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Highly efficient two-step synthesis of (*Z*)-2-halo-1-iodoalkenes from terminal alkynes†

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Received 28th June 2010, Accepted 8th September 2010
DOI: 10.1039/c0cc02156c

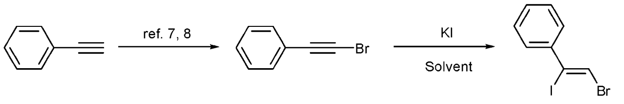
The easily accessible haloalkynes can be converted to (*Z*)-2-halo-1-iodoalkenes in high yields with excellent regio- and stereo-selectivity. The method shows good functional group compatibility. The resulting products could find broad applications.

Vinyl halides are one of the most important intermediates in organic synthesis and are often employed for transition-metal-catalyzed cross-coupling reactions. The dihaloalkenes are attracting more and more attention as it has been possible to construct multifunctional and dissymmetrical compounds in the past decades.[1,2] Vicinal hetero-dihaloalkenes, such as 2-chloro-1-iodoalkene and 2-bromo-1-iodoalkene, are one of the most versatile building blocks, and their preparations are mainly through the halogenation using iodine monochloride or iodine monobromide with alkynes. However, the poor selectivity and difficult separation in the preparation course prevent them from being widely used in organic synthesis. Although some methodologies have been developed for the more efficient and selective halogenation of alkynes,[3] there is still no efficient method to prepare the (*Z*)-2-halo-1-iodoalkenes.[4] Herein, we wish to present the first example of a facile two-step synthesis of the (*Z*)-2-halo-1-iodoalkenes from the simple terminal alkynes in moderate to excellent yields in a highly regio- and stereoselective manner.[5] The reactions proceeded with haloalkynes,[6] which were prepared by reported methods with high yields (87–99%).[7,8]

With the haloalkynes in hand, we then examined the second step, transforming the haloalkyne **1** into the desired product 1,2-dihaloalkene **2** in detail to tune the reaction conditions. As summarized in Table 1, bromoalkyne (**1a**) was used as the starting material for the model reaction. Initially, we added different transition metals in the reaction by assuming the reaction is a catalytic process (Table 1, entries 1–4). However, the control experiment results showed that the bromoalkyne (**1a**) can be effectively converted to the (*Z*)-2-bromo-1-iodoalkene (**2a**) without addition of any transition metals (entry 5), which implies that it's a noncatalytic reaction. Indeed, some transition metals can even prohibit or depress the reaction (entries 1, 2). The solvent played an important role and acetic anhydride is the solvent of choice for the reaction (entries 5–10). Alkaline iodine was the best iodine source, both KI and NaI can work equally well (entries 5, 12). Lower temperature and shorter time decreased the reaction yields (entries 16–18), for example, only trace product was formed when the reaction was conducted at room temperature (entry 16). It is notable that the reaction can be simplified in a one-pot style starting from phenylacetylene, which eventually afforded the corresponding product **2a** in 84% yield (Table 1, entry 19).

With the success in finding the optimum reaction conditions (Table 1, entry 5), the scope and the utility of this method with other haloalkynes in the standard conditions were then investigated in detail. As summarized in Scheme 1, aromatic alkynyl bromides with either an electron-donating or electron-withdrawing group on the benzene ring were able to generate the corresponding products in good to excellent yields (**2a–o**). Substitution at the 2-position of the aromatic ring had a slight impact and the CF_3 substituted substrate required prolonged reaction time (**2g** and **2k**). The reaction conditions were compatible with alkyl, methoxy, fluoro, chloro, bromo, nitro, and trifluoromethyl group (**2b–l**). Especially, the di-electron-withdrawing group substituted substrate gave excellent yield (**2l**). Furthermore, diyne bromide can be converted into the corresponding product **2m** in good yield as well. In addition to bromoalkynes, chloroalkynes were also shown to

Table 1 The reaction of KI with bromoalkyne[a]



1a **2a**

Entry	Solvent	Additive	Iodine source	Yield (%)[b]
1	Ac_2O	$Pd(OAc)_2$	KI	n.p.
2	Ac_2O	CuI	KI	30
3	Ac_2O	AgOAc	KI	95
4	Ac_2O	$FeCl_3$	KI	96
5	**Ac_2O**	**—**	**KI**	**95**
6	DMF	—	KI	trace
7	HOAc	—	KI	85
8	1,4-dioxane	—	KI	trace
9	Water	—	KI	trace
10	DMSO	—	KI	20
11	Ac_2O	—	HI	50
12	Ac_2O	—	NaI	94
13	Ac_2O	—	$N(Bu)_4I$	56
14[c]	Ac_2O	—	I_2	9
15	Ac_2O	—	NIS	n.p.
16[d]	Ac_2O	—	KI	trace
17[e]	Ac_2O	—	KI	55
18[f]	Ac_2O	—	KI	78
19[g]	Ac_2O	—	KI	84

[a] Reaction conditions: phenylethynyl bromide (1.0 mmol), KI (1.5 mmol), solvent (2.0 mL) at 120 °C for 6 h. [b] Isolated yield. [c] The addition product of I_2 was obtained in 88% yield. [d] Room temperature. [e] At 60 °C. [f] 3 h. [g] The one-pot method from phenylacetylene to the product, please see the supporting information.

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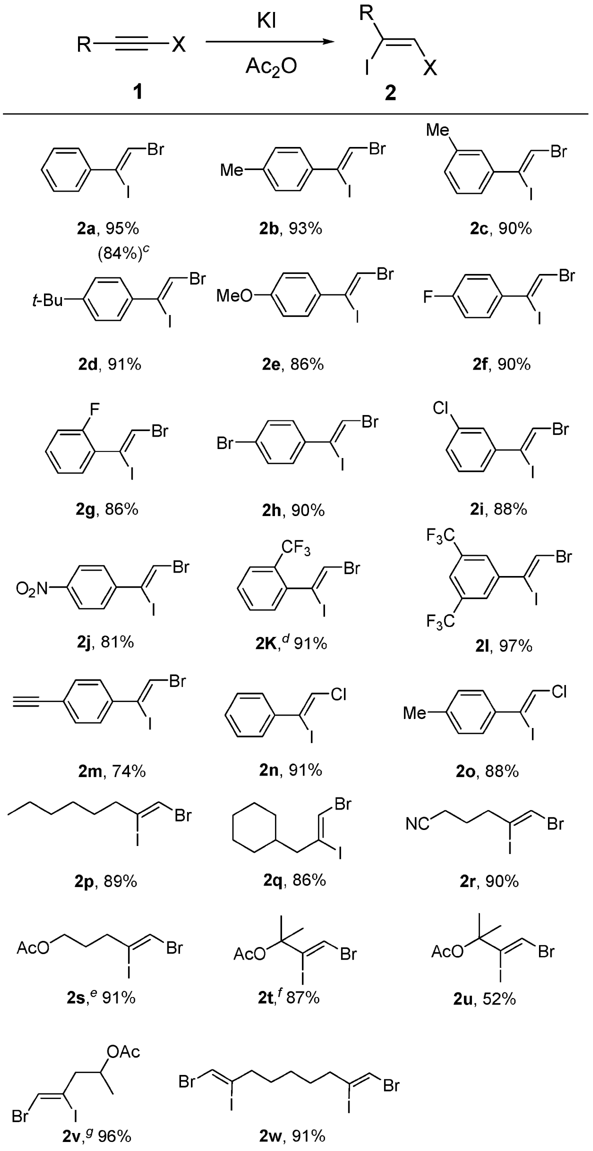
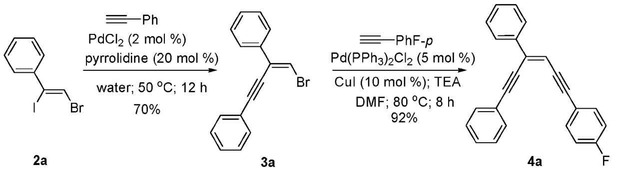
† Electronic supplementary information (ESI) available: Experimental section, characterization of all compounds, copies of ^1H and ^{13}C NMR spectra for isolated compounds. See DOI: 10.1039/c0cc02156c



Scheme 1 The scope of halogenation of haloalkynes[a,b]. [a] *Reaction conditions*: haloalkyne (1 mmol), KI (1.5 mmol), acetic anhydride (2.0 mL) at 120 °C for 6 h. [b] Isolation yield and the ratio of *Z*/*E* isomers was above 99 : 1 determined by GC. [c] 10 mmol scale of the reaction. [d] 24 h. [e] The substrate was 1-bromo-5-chloropent-1-yne. [f] The substrate was 4-bromo-2-methylbut-3-yn-2-ol. [g] The substrate was 5-bromopent-4-yn-2-ol.



Scheme 2 The Sonogashira reaction of **2a** and **3a**.

be highly effective substrates for the transformation; the corresponding products (*Z*)-2-chloro-1-iodoalkenes can be obtained in excellent yields as well (**2n** and **2o**). Except for the aryl haloalkynes, the alkyl haloalkynes were also found to be suitable substrates for the standard conditions (**2p–w**). When the aliphatic alkynes bearing cyclohexyl, cyano, chloro, hydroxyl and ester group were employed, the reaction proceeded in moderate to excellent yields (**2q–v**). In the case of the aliphatic alkyne bearing chloro and hydroxyl groups, the functionalization proceeded simultaneously at both the alkyne and hydroxyl, chloro moieties (**2s**, **2t** and **2v**). Furthermore, diene formation was performed in excellent yield (**2w**). To further explore its potential application, we scaled up the reaction in a 10 mmol scale; the product could be formed in 84% yield (**2a**).

With a viable route to the (*Z*)-2-halo-1-iodoalkenes, we then worked on exploring their potential applications as building blocks for the synthesis of highly substituted alkenes. For example, by elaborately designing, the (*Z*)-2-bromo-1-iodoalkene **2a** can be selectively cross-coupled with two different alkynes in order in good yields through the Sonogashira reaction, as iodine and bromine atoms in the molecule have quite different reaction activities (Scheme 2). The (*Z*)-bromo-enyne **3a**, with the bromine functional group on the terminal C=C double bond, is a very useful intermediate in organic synthesis;[9] and the dissymmetric enediyne **4a** is a key framework for the preparation of a variety of target compounds with applications ranging from natural products and pharmaceuticals to molecular organic materials.[10,11]

In conclusion, a convenient and practical route to synthetically useful (*Z*)-2-halo-1-iodoalkenes from the simple terminal alkynes in high yields with excellent regio- and stereoselectivity was described. The method shows excellent functional group compatibility. Moreover, the useful intermediate was briefly transformed to the conjugated (*Z*)-haloenyne and (*Z*)-dissymmetric enediyne in good yields. The use of these precursors for multifunctional synthesis and further applications is in progress and will be reported in due course.

This work was supported by the National Natural Science Foundation of China (Nos. 20625205, 20772034, and 20932002), National Basic Research Program of China (973 Program) (No. 2011CB808603) and the Doctoral Fund of the Ministry of Education of China (20090172110014).

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