences, *Zhejiang University of Technology*, *Hangzhou*, *P. R. China*
E-mail: *jieyan87@zjut.edu.cn*
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Abstract

An efficient *α*-phosphoryloxylation of ketones has been developed. When ketones were treated with (diacetoxyiodo)benzene and phosphates in CH_2Cl_2 at room temperature, the *α*-phosphoryloxylaction of ketones was easily be carried out, providing the ketol phosphates in good yields.

Keywords: α-Phosphoryloxylation, Ketol Phosphate, (Diacetoxyiodo)benzene, Synthesis

1. Introduction

Hypervalent iodine reagents have found broad application in organic chemistry and nowadays frequently used in synthesis due to they are nonmetallic oxidation reagents and avoid the issues of toxicity of many transition metals commonly involved in such processes [1-10]. They offer high potential for the improvement of known reactions not only from the environmental point of view，they are also potentially interesting reagents for the development of completely new synthetic transformations. Among hypervalent iodine reagents, [hydroxy (tosyloxy)iodo]benzene (Koser's reagent) is the most popular and useful reagent for the direct α-tosyloxylation of ketones, and with which the *α*-tosyloxylation of ketones has been extensively studied especially in recent years [11-17]. However, to our knowledge, the analogue reaction of ketones for *α*-phosphoryloxylation has been rather limited and only two methods for preparation of the important ketol phosphates have been known. Using the hypervalent iodine reagent, [hydroxyl ((bis(phenyloxy) phphoryl)-oxy)iodo]benzene to react with ketones was the main method which was reported by Koser's group in 1988, in this process hypervalent iodine reagent must be pre-prepared from (diacetoxyiodo)benzene and diphenyl phosphate [18-19]. The reaction of the prepared hypervalent iodine reagent with terminal alkynes in aqueous MeCN was another protocol for preparation of ketolphosphates [20]. In order to extend the scope of α-phosphoryloxylation of ketones and to prepare more ketol phosphates, the development of a simple, mild and efficient *α*-phosphoryloxylation of ketones is a much-sought process. Herein we would like to report an efficient one-pot *α*-phosphoryloxylation of ketones and a series of ketol phosphates have been prepared in good yields.

2. Results and Discussions

At the beginning, we investigated the "one pot" procedure to improve Koser's method due to the preparation of [hydroxyl((bis(phenyloxy)phosphoryl)oxy)iodo]bezene and its reaction with ketones were separated in two steps. When one equivalent of (diacetoxyiodo)benzene (DIB), diphenyl phosphate and acetophenone were mixed in CH_2Cl_2 at room temperature and stirred for 24 h, the desired product of α-phosphoryloxyl acetophenone was separated in 38% yield after separation. Then, a series of experiments were performed on the reaction of (diacetoxyiodo)benzene, diphenyl phosphate and acetophenone to determine the suitable reaction conditions (**Scheme 1**), the results are summarized in **Table 1**.

The results indicate that the yield depended on solvent and CH_2Cl_2 was found to be the most preferred (entries 1-5). When (diacetoxyiodo)benzene and diphenyl phosphate reached to two equivalents, the yield was increased to 43% (entry 6); while two equivalents of acetophenone were used to reacted with one equivalent of (diacetoxyiodo)benzene and diphenyl phosphate, the reaction got the higher yield of 48% (entry 7). We found that the

$$PhCOCH_3 + PhI(OAc)_2 + HOPO(OPh)_2 \xrightarrow{RT} PhCOCH_2OPO(OPh)_2$$

Scheme 1

Table 1. Optimization of the α-phosphoryloxylation of acetophenone.

Entry	Acetophenone (equiv.)	DIB (equiv.)	Diphenyl phosphate (equiv.)	Solvent (2 mL)	Time (h)	Yield (%)[a]
1	1	1	1	CH_3CN	24	10
2	1	1	1	THF	24	20
3	1	1	1	CH_3OH	24	9
4	1	1	1	CF_3CH_2OH	24	9
5	1	1	1	CH_2Cl_2	24	38
6	1	2	2	CH_2Cl_2	24	43
7	2	1	1	CH_2Cl_2	24	48
8	2	1	1	CH_2Cl_2	2	8[b]
9	2	1	1	CH_2Cl_2	4	13[b]
10	2	1	1	CH_2Cl_2	8	45[b]
11	2	1	1	CH_2Cl_2	12	69[b]
12	2	1	1	CH_2Cl_2	16	72[b]
13	2	1	1	CH_2Cl_2	24	80[b]

[a]Isolated yield; [b]Measured by 1H NMR.

product of α-phosphoryloxyl acetophenone was partly decomposed in separation and the yield was decreased much, then we used ^{1}H NMR technique to show the true yield and after 24 h the reaction reached the highest yield of 80% (entries 8-13).

Under the optimum reaction conditions, the reaction of a series of ketones (1) with (diacetoxyiodo)benzene and phosphate (2) in CH_2Cl_2 at room temperature was investigated (**Scheme 2**), and several ketol phosphates (3) were obtained which all were characterized by ^{1}H NMR, ^{13}C NMR, IR and MS spectra, the results are summarized in **Table 2**. It is shown that the α-phosphoryloxylaction of ketones was easily carried out at room temperature and complete in 24 h, most provided the corresponding ketol phosphates in good to excellent yields. In comparison with other ketones, β-diketone **1e** and **1f** usually needed much less time in the reaction and got the products in excellent yields due to the high activity of α-hydrogen (entries 5-6,8).

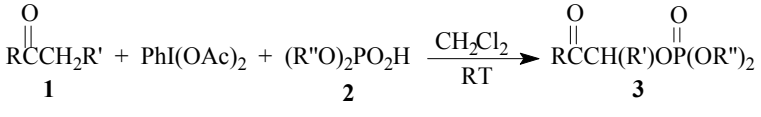
The proposed mechanism for the *α*-phosphoryloxylaction of ketones is similar to the literature procedure [21], which is shown as follows (**Scheme 3**).

3. Experimental

IR spectra were recorded on a Thermo-Nicolet 6700 instrument, NMR spectra were measured on a Bruker ANANCE Ⅲ (500 MHz) spectrometer, and Mass spectra were determined on Thermo-ITQ 1100 mass spectrometer. Ketones, (diacetoxyiodo)benzene and phosphate are commercially available.

4. A Typical Procedure for *α*-Phosphoryloxylation of Ketones

A mixture of acetophenone (1a) (0.5 mmol), (diacetoxy iodo)benzene (0.25 mmol) and diphenyl phosphate (2a) (0.25 mmol) in CH_2Cl_2 (2 mL) was stirred at room temperature for 24 h, then H_2O (5 ml) and sat. aq Na_2CO_3



1

1a: R=Ph, R'=H
1b: R=Me, R'=H
1c: R=*p*-NO_2-C_6H_4, R'=H
1d: R, R'=-$(CH_2)_4$-
1e: R=Ph, R'=PhCO
1f: R=Ph, R'=MeCO

2

2a: R"=Ph
2b: R"=Bz
2c: R"=*p*-NO_2-C_6H_4

3

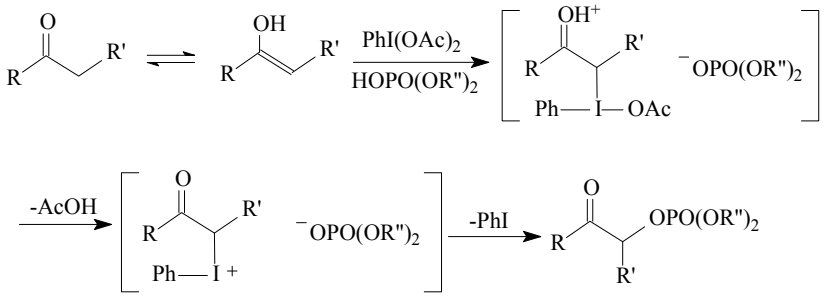
3a: R=Ph, R'=H, R"=Ph
3b: R=Me, R'=H, R"=Ph
3c: R=*p*-NO_2-C_6H_4, R'=H, R"=Ph
3d: R, R'=-$(CH_2)_4$-, R"=Ph
3e: R=Ph, R'=PhCO, R"=Ph
3f: R=Ph, R'=MeCO, R"=Ph
3g: R=Ph, R'=H, R"=Bz
3h: R=Ph, R'=MeCO, R"=Bz
3i: R=Ph, R'=H, R"=*p*-NO_2-C_6H_4

Scheme 2

Table 2. The result of the α-phosphoryloxylation of ketone.

Entry	Ketone (1)	Phosphate (2)	Ketol phosphate (3)	Time (h)	Yield (%)[a]
1	1a	2a	3a	24	80
2	1b	2a	3b	24	70
3	1c	2a	3c	28	68
4	1d	2a	3d	24	92
5	1e	2a	3e	45 (min)	90
6	1f	2a	3f	45 (min)	91
7	1a	2b	3g	24	50
8	1f	2b	3h	45 (min)	92
9	1a	2c	3i	24	69

[a] Measured by 1H-NMR.



Scheme 3

(1 mL) were added. After separation, the water layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give the residue with which the yield of α-phosphoryloxyl acetophenone (3a) was determined in 80% by ^{1}H NMR technique. The residue was purified on a silica gel plate using (4:1 hexane-ethyl acetate) as eluant to give **3a** in the yield of 48%.

3a: Oil (Lit.[18]); ^{1}H NMR (500 MHz, $CDCl_3$): 7.89 - 7.87 (m, 2H), 7.62 - 7.59 (m, 1H), 7.49 - 7.46 (m, 2H), 7.37 - 7.34 (m, 4H), 7.30 - 7.26 (m, 4H), 7.22 - 7.19 (m, 2H), 5.46 (d, J = 10.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): 191.20(d, J = 5.0 Hz), 150.40 (d, J = 7.5 Hz), 134.04, 133.72, 129.78, 128.88, 127.78, 125.51, 120.18 (d, J = 5.0 Hz), 69.90 (d, J = 5.0 Hz); IR (film, cm^{-1}): 1709, 1594, 1489, 1291, 1222, 1189, 1102, 1026; MS (EI, m/z, %): 369 (M+1, 3.5), 275 (100).

3b: Oil (Lit.[18]); ^{1}H NMR (500 MHz, $CDCl_3$): 7.38 - 7.34 (m, 4H), 7.28 - 7.26 (m, 2H), 7.23 - 7 .22 (m, 4H), 4.72 (d, J = 9.5 Hz, 2H), 2.16(s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 201.39 (d, J = 6.3 Hz), 150.17 (d, J = 6.3 Hz), 129.72, 125.50, 119.94 (d, J = 5.0 Hz), 71.54 (d, J = 6.3 Hz), 25.78; IR (film, cm^{-1}): 1739, 1194, 1092, 1024; MS (EI, m/z, %): 307 (M+1, 2), 250 (100).

3c: Oil; ^{1}H NMR (500 MHz, $CDCl_3$): 8.31 (d, J = 9.0 Hz, 2H), 8.04 (d, J = 8.5 Hz, 2H), 7.36 (d, J = 7.5 Hz, 4H), 7.28 - 7.22 (m, 6H), 5.44 (d, J = 10.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): 196.26, 150.30, 141.33, 136.46, 134.89, 130.90, 129.04, 125.66, 123.98, 120.07 (d, J = 5.0 Hz), 69.99 (d, J = 5.0 Hz); IR (film, cm^{-1}): 1693, 1527, 1346, 1261, 1188, 1101; MS (EI, m/z, %): 413 (M, 2), 94 (100); HRMS: $C_{20}H_{16}NO_7P$ calcd.: 413.0664, found: 413.0632.

3d: Oil (Lit.[18]); ^{1}H NMR (500 MHz, $CDCl_3$): 7.37 - 7.32 (m, 6H), 7.25 - 7.19 (m, 4H), 5.03 - 4.98 (m, 1H), 2.59 - 2.55 (m, 1H), 2.37 - 2.31 (m, 2H), 2.0 - 2.02 (m, 1H), 1.95 - 1.92 (m, 1H), 1.86 - 1.80 (m, 1H), 1.75 - 1.60 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): 203.58, 150.62 (d, J = 6.3 Hz), 150.44 (d, J = 7.5 Hz), 129.72 (d, J = 10.0 Hz), 129.58, 125.45, 120.43 (d, J = 3.8 Hz), 120.28 (d, J = 5.0 Hz), 81.36 (d, J = 7.5 Hz), 40.51, 35.03 (d, J = 5.0 Hz), 26.88, 23.34; IR (film, cm^{-1}): 1734, 1284, 1221, 1190, 1069, 1026; MS (EI, m/z, %): 346 (M+, 1), 94 (100).

3e: Oil (Lit.[18]); ^{1}H NMR (500 MHz, $CDCl_3$): 8.09 - 8.04 (m, 4H), 7.55 - 7.52 (m, 2H), 7.41 - 7.38 (m, 4H), 7.33 - 7.27 (m, 4H), 7.24 - 7.242 (m, 4H), 7.19 - 7.15 (m, 2H), 6.90 (d, J = 9.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 190.35 (d, J = 5.0 Hz), 150.22 (d, J = 7.5 Hz), 134.29 (d, J = 12.5 Hz), 133.73, 129.76 (d, J = 16.3 Hz), 129.42, 128.80 (dd, J = 10.0, 3.8 Hz), 127.50, 125.70,

120.21 (d, J = 5.0 Hz), 84.06 (d, J = 6.3 Hz); IR (film, cm^{-1}): 1711, 1682, 1294, 1230, 1186, 1163, 1091, 1011; MS (EI, m/z, %): 472 (M+, 2), 94 (100).

3f: Oil; ^{1}H NMR (500 MHz, $CDCl_3$): 7.94 (dd, J = 8.0, 1.0 Hz, 2H), 7.61 - 7.58 (m, 1H), 7.45 - 7.42 (m, 2H), 7.37 - 7.31 (m, 2H), 7.28 - 7.20 (m, 5H), 7.17 - 7.14 (m, 3H), 6.11 (d, J = 8.5 Hz, 1H), 2.22 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 190.35 (d, J = 5.0 Hz), 150.22 (d, J = 7.5 Hz), 134.29 (d, J = 12.5 Hz), 133.73, 129.76 (d, J = 16.3 Hz), 129.42, 128.80 (dd, J = 10.0, 3.8 Hz), 127.50, 125.70, 120.21 (d, J = 5.0 Hz), 84.06 (d, J = 6.3 Hz); IR (film, cm^{-1}): 1730, 1688, 1218, 1024; MS (EI, m/z, %): 410 (M+, 1), 105 (100); HRMS: $C_{22}H_{19}O_6P$ calcd.: 410.0919, found: 410.0889.

3g: Oil; ^{1}H NMR (500 MHz, $CDCl_3$): 7.84 (d, J = 8.0 Hz, 2H), 7.58 - 7.52 (m, 1H), 7.47 (d, J = 8.0 Hz, 2H), 7.34 - 7.30 (m, 10H), 5.22 (d, J = 10.0 Hz, 2H), 5.18 (dd, J = 8.0, 6.0 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): 191.99 (d, J = 5.0 Hz), 135.67 (d, J = 6.3 Hz), 133.89, 128.80, 128.51, 128.02, 127.68, 69.70 (d, J = 5.0 Hz), 68.67 (d, J = 5.0 Hz); IR (film, cm^{-1}): 1708, 1279, 1234, 1116, 1014; MS (EI, m/z, %): 397 (M+, 1), 199 (100); HRMS: $C_{22}H_{21}O_5P$ calcd.: 396.1127, found: 396.1121.

3h: Oil; ^{1}H NMR (500 MHz, $CDCl_3$): 7.98 (d, J = 7.5 Hz, 2H), 7.59 (t, J = 7.5 Hz, 1H), 7.42 (t, J = 8.0 Hz, 2H), 7.38 - 7.29 (m, 10H), 5.97 (d, J = 8.0 Hz, 1H), 5.15 (d, J = 9.0 Hz, 2H), 5.10 - 5.01 (m, 2H), 2.22 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 191.99 (d, J = 5.0 Hz), 135.67 (d, J = 6.3 Hz), 133.89, 128.80, 128.51, 128.02, 127.68, 69.70 (d, J = 5.0 Hz), 68.67 (d, J = 5.0 Hz); IR (film, cm^{-1}): 1708, 1279, 1234, 1116, 1014; MS (EI, m/z, %): 439 (M+1, 2), 105 (100); HRMS: $C_{24}H_{23}O_6P$ calcd.: 438.1232, found: 438.1201.

3i: Oil; ^{1}H NMR (500 MHz, $CDCl_3$): 8.28 (d, J = 9.0 Hz, 4H), 7.87 (d, J = 7.5 Hz, 2H), 7.64 - 7.62 (m,1H), 7.52 - 7.45 (m, 6H), 5.57 (d, J = 12.5Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): 190.55 (d, J = 3.8 Hz), 154.55 (d, J = 6.3 Hz), 145.19, 134.41, 132.98, 128.98, 127.62, 125.72, 120.86 (d, J = 2.5 Hz), 70.79 (d, J = 6.3 Hz); IR (film, cm^{-1}): 1713, 1614, 1591, 1518, 1491, 1344, 1290, 1248, 1215, 1109; MS (EI, m/z, %): 458 (M+, 1), 105 (100); HRMS: $C_{20}H_{15}N_2O_9P$ calcd.: 458.0515, found: 458.0488.

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6. References

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