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Synthesis of α-Arylphosphonates using Copper-Catalyzed α-Arylation and Deacylative α-Arylation of β-Ketophosphonates

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Abstract: Efficient methods for the direct arylation and deacylative arylation of β-ketophosphonates with iodoarenes in presence of a copper(I) or a copper(II) salt as the catalysts have been developed. The corresponding α-arylphosphonates were obtained in high yields. A tentative mechanism for the deacylative arylation reaction was proposed on the basis of the experimental data.

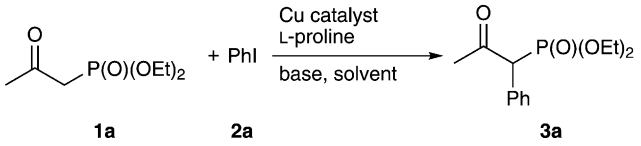
Keywords: arylation; α-arylphosphonates; coupling; deacylation; iodoarenes

α-Aryl-substituted methylphosphonate and β-ketophosphonate derivatives are frequently used as anti-inflammatory agents.[1] For example, they have been shown to be potent dual inhibitors of neutrophil cathepsin G and mast cell chymase, which are associated with asthma and chronic obstructive pulmonary diseases.[1a–c] They are also useful precursors for the synthesis of other biologically active compounds.[1b] In organic chemistry, these compounds are vital starting materials for the synthesis of alkene derivatives.[2] Traditional methods for the synthesis of α-arylmethylphosphonates involve the reaction of arylmethyl halides[3a] or arylmethylpyridinium iodides[3b] with trialkyl phosphites and the Michaelis–Arbuzov rearrangement of arylmethylphosphites.[3c,d] Other reported methods include the rhodium-catalyzed coupling reaction of $(EtO)_2P(O)CH_2ZnI$ and PhI,[3e] and the coupling reaction of chloromethylphosphonates with aryl bromide mediated by CuI and *t*-BuLi.[3f] As for the synthesis of α-aryl-substituted β-ketophosphonates, only a handful of reports is available, namely, the addition of trialkyl phosphites in the presence of $TiCl_4$,[3g] or dialkyl phosphites in the presence of DBU/TMSCl,[3h] to nitroalkenes followed by *m*-CPBA oxidation; the reaction of diethyl phosphonocarboxylic acid chlorides and organocuprates or Grignard reagents,[3i] the rearrangement of substituted epoxyphosphonates,[3j] and the reaction of arylsulfonyl epoxides and sodium dialkyl phosphates.[3k] As summarized above, most of these reported methods for the synthesis of these two types of compounds require either drastic reaction conditions or some special reagents. Moreover, to the best of our knowledge, there is no general method for the synthesis α-aryl-substituted methylphosphonates and β-ketophosphonates from a common starting material using readily available catalysts.

As part of our ongoing efforts in developing novel synthetic methods for α-substituted phosphonates,[4] we became interested in the synthesis of α-aryl-substituted phosphonates through the direct α-arylation of the readily available β-ketophosphonates. Although there is no such precedence in the literature, there are a few reports on the direct α-arylation of active methylene compounds.[5] For example, Ma and coworkers have reported a copper-catalyzed coupling of β-keto esters and aryl iodides.[5a–d] Inspired by these reports, we envisioned that α-aryl-substituted β-ketophosphonates could be synthesized from β-ketophosphonates and aryl halides with a suitable catalyst. Herein we report a copper-catalyzed direct synthesis of α-aryl-substituted β-ketophosphonates and methylphosphonates from β-ketophosphonates and aryl iodides *via* a cross-coupling reaction and a cascade cross-coupling and deacylation reaction, respectively. We believe this is the first method where these two types of compounds are prepared from a common β-ketophosphonate derivative.

With diethyl (2-oxopropane)phosphonate (**1a**) and iodobenzene (**2a**) as the model substrates, we first studied the α-arylation reaction using the reaction conditions similar to those reported by Ma and coworkers.[5a] The results of this study are summarized in Table 1. As shown by the results, in presence of CuI (20 mol%), L-proline (40 mol%) and Cs_2CO_3 (3 equiv.) in DMSO, the desired α-arylated product **3a** was isolated with 64% yield after reacting for 24 h at 50 °C (entry 1). While copper(I) bromide (entry 2), copper(II) acetate monohydrate (entry 3), copper(II) sulfate pentahydrate (entry 4), and copper(II) tosylate monohydrate (entry 5) all catalyze this coupling reaction, their reactivity is much lower. Screening of the

Table 1. Optimization of the reaction conditions for the arylation of **1a**.[a]



1a **2a** **3a**

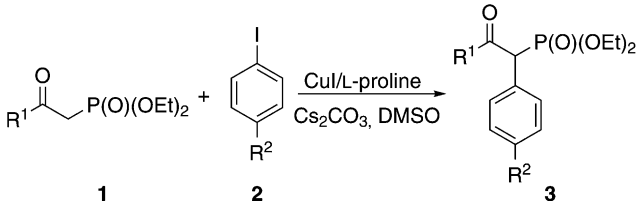
Entry	Catalyst	Solvent	Base	Yield [%][b]
1	CuI	DMSO	Cs_2CO_3	64
2	CuBr	DMSO	Cs_2CO_3	24
3	$Cu(OAc)_2·H_2O$	DMSO	Cs_2CO_3	31
4	$CuSO_4·5H_2O$	DMSO	Cs_2CO_3	38
5	$Cu(OTf)_2·H_2O$	DMSO	Cs_2CO_3	35
6	CuI	DMF	Cs_2CO_3	61
7	CuI	dioxane	Cs_2CO_3	0
8	CuI	toluene	Cs_2CO_3	0
9	CuI	DMSO	K_2CO_3	0
10	CuI	DMSO	KOH	19
11	CuI	DMSO	$K_3PO_4·3H_2O$	24
12[c]	CuI	DMSO	Cs_2CO_3	0
13[d]	CuI	DMSO	Cs_2CO_3	0
14[e]	CuI	DMSO	Cs_2CO_3	84
15[f]	CuI	DMSO	Cs_2CO_3	61

[a] Unless otherwise indicated, all reactions were conducted with **1a** (1.2 mmol), **2a** (1.0 mmol), the copper salt (20 mol%), L-proline (40 mol%), and the specified base (3.0 mmol) in the indicated solvent (1.0 mL) under an N_2 atmosphere at 50 °C for 24 h.
[b] Yield of the isolated product.
[c] No L-proline was added.
[d] PPh_3 was used instead of L-proline.
[e] The reaction was carried out 70 °C.
[f] The reaction was carried out in bromobenzene at 90 °C.

solvents revealed that good reactivity was also obtained in DMF (entry 6). However, no reaction was observed in dioxane and toluene (entries 7 and 8). Similarly, other bases tested in this reaction, such as K_2CO_3 (entry 9), KOH (entry 10), and $K_3PO_4·3H_2O$ (entry 11), are not effective. It is also noteworthy that the reaction did not proceed in absence of L-proline (entry 12) or when L-proline was replaced with PPh_3 (entry 13). Gratifyingly, the yield of this arylation reaction may be improved to 84% by carrying out the reaction at 70 °C (entry 14). Under these optimized reaction conditions, less reactive bromobenzene also affords compound **3a** in 61% yield (entry 15).

Next, we studied the scope of reaction with different iodobenzenes bearing electron-withdrawing or electron-donating functional groups (Table 2). As shown by the results, this catalytic system tolerates iodobenzenes with both an electron-withdrawing group and an electron-donating group at the *para*-position of the benzene ring and different β-ketophophonate starting materials to afford the desired α-arylated β-ketophosphonates **3a–3k** in good yields (74–84%, entries 1–11). Interestingly, for 1,4-diiodobenzene

Table 2. Copper(I) iodide-catalyzed arylation of β-ketophosphonates.[a]



1 **2** **3**

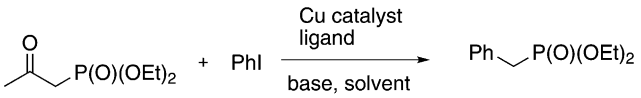
Entry	R^1	R^2	Time [h]	Product	Yield [%][b]
1	Me	H	24	**3a**	84
2	Me	F	26	**3b**	81
3	Me	Br	26	**3c**	74
4	Me	I	24	**3d**	81
5	Me	CO_2Et	24	**3e**	81
6	Me	CN	22	**3f**	81
7	Me	NO_2	20	**3g**	80
8	Me	Me	26	**3h**	82
9	Me	MeO	26	**3i**	83
10	Et	H	24	**3j**	81
11	Ph	H	24	**3k**	75

[a] All reactions were conducted with **1a** (1.2 mmol), **2** (1.0 mmol), CuI (20 mol%), L-proline (40 mol%), and Cs_2CO_3 (3.0 mmol) in DMSO (1.0 mL) under an N_2 atmosphere at 70 °C for the indicated reaction times.
[b] Yield of the isolated product.

(entry 4), we only observed the monoarylated **3d**. No trace of the diarylated product was detected even when the reaction was carried out in the presence of 6 equivalents of Cs_2CO_3 and 3 equivalents of **1a** after 48 h (data not shown).

During the course of the above study, we noted that Cu(II) salts also can catalyze the arylation reaction (Table 1, entries 3–5), albeit in lower efficiency as compared to CuI. Because Cu(II) salts are cheaper than CuI, it was our intention to optimize the reaction conditions to improve the efficiency of the Cu(II)-catalyzed arylation. Since higher temperature works better for CuI (Table 1, entry 14), we attempted the copper(II) acetate monohydrate-catalyzed coupling reaction at higher temperature. Surprisingly, increasing the reaction temperature to 110 °C led to the formation of the deacylated coupling product **4a** in 72% yield; whereas the expected **3a** was only isolated in 12% yield (Table 3, entry 1). This result represents the first catalytic method for the direct preparation of arylmethylketophosphonates from readily available β-ketophosphonates. In this regard, it should be pointed out that palladium acetate-catalyzed deacylative coupling between β-keto esters and aryl halides[6] and copper(I) iodide-catalyzed deacylative coupling between β-keto esters[7] or 1,3-diketones[8] and aryl halides have been reported recently. Nevertheless, deacylative coupling reaction of β-ketophosphonates is un-

Table 3. Optimization of the reaction conditions for the deacylative α-arylation of **1a**.[a]



1a **2a** **4a**

Entry	Catalyst	Solvent	Base	Yield [%][b]
1[c]	$Cu(OAc)_2 \cdot H_2O$	DMSO	Cs_2CO_3	72[d]
2[e]	$Cu(OAc)_2 \cdot H_2O$	DMSO	K_2CO_3	61
3	$Cu(OAc)_2 \cdot H_2O$	DMSO	K_2CO_3	89
4[f]	$Cu(OAc)_2 \cdot H_2O$	DMSO	K_2CO_3	53
5	$Cu(OAc)_2 \cdot H_2O$	DMSO	Cs_2CO_3	51
6	$Cu(OAc)_2 \cdot H_2O$	DMSO	KOH	41
7	$Cu(OAc)_2 \cdot H_2O$	DMSO	$K_3PO_4 \cdot 3H_2O$	62
8	$Cu(OAc)_2 \cdot H_2O$	EG[g]	K_2CO_3	0
9	$Cu(OAc)_2 \cdot H_2O$	toluene	K_2CO_3	0
10	$Cu(OAc)_2 \cdot H_2O$	DMF	K_2CO_3	trace
11	CuI	DMSO	K_2CO_3	49
12	$Cu(OTf)_2 \cdot H_2O$	DMSO	K_2CO_3	57
13	$Cu(NO_2)_2 \cdot H_2O$	DMSO	K_2CO_3	52
14[8h]	$Cu(OAc)_2 \cdot H_2O$	DMSO	K_2CO_3	13

[a] Unless otherwise indicated, all reactions were conducted with **1a** (1.2 mmol), **2a** (1.0 mmol), the copper salt (10 mol%), 2,2′-bipyridine (20 mol%), and the specified base (5.0 mmol) in the indicated solvent (1.0 mL) at 110 °C for 24 h.
[b] Yield of the isolated product.
[c] The reaction was carried out with L-proline (40 mmol%) as the ligand.
[d] Compound **3a** was also isolated in 12% yield in this case.
[e] No ligand was added.
[f] Phenanthrene was used as the ligand.
[g] EG = ethylene glycol.
[h] Bromobenzene was used at 130 °C.

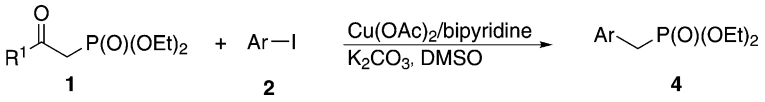
precedented and copper(II) salts have never been used for such a purpose.

When K_2CO_3 was used as the base, the reaction also proceeded without L-proline to yield **4a** in 61% yield (entry 2). When 2,2′-bipyridine was used as the ligand, the yield was improved to 89% (entry 3). However, using phenanthrene as the ligand showed no improvement in the yield of **4a** (entry 4). It should be pointed out that, although the deacylation is most favorable with 5 equivalents of K_2CO_3, it does proceed with a lower amount of base. For example, with 0.5, 1.0, 2.0, 3.0, and 4.0 equivalents of K_2CO_3, product **4a** was obtained in 12%, 23%, 38%, 51%, and 72% yields, respectively (data not shown). Other bases, such as Cs_2CO_3, KOH, and $K_3PO_4 \cdot 3H_2O$ are less effective in promoting the reaction (entries 5-7). Similarly, this reaction does not work in solvents like ethylene glycol, toluene, and DMF (entries 8–10). Under the optimized conditions, copper(I) iodide, copper(II) tosylate monohydrate, and copper(II) nitrate monohydrate also led to the deacylative α-arylation product **4a**, albeit in lower yields (entries 11–13). Replacing iodobenzene with bromobenzene afforded **4a** in only 13% yield even at 130 °C (entry 14).

Then we further investigated the scope of this deacylative arylation reaction (Table 4) under the optimized conditions. Besides iodobenzene (entry 1), iodobenzene derivatives bearing an electron-withdrawing group, such as, 4-fluoro (entry 2), 4-bromo (entry 3), 4-iodo (entry 4), 4-ethoxycarbonyl (entry 5), 4-cyano (entry 6), and 4-nitro (entry 7), all undergo the expected reaction smoothly to provide the corresponding deacylated cross-coupling products **4b**–**4g** in high yields (85–91%). Again 1,4-diiodobenzene (entry 4) gave only the monoarylated phosphonate **4d**. No formation of diarylated product was observed. Nonetheless, with iodobenzenes bearing an electron-donating group, such as 4-methyl and 4-methoxy groups, no deacylative arylation products, such as, **4h** and **4i**, could be isolated. Only low yields of the arylation products **3h** and **3i** were obtained, respectively (Table 4, entries 8 and 9). On the other hand, 1-iodonaphthalene underwent this reaction smoothly to provide corresponding deacylated cross-coupling product **4h** in 92% yield (entry 10). This deacylative arylation reaction may also be applied to other β-ketophosphonate substrates. When the terminal methyl group of **1a** was changed to ethyl (**1b**, entry 11) and phenyl (**1c**, entry 12) groups, reactions with iodobenzene under similar conditions produced the expected deacylated product **4a** in 85% and 93% yields, respectively.

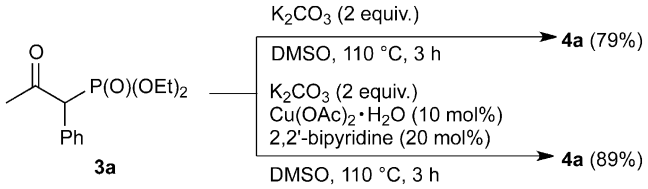
Although the mechanism of the reported copper- or palladium-catalyzed deacylative coupling reactions[6–8] remains elusive, a C–C bond activation[9] was proposed to be a possible mechanism in the deacylative arylation of 1,3-diketones.[8] In order to find out the possible mechanism of the current reaction, some additional experiments were carried out. Firstly, four separate reactions were carried out with the authentic α-phenyl-substituted β-ketophosphonate **3a**, which is a potential intermediate in the deacylative arylation reaction. As shown in Scheme 1, in the presence of 2 equivalents of K_2CO_3, the reaction of **3a** at 110 °C in DMSO for 3 h led to the full conversion of **3a**, and **4a** was isolated in 79% yield. Similarly, in the presence of 2 equivalents of K_2CO_3 and 10 mol% of $Cu(OAc)_2 \cdot H_2O$, as well as 20 mol% of 2,2′-bipyridine, **4a** was isolated in 89% yield (Scheme 1). However, under these conditions, no reaction was observed without the addition of any of these reagents. Similarly, $Cu(OAc)_2 \cdot H_2O$ alone cannot catalyze the conversion of **3a** under these conditions (data not shown). It is also noteworthy that we did not observe any dephosphorylation product, such as $PhCH_2COMe$, in all these cases. These results indicate that, if **3a** is formed, the deacylation is mainly due to the action of K_2CO_3. However, $Cu(OAc)_2$ also promotes the deacylation reaction in the presence of the ligand (2,2′-bipyridine).

Table 4. Synthesis of **4** from reaction of **1** and **2** with $Cu(OAc)_2 \cdot H_2O$.[a]

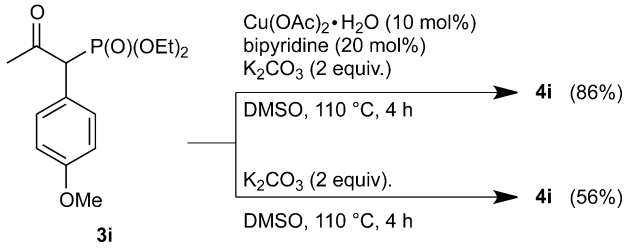


Entry	R^1	Ar	Time [h]	Product	Yield [%][b]
1	Me	C_6H_5	24	**4a**	89
2	Me	4-F-C_6H_4	40	**4b**	85
3	Me	4-Br-C_6H_4	34	**4c**	86
4	Me	4-I-C_6H_4	26	**4d**	88
5	Me	4-EtO_2C-C_6H_4	28	**4e**	87
6	Me	4-CN-C_6H_4	27	**4f**	90
7	Me	4-NO_2-C_6H_4	32	**4g**	91
8	Me	4-Me-C_6H_4	48	**4h**	0[c]
9	Me	4-MeO-C_6H_4	48	**4i**	0[d]
10	Me	1-naphthyl	35	**4j**	92
11	Et	C_6H_5	24	**4a**	85
12	Ph	C_6H_5	24	**4a**	93

[a] All reactions were conducted with **1** (1.2 mmol), **2** (1.0 mmol), K_2CO_3 (5.0 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.10 mmol, 10 mol%), and 2,2′-bipyridine (0.20 mmol, 20 mol% in DMSO (1.0 mL) at 70 °C for the indicated reaction times.
[b] Yield of the isolated product.
[c] Only the coupling product **3h** was obtained in 28% yield.
[d] The coupling compound **3i** was obtained in 30% yield with a trace amount of **4i**.



Scheme 1. Deacylation of **3a** under various conditions.

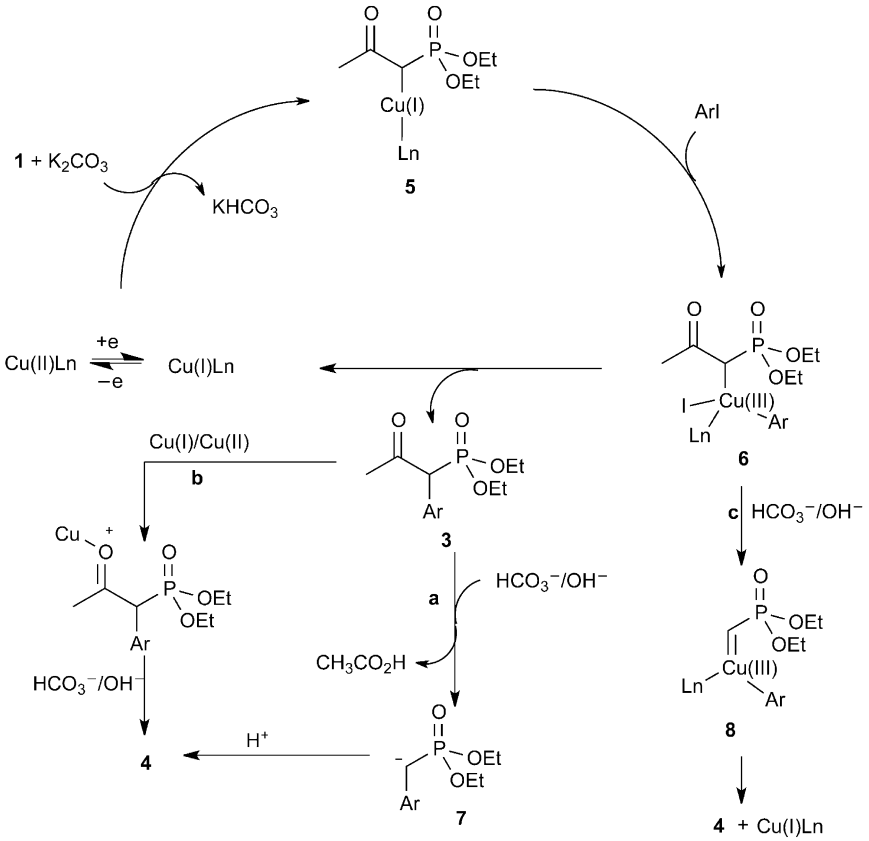


Scheme 2. Deacylation of **3i**.

Next, the deacylation of compound **3i** was studied. As we have mentioned previously, the direct deacylative coupling of 1-iodo-4-methoxybenzene and **1a** fails to proceed (Table 4, entry 9). However, the deacylation of **3i** works well in the presence of $Cu(OAc)_2$/K_2CO_3 or K_2CO_3 alone (Scheme 2). The data again verify that, although the reaction takes place with K_2CO_3 alone, $Cu(OAc)_2$/2,2′-bipyridine is also a promoter of the deacylation reaction. These data also hint that the direct deacylative arylation reaction is a cascade reaction beginning with the arylation reaction.

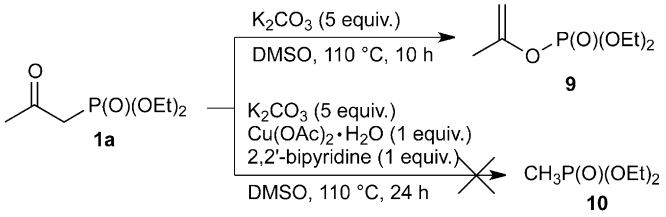
On the basis of these facts and the mechanism proposed for deacylative arylation of 1,3-diketones,[8] a plausible mechanism (Scheme 3) is proposed to account for the above deacylation reaction. As shown in Scheme 3, Cu(I) formed *in situ* from Cu(II) acetate reacts with **1** in the presence of K_2CO_3 to give the Cu(I) intermediate **5**. Oxidative addition of iodoarene to **5** forms a Cu(III) intermediate **6**. Intermediate **6** may undergo a reductive elimination to yield the coupling reaction product **3** and simultaneously regenerate the Cu(I) species to complete the catalytic cycle. As our data show, compound **3** may be decarboxylated by K_2CO_3 directly to generate the carbanion intermediate **7** (pathway a), which produces the deacylative product **4** after protonation. On the other hand, by acting as a Lewis acid, Cu salts may enhance the efficiency of the deacylation of **3** (pathway b). Alternatively, intermediate **6** may react with K_2CO_3 directly to generate a copper(III) intermediate **8**,[8] which undergoes rearrangement and elimination to yield product **4** and the copper(I) to complete the catalytic cycle (pathway c). Both pathways b and c can account for the observed acceleration of the deacylation reaction in the presence of the copper catalyst (Scheme 1 and Scheme 2).

To provide further support of this mechanism and to clarify the role of copper in the deacylation process, several additional experiments were carried out. Firstly, the deacylation of compound **3a** was studied with K_2CO_3 (2 equiv.) and different Lewis acids (10 mol%), such as $La(NO_3)_3 \cdot 6H_2O$, $Fe(NO_3)_3 \cdot 6H_2O$, $Ni(NO_3)_2 \cdot 6H_2O$, and $Cu(OAc)_2 \cdot H_2O$ under the opti-



Scheme 3. Proposed mechanism for the deacylative arylation reaction (Ln = ligand).

mized reaction conditions (DMSO, 110 °C), and the corresponding deacylative product **4a** was obtained in 59%, 51%, 51%, and 0% yields, respectively. Comparing these data with those reported in Scheme 1, it is clear that these Lewis acids do not promote the deacylation of compound **3a** since the obtained yields are worse than that obtained with K_2CO_3 alone (79%). Thus, it is unlikely that $Cu(OAc)_2 \cdot H_2O$ is behaving as a Lewis acid in promoting the deacylation reaction and, therefore, pathway b in Scheme 3 is unlikely. Secondly, the deacylation reaction of β-ketophosphonate **1a**, which is the substrate used in this deacylative coupling reaction, was carried out. As shown in Scheme 4, upon the treatment with K_2CO_3 (5 equiv.) in DMSO at 110 °C for 10 h, no formation of the desired deaceylated product **10** was observed; instead, the rearranged product **9** was obtained in low yield.[10] Formation of **9** may be rationalized through a rearrangement of the enolate intermediate formed from **1a** under the action of a base. Similarly, the attempted deacylation using a stoichiometric amount of $Cu(OAc) \cdot H_2O$ under the optimized reaction conditions also failed (Scheme 4). Moreover, compounds **11** and **12**[11] (Figure 1) failed to deacylate under the optimized reaction conditions, too. These results again demonstrate that the presence of an α-aryl group is essential for the deacylation of β-ketophosphonates. These results are in agreement with both pathways a and c. Most likely both pathways are working under the reaction conditions. For pathway a, the aryl group can stabilize the carbanion intermediate **7** to facilitate the direct deacylation of **3** by



Scheme 4. Attempted deacylation of **1a**.

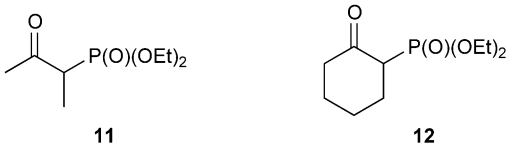


Figure 1. Compounds attempted for the deacylation reaction.

K_2CO_3. For pathway c, the presence of an aryl group can facilitate the insertion of the copper(I) reagent into the carbon-aryl bond of **3** to form the intermediate **6**, which may deacylate through **8**. Copper(II) acetate itself cannot insert into **3** to generate **6** and, therefore, it alone cannot deacylate compound **3** (*vide supra*).

In conclusion, we have described an efficient synthesis of α-aryl substituted β-ketophosphonates and methylphosphonates from β-ketophoxphonates and aryl iodides *via* an arylation reaction and a tandem arylation and deacylation reaction, respectively, using Cu(I) or Cu(II) salts as the catalysts. The corresponding α-aryl-substituted β-ketophosphonates and α-arylmethylphosphonates were obtained in high yields. A plausible mechanism of this reaction is proposed and the role of the base and the Cu(II) salt in the deacylation reaction is discussed.

Experimental Section

General Procedure for the α-Arylation of β-Ketophophonates

A mixture of β-ketophosphonate **1** (1.2 mmol), iodobenzene **2** (1.0 mmol), CuI (0.2 mmol, 20 mol%), L-proline (0.4 mmol, 40 mol%) and Cs_2CO_3 (3.0 mmol) in DMSO (1.0 mL) was stirred under N_2 at 70 °C. Upon the completion of the reaction (monitored by TLC) and after being cooled to room temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl (2.0 mL). The mixture was extracted with ethyl acetate (3×5 mL). The organic layers were combined and dried over sodium sulfate. The drying agent and the solvent were then removed and the residue was purified by flash column chromatography on silica gel to afford product **3**. All the known compounds (**3a**,[3i] **3j**,[3i] and **3k**[12a]) gave satisfactory spectroscopic data that are in agreement with the reported data in the literature. All the new compounds were fully characterized.[13]

General Procedure for the α-Arylation and Deacylation Reaction

A mixture of β-ketophophonates **1** (1.2 mmol), iodobenzenes **2** (1.0 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.10 mmol, 10 mol%), 2,2′-bipyridine (0.20 mmol, 20 mol%) and K_2CO_3 (5.0 mmol) in DMSO (1.0 mL) was stirred under N_2 at 110 °C. Upon the completion of the reaction (monitored by TLC) and after being cooled to room temperature, the reaction was quenched with saturated aqueous NH_4Cl (2.0 mL). The mixture was extracted with ethyl acetate (3×5 mL). The organic layers were combined and dried over sodium sulfate. The drying agent and the solvent were then removed and the residue was purified by flash column chromatography on silica gel to afford compounds **4**. All the known compounds (**4a**,[3c] **4b**,[12b] **4c**,[12c] **4d**,[12d] **4e**,[12e] **4f**,[12f] **4g**,[12g] **4i**,[3e,12b] and **4j**[12h]) gave satisfactory spectroscopic data that are in agreement with the reported data in the literature.

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