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Copper Catalyzed Decarboxylative Alkynylation of Quaternary α-Cyano Acetate Salts

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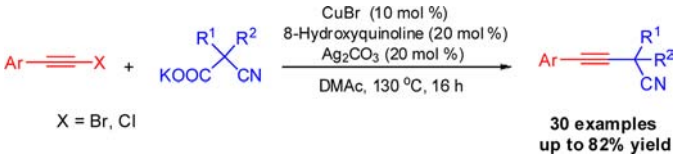
ABSTRACT



Cu-catalyzed decarboxylative alkynylation of quaternary α-cyano acetate salts with alkynyl bromides and alkynyl chlorides is described. This new reaction can be used for preparing functionalized butynenitrile derivatives.

Transition-metal-catalyzed decarboxylative cross-coupling reactions are widely studied in organic synthesis as a novel method.[1] These reactions can be used to construct carbon−carbon[2] and carbon−heteroatom[3] bonds to synthesize a variety of organic molecules. A number of studies on the decarboxylative coupling reactions of aromatic,[2a−l,4] alkenyl,[2m,5] and alkynyl[2n,o,6] carboxylic acids have been

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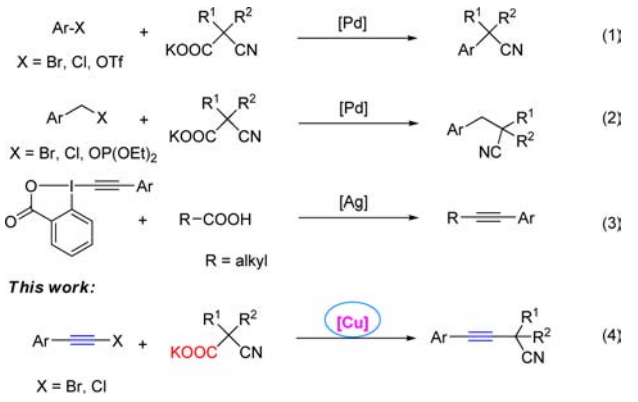
Scheme 1. Decarboxylative Coupling Reactions of Aliphatic Carboxylic Acids

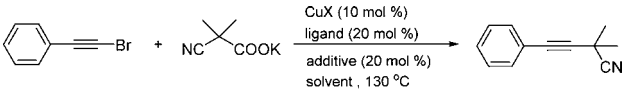


reported. More recently, Liu,[7] Li,[8] and others[9] including our group[10] examined transition-metal-catalyzed decarboxylative coupling reactions involving the breaking of C_{sp^3}–COOH bonds. Such reactions are synthetically useful for making aliphatic compounds but have been less studied. In particular, a Cu-catalyzed decarboxylative coupling involving the breaking of a C_{sp^3}–COOH bond is still a challenge.[11]

According to the previous studies, the decarboxylative coupling reactions of α-cyano acetate salts need Pd as the catalyst. For instance, Liu et al. developed a method to synthesize α-aryl nitriles through the palladium-catalyzed decarboxylative coupling of cyanoacetate salts with aryl halides [Scheme 1, eq 1].[7b] More recently, they found that a similar catalytic reaction can be achieved with benzyl halides [Scheme 1, eq 2].[7d] Moreover, Li et al. reported the silver-catalyzed decarboxylative alkynylation of aliphatic carboxylic acids with ethynylbenziodoxolones [Scheme 1, eq 3].[8c] Herein, we reported the first case a Cu-catalyzed decarboxylative alkynylation of quaternary α-cyano acetate salts to synthesize butynenitrile derivatives [Scheme 1, eq 4] that represent interesting organic intermediates.[12]

Our study began by examining the cross-coupling of (bromoethynyl)benzene with potassium cyanoacetate. Unfortunately, the desired product was not observed despite many attempts, as we only obtained the rapid homocoupling product of the alkynylbromide. When we used potassium 2-cyano-2-methylpropanoate instead of potassium cyanoacetate with CuI as the catalyst and DMAc (*N*,*N*-dimethylacetamide) as the solvent, the target

Table 1. Optimization of the Reaction Conditions[a]



entry	CuX	ligand	solvent	additive	yield (%)
1	CuI	–	DMAc	–	13
2	CuBr	–	DMAc	–	34
3	CuCl	–	DMAc	–	33
4	Cu_2O	–	DMAc	–	15
5	CuBr	–	DMAc	Ag_2CO_3	40
6	$Cu(OAc)_2$	–	DMAc	Ag_2CO_3	26
7	$Cu(CH_3CN)_4PF_6$	–	DMAc	Ag_2CO_3	24
8	$CuBr_2$	–	DMAc	Ag_2CO_3	36
9	CuBr	1,10-phen	DMAc	Ag_2CO_3	20
10	CuBr	TMEDA	DMAc	Ag_2CO_3	27
11	CuBr	L-proline	DMAc	Ag_2CO_3	36
12	CuBr	1-napthol	DMAc	Ag_2CO_3	21
13	CuBr	8-hydroxyquinoline	DMAc	Ag_2CO_3	60
14	CuBr	pyridine	DMAc	Ag_2CO_3	43
15	CuBr	Ph_3P	DMAc	Ag_2CO_3	36
16	CuBr	8-hydroxyquinoline	DMF	Ag_2CO_3	59
17	CuBr	8-hydroxyquinoline	mesitylene	Ag_2CO_3	40
18	CuBr	8-hydroxyquinoline	diglyme	Ag_2CO_3	39
19	CuBr	8-hydroxyquinoline	NMP	Ag_2CO_3	50
20[b]	CuBr	8-hydroxyquinoline	DMAc	Ag_2CO_3	84(81[c])
21[b]	CuBr	8-hydroxyquinoline	DMAc	Ag_2O	76
22[b]	CuBr	8-hydroxyquinoline	DMAc	$AgNO_3$	60
23[b]	CuBr	8-hydroxyquinoline	DMAc	–	48
24[b]	–	8-hydroxyquinoline	DMAc	Ag_2CO_3	8

[a] Yield determined by GC methods using benzophenone. All reactions were performed by using potassium 2-cyano-2-methylpropanoate (0.5 mmol) and (bromoethynyl)benzene (0.75 mmol), under an argon atmosphere for 16 h. [b] (Bromoethynyl)benzene (1.5 mmol). [c] Isolated yield.

product was detected, although the yield was only 13% (Table 1, entry 1). To improve the reaction, we examined the effects of different Cu salts and silver carbonate (entries 2−8). We found that CuBr was optimal, and Ag_2CO_3 could promote the reaction. However, common *N*-ligands, such as 1,10-phenanthroline, TMEDA (*N*,*N*,*N*′,*N*′-tetramethylethylenediamine), and L-proline, all failed to promote the reaction (entries 9−11). We also tried other types of ligands, such as 1-naphthol, 8-hydroxyquinoline, pyridine, and Ph_3P (entries 12−15), and found that 8-hydroxyquinoline can increase the yield to 60% (entry 13). Next, we examined the effects of different solvents. Most of the solvents that we investigated gave poor results (entries 16−19). To improve the yield, we increased the loading of (bromoethynyl)benzene to 3 equiv and obtained a good yield of 84% (entry 20). A brief survey of additives was undertaken in which the optimal result was achieved using Ag_2CO_3 (entries 21−22). We found that the yield dropped to 48% in the absence of Ag_2CO_3 (entry 23) and the yield was only 8% without CuBr (entry 24).

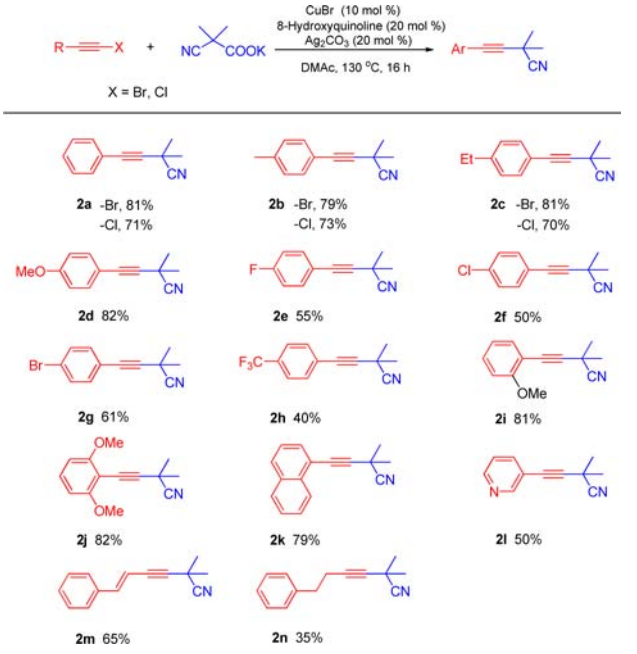


Figure 1. Decarboxylative alkynylation of potassium 2-cyano-2-methylpropanoate. All reactions were performed by using α-cyano acetate salts (0.5 mmol) and alkynyl halides (1.5 mmol), under an argon atmosphere for 16 h. Yields are isolated.

With the above optimized conditions in hand, we explored the scope of this reaction with various alkynyl halides (Figure 1). To our satisfaction, the reaction took place easily to give a good yield and was applicable to a broad range of alkynyl bromides and chlorides. For phenylethynyl bromide substrates, electron-donating groups alkyl (**2a**, **2c**) and ether (**2d**, **2i**, **2j**) can all react with good yields of 79−82%. Phenylethynyl bromides carrying electron-withdrawing groups including fluoro (**2e**), chloro (**2f**), bromo (**2g**), and trifluoromethyl (**2h**) are all amenable substrates. An *ortho*-substituted substrate (**2i**, **2j**) can be well tolerated. Naphthyl-1-ethynyl bromide (**2k**), pyridine-3-ethynyl bromide (**2l**), and (4-bromobut-1-en-3-ynyl)-benzene (**2m**) can also react with good yields. However, an alkyl-substituted product (**2n**) was obtained in low yield (35%).

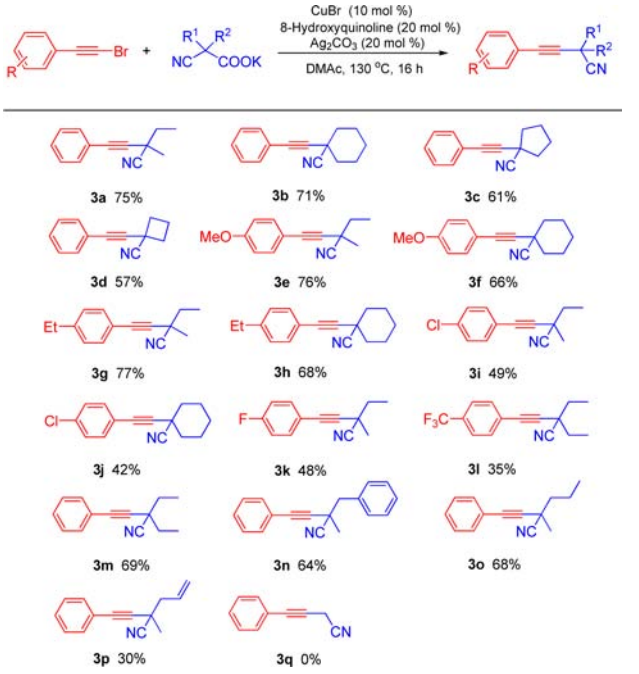


Figure 2. Decarboxylative alkynylation of α-cyano acetate salts. All reactions were performed by using α-cyano acetate salts (0.5 mmol) and alkynyl halides (1.5 mmol), under a argon atmosphere for 16 h. Yields are isolated.

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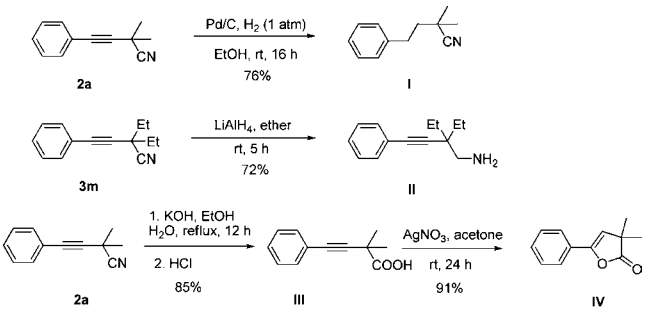
We next explored the scope of the quaternary α-cyano acetate salts (Figure 2). Potassium 2-cyano-2-methylbutanoate (**3a**, **3g**, **3i**), potassium 2-cyano-2-methylpentanoate (**3l**, **3m**), and potassium 2-cyano-2-ethylbutanoate (**3o**) can react with moderate to good yields ranging from 35 to 75%. Potassium 1-cyanocyclohexanecarboxylate (**3b**, **3f**, **3h**), potassium 1-cyanocyclopentanecarboxylate (**3c**), and potassium 1-cyanocyclobutanecarboxylate (**3d**) were all amenable to decarboxylative alkynylation. Potassium 2-cyano-2-methyl-3-phenylpropanoate (**3n**) can react with a moderate yield of 64%. Potassium 2-cyano-2-methylpent-4-enoate (**3p**) gave a low yield of 30%. However, α-cyano acetate containing active H failed to give any desired product (**3q**) under the above experimental conditions.

The obtained butynenitrile derivatives were subjected to a series of applications (Scheme 2). We chose α-cyano alkynes for selective hydrogenation. The α-cyano alkyne **2a** was successfully reduced to an alkyl nitrile (**I**) at room temperature. α-Cyano alkyne **3m** was also selectively reduced to a *β*-amine alkyne (**II**) by $LiAlH_4$. Next, 3,3-dimethyl-5-phenyl-2(3*H*)-furanone (**IV**) was obtained by hydrolysis of α-cyano alkyne **2a** and further reaction of α-carboxyl alkyne **III** with silver nitrate. Thus, our method provides an efficient protocol for the preparation of a furanone derivative.

Finally, we performed experiments to study the mechanism of this reaction. When this reaction was carried out under the standard conditions in the presence of 1 equiv of TEMPO, a radical trap, we only detected a trace amount of product (see Supporting Information). We suspect that the process of free radicals may be present in the mechanism of this reaction. Clarification of the detailed mechanism is a goal in our future research.

In conclusion, we have successfully developed a Cu-catalyzed decarboxylative alkynylation of quaternary α-cyano acetate salts. This new reaction was applicable not only for alkynyl bromides but also for alkynyl chlorides. With this new and simple method, we can synthesize a series of butynenitrile derivatives. Through further transformations, butynenitrile derivatives can be converted to alkyl nitriles, *β*-amine alkynes, α-carboxyl alkynes, and even furanone derivatives.

Scheme 2. Further Synthetic Transformation of Some Products



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

The authors declare no competing financial interest.