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Copper-Mediated Oxidative Decarboxylative Coupling of Arylpropiolic Acids with Dialkyl H-Phosphonates in Water

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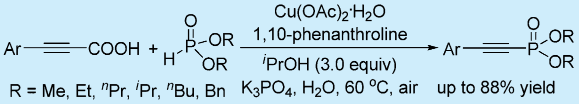
Supporting Information

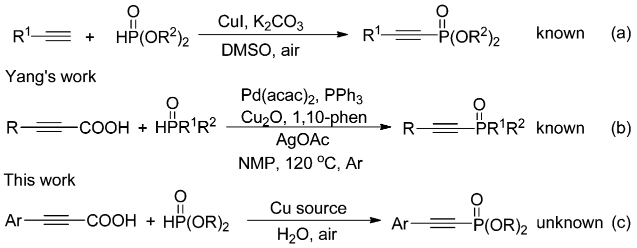
ABSTRACT: An efficient, mild, and generally applicable protocol for copper-mediated oxidative decarboxylative coupling of arylpropiolic acids with dialkyl H-phosphonates in water has been developed. Note that the reaction could proceed smoothly under air at relatively low temperature (60 °C), and the addition of isopropanol could successfully suppress the decomposition of dialkyl H-phosphonates in water.



The phosphorus-containing compounds are of great importance in organic synthesis, pharmaceuticals, and bioactive products.[1−3] Among them, alkynylphosphonates have attracted intense attention, because they could provide valuable scaffolds for the synthesis of other sophisticated phosphorus-containing heterocycles through conjugate-addition or cycloaddition reactions.[4] However, the traditional routes to alkynylphosphonates such as the Michaelis−Arbuzov reaction and the Michaelis−Becker reaction usually suffer from the prior preparation of original materials and poor tolerance of functional groups, thus restraining the applications of these methodologies.[3b,5]

In recent years, the transition-metal-catalyzed C$_{sp}$−P bond-forming reaction has emerged as one of the most reliable and robust tools for the synthesis of alkynylphosphonates.[6] In 2009, Han and Zhao reported the first successful copper-catalyzed oxidative coupling of terminal alkynes with H-phosphonates in DMSO, affording the corresponding alkynylphosphonates in high yields (Scheme 1a).[6a] On the other hand, the decarboxylative coupling reaction as a new synthetic strategy has wide applications in the construction of C−C and C−heteroatom bonds.[7,8] Particularly, arylpropiolic acids are usually solid-state without pungent smell and easy to prepare, store, and transport.[9] Therefore, taking arylpropiolic acids instead of terminal alkynes would make the reaction safer and easier to operate.[10,11] Following this viewpoint, in 2011, Yang's group fulfilled the reaction of arylpropiolic acids and diphenylphosphine oxide in NMP with the assistance of a Pd/Cu cocatalyst system (Scheme 1b).[12] However, this reaction did not work well for the dialkyl H-phosphonate, affording the product in a yield of 42%.

Scheme 1. Transition-Metal-Catalyzed C$_{sp}$-P Bond Forming Reaction



On the other hand, water as an ideal green solvent can potentially provide benefits for chemical syntheses in terms of resource economy, energy efficiency, and health and environmental safety.[13] As we know, dialkyl H-phosphonates tend to decompose to phosphorous acid and isopropanol in water, and therefore, the reaction involving dialkyl H-phosphonates in water would be rich in challenges. Just recently, we have realized the reaction of aryl halides with diisopropyl H-phosphonate in neat water using isopropanol as the additive, which successfully suppressed the decomposition of dialkyl H-phosphonates.[14] In this work, we attempt to develop a mild, simple, and green protocol for the copper-mediated oxidative decarboxylative coupling of arylpropiolic acids with dialkyl H-phosphonates in water under air (Scheme 1c). In this reaction, the effect of isopropanol as the additive on the decomposition of dialkyl H-phosphonates in water would also be discussed.

Initially, we performed a reaction of phenylpropiolic acid (**1a**) with diisopropyl H-phosphonate (**2a**) in water under air in the presence of 2 equiv of Cu(OAc)$_2$·H$_2$O and 2 equiv of K$_3$PO$_4$, and the desired product was obtained in 28% yield (Table 1, entry 1). Subsequently, we checked some commercially available ligands (e.g., TMEDA, Et$_3$N, DABCO, 2,2′-bipyridine, and 1,10-phenanthroline), and when 1,10-phenanthroline was used the yield of desired product could be up to 71% (Table 1, entries 2−6). Then, the reaction conditions were further optimized by the addition of different additives (Table 1, entries 7−11). When the traditional surfactant TBAB was added, the yield slightly increased to 75% yield (Table 1, entry 7). To our delight, the simple bulky

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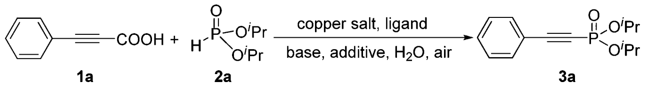
Table 1. Optimization of the Reaction Conditions[a]



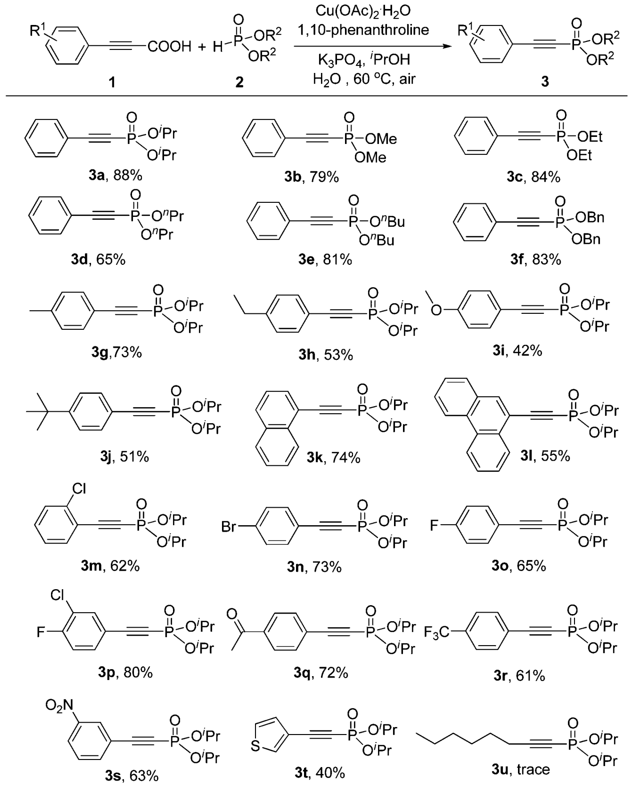
entry	copper salt	ligand	additive	yield (%)[b]
1	$Cu(OAc)_2{\cdot}H_2O$	–	–	28
2	$Cu(OAc)_2{\cdot}H_2O$	TMEDA	–	34
3	$Cu(OAc)_2{\cdot}H_2O$	Et_3N	–	21
4	$Cu(OAc)_2{\cdot}H_2O$	DABCO	–	20
5	$Cu(OAc)_2{\cdot}H_2O$	2,2′-Bipyridine	–	10
6	$Cu(OAc)_2{\cdot}H_2O$	1,10-Phen	–	71
7[c]	$Cu(OAc)_2{\cdot}H_2O$	1,10-Phen	TBAB	75
8	$\mathbf{Cu(OAc)_2{\cdot}H_2O}$	**1,10-Phen**	**^{i}PrOH**	**88**
9	$Cu(OAc)_2{\cdot}H_2O$	1,10-Phen	^{t}BuOH	83
10	$Cu(OAc)_2{\cdot}H_2O$	1,10-Phen	^{n}BuOH	79
11	$Cu(OAc)_2{\cdot}H_2O$	1,10-Phen	^{t}AmOH	82
12[d]	$Cu(OAc)_2{\cdot}H_2O$	1,10-Phen	^{i}PrOH	84
13[e]	$Cu(OAc)_2{\cdot}H_2O$	1,10-Phen	^{i}PrOH	66
14[f]	$Cu(OAc)_2{\cdot}H_2O$	1,10-Phen	^{i}PrOH	73
15[g]	$Cu(OAc)_2{\cdot}H_2O$	1,10-Phen	^{i}PrOH	37
16	$Cu(OTf)_2$	1,10-Phen	^{i}PrOH	70
17	$CuSO_4{\cdot}5H_2O$	1,10-Phen	^{i}PrOH	71
18	$CuCl_2$	1,10-Phen	^{i}PrOH	77

[a] Reaction conditions: phenylpropiolic acid **1a** (0.2 mmol), diisopropyl H-phosphonate **2a** (0.4 mmol), copper salt (2.0 equiv), ligand (2.5 equiv), K_3PO_4 (2.0 equiv), additive (3.0 equiv), and H_2O (2.5 mL) at 60 °C under air for 24 h. [b] Isolated yield. [c] TBAB (1.0 equiv) was used. [d] At 80 °C. [e] At 40 °C. [f] 1 equiv of $Cu(OAc)_2{\cdot}H_2O$ was used. [g] 20 mol % of $Cu(OAc)_2{\cdot}H_2O$ was used.

alkyl alcohols (e.g., ^{i}PrOH, ^{t}BuOH, ^{n}BuOH and ^{t}AmOH) were found to be particularly beneficial for this reaction (Table 1, entries 8−11). Remarkably, ^{i}PrOH as the additive could afford the desired product in a yield of up to 88%, which may be attributed to its suppressive role for the decomposition of the diisopropyl H-phosphonate in water and phase transfer catalytic property (Table 1, entry 8). Finally, some controlling experiments were performed. For example, performing the reaction at higher temperature of 80 °C or lower temperature of 40 °C, changing the amount of $Cu(OAc)_2{\cdot}H_2O$ to 1 equiv or even substoichiometric amount (20 mol %), did not afford the products in higher yields (Table 1, entries 12−15). Other copper sources such as $Cu(OTf)_2$, $CuSO_4{\cdot}5H_2O$, and $CuCl_2$ were also checked, but they could only give slightly lower yields of 70, 71, and 77%, respectively (Table 1, entries 16−18).

With optimized conditions in hand, we next explored the scope of the substrates and the results are summarized in Scheme 2. First, the reaction could well tolerate diverse dialkyl H-phosphonates and afford the corresponding products in moderate to good yields of 65−88% (Scheme 2, **3a−3f**). The scope of arylpropiolic acids bearing various functional groups was then checked, and the electronic effect had an obvious influence on this decarboxylative coupling (Scheme 2, **3g−3s**). For example, electron-rich arylpropiolic acids have a relatively lower reactivity, only affording the corresponding products in moderate yields ranging from 42 to 53%, accompanied by the generation of diynes as the byproducts (Scheme 2, **3h−3j**). It was exceptional that 4-methylphenylpropiolic acid could generate the desired product in a good yield of 73% (Scheme 2, **3g**). On the contrary, both electron-poor and electron-neutral arylpropiolic acids could well be coupled with diisopropyl H-phosphonate (**2a**) affording the products in moderate to good yields (Scheme 2, **3k−3s**). Functional groups (e.g., F, Cl, Br, CH_3CO, NO_2, and CF_3) could well be tolerated in this reaction (Scheme 2, **3m−3s**), and particularly, the arylpropiolic acid bearing two halogen atoms could be converted to the desired product in a yield of 80% (Scheme 2, **3p**). The heterocyclicpropiolic acid could also afford the desired product in a yield of 40% (Scheme 2, **3t**). In addition, alkylpropiolic acid, 2-octynoic acid was also checked, but unfortunately, only trace amount of the product was detected by GC−mass analysis (Scheme 2, **3u**).

Scheme 2. Decarboxylative Coupling of Propiolic Acids with H-Phosphonates[a,b]

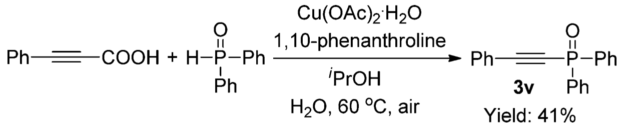


[a] Reaction conditions: arylpropiolic acid **1** (0.2 mmol), H-phosphonate **2** (0.4 mmol), $Cu(OAc)_2{\cdot}H_2O$ (2.0 equiv), 1,10-phenanthroline (2.5 equiv), K_3PO_4 (2.0 equiv), ^{i}PrOH (3.0 equiv), and H_2O (2.5 mL) at 60 °C under air for 24 h. [b] Isolated yield.

To further extend the scope of this reaction, the alkynylation of diphenylphosphine oxide was explored (Scheme 3). Under base-free conditions, the reaction could afford the desired product in a yield of 41%, presumably because of its insolubility in water.

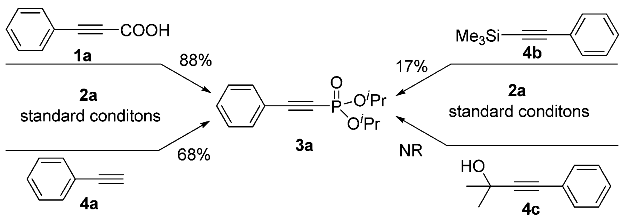
To reveal the advantage of this methodology, the reactions of diisopropyl H-phosphonate (**2a**) with some other common acetylene sources such as phenylacetylene (**4a**), 1-phenyl-2-(trimethylsilyl)acetylene (**4b**), and 2-methyl-4-phenylbut-3-yn-2-ol (**4c**) were carried out under the optimized conditions

Scheme 3. Decarboxylative Coupling of Propiolic Acid with Diphenylphosphine Oxide



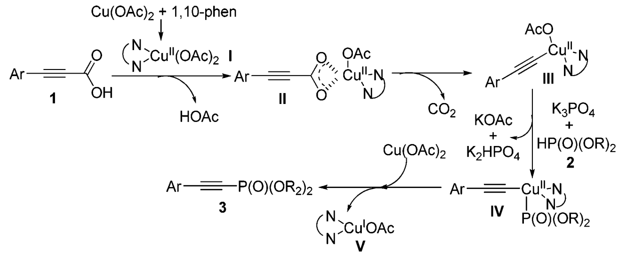
(Scheme 4). However, these reactions either gave the desired product (**3a**) in lower yields (**4a** and **4b**) or did not take place at all (**4c**). The unique features of arylpropiolic acids may be attributed to the better water solubility and coordination of their anions generated in situ to the active Cu(II) species.

Scheme 4. Comparative Experiments of Different Acetylene Sources



On the basis of these experimental results and previous reports,[15] a possible mechanism for copper-mediated decarboxylative coupling of arylpropiolic acids with dialkyl H-phosphonates is outlined as Scheme 5. First, the coordination of 1,10-phenanthroline to Cu(OAc)$_2$ could generate active copper(II) intermediate **I**, and the ligand exchange between intermediate **I** and the arylpropiolic acid (**1**) took place to form the copper(II) intermediate **II**, which would undergo the decarboxylative reaction to afford the copper(II) intermediate **III** and release one molecular CO$_2$. Then, the reaction of the intermediate **III** with a phosphonate anion generated from H-phosphonate (**2**) and K$_3$PO$_4$ took place affording the copper(II) intermediate **IV**. Finally, the reductive elimination of the intermediate **IV** would lead to the desired products (**3**) and the copper(I) species **V** to fulfill the reaction.

Scheme 5. Proposed Mechanism



In conclusion, we have developed an efficient and facile protocol for copper-mediated decarboxylative coupling of arylpropiolic acids with dialkyl H-phosphonates. It is worth noting that the reaction proceeded smoothly in water under mild conditions (at 60 °C under air) and could tolerate various functional groups. Remarkably, the decomposition of dialkyl H-phosphonates in water was effectively suppressed by the addition of isopropanol. This new and green synthetic protocol for alkynylphosphonates may have wide applications to the industrial process in the future.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General experimental procedure and characterization data of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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