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Regio- and stereoselective iodoarylation of arylacetylenes using molecular iodine promoted by hypervalent iodine

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ABSTRACT

Iodoarylation of arylacetylenes with electron-rich arenes using a simple reagent system: I_2 and $PhI(OCOPh)_2$ proceeded regio- and stereoselectively to give trans adducts, 1,1-diaryl-2-iodoethenes, in good to high yields.

Catalytic functionalization of aromatic C–H bonds via formation of a new carbon–carbon bond between arenes and alkynes has received significant attention. The process provides a direct synthesis of various functionalized aromatic compounds bearing conjugated carbon–carbon double bonds in one step, which is the useful alternative to Heck-type coupling reactions of aromatic halides and olefins. To date, various methods for the functionalization of arenes with alkynes have been developed,[1] which are catalyzed by transition metals or Lewis acids.

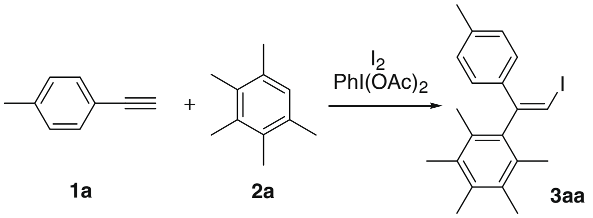
Although such metal-catalyzed carbon–carbon bond formation reactions are excellent and very powerful methods, there are some limitations, for instance, special caution for handling metal catalysts under inert atmosphere and requirement of activated substrates or strong acidic or severe conditions. These drawbacks of the transition metal-catalyzed reaction of arenes with alkynes have directed our attention to develop a more convenient and new synthetic method for the functionalization of arenes without using any transition metal catalysts.

Iodine is a unique element which acts as a weak oxidizer at the same time as a reducing agent. Iodine molecule (I_2) shows an electrophilic property, but the reactivity in the addition reaction is low. In the iodination reaction of arenes with I_2, we have found that the reaction of arenes with I_2 proceeds smoothly in the presence of potassium peroxodisulfate ($K_2S_2O_8$) as an oxidant to give iodoarenes in good yields.[2] To explore the use of molecular iodine, we extended the iodination reaction to iodoarylation of alkynes. It was assumed that an alkyne would be first activated by iodine and then would undergo electrophilic substitution with an arene. Iodoarylation of alkynes itself is a rare reaction. To the best of our knowledge, there are no reports on the iodoarylation of alkynes using molecular iodine except for an elaborated, expensive iodine source, bis(pyridine)iodonium(I) tetrafluoroborate (IPy_2BF_4).[3] Here, we report a convenient and very simple reagent system of molecular iodine and hypervalent iodine compounds for iodoarylation reaction of alkynes, providing regio- and stereoselective synthesis of 1,1-diaryl-2-iodoethenes.

Iodoarylation of alkynes is accompanied by generation of proton and competes with protonation of alkynes. Actually, the iodoarylation of an alkyne with pentamethylbenzene (**2a**) using an $I_2/K_2S_2O_8$ reagent system was found to produce a hydroarylation product as a by-product along with a desired iodoarylation product. However, the contamination of the iodoarylation product with the inseparable by-product caused many difficulties in separation and purification processes. (Diacetoxyiodo)benzene, $PhI(OAc)_2$, is a promising reagent which has both functions of oxidizing iodine and of trapping proton with acetate anion. Thus, we considered the use of $PhI(OAc)_2$, which is the most commercially available hypervalent iodine compound and is widely used one in organic synthesis.

Initial work was concentrated on the efficiency of the iodoarylation of *p*-methylphenylacetylene (**1a**) with pentamethylbenzene (**2a**) in the presence of I_2 and $PhI(OAc)_2$ (Scheme 1).

Iodoarylation reaction of **1a** (1 mmol) and **2a** (1 mmol) was carried out using 1.25 mmol each of I_2 and $PhI(OAc)_2$. The results are given in Table 1. The reaction in 1,2-dichloroethane (DCE) at 45 °C for 28 h gave pure 1-iodo-2-(pentamethylphenyl)-2-(4-methylphenyl)ethene (**3aa**), but the yield was low (12%) (entry 1). Increasing the amount of **2a** and $PhI(OAc)_2$, the reaction was con-



Scheme 1.

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Table 1

Iodoarylation reaction of **1a** with **2a**[a]

Entry	**2a** (mmol)	$PhI(OAc)_2$ (mmol)	Solvent	Temp (°C)	Time (h)	Yield of **3aa**[b] (%)
1	1	1.25	DCE	45	28	12
2	5	3	AcOH	60	48	23
3	5	3	CH_3CN	60	48	52
4	10	3	CH_3CN[c]	82	65	78
5	10	3	AcOEt[c]	82	65	13

[a] Reaction conditions: **1a** (1 mmol), **2a**, I_2 (1.25 mmol), $PhI(OAc)_2$, and a solvent (2 mL).

[b] Isolated yield based on **1a**.

[c] 4 mL was used.

ducted in AcOH or MeCN at 60 °C (entries 2 and 3), indicating that MeCN gave a better result. Extension of the reaction time and a higher temperature improved the yield of **3aa** to give the best result (78%) (entry 4). Using the conditions of entry 4, the reaction in AcOEt instead of MeCN resulted in a low yield (13%) of **3aa** (entry 5).

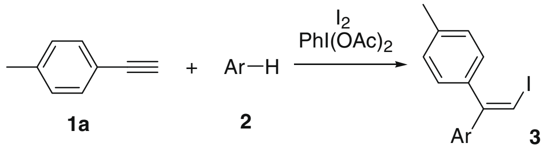
We attempted to determine the stereochemistry of iodoarylation product **3aa** by NOE experiments, but only a small enhancement (3%) of the vinylic proton was observed when the *ortho* methyl proton was irradiated. This may be attributed to the deviation of the pentamethylphenyl ring from the olefinic plane. Then, we estimated the chemical shift of the vinylic proton according to the literature.[4] The calculation of the chemical shift concerning the vinylic proton of **3aa** gives 6.57 ppm for the *E* isomer and 6.84 ppm for the *Z* isomer. Therefore, the observed chemical shift of 6.31 ppm indicates that the stereochemistry of **3aa** is *E*. This result suggests that the iodoarylation of arylalkynes proceeds with trans addition.

Using the conditions of entry 4 as listed in Table 1, we conducted the iodoarylation of **1a** with several electron-rich arenes. The results are given in Table 2. The reaction with mesitylene (**2b**), durene (**2c**), and bromomesitylene (**2d**) gave the corresponding iodoarylation products **3** in moderate yields (entries 1–3).

In order to increase the reactivity of the hypervalent iodine reagent, the derivative of benzoic acid, $PhI(OCOPh)_2$,[5] was employed in the iodoarylation reaction under the same conditions as $PhI(OAc)_2$. To our delight, $PhI(OCOPh)_2$ improved the yield of the iodoarylation product to afford **3aa** in 86% yield (see, Table 3, entry 1). Then, we furthermore conducted the iodoarylation reaction using $PhI(OCOPh)_2$. The outline of the reaction is drawn in Scheme 2 and the results are given in Table 3. In the reaction of 4-methylphenylacetylene (**1a**), electron-rich mesitylene (**2b**) gave the product **3ab** in high yield (entry 2). The reaction of **1a** with durene (2**c**) and 2-bromomesitylene (**2d**) gave **3ac** and **3ad** in 56 and 42% yields, respectively (entries 3 and 4). The reaction with *p*-xylene (**2e**) gave low yield (entry 5) of iodoarylation product **3ae** owing to the formation of inseparable, polar substances. Similarly, the reactions of phenylacetylene (**1b**) and 4-fluorophenylacetylene (**1c**) also afforded iodoarylation products **3** in moderate to high yields.

Table 2

Iodoarylation reaction of **1a** with several arenes **2**[a]



Entry	Arene **2**	Temp (°C)	Time (h)	Yield[b] (%)
1	Mesitylene (**2b**)	82	65	62
2	Durene (**2c**)	82	65	40
3	Bromomesitylene (**2d**)	82	65	26[c]

[a] Reaction conditions: **1a** (1 mmol), **2** (10 mmol), I_2 (1.25 mmol), $PhI(OAc)_2$ (3 mmol), and MeCN (4 mL).

[b] Isolated yield based on **1a**.

[c] A mixture of *E*- and *Z*-isomers.

Table 3

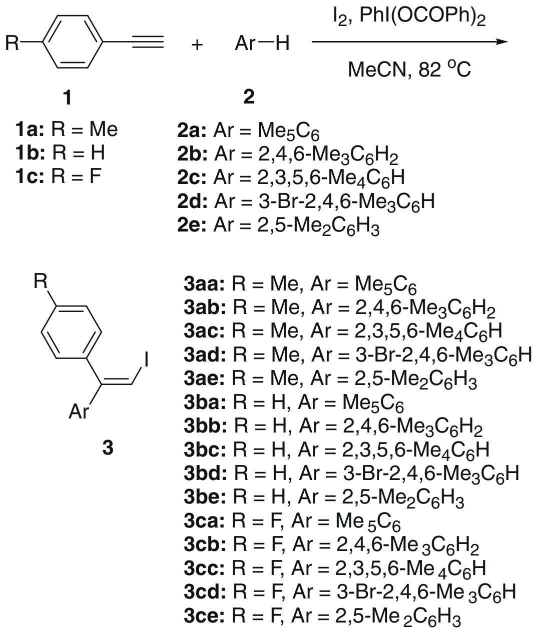
The reaction of alkyne **1** with arenes **2** in the presence of $PhI(OCOPh)_2$[a]

Entry	Alkyne **1**	ArH **2**	Time (h)	Product **3**	Yield[b] (%)
1	**1a**	**2a**	65	**3aa**	86
2	**1a**	**2b**	65	**3ab**	75
3	**1a**	**2c**	67	**3ac**	56
4	**1a**	**2d**	72	**3ad**	42[c]
5	**1a**	**2e**	72	**3ae**	33[c]
6	**1b**	**2a**	65	**3ba**	71
7	**1b**	**2b**	70	**3bb**	61
8	**1b**	**2c**	73	**3bc**	59
9	**1b**	**2d**	76	**3bd**	32
10	**1b**	**2e**	72	**3be**	24
11	**1c**	**2a**	72	**3ca**	69
12	**1c**	**2b**	72	**3cb**	67
13	**1c**	**2c**	73	**3cc**	56
14	**1c**	**2d**	76	**3cd**	27
15	**1c**	**2e**	76	**3ce**	23

[a] Reaction conditions: **1** (1 mmol), **2** (10 mmol), I_2 (1.25 mmol), $PhI(OCOPh)_2$ (3 mmol), MeCN (6 mL) at 82 °C.

[b] Isolated yield based on **1**.

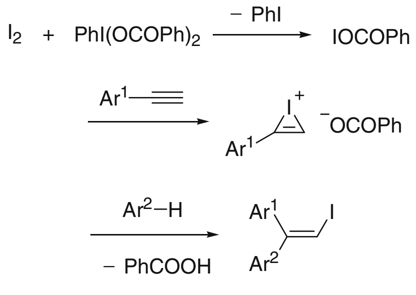
[c] A mixture of *E*- and *Z*-isomers.



Scheme 2.

A reaction path is proposed as shown in Scheme 3. The iodoarylation of an arylalkyne is initiated by oxidation of iodine with $PhI(OCOPh)_2$ giving a hypoiodite, IOCOPh.[6] The in situ-generated IOCOPh adds the arylalkyne to form a cyclic iodonium benzoate, which undergoes aromatic electrophilic substitution with an electron-rich arene to afford a final product, accompanying deprotonation with benzoate anion. Although the regioselectivity is derived from a larger cationic character at the carbon bearing the aryl group in the cyclic iodonium ion, the stereoselectivity can be explained by the contribution of the cyclic iodonium ion. Its presence is an important factor to cause trans addition giving the stereochemically defined product.[7]

In conclusion, we have demonstrated that arylacetylenes undergo regio- and stereoselective iodoarylation in the presence of a simple reagent system composed of I_2 and $PhI(OCOPh)_2$. Iodine group is particularly useful for further elaboration by merging the iodoalkene structures with metal-catalyzed cross-coupling



Scheme 3.

reactions.[8] Because of its simple and convenient procedure further applications are now under progress.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.06.015.

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