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Transition-Metal-Free Homocoupling of 1-Haloalkynes: A Facile Synthesis of Symmetrical 1,3-Diynes

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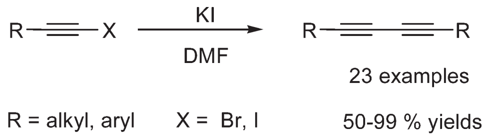

Symmetrical 1,3-diyne compounds can be easily synthesized via a transition-metal-free homocoupling reaction of 1-haloalkynes without base and oxidant. The method shows excellent functional group compatibility and high yields.

1,3-Diyne compounds are versatile building blocks in the construction of linearly π-conjugated acetylenic oligomers and polymers,[1] natural products,[2] electronic and optical materials,[3] and molecular recognition systems.[4] They are obtained either by Cu-mediated homocoupling reactions including Glaser coupling,[5] Eglinton coupling,[6] Hay coupling,[7] and related modified methods,[8,9] or by Pd-catalyzed homocoupling reactions.[10,11] Compared to the copper and palladium catalysis other transition-metal mediated homocoupling reactions for the synthesis of 1,3-diynes are still limited.[12] However, transition-metal reagents are often expensive and poisonous, and they often required air-sensitive and expensive phosphine ligand and amine reagent. Few studies are focused on the formation of 1,3-diynes without transition metal.[13] One example is the transition-metal-free oxidative homocoupling reaction of alkynylmagnesium compounds reported by Knochel.[13a] For the environmental and economical consideration, development of a transition-metal-free system for the synthesis of 1,3-diynes is an attractive route.

Haloalkynes are high-value synthons widely used in synthetic organic chemistry.[14,15] On the basis of these promising potentialities of 1-haloalkynes, herein we present a highly efficient protocol for the synthesis of symmetrical 1,3-diynes from 1-haloalkynes without any transition-metal, base, and oxidant.

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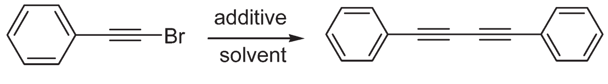
TABLE 1. Screening of Reaction Conditions for Transition-Metal-Free Homocoupling of Phenylethynyl Bromide[a]



1a **2a**

entry	solvent	additive	yield (%)[b]
1	1,4-dioxane		n.p.
2	1,4-dioxane	KI	20
3	Ac_2O	KI	6
4	HOAc	KI	trace
5	DMF	KI	94
6	water	KI	15
7	DMSO	KI	80
8	toluene	KI	trace
9[c]	DMF	HI	n.p.
10	DMF	NaI	88
11	DMF	n-Bu_4NI	75
12	DMF	NaBr	n.p.
13	DMF	LiCl	n.p.
14[d]	DMF	KI	25
15[e]	DMF	KI	42
16[f]	DMF	KI	81
17[g]	DMF	KI	80
18[h]	DMF		n.p.

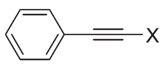
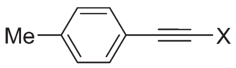
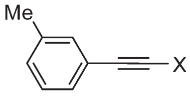
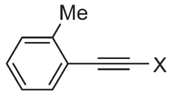
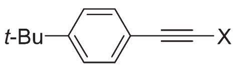
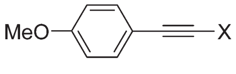
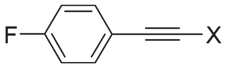
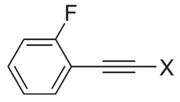
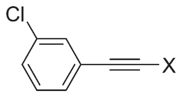
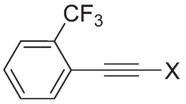
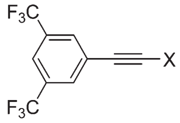
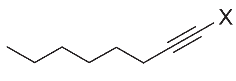
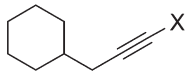
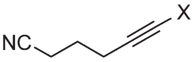
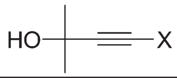
[a] Reaction conditions: bromoalkyne (1 mmol), additive (3 mmol), solvent (2.0 mL) at 120 °C for 12 h. [b] Isolated yield. [c] 47% aqueous hydroiodic acid solution. [d] 80 °C. [e] 2 h. [f] KI (2 mmol). [g] N_2 protection. [h] The substrate was 1-(2-iodoethynyl)benzene.

As a starting point for the development of our transition-metal-free methodology we chose phenylethynyl bromide (**1a**) to study the homocoupling reaction. As shown in Table 1, the reaction did not proceed without additives (Table 1, entry 1). To our delight, we found that the reaction performed with addition of KI (Table 1, entry 2). The reaction showed a strong solvent dependence. Among the solvents used, DMF and DMSO were proved appropriate (Table 1, entries 3−8). A variety of common additives were tried (Table 1, entries 9−13), and the results showed that when NaI or n-Bu_4NI was employed the reaction could afford **2a** in good yields. The lower temperature disfavored the reaction, and **2a** was obtained in 42% yield after 2 h (Table 1, entries 14 and 15). Moreover, a decrease in the amount of KI led to a decrease in the yield (Table 1, entry 16). It is noteworthy that the reaction proceeded well under nitrogen atmosphere (Table 1, entry 17). The iodoalkyne did not afford the product without any additive (Table 1, entry 18). After some attempts, we considered that the optimized reaction conditions are the following: **1a** (1 mmol) with KI (3 mmol) and DMF (2 mL) at 120 °C for 12 h (Table 1, entry 5).

To test the scope of this transition-metal-free homocoupling reaction, we subjected a variety of alkynyl bromides and iodides to the reaction conditions (Table 2). In general, alkynyl iodides gave 1,3-diynes in better yields as compared to the corresponding alkynyl bromides. Both electron-rich and electron-deficient aromatic 1-haloalkynes afforded the corresponding products in good to excellent yields (Table 2, entries 1−19). The treatment of alkyl-substituted substrates afforded the corresponding products in moderate to high yields (Table 2, entries 20−23). For the para-electron-rich substituted aromatic 1-haloalkynes, the coupling yields gradually decreased from H to methoxy group (Table 2, entries 1−4 and 7−9). Clearly, the electronic effect plays an

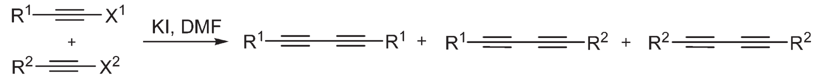
TABLE 2. Scope of Transition-Metal-Free Homocoupling of 1-Haloalkynes[a]

1 **2**

entry	substrate	X	product	yield (%)[b]
1		Br (**1a**)	(**2a**)	94
2		I (**1b**)		97
3		Br (**1c**)	(**2b**)	83
4		I (**1d**)		90
5		Br (**1e**)	(**2c**)	85
6		Br (**1f**)	(**2d**)	73
7		Br (**1g**)	(**2e**)	86
8		Br (**1h**)	(**2f**)	72
9		I (**1i**)		75
10		Br (**1j**)	(**2g**)	89
11		I (**1k**)		93
12		Br (**1l**)	(**2h**)	80
13		I (**1m**)		92
14		Br (**1n**)	(**2i**)	78
15		I (**1o**)		96
16		Br (**1p**)	(**2j**)	87
17		I (**1q**)		93
18		Br (**1r**)	(**2k**)	85
19		I (**1s**)		99
20		Br (**1t**)	(**2l**)	75
21		I (**1u**)		94
22		Br (**1v**)	(**2m**)	50
23		Br (**1w**)	(**2n**)	53
24		Br (**1x**)	(**2o**)	64

[a] Reaction conditions: 1-haloalkyne (1 mmol), KI (3 mmol), DMF (2.0 mL) at 120 °C for 12 h. [b] Isolated yield.

SCHEME 1. The Cross-Coupling of Haloalkynes



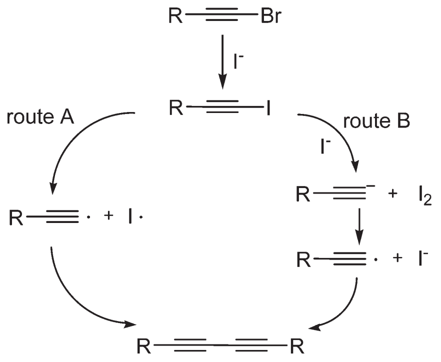
R^1 = MeOPh, R^2 = Ph X^1 = Br, X^2 = Br	**2f** 22%	**2ah** 53%	**2a** 25%
X^1 = I, X^2 = Br	**2f** 5%	**2ah** 35%	**2a** 60%
R^1 = MeOPh, R^2 = *o*-FPh X^1 = Br, X^2 = I	**2f** 9%	**2hl** 34%	**2g** 57%
R^1 = MeOPh, R^2 = C_6H_{13} X^1 = I, X^2 = Br	**2f** 17%	**2ht** 62%	**2l** 21%
R^1 = $C(CH_3)_2OH$, R^2 = C_6H_{13} X^1 = Br, X^2 = I	**2o** 13%	**2tx** 42%	**2l** 45%
R^1 = Ph, R^2 = C_6H_{13} X^1 = I, X^2 = I	**2a** 54%	**2at** 35%	**2l** 5%
R^1 = Ph, R^2 = MePh X^1 = I, X^2 = Br	**2a** 25%	**2ac** 56%	**2b** 19%

important role. It should be pointed out that the carbon−halogen bonds tolerated the substrate reactivity and the halogen-containing products were afforded smoothly (Table 2, entries 10−15). Substitution at the ortho-position of the aromatic ring had some impact on the yields (Table 2, entries 3−6 and 10−13). 3,5-Bis(trifluoromethyl)-substituted phenylethynyl iodide almost gave a quantitative yield (Table 2, entry 19). Luckily, the standard conditions were compatible with aliphatic alkynyl halides, and the functional group on 1-haloalkyne could be tolerated as nitrile, hydroxyl, and so on, albeit in lower yields (Table 2, entries 20−24).

With regard to the versatile utility of unsymmetrical 1,3-diynes in synthetic chemistry, remarkable progress has been made in the transition-metal-catalyzed cross-coupling of alkynes.[16] Therefore, an attempt at cross-coupling reactions of alkynylbromide or iodide with different alkynyl bromide or iodide were investigated briefly and resulted in a statistical distribution of diynes along with the cross-coupled products (Scheme 1, GC ratio).

The mechanism of this reaction was proposed on the basis of the previous reports and our present results.[17] Two alternative routes (A and B) as outlined in Scheme 2 have been considered. First, the substitution of 1-bromoalkyne with KI to form the 1-iodoalkyne intermediate. In route A the 1-iodoalkyne was decomposed to alkyne radical and iodine radical, which then homocoupled to form the symmetric 1,3-diynes and iodine. In route B the 1-iodoalkyne intermediate was transformed to alkyne negative ion and iodine via a redox process, followed to produce the alkyne radical through a redox process, and then gave rise to the product. On the other hand, compound **2a** could not be obtained from **1b** without any additive (Table 1, entry 18). Thus, the formation of product through route B is predicted.

SCHEME 2. A Plausible Mechanism



In conclusion, we have successfully developed an efficient synthetic approach to symmetrical 1,3-diynes from 1-haloalkynes under transition-metal-free conditions in DMF solvent. Especially, the homocoupling of 1-iodoalkynes is more effective for synthesis of the symmetrical 1,3-diynes. Although the haloalkynes are usually prepared from terminal alkynes by halogenation, the absence of any transition-metal and base can make the method more valuable. Further investigations on the scope and limitation of the coupling reaction and mechanistic studies are underway.

Experimental Section

General Procedure for the Synthesis of 1,4-Diphenylbuta-1,3-diyne (2a). 1-(2-Bromoethynyl)Benzene (**1a**, 1 mmol) and KI (3 mmol) in DMF (2 mL) were stirred at 120 °C for 12 h in a 25 mL Schlenk tube. Water (8 mL) was added after completion of the reaction, the aqueous solution was extracted with diethyl ether (3 × 5 mL), and the combined extract was dried with anhydrous $MgSO_4$. The solvent was removed and the crude product was separated by column chromatography to give a pure sample of

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[16] For selective examples, see: (a) Negishi, E.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979–2017. (b) Shi, W.; Luo, Y.; Luo, X.; Chao, L.; Zhang, H.; Wang, J.; Lei, A. *J. Am. Chem. Soc.* **2008**, *130*, 14713–14720. (c) Marino, J. P.; Nguyen, H. N. *J. Org. Chem.* **2002**, *67*, 6841–6844. (d) Luu, T.; Morisaki, Y.; Cunningham, N.; Tykwinski, R. R. *J. Org. Chem.* **2007**, *72*, 9622–9629. (e) Negishi, E.; Hata, M.; Xu, C. *Org. Lett.* **2000**, *2*, 3687–3689. (f) Kim, S.; Kim, S.; Lee, T.; Ko, H.; Kim, D. *Org. Lett.* **2004**, *6*, 3601–3604. (g) Yin, W.; He, C.; Chen, M.; Zhang, H.; Lei, A. *Org. Lett.* **2009**, *11*, 709–712.

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2a. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50−7.53 (m, 4H), 7.30−7.36 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.4, 129.1, 128.4, 121.7, 81.5, 75.8. MS (EI) *m*/*z* 88, 101, 126, 150, 174, 202.

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Supporting Information Available: Compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.