Tetrahedron 68 (2012) 6413–6419

Contents lists available at SciVerse ScienceDirect

Tetrahedron

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

Copper-catalyzed decarboxylative coupling of aryl halides with alkynyl carboxylic acids performed in water

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ARTICLE INFO

Article history:
Received 25 April 2012
Received in revised form 24 May 2012
Accepted 1 June 2012
Available online 13 June 2012

Keywords:
Coupling reactions
Alkynyl carboxylic acids
Aryl halides
Low-cost
Copper catalysis

ABSTRACT

Most alkynes are volatile liquids, which are relatively difficult to use and to transport. In contrast, alkynyl carboxylic acids offer a stable and attractive alternative for the alkynylation reactions. Here, we employed alkynyl carboxylic acids as reaction partners for the alkynylation of aryl halides. Copper-catalyzed decarboxylative coupling, including various challenging aryl bromides with phenylpropiolic acid, was performed in water without using co-solvents with good yields. Our approach provides a low-loading, low-cost, stable and environmentally friendly copper catalyst system for decarboxylative coupling.

1. Introduction

Transition metal-catalyzed cross-coupling reactions are extremely useful in organic synthesis of materials or drugs for modern chemical and medical applications, because they offer a powerful means for the construction of many carbon–carbon bonds.[1] In particular, the Sonogashira reaction of terminal alkynes with aryl and alkenyl halides is an effective approach for the preparation of acetylene derivatives.[2] As a result, enormous effort has been devoted to improve catalytic activity and expand the scope of substrates of this useful reaction, which was first reported by Sonogashira in 1975.[3,4] However, most of the alkynes are volatile liquids, which are relatively difficult to use and transport.[5] Therefore, the use of some other readily available substrates rather than terminal alkynes for the straightforward synthesis of arylalkynes, remains a practical challenge.[5] Recently, alkynyl carboxylic acids were found to represent a promising alternative to terminal alkynes for coupling reactions.[6] In 2008, P. H. Lee and co-workers developed the first example of such decarboxylative coupling in the presence of $Pd_2(dba)_3$ and phosphine-ligands, including dppf and dppb.[6a] In addition, Kim and Lee also found that $Pd_2(dba)_3$ together with PPh_3 or Xantphos could also catalyze the couplings in high yields.[6b] Very recently, Li found that combination of $Pd(OAc)_2$ and Xphos could catalyze decarboxylative coupling reactions of alkynyl carboxylic acids with a wide range of aryl halides.[6c] Furthermore, Song and Lee have prepared the symmetrical and unsymmetrical diarylalkynes from propiolic acid using decarboxylative coupling using $Pd(PPh_3)_2Cl_2$/dppb catalytic system.[6d] However, these protocols were limited to academic use owing to the high cost of palladium complexes. There are two routes to solve the problem of catalyst expense: one method is to reduce the catalytic loading of the palladium catalyst or alternatively, to introduce cheaper catalysts, preferably those with lower toxicity than palladium to facilitate downstream processing. Encouragingly, You and his co-workers recently developed the first example of such decarboxylative coupling in the presence of commercially available CuI and 1,10-phenanthroline (phen), although the catalyst loading is high (10 mol %) and reaction conditions are slightly harsh (130 °C).[6f] Recently, we just reported that $Fe(acac)_3$/CuI showed better catalytic activity with low-loading catalyst,[6g] however, the reaction temperature of this protocol was still high (140 °C). After screening various ligands, we found that copper-catalyzed decarboxylative coupling between aryl halide and alkynyl carboxylic acids could be conducted efficiently in DMSO at 90 °C using PPh_3 as the ligand.[6h] With the further effort, we just found the reaction could be performed in water and good results were obtained. Considering that the current methodology was more useful and practical, herein, we want to disclose all of findings about the copper-catalyzed decarboxylative coupling as a full paper.

Water is considered as the 'green' solvent and has low-cost. It is also safer than the usual solvents, which are often inflammable and

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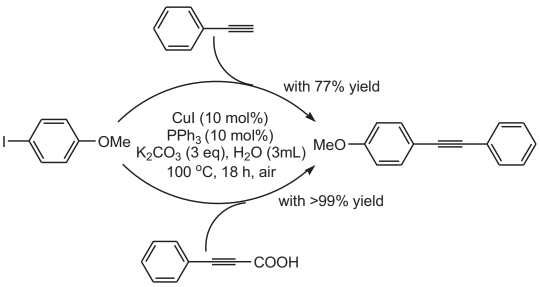
http://dx.doi.org/10.1016/j.tet.2012.06.003

explosive. From an industrial point of view, the use of a two-phase system allows an easy separation of the products from the water-soluble organometallic catalyst by simple phase separation.[7] More importantly, the development of organic reactions in water is helpful to understand the nature of the enzymes-catalyzed reaction performed in the human body. With our increasing interest in various cross-coupling reactions,[8] we describe our efforts on the development of the low-loading, low-cost, stable and environmentally friendly copper catalyst system for such decarboxylative coupling.

2. Results and discussion

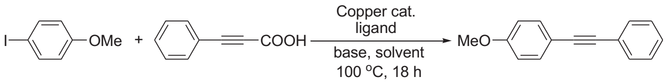
Initially, we chose phenylacetylene as the cross-coupling partner and examined its reaction with 4-iodoanisole in the presence of CuI and PPh_3 in water.[9] The desired product was obtained in moderate yield (77%) as shown in Scheme 1. Considering the poor solubility of the phenylacetylene in water, phenylpropiolic acid was then chosen as the alternative partner. Without any need for further optimization, treatment of 4-iodoanisole with phenylpropiolic acid afforded the corresponding product in quantitative yield.



Scheme 1. Copper-catalyzed alkynylation of 4-iodoanisole in the presence of different alkyne partners.

Table 1

Screening catalytic conditions in decarboxylative coupling between 4-iodoanisole and phenylpropiolic acid performed in water[a]



Entry	Cat. (mol %)	Ligand (mol %)	Solvent	Base	Yield[b] (%)
1[c]	CuI (10)	PPh_3 (10)	Water	K_2CO_3	>99
2	$Pd(OAc)_2$ (10)	PPh_3 (10)	Water	K_2CO_3	Trace
3[d]	Pd–Cu (10)	PPh_3 (10)	Water	K_2CO_3	Trace
4[e]	CuI (10)	PPh_3 (10)	Water	K_2CO_3	30
5	CuI (10)	Phen (10)	Water	K_2CO_3	5
6	CuI (10)	Oxine (10)	Water	K_2CO_3	8
7	CuI (10)	Binol (10)	Water	K_2CO_3	Trace
8	CuI (10)	PCy_3 (10)	Water	K_2CO_3	<5
9	CuI (10)	$P(OPh)_3$ (10)	Water	K_2CO_3	<5
10	CuI (10)	—	Water	K_2CO_3	<5
11	CuI (10)	PPh_3 (10)	Water	K_3PO_4	98
12	CuI (10)	PPh_3 (10)	Water	Et_3N	97
13	CuI (10)	PPh_3 (10)	Water	Cs_2CO_3	96
14	CuI (10)	PPh_3 (10)	Water	NaOAc	39
15	CuI (5)	Phen (10)	Water	K_2CO_3	>99
16	CuI (5)	Phen (5)	Water	K_2CO_3	91
17	CuI (2)	PPh_3 (2)	Water	K_2CO_3	83
18	CuI (2)	PPh_3 (4)	Water	K_2CO_3	93
19	$Cu(acac)_2$ (2)	PPh_3 (4)	Water	K_2CO_3	80
20	CuBr (2)	PPh_3 (4)	Water	K_2CO_3	92
21	Cu (2)	PPh_3 (4)	Water	K_2CO_3	90
22[f]	CuI (2)	PPh_3 (4)	Water	K_2CO_3	99
23[f,g]	CuI (2)	PPh_3 (4)	NMP	K_2CO_3	11
24[f,g]	CuI (2)	PPh_3 (4)	DMF	K_2CO_3	97
25[f,g]	CuI (2)	PPh_3 (4)	Dioxane	K_2CO_3	78
26[f,g]	CuI (2)	PPh_3 (4)	Toluene	K_2CO_3	29
27[f,g]	CuI (2)	PPh_3 (4)	DMSO	K_2CO_3	>99

[a] Reaction conditions: 4-iodoanisole (0.3 mmol), phenylpropiolic acid (0.4 mmol), base (0.9 mmol), water (3 mL), 100 °C, 18 h, under air.
[b] Isolated yield (based on 4-iodoanisole).
[c] CuI (99.999%) from Aldrich was employed.
[d] $Pd(OAc)_2$ (10 mol %), CuI (10 mol %).
[e] 80 °C.
[f] 24 h, in Ar.
[g] 90 °C.

We continued our investigation using phenylpropiolic acid and 4-iodoanisole as model substrates. First, in order to confirm our promising initial result and to attempt to exclude the influence of metal contaminant, we carried out experiments in new flasks with new stirring bars and new caps. We found that CuI of higher purity (99.999%, from Aldrich) and K_2CO_3 (99.0%, from Alfa) could catalyze this coupling in high yield (>99%) (Table 1, entry 1) (for certificate of analysis, see the Supplementary data). In comparison, traditional Pd species, such as $Pd(OAc)_2/PPh_3$ and $Pd(OAc)_2/CuI/PPh_3$ could not show any catalytic activity in this reaction (Table 1, entries 2 and 3). Lower reaction temperature led to poor result (Table 1, entry 4). Subsequently, various readily available ligands were employed, including other monodentate P-ligands (PCy_3 and $P(OPh)_3$), O,O-ligands (binaphthol (binol)), N,N-ligand (1,10-phenanthroline (phen)) and N,O-ligand (8-hydroxquinoline) (Table 1, entries 5–9). Commercially available PPh_3 afforded the best catalytic results. Control experiments confirmed that CuI alone in the absence of ligand was unable to catalyze the coupling reaction (Table 1, entry 10). With the optimized CuI/PPh_3 catalytic system in hand, we then screened other various catalytic conditions. First, various inorganic and organic bases were tested: K_3PO_4, Cs_2CO_3 and Et_3N as the base also resulted in almost quantitative desired product (Table 1, entries 11–13). However, NaOAc as the base afforded the corresponding product in only 39% yield (Table 1, entry 14). Subsequently, varying amounts of CuI and PPh_3 were investigated (Table 1, entries 15–18). The best ratio of CuI and PPh_3 was 1:2 (Table 1, entry 18). Subsequently, different copper sources were evaluated at low-catalyst loading (2 mol %), including $Cu(acac)_2$, CuBr and Cu powder (Table 1, entries 19–21). The best result was generated from CuI-catalyzed coupling. Finally, longer reaction time (24 h) under argon atmosphere gave exclusively the desired product in almost quantitative yield (Table 1, entry 22). Under the same conditions, the commonly-used solvents, such as NMP, dioxane, toluene, DMF and DMSO, were employed into the reaction (Table 1, entries 23–27) and DMSO afforded the quantitative product (Table 1, entry 27).[6h]

With optimized conditions now in hand, we explored the scope of this process with respect to a wide array of aryl halides as summarized in Table 2. It can be seen that whether the reactions were performed in DMSO or water, high yields of desired products were obtained. Only several entries showed the obvious difference. Generally, high yields were obtained with substrates, regardless of the positions of aryl substituent (Table 2, entries 1–3). It is noteworthy that the ester group was sensitive in water and lower yield was obtained comparing with the yield in DMSO (40% vs 99%, Table 2, entry 4). In addition, for the aryl iodides with electron-deficient or electron-rich substituents, the desired products were acquired with good to excellent yields (Table 2, entries 5–13). It is of particular relevance that the reaction conditions were compatible with the presence of different functional groups, such as ketone, amino and nitro groups (Table 2, entries 5, 12, 13), which may then be subject to further synthetic transformations. When 2-butynoic acid was used as the substrate, the desired product was obtained in 23% yield using water as solvent and 86% yield was got using DMSO as the solvent (Table 2, entry 14). In comparison, 2-octynoic acid as the alkyne partner gave excellent results (Table 2, entries 15–19). We were pleased to discover that the substituted phenylpropiolic acids