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Selective Synthesis of *o*-Acylbenzylphosphonates by Insertion Reactions of Arynes into *β*-Ketophosphonates

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Received April 24, 2009

A mild method for selective synthesis of *o*-acylbenzylphosphonates has been developed by the reactions of arynes with *β*-ketophosphonates. In the presence of CsF and THF, the carbon−carbon *σ*-bonds of 2-*oxo*propylphosphonates were selectively cleaved and added to arynes providing the corresponding 2-acylbenzylphosphonates in moderate to good yields.

Aryne chemistry is an important topic in organic chemistry because arynes are highly strained and kinetically unstable molecules emerging as valuable reactive intermediates in organic synthesis.[1−10] However, the generation of arynes in situ from the traditional aryne precursors is often conducted under harsh conditions.[1] Moreover, the traditional aryne precursors are prepared with difficulty. These drawbacks limit their applications in organic synthesis. Recently, many efficient methods have been developed on the basis of *o*-silyl aryltriflates because *o*-silyl aryltriflates could be readily prepared, and be converted into benzynes in situ under mild conditions.[1d−1f,2−10] These efficient transformations involve insertion of arynes into various nucleophilic−electrophilic *σ*-bonds, such as hydrogen−heteroatom, hydrogen−carbon, heteroatom−heteroatom, heteroatom−carbon, and carbon−carbon *σ*-bonds, for the straightforward synthesis of substituted arenes.[1,3−9] In 2001, Shirakawa and Hiyama first reported that palladium could promote the insertion of arynes into C−Sn *σ*-bonds to afford ortho-substituted arylstannanes using *o*-silyl aryltriflates as the aryne precursors.[3] Shortly after, a variety of nucleophilic−electrophilic *σ*-bonds were developed for these purposes.[1f,4−9] However, only a few papers on the insertion of an aryne into a carbon−carbon *σ*-bond have been published.[5−8] Stoltz and co-workers have described an efficient and direct acyl-alkylation of arynes with keto esters involving the net insertion of an arene unit into the α,*β*-C−C *σ*-bond of *β*-ketoester in the presence of CsF and MeCN.[5] Subsequently, Yoshida and Kunai extended the scopes to *β*-dicarbonyls,[6] α-cyanocarbonyl,[7] *p*-toluenesulfonylacetonitrile, and malononitrile[8] using the KF/18-crown-6/THF system. Very recently, Huang and co-workers also found that *β*-keto sulfones were suitable substrates for the insertion reaction with arynes under the same conditions.[9] Thus, the development of some new alternative carbon−carbon *σ*-bonds for the insertion reaction with arynes is still interesting. Yoshida and Kunai have reported the carbophosphinylations

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DOI: 10.1021/jo900847u Published on Web 06/15/2009

SCHEME 1

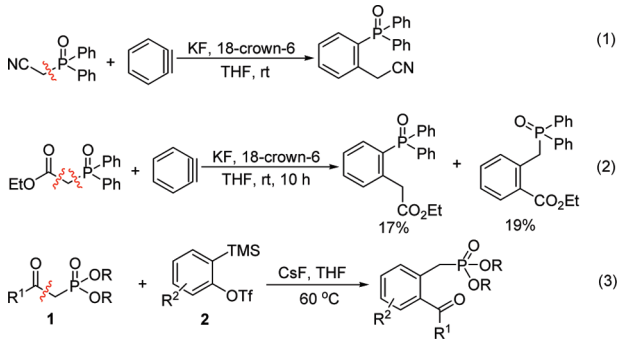
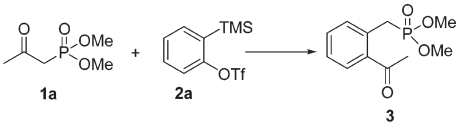


TABLE 1. Screening Conditions[a]



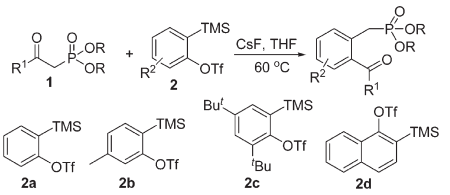
entry	fluoride	solvent	*t* (°C)	time (h)	yield (%)[b]
1	CsF	THF	60	15	84
2	CsF	MeCN	60	21	67
3	CsF	CH_2ClCH_2Cl	60	21	55
4	CsF	toluene	60	20	31
5[c]	KF	THF	60	15	33
6	TBAF	THF	60	15	mixture
7	CsF	THF	25	15	75
8	CsF	THF	100	21	50
9[d]	CsF	THF	60	15	60

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.25 mmol), base (4 equiv), and solvent (2 mL). [b] Isolated yield based on substrate **1a**. [c] 18-Crown-6 (2 equiv) was added. [d] CsF (2 equiv).

of arynes with cyanomethyldiphenylphosphine oxide (eq 1 in Scheme 1).[4j] Although both the selectivity and yield were not satisfactory among the reaction of benzyne with ethyl 2-(diphenylphosphine oxide)acetate, insertion of arynes into the carbon−carbon σ-bond was observed (eq 2). The results prompted us to explore the feasibility of the carbon−carbon σ-bond insertion between phosphine-contained compounds and arynes. After a series of trials, we found that 2-oxopropylphosphonates were suitable substrates for the carbon−carbon σ-bond insertion with arynes to afford the corresponding 2-acylbenzylphosphonates in moderate to good yields. Here, we report our results on the insertion reactions of arynes to the α,β-C−C σ-bonds of β-ketophosphonates (eq 3).

As shown in Table 1, the reaction of dimethyl 2-oxopropylphosphonate (**1a**) with 2-(trimethylsilyl)phenyl triflate (**2a**), a benzyne precursor, was investigated to optimize the reaction conditions. Initially, a number of solvents, including THF, MeCN, CH_2ClCH_2Cl, and toluene, were tested (entries 1−4), and THF was found to be the most effective (entry 1). While in THF the reaction between substrate **1a** and benzyne **2a** was conducted smoothly to afford the corresponding product **3** in an 84% yield, the other three solvents reduced the yield to 67%, 55%, and 31%, respectively (entries 2−4). Subsequently, two other fluorides, KF and TBAF, were evaluated (entries 5 and 6). The results indicated that they both were inferior to CsF. Among the reaction temperature and amount of CsF examined (entries 2 and 7−9), 60 °C combined with 4 equiv of CsF gave the best results (entry 1).

TABLE 2. Insertion Reactions of Arynes 2 into β-Ketophosphonates 1 in the Presence of CsF and THF[a]



Entry	1	2	Product	Yield[b]
1[c]	**1a**	**2b**	**4**	74% (19 h)
2[d]	**1a**	**2c**	**5**	37% (51 h)
3[e]	**1a**	**2d**	**7**	71% (19 h)
4	**1b**	**2a**	**8**	54% (37 h)
5	**1c**	**2a**	**9**	59% (37 h)
6	**1d**	**2a**	**10**	54% (37 h)
7	**1e**	**2a**	**11**	74% (23 h)
8	**1f**	**2a**	**12**	65% (67 h)
9	**1g**	**2a**	**13**	51% (45 h)
10	**1h**	**2a**	**14**	67% (30 h)
11	**1i**	**2a**	**15**	44% (37 h)
12	**1j**	**2a**	**16**	69% (11 h)

[a] Reaction conditions: **1** (0.2 mmol), **2** (0.25 mmol), CsF (4 equiv), and THF (2 mL) at 60 °C. [b] Isolated yield. The reaction time is given in the parenthesis. [c] Dimethyl 2-acetyl-4-methylbenzylphosphonate/dimethyl 2-acetyl-5-methylbenzylphosphonate = 1:1.2. [d] Another product, dimethyl 1-(3,5-di-*tert*-butylphenyl)-2-oxopropylphosphonate 6, was isolated in 17% yield. [e] Dimethyl (2-acetylnaphthalen-1-yl)methylphosphonate/dimethyl (1-acetylnaphthalen-2-yl)methylphosphonate = 3.4:1.

With the optimal conditions in hand, the scopes of both arynes and β-ketophosphonates were explored (Table 2).

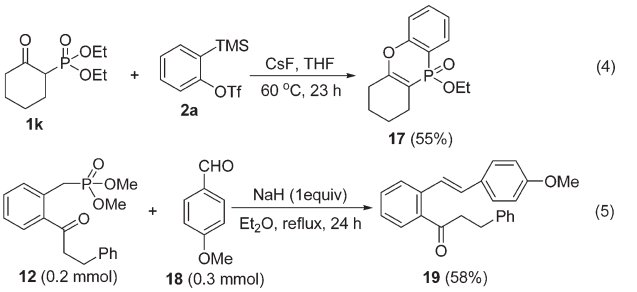
Initially, three other *o*-silyl aryltriflates **2b**−**d** reacted with dimethyl 2-oxopropylphosphonate (**1a**) were investigated in the presence of CsF and THF. Treatment of substrate **1a** with *o*-silyl aryltriflates **2b** or **2d**, CsF, and THF afforded the desired products in good yields (entries 1 and 3). It is worth noting that 37% yield of the desired product **5** is still isolated from bulky *o*-silyl aryltriflate **2c** together with 17% yield of a side product **6**, dimethyl 1-(3,5-di-*tert*-butylphenyl)-2-oxopropylphosphonate (entry 2). Subsequently, a variety of *β*-ketophosphonates **1b**−**j** were examined for the reaction with 2-(trimethylsilyl)phenyl triflate (**2a**) (entries 4−12). The results demonstrated that several functional groups, such as alkenyl, chloro, iodo, and methoxy groups, were tolerated well under the standard conditions. Alkenyl *β*-ketophosphonates **1b**−**d**, for instance, underwent the reaction with aryne **2a**, CsF, and THF, respectively, to afford the target products in moderate yields (entries 4−6). To our delight, the standard conditions were compatible with substrate **1e** with a chloroalkyl group (entry 7). We were pleased to observe that 2-oxobutylphosphonates **1f**−**i**, bearing substituted phenyl groups at the 4-position, were still suitable substrates for the reaction with aryne **2a** in moderate yields, and substituents on the aromatic ring were tolerated (entries 8−11). Interestingly, the reaction of diethyl 2-oxocyclopentylphosphonate (**1j**) with aryne **2a** afforded a seven-membered-ring product **16**, diethyl 6,7,8,9-tetrahydro-9-oxo-5*H*-benzo[7]annulen-5-yl-5-phosphonate, in 69% yield (entry 12).

To our surprise, diethyl 2-oxocyclohexylphosphonate (**1k**) underwent addition, not insertion/deletion of α,*β*-C−C *σ*-bond, with aryne to form the corresponding product **17** in 55% yield (eq 4 in Scheme 2). We have tested the product **3** as a synthetic intermediate to undergo the Wittig reaction with 4-methoxybenzaldehyde (**18**) (eq 5). In the presence of NaH, treatment of dimethyl (2-acetylphenyl)methylphosphonate (**3**) with aldehyde **18** in DMF afforded the desired 1-(2-(4-methoxystyryl)phenyl)ethanone (**19**) in 58% yield.[11]

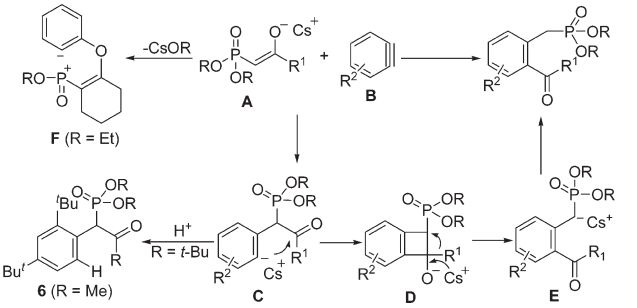
A possible mechanism was proposed as outlined in Scheme 3 on the basis of the reported mechanism and the present results. Nucleophilic attack of an enolate intermediate **A**, which is generated in situ from the reaction of *β*-ketophosphonate **1** with CsF, to aryne **B** occurs to produce an aryl anion **C**. Intermediate **C** undergoes intramolecular nucleophilic attack to carbonyl moiety to afford intermediate **D**, followed by ring expansion of intermediate **D** to give intermediate **E**. Protonation of intermediate **E** affords the product. An aryl anion **C** reacts with a hydrogen cation to yield **6** when the ortho-position has a bulky group (entry 2 in Table 2). Intermediate **F** may be readily generated from addition of the oxygen atom of the enolate intermediate **A** to an aryne, followed by attack at an RO-decomposed phosphorus to afford the product **17**.

In conclusion, we have demonstrated that the carbon−carbon *σ*-bonds of *β*-ketophosphonate compounds could be readily cleaved and added to arynes under mild conditions. Importantly, these products with a phosphonate group are crucial synthetic intermediates, such as the known Wittig reagents,[11] which provide an attractive and useful route to introduce new groups for the synthesis of new bioactive products. Moreover, the known phosphonate-contianed compounds often display a multitude of robust biologically important properties serving as pharamacological agents.

SCHEME 2



SCHEME 3. A Working Mechanism



Experimental Section

Typical Experimental Procedure for the Insertion Reactions of Arynes (2) into *β*-Ketophosphonates (1). A mixture of *β*-ketophosphonate **1** (0.2 mmol), aryne **2** (0.25 mmol), CsF (4 equiv), and THF (2 mL) was stirred at 60 °C under argon atmosphere for the indicated time until complete consumption of starting material as monitored by TLC and GC-MS analysis. After the reaction was finished, the mixture was filtered by a crude column with ethyl acetate as eluent, and evaporated under vacuum. The residue was purified by flash column chromatography (hexane/ethyl acetate) to afford the desired product.

Dimethyl 2-(3-phenylpropanoyl)benzylphosphonate (12): colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.59 (d, *J* = 7.5 Hz, 1H), 7.36−7.42 (m, 2H), 7.25−7.31 (m, 5H), 7.19 (t, *J* = 7.0 Hz, 1H), 3,67 (d, *J* = 24.0 Hz, 2H), 3.63 (d, *J* = 10.5 Hz, 6H), 3.27 (t, *J* = 7.8 Hz, 2H), 3.07 (t, *J* = 7.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 29.4 (d, *J* = 136.3 Hz, 1C), 30.1, 43.1, 52.7 (d, *J* = 6.3 Hz, 2C), 126.1, 127.0 (d, *J* = 3.8 Hz, 1C), 128.5, 128.5, 128.6 (d, *J* = 3.8 Hz, 1C), 131.0 (d, *J* = 10.0 Hz, 1C), 131.3 (d, *J* = 3.8 Hz, 1C), 132.5 (d, *J* = 6.3 Hz, 1C), 138.4 (d, *J* = 6.3 Hz, 1C), 141.3, 203.5; IR (KBr, cm^{-1}) 1675; LRMS (EI, 70 eV) *m*/*z* (%) 332 (M^+, 71), 227 (49), 200 (67), 149 (15), 118 (31), 131 (42), 104 (65), 91 (100); HRMS (EI) for $C_{18}H_{21}O_4P$ (M^+) calcd 332.1178, found 332.1176.

1-(2-(4-Methoxystyryl)phenyl)-3-phenylpropan-1-one (19): colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.68 (d, *J* = 7.5 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.41−7.47 (m, 3H), 7.36 (d, *J* = 15.0 Hz, 1H), 7.28−7.30 (m, 3H), 7.18−7.23 (m, 3H), 6.89−6.96 (m, 3H), 3.84 (s, 3H), 3.25 (t, *J* = 7.5 Hz, 2H), 3.06 (t, *J* = 7.5, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 30.4, 43.1, 55.3, 114.1, 124.7, 126.1, 126.8, 127.0, 128.1, 128.1, 128.4, 128.5, 130,0, 131.2 (2C), 137.2, 137.6, 141.0, 159.5, 204.3; IR (KBr, cm^{-1}) 1683; LRMS (EI, 70 eV) *m*/*z* (%) 342 (M^+, 100), 251 (64), 237 (35), 221 (32), 165 (37), 121 (49);

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HRMS (ESI) for $C_{24}H_{22}NaO_2$ (M^+) calcd 365.1513, found 365.1513.

Acknowledgment. We thank the New Century Excellent Talents in University (No. NCET-06-0711), Scientific Research Fund of Hunan Provincial Education Department (Nos. 08B053 and 08A037), Opening Fund of KLCBTCMR (No. KLCBTCMR2008-11), Hunan Normal University (No. 080605), and National Natural Science Foundation of China (No. 20872112) for financial support.

Supporting Information Available: Analytical data and spectra (^1H and ^{13}C NMR) for all the products **3**−**17** and **19**; typical procedure for the insertion reactions of arynes into β-ketophosphonates. This material is available free of charge via the Internet at http://pubs.acs.org.