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Efficient Fe/I₂/NaI mediated synthesis of alkenyl iodides through direct coupling of alcohols and alkynes

Ming-Ming Li^{a,b}, Qiang Zhang^{a,b}, Hui-Lan Yue^{a,b}, Lei Ma^c, Jian-Xin Ji^{a,*}

ABSTRACT

^a Chengdu Institute of Biology, Chinese Academy of Sciences, Chengdu 610041, China

^b Graduate University of the Chinese Academy of Sciences, Beijing 100049, China

^c Center for Drug Evaluation, State Food and Drug Administration, Beijing 100038, China

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Alkenyl iodides are highly valuable structural motifs and widely serve as important intermediates in the synthesis of various natural products, pharmaceuticals, and polymers.¹ The iodide moiety is commonly regarded as the key element which provides simple and convenient avenues for further structural elaboration through transition-metal-catalyzed cross-coupling reactions, such as Heck, Suzuki, Stille, Sonogashira, and Negishi reactions.^{1b,2} In general, the strategies for the construction of alkenyl iodides are mostly based on iodination or hydroiodination of alkynes,³ allenes,⁴ propargylic alcohols, and their derivatives⁵ with iodinating reagents such as HI, I2, or N-iodosuccinimide. From a synthetic standpoint, iodoalkylation of alkynes could supply more versatile functionalized alkenyl iodides. So far, various methods have been developed over the past decades.^{6–9} Typically, the iodoalkylation of alkynes was achieved through two steps (i) the addition of organometallic reagents or unsaturated compounds such as vinyl ether to alkynes mediated by Zr, Ti, or Ni salts for the preparation of alkenyl organometallics, and (ii) treatment of the alkenyl organometallics with I₂ generated alkenyl iodides.⁶ Alternative procedures including intramolecular electrophilic cyclization of complicated alkynes such as 1,5-divnes or 1,5-envnes,⁷ AIBN or zinc powder mediated radical addition of perfluoroalkyl iodides to alkynes,⁸ and the use of ketones and aldehydes reacted with activated alkynes and iodide salts to access alkenyl iodides have also been developed.⁹ Nevertheless, most of these methods suffer from limitations such as the need of extra steps to prepare active starting materials, drastic reaction conditions, and the use of expensive and toxic metal catalysts. Therefore, the development of simple and efficient methods for the iodoalkylation of alkynes is still highly desirable.

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A new and efficient method for the synthesis of alkenyl iodides through direct coupling of alcohols and

alkynes has been developed in the presence of iron powder, I₂, and NaI. This methodology not only provides

an attractive approach to alkenyl iodides, but also expands the application of iron in synthetic chemistry.

Iron as an abundant, cheap, and environmentally benign metal, has displayed excellent reactivity for the formation of carbon–carbon and carbon–heteroatom bonds.¹⁰ Recently, a new synthetic strategy for preparing alkenyl chlorides and alkenyl bromides through coupling reaction of benzyl alcohols and alkynes has been developed, in which FeCl₃ and FeBr₃ were employed not only as promoters to accomplish the formation of chemical bonds but also as halide sources (Eq. 1).^{11a–c} However, alkenyl iodides could not be afforded by this procedure due to the highly labile feature of Fel₃.¹² Herein, we report a new and efficient iron powder, l₂, and Nal mediated method for the synthesis of alkenyl iodides from al-kynes and alcohols under

Previous work
$$R^2 \longrightarrow R^3 \longrightarrow R^$$







^{*} Corresponding author. Tel.: +86 28 82855463; fax: +86 28 82855223. *E-mail address:* jijx@cib.ac.cn (J.-X. Ji).

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mild conditions (Eq. 2).

In an initial experiment, benzhydrol 1a and phenylacetylene 2a were chosen as model substrates to examine the activity of various iron and iodinating reagents including FeI₂, iron powder/HI, iron powder/NaI, and iron powder/I₂ in 1,2-dibromoethane (DBE)¹³ at 55 °C. No desired product **3a** was detected in the presence of iron powder/HI and iron powder/NaI (Table 1, entries 2 and 3). To our delight, the desired alkenyl iodide 3a was produced in 28% and 32% yields by the promotion of Fel₂ and iron powder/l₂, respectively, (Table 1, entries 1 and 4). Considering iron powder and I₂ are cheaper and easily available reagents, further optimization of the reaction using iron powder and I₂ was conducted. The results suggested that the increase of iron powder and I₂ loading greatly improved this iodoalkylation reaction, and good yield of 3a was obtained when NaI was employed as the additive (Table 1, entries 5-10). Further investigation showed that solvents had a strong effect on this process, halogenated solvents such as 1.2-dichloroethane. DBE, and dichloromethane worked more efficiently for this transformation than non-halogenated solvents, and DBE was found to be the most effective (Table 1, entries 9, 11–15). After an extensive screening, the best yield (88%) was obtained by employing iron powder (1 equiv), I₂ (1 equiv), and NaI (2 equiv) in DBE at 55 °C (Table 1, entry 9).

Under the optimal reaction conditions, the generality of the process was tested by using various alcohols with alkynes and the results are summarized in Table 2. In general, the desired products were produced with *E* isomers as the main products, which can be explained from the preferred trans attack of the iodide ion to the alkenyl carbocation. Dibenylmethanols with either electron-donating or -withdrawing groups attached to the benzene ring were suitable for this protocol, and the corresponding products were obtained in good to excellent yields (**3a**–**e**). Benzylic alcohols could also be used in the reaction to give the expected alkenyl iodides (**3f** and **3g**). In addition, allylic alcohols such as (*E*)-1,3-diphenylprop-2-en-1-ol, cyclohex-2-enol, and 4,4-dimethyl-cyclohex-2-enol reacted smoothly with alkynes, affording 1-iodo-1,4-diene derivatives in good yields (**3h–1**). With respect to alkynes, electron-rich

Table 1

Screening of the reaction conditions^{a,b}

	$Ph \rightarrow Ph \rightarrow$	conditions Ph	Ph I I
	1a 2a	3	a
Entry	Iron/iodinating reagents (equiv)	Solvent	Yield ^b (%)
1	Fel ₂ (0.5)	DBE	28
2	Fe (0.5)/HI (1)	DBE	0 ^c
3	Fe (0.5)/NaI (1)	DBE	0
4	Fe (0.5)/I ₂ (0.5)	DBE	32
5	Fe (0.5)/I ₂ (0.75)	DBE	29
6	Fe (0.75)/I ₂ (0.75)	DBE	45
7	Fe $(1)/I_2(1)$	DBE	56
8	Fe (1)/I ₂ (1)/NaI (1)	DBE	68
9	Fe (1)/I ₂ (1)/NaI (2)	DBE	88
10	Fe (1)/I ₂ (1)/NaI (3)	DBE	57
11	Fe (1)/I ₂ (1)/NaI (2)	CICH ₂ CH ₂ CI	79
12	Fe (1)/I ₂ (1)/NaI (2)	CH_2Cl_2 (reflux)	77
13	Fe (1)/I ₂ (1)/NaI (2)	Toluene	39
14	Fe (1)/I ₂ (1)/NaI (2)	CH₃OH	0
15	Fe (1)/I ₂ (1)/NaI (2)	CH ₃ CN	0
16	Fe (1)/I ₂ (1)/KI (2)	DBE	60
17	Fe (1)/I ₂ (1)/HI (2)	DBE	74 ^c

^a Reaction conditions: benzhydrol **1a** (0.5 mmol), phenylacetylene **2a** (1.5 mmol), iron/iodinating reagents, solvent (1.0 mL), 55 °C, 8 h.

^b Isolated yields of the *E*:*Z* mixtures.

^c 47% aqueous HI was used.

Table 2

Results for reactions of alkynes with various alcohols^{a,b}



^a Reaction conditions: alcohols 1 (0.5 mmol), alkynes 2 (1.5 mmol), I₂ (0.5 mmol), iron powder (0.5 mmol), Nal (1.0 mmol), DBE (1.0 mL), 55 °C, 8–12 h.
 ^b Isolated yields of the *E:Z* mixtures; the *E:Z* ratio was determined by ¹H NMR spectroscopy.

aromatic alkynes generally exhibited better reactivity than electron-deficient ones (**3m**–**p**). Notably, internal aromatic alkynes such as 1-phenyl-1-propyne and 1-phenyl-1-butyne were also tolerated

(3)



Scheme 1. Postulated reaction pathways.

in this process, leading to the corresponding products in moderate yields (**3q** and **3r**). Nevertheless, when aliphatic alkynes were used as the substrates, none of the desired products were detected.

In the course of our investigation on the mechanism of this reaction, dimeric ether **4a** was observed and isolated together with the product **3a** when the reaction of benzhydrol **1a** and phenylacetylene **2a** was conducted in the presence of iron powder, I₂, and NaI (Eq. 3). Furthermore, the product **3a** was obtained in an 81% isolated yield when a separate experiment was performed between dimeric ether **4a** and phenylacetylene **2a** under the standard conditions (Eq. 4). These results suggested that dimeric ether **4** might be an intermediate in this iodoalkylation reaction. Nevertheless, the direct iodoalkylation of alkynes with alcohols and iodinating reagents could not be excluded at present stage.^{11c-e}

Although the detailed mechanism is unclear, based on the above results and previous studies,¹¹ we proposed two postulated pathways of this reaction shown in Scheme 1. One pathway was a direct alkylation of alkyne **2** with alcohol **1** to generate alkenyl cation **5**, which was attacked by iodide ion to form alkenyl iodides **3**. In another probable pathway, the starting alcohol **1** was firstly converted to the corresponding dimeric ether **4**. Then, the alkylation of alkyne **2** by dimeric ether **4** was proceeded to give alkenyl cation **5**. Finally, the iodination of alkenyl cation **5** delivered the desired product **3**.

In summary, we have successfully developed a convenient and efficient method for the synthesis of alkenyl iodides through direct coupling of various alcohols with alkynes in the presence of iron powder, I₂, and NaI under mild conditions. The present protocol not only provides a green and attractive approach to alkenyl iodides, but also expands the application of iron in synthetic chemistry. Further investigation of the detailed reaction mechanism and synthetic applications are ongoing.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.11.037.

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