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# Mild and efficient oxy-iodination of alkynes and phenols with potassium iodide and *tert*-butyl hydroperoxide

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## ABSTRACT

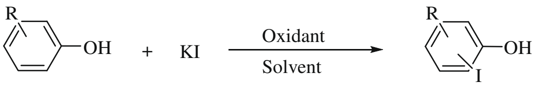
An efficient synthesis of 1-iodoalkynes and iodophenols was easily achieved by employing simple KI and TBHP. The reaction does not involve the use of a metal and base combination. A variety of substituted alkynes and phenols were prepared with good to excellent yield.

Iodoalkynes are useful synthetic precursors in organic chemistry[1] and are found to possess several biological activities.[2] Numerous methods have been developed for the preparation of 1-iodoalkynes employing various metal catalysts,[3] anodic oxidation,[4] hypervalent iodonium salts,[5] ionic liquids,[6] bases,[7] phase transfer catalysts (PTC),[8] ultrasound,[9] iodine oxide,[10] Grignard reagent,[11] and *n*-BuLi.[12] Similarly, iodophenols are used as building blocks for the synthesis of various organic compounds that have importance in medicine, bio-chemistry, and pharmaceutics[13] and are useful for C–C and C–N bond forming reactions.[14] Several reports have appeared for the iodination on phenols using iodinating agents such as, *N*-iodosuccinimide, bis(pyridinium)iodonium(I) tetrafluoroborate ($IPy_2BF_4$), iodochloride (ICl), and potassium iodide (KI).[15] Though, these reagents are excellent iodinating agents, they have disadvantages, like involving the complex synthetic processes, use of expensive reagents and moreover generates considerable amount of waste materials.

Molecular halogens and related reagents are well known for various organic transformations due to their simple operation and low cost.[16] Several reports have appeared recently on the use of iodine and iodine-based reagents for the electrophilic iodination of organic compounds.[17] The main drawback of these methods is the use of only 50% of iodine for the iodination. On the other hand, oxidative-iodination proves to be more promising where 100% iodine atom-economy is achieved. Though some amount of work has been achieved on the oxidative-iodination of phenols, less is explored on the oxidative-iodination of alkynes.

As part of our ongoing study on iodine/iodide-mediated oxidative functionalization, we have recently shown that the catalytic amount of KI in combination with TBHP works well for the amidation of aldehydes and alcohols, selective oxidation of aromatic amines to nitro compounds, oxidative conversion of alcohols and aldehydes into nitriles and oxidative esterification of aldehydes and alcohols.[18] In continuation, we would like to present a mild and efficient method for the oxidative-iodination of alkynes and phenols as shown in Eqs. 1 and 2.

$$\mathrm{R{-}C{\equiv}C{-}H} \quad + \quad \mathrm{KI} \xrightarrow[\text{Solvent}]{\text{Oxidant}} \mathrm{R{-}C{\equiv}C{-}I} \qquad (1)$$



(2)

Initial optimizations were carried out by treating phenyl acetylene under different reaction conditions and the results are tabulated in Table 1. No product was observed with the blank reactions in the absence of either oxidant or iodine source (Table 1, entries 1 and 2). Under similar reaction conditions, with 1.1 equiv of KI and 1.5 equiv of TBHP, 91% of the desired 1-iodoalkyne was obtained (Table 1, entry 3), which clearly proves that both KI and TBHP are essential for the formation of product. Among the various solvents screened, methanol provided the best results (Table 1, entries 3–7). Reaction with $H_2O_2$ as an oxidant in both methanol and $CH_3CN$ does not yield the required product (Table 1,

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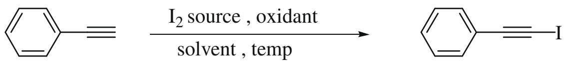
entries 8 and 9). We could not observe the desired product when the reaction was carried out with $I_2$ and TBHP, instead we observed that 1,2-diiodo-vinylbenzene was the major product (Table 1, entry 10), which was also observed even in the absence of TBHP.

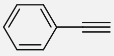
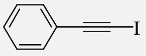
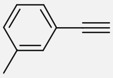
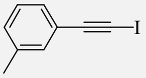
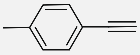
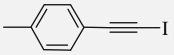
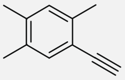
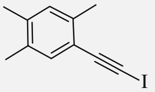
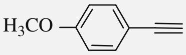
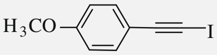
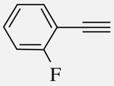
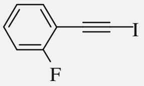
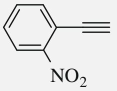
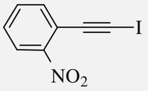
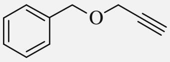
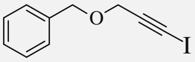
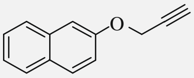
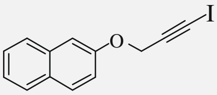
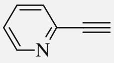
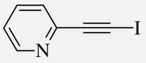
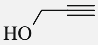
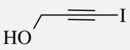
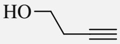
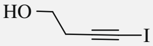
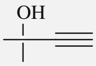
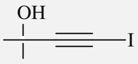
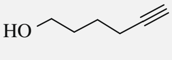
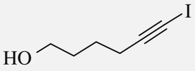
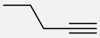
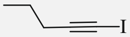
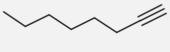
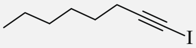
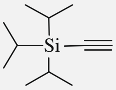
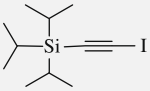
**Table 1**
Optimization condition for the synthesis of 1-iodoalkynes[a]



| S. No. | Iodine source (mmol) | Oxidant (mmol) | Solvent | Conversion[b] (%) |
|---|---|---|---|---|
| 1 | KI (1.1) | – | $CH_3OH$ | – |
| 2 | – | TBHP (1.5) | $CH_3OH$ | – |
| 3 | KI (1.1) | TBHP (1.5) | $CH_3OH$ | 91 (99) |
| 4 | KI (1.1) | TBHP (1.5) | $CH_3CN$ | 75 (98) |
| 5 | KI (1.1) | TBHP (1.5) | $H_2O$ | 16 (95) |
| 6 | KI (1.1) | TBHP (1.5) | DCM | 04 (96) |
| 7 | KI (1.1) | TBHP (1.5) | Ph $CH_3$ | 53 (70) |
| 8 | KI (1.1) | $H_2O_2$ (1.5) | $CH_3CN$ | – |
| 9 | KI (1.1) | $H_2O_2$ (1.5) | $CH_3OH$ | 01 (81) |
| 10 | $I_2$ (1.1) | TBHP (1.5) | $CH_3OH$ | –[c] |

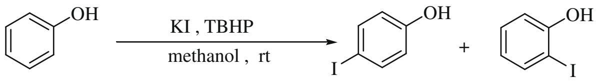
[a] Reaction conditions: phenyl acetylene (1 mmol), solvent (3 mL), 6 h, rt.
[b] Conversion based on GC. Selectivity mentioned in parentheses.
[c] 1,2-Diiodo-vinylbenzene was the major product (72% selectivity).

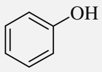
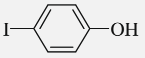
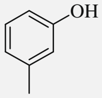
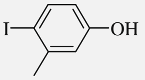
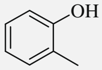
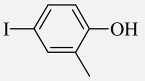
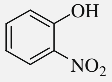
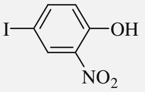
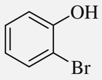
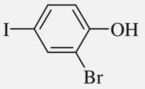
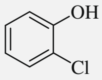
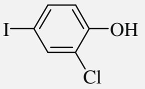
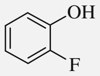
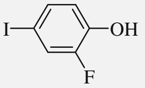
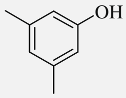
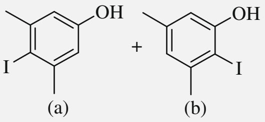
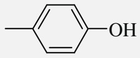
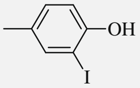
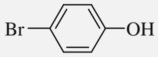
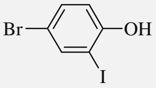
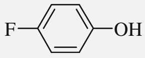
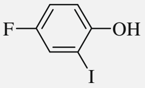
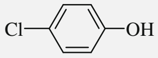
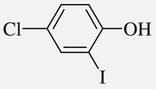
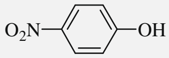
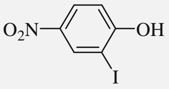
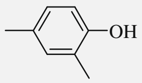
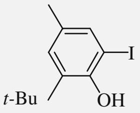
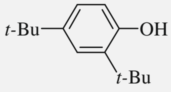
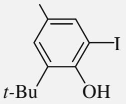
**Table 2**
Synthesis of 1-iodoalkynes using KI-TBHP[a]

| Entry | Substrate | Product | Yield (%) | |
|---|---|---|---|---|
| | | | GC | Isolated |
| 1 |  |  | 91 | 89 |
| 2 |  |  | 90 | 88 |
| 3 |  |  | 91 | 89 |
| 4 |  |  | 85 | 83 |
| 5 |  |  | 90 | 89 |
| 6 |  |  | 80 | 78 |
| 7 |  |  | 65 | 63 |
| 8 |  |  | 66 | 64 |
| 9 |  |  | 63 | 62 |
| 10 |  |  | 78 | 77 |
| 11 |  |  | 83 | 81 |
| 12 |  |  | 98 | 95 |
| 13 |  |  | 98 | 97 |
| 14 |  |  | 80 | 79 |
| 15 |  |  | 65 | 63 |
| 16 |  |  | 81 | 79 |
| 17 |  |  | 68 | 66 |

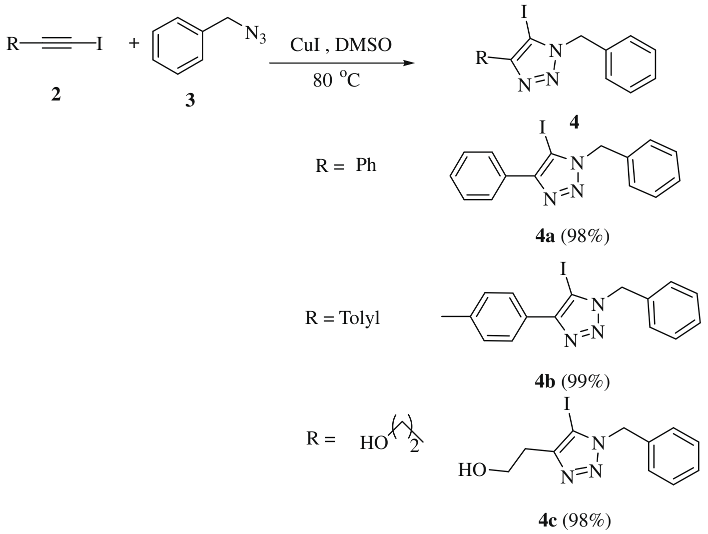
[a] Reaction conditions: alkyne (1 mmol), KI (1.1 mmol), TBHP (1.5 mmol), $CH_3OH$ (3 mL), 6 h at rt.

**Table 3**
Iodination of phenols[a]



| Entry | Substrate | Product | Yield (%) | |
|---|---|---|---|---|
| | | | GC | Isolated |
| 1 |  |  | 80 | 78 |
| 2 |  |  | 71 | 69 |
| 3 |  |  | 82 | 80 |
| 4 |  |  | 78 | 76 |
| 5 |  |  | 82 | 80 |
| 6 |  |  | 89 | 87 |
| 7 |  |  | 93 | 92 |
| 8 |  |  | *a* = 53<br>*b* = 22 | *a* = 51<br>*b* = 21 |
| 9 |  |  | 72 | 71 |
| 10 |  |  | 58 | 55 |
| 11 |  |  | 60 | 59 |
| 12 |  |  | 66 | 65 |
| 13 |  |  | 66 | 64 |
| 14 |  |  | 66 | 65 |
| 15 |  |  | 90 | 88 |

[a] Reaction conditions: phenol (1 mmol), KI (1.1 mmol), TBHP (1.5 mmol), $CH_3OH$ (3 mL), 8 h at rt.



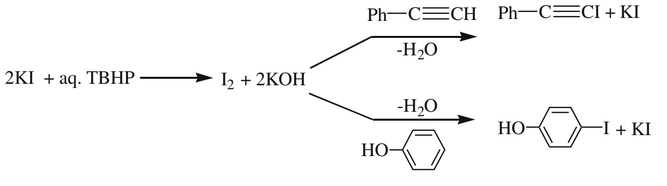
**Scheme 1.** Synthesis of 5-iodo-1,4-disubstituted-1,2,3-triazoles.

To explore the generality and scope of the reaction, the reaction was carried out with various aromatic and aliphatic alkynes under the optimized reaction condition and the results are shown in Table 2.[19] The yields varied from good to excellent for aromatic alkynes. Generally aromatic alkynes having electron-donating groups gave excellent yields (Table 2, entries 1–5). Aromatic alkynes with electron-withdrawing substituents in *ortho* position gave the desired 1-iodoalkynes in moderate yields (Table 2, entries 6 and 7). The reaction proceeds well even with alkynes having different functional groups like alcohol and ether with moderate yields (Table 2, entries 8 and 9). When a hetero-aromatic alkyne was taken as the substrate (2-ethynylpyridine), the yield was good and gave 77% of the desired product (Table 2, entry 10). The yields were excellent, when iodination was carried out with aliphatic alkynes having alcohol moiety (Table 2, entries 11–14). Simple aliphatic alkynes gave moderate yields (Table 2, entries 15–17).

To widen the scope of this methodology, we have applied the same protocol for the iodination of phenols and the results are shown in Table 3.[20] Good to excellent yields were observed with both phenols having electron-withdrawing groups and electron-donating substrates. Usually, iodination takes place at *para*-position. But when a substituent was present at *para*-position, iodo substitution occurs at *ortho* position.

The synthetic utility of 1-iodoalkynes was tested by carrying out the 1,3-dipolar cyclo-addition between 1-iodoalkynes and benzyl azide resulting in 5-iodo-1,4-disubstituted-1,2,3-triazoles in very good yields (Scheme 1).[21]

On the basis of the above-mentioned results, we tentatively propose the mechanism as shown in Scheme 2. In the first step TBHP oxidizes the potassium iodide to generate molecular iodine and base, which subsequently iodinates phenylacetylene and phenols. This hypothesis was further confirmed by performing the reaction with iodine under alkaline conditions. For example, the reaction with phenylacetylene, iodine and base ($K_2CO_3$) in 1:1:1 ratio led to 85% of the desired product. On the other hand, 45% of the desired product was observed with 1:0.5:1 ratio of phenylacetylene, iodine, and base. Similarly the reaction with phenylacetylene, iodine, and KOH provided 62% of the desired product. This clearly demonstrates that under the present oxidative conditions, the generated KI is oxidized to iodine leading to complete consumption of iodide, thus accounting for 100% atom-economy of iodide.



**Scheme 2.** Plausible reaction mechanism.

In conclusion, we have developed an efficient method for the synthesis of 1-iodoalkynes and iodophenols with KI and TBHP. This method does not require the combination of a metal and base. The synthetic utility of 1-iodoalkynes has been tested for the preparation of triazoles.

## Acknowledgment

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## Supplementary data

Supplementary data (general experimental methods, GC–MS and $^1$H NMR) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.02.074.

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19. *General procedure for synthesis of 1-iodoalkynes:* To a solution of alkyne (1.0 mmol), potassium iodide (1.1 mmol), in methanol (3 mL) was added 70% aqueous TBHP (1.5 mmol) dropwise over a period of 30 min and stirred at room temperature. Progress of the reaction was monitored by TLC and the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$, washed with brine, extracted with ethyl acetate, and dried with anhydrous $Na_2SO_4$. Removal of the solvent under vacuum afforded the crude product, which was purified by column chromatography by using a hexane/ethyl acetate mixture and analyzed by $^1$H NMR spectroscopy, gas chromatography, and GC–MS.
20. *General procedure for synthesis of iodophenols:* To a solution of phenol (1.0 mmol), potassium iodide (1.1 mmol), in methanol (3 mL) was added 70% aqueous TBHP (1.5 mmol) dropwise over a period of 30 min and stirred at room temp. Progress of the reaction was monitored by TLC and the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$, washed with brine, extracted with ethyl acetate, and dried with anhydrous $Na_2SO_4$. Removal of the solvent under vacuum afforded the crude product, which was purified by column chromatography by using a hexane/ethyl acetate mixture and analyzed by $^1$H NMR spectroscopy, gas chromatography, and GC–MS.
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