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A mild CuI-catalyzed Glaser-type homo-coupling reaction using α,α-dibromo-β-dicarbonyl compounds as oxidants

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ABSTRACT

Exploration of α,α-dibromo-β-dicarbonyl compounds as novel organic oxidants for the mild Cu(I)-catalyzed Glaser-type homo-coupling reaction has been achieved, which provides an alternatively efficient pathway for the construction of 1,3-conjugated structures. In addition, the mechanism of this reaction was investigated.

1. Introduction

Oxidative homo-coupling of terminal alkynes provides an easy and efficient access to 1,3-conjugated structures, which are an important class of building blocks with diverse applications in organic chemistry and functional materials,[1] such as for the synthesis of natural products,[2] pharmaceuticals,[3] π-conjugated acetylenic polymers,[4] and carbon-rich materials.[5] The first example of this reaction was reported by Glaser in 1869 via the treatment of terminal alkynes with Cu(I) salt in the presence of aqueous ammonia followed by air oxidation.[6] Almost one century later, two important modifications for Glaser reaction were developed by Eglinton and Hay, respectively.[7] Nowadays, a significant number of catalyst systems have been explored for this reaction, including palladium,[8,9] nickel,[10] copper,[11] cobalt,[12a] and gold[12b] catalyst systems. Among them, the copper-mediated Glaser-type coupling reactions represent the most promising methods for the synthesis of 1,3-diynes due to its economy and environmental friendliness. However, despite many copper-catalytic systems have been developed over the past decades, most of them usually required large amounts of copper salts, excessive oxidants, poisonous ligands, high reaction temperature,[13] special reaction medium,[14] or palladium complexes as co-catalysts. Recent efforts have brought about the development of several improved methods that use air as oxidant and permit the copper-catalyzed homo-coupling reactions undergoing either under mild conditions with the assistance of a ligand and base[15] or at high reaction temperature without additives.[16] In addition, a few efficient solvent-free and heterogeneous copper-catalytic systems have also been developed.[17] Given the importance of the 1,3-diyne derivatives in organic chemistry and functional materials, further exploration of mild and efficient methods for diversely synthesis of these compounds would be valuable.

α,α-Dibromo-β-dicarbonyl compounds are a series of less investigated reagents in organic synthesis that possess a similar structure with NBS.[18] We reasoned that these compounds would be prone to release one bromonium ion or two under Lewis acid or base conditions and could be used as oxidants or brominating agents[19] for the development of novel reaction methods (Eq. 1). Inspired by the pioneering works reported by Rossi and Zhang's groups in which chloroacetone and ethyl bromoacetate combined with Pd complexes were used as efficient catalytic systems for the Glaser-type coupling,[8,20] recently we launched a study to examine the conversion of terminal alkynes to 1,3-conjugated compounds via using a α,α-dibromo-β-dicarbonyl compound as oxidant. We were gratified to find that the high reactivity of these compounds allows the homo-coupling of terminal alkynes to proceed with catalytic amount of CuI in air at room temperature. Furthermore, the preliminary mechanistic study revealed that the α,α-dibromo-

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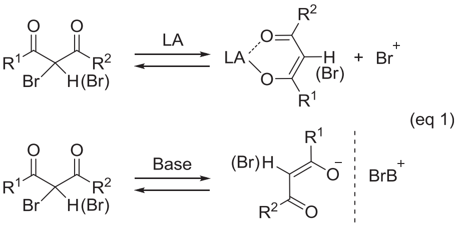
β-dicarbonyl compound most likely serve as both oxidant and ligand in this coupling reaction. Herein, we wish to report our study results on this topic.

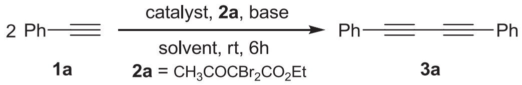


(1)

2. Results and discussion

At our starting point for the development of this methodology, phenylacetylene (**1a**, 1.0 equiv) was chosen as the model substrate, CuI (15 mol %), ethyl α,α-dibromoacetoacetate (**2a** 30 mol %), and triethylamine (2.0 equiv) were selected as the catalyst, oxidant, and base, respectively (Table 1, entry 1). To our delight, the desired homo-coupling product **3a** was obtained in 52% yield in dichloromethane at room temperature. Encouraged by this initial result, extensive examination of the catalyst loading, oxidant loading, and base loading were conducted (Table 1, entries 2–7). Gratifyingly, the yield of **3a** could be improved to 95% under the optimized conditions, which employed 30 mol % CuI, 30 mol % **2a**, and 200 mol % triethylamine (Table 1, entry 3). Further investigation of solvent effects under the latter conditions revealed that dichloromethane is the most suitable solvent (Table 1, entries 3 and 8–14). Other copper salts, such as $Cu(OAc)_2 \cdot H_2O$, $Cu(acac)_2$, CuCl, and CuBr were proved to be less effective or ineffective to promote this transformation (Table 1, entries 15–18). Similar yields were obtained when triethylamine was replaced by DBU or piperidine (Table 1, entries 19 and 20). In contrast, employing either NaOAc or Cs_2CO_3 as the base, the reaction proceeded very slowly and low yields were achieved (Table 1, entries 22 and 23). Control experiments indicated that the combination of CuI, ethyl α,α-dibromoacetoacetate (**2a**), and triethylamine were essential for this coupling reaction (Table 1, entries 24–26). Furthermore, the reaction could proceed smoothly under argon atmosphere at longer reaction time (Table 1, entry 27), which suggests that ethyl α,α-dibromoacetoacetate (**2a**) acts as an oxidant and oxygen can accelerate this oxidative coupling reaction.[21]

Table 1
Optimization of homo-coupling reaction conditions[a]



Entry	Catalyst (mol %)	**2a** (mol %)	Base (mol %)	Solvent	Yield (%)[b]
1	CuI (15)	30	Et_3N (200)	DCM	52
2	CuI (25)	30	Et_3N (200)	DCM	87
3	**CuI (30)**	**30**	**Et_3N (200)**	**DCM**	**95**
4	CuI (30)	25	Et_3N (200)	DCM	88
5	CuI (30)	50	Et_3N (200)	DCM	60
6	CuI (30)	30	Et_3N (300)	DCM	75
7	CuI (30)	30	Et_3N (100)	DCM	56
8	CuI (30)	30	Et_3N (200)	Toluene	65
9	CuI (30)	30	Et_3N (200)	DMF	66
10	CuI (30)	30	Et_3N (200)	THF	66
11	CuI (30)	30	Et_3N (200)	DMSO	81
12	CuI (30)	30	Et_3N (200)	CH_3OH	39
13	CuI (30)	30	Et_3N (200)	CH_3CN	64
14	CuI (30)	30	Et_3N (200)	CH_3NO_2	62
15	$Cu(OAc)_2$(30)	30	Et_3N (200)	DCM	78
16	$Cu(acac)_2$ (30)	30	Et_3N (200)	DCM	0
17	CuCl (30)	30	Et_3N (200)	DCM	32
18	CuBr (30)	30	Et_3N (200)	DCM	30
19	CuI (30)	30	DBU (200)	DCM	94
20	CuI (30)	30	piperidine (200)	DCM	92
21	CuI (30)	30	DABCO (200)	DCM	44
22[c]	CuI (30)	30	NaOAc (200)	DCM	29
23[c]	CuI (30)	30	Cs_2CO_3 (200)	DCM	31
24	—	30	Et_3N (200)	DCM	0
25	CuI (30)	—	Et_3N (200)	DCM	5
26	CuI (30)	30	—	DCM	0
27[d]	CuI (30)	30	Et_3N (200)	DCM	89

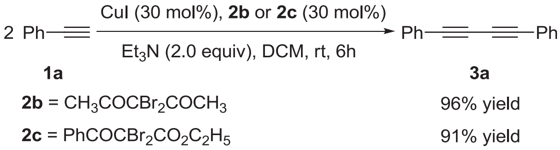
[a] Reaction conditions: phenylacetylene (0.55 mmol), solvent (2.0 mL), room temperature, 6 h, in air.

[b] Isolated yield.

[c] 48 h.

[d] 26 h, under argon.

Subsequently, other activated dibromides, such as α,α-dibromoacetylacetone (**2b**) and ethyl α,α-dibromobenzoylacetate (**2c**), were examined for this coupling reaction (Scheme 1). Expectedly, under the optimal reaction conditions (Table 1, entry 3), either **2b** or **c** can serve as oxidant and gave the corresponding homo-coupling product **3a** in 96% and 91% yields, respectively.



Scheme 1. Other dibromides for homo-coupling of **1a**.

With a suitable set of reaction conditions developed, the substrate scope and limitations of this copper-catalyzed oxidative coupling reaction were then investigated (Table 2). Gratifyingly, it was found that the present catalytic system showed good substrate compatibility with various aliphatic and electron-rich aromatic alkynes, providing the corresponding homo-coupling products in good to excellent yields (Table 2, **3a**–**d** and **3f**–**r**). Heteroaromatic terminal alkynes, such as 3-ethynylpyridine (**1s**) and 2-ethynyl thiophene (**1t**), also underwent this Glaser-type dimerization smoothly and afforded the desired products **3s** and **t** in 88% and 83% yields, respectively. Functional groups, including aromatic fluoro or methoxy groups, etheric groups, C=C double bond, hydroxyl, trimethylsilyl, cyclopropyl, and acetal, tolerate the reaction conditions very well (Table 2, **3d**, **e**, and **h**–**r**). Intriguingly, when the electron-poor terminal aromatic alkynes **1e**, **u**, and **v**, which bear a fluorine, chlorine atom or nitryl group at the *para*-position of the phenyl ring, were subjected to the optimized coupling conditions, a quite opposite result was obtained. **1e** was compatible with the optimal reaction conditions and gave the desired 1,3-diyne product **3e** in 87% yield. In contrast, **1u** and **v** were found to be kept intact even under the prolonged reaction time and heating condition.[22] Further employment of 1-(4-ethynyl-phenyl)-ethanone **1w** and 4-ethynylbenzoic acid methyl ester **1x** as substrates also failed to give the desired homo-coupling products. Although the exact reason for such a dramatic difference in reactivity between **1e**, **u**, **v**, **w**, and **x** is unclear, the electronic properties of these substituents should be responsible for the results being observed. Furthermore, it is worth noting that the present catalyst system is more efficient for homo-coupling of electron-rich terminal alkynes (Table 2, **3f**–**j**) in comparison with the previously reported catalytic systems, in which the terminal aliphatic alkynes are less reactive in the Glaser coupling due to its weak acidity.[7a,17h,23]