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Metal-free regioselective hydrobromination of alkynes through C—H/C—Br activation

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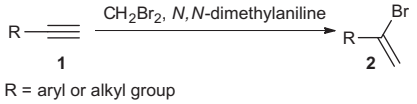
ABSTRACT

A metal-free regioselective hydrobromination of alkynes has been developed to provide the Markovnikov-type vinyl bromides in good yields using dibromomethane/*N*,*N*-dimethylaniline as in-situ 'HBr' source. This protocol also represents an elegant example of the activation of sp^2 C—H and C—Br bonds in one pot, in which 'HBr' is generated and transferred under mild metal-free conditions. *D*-incorporated experiments were employed to investigate the reaction mechanism and a plausible reaction path was proposed.

Introduction

Vinyl bromides play an important role in organic synthesis. They often emerge as versatile substrates in a variety of chemical transformations.[1–4] Conventional procedures for the preparation of these compounds depend on the addition of HBr gas to alkynes, however, the direct use of toxic and corrosive HBr gas hinders their applications in synthetic processes.[5] To avoid experimental hazard, many efforts have been made to develop in-situ 'HBr' systems in place of HBr gas for the synthesis of vinyl bromides using non- or low toxicity/causticity and easily-handled liquids or solids.[6–9] In the year 2003, Weiss reported an efficient system for the hydrobromination of alkynes using quaternary ammonium bromide and trifluoroacetic acid.[6] Subsequently, Thongsornkleeb and co-workers utilized LiBr-TMSCl-TEAB to prepare vinyl bromides.[7] The notable recent advancement was achieved by Hoveyda and co-workers, they developed a Ni-catalyzed hydrobromination of alkynes using *N*-bromosuccinimide and diisobutylaluminum hydride as in-situ 'HBr' source, which was smoothly performed to produce vinyl bromides in high yields with high α-selectivity (95% to >98%).[8] Despite those advances, highly selective and metal-free synthetic methods to give 2-bromo-1-alkenes of great synthetic importance are still desirable.



1 2 (1)

R = aryl or alkyl group

Herein, we report a novel alternative procedure for the synthesis of vinyl bromides employing CH_2Br_2/*N*,*N*-dimethylaniline as in-situ 'HBr' source (Eq. 1). This protocol also represents an elegant example of combining successfully C—H bond activation, C—Br bond cleavage, and hydrobromination of alkynes, in which the in-situ 'HBr' is generated and transferred under metal-free conditions. To the best of our knowledge, there is no precedent for C—H bond and C—Br bond cleavage under metal-free conditions to synthesize vinyl bromides.

Results and discussion

During studies on the three-component coupling reaction of phenylacetylene, dichloromethane, and *N*,*N*-dimethylaniline to produce propargylamines,[10] we accidentally found the formation of (1-bromovinyl)benzene **2a** via hydrobromination of alkynes using CH_2Br_2 instead of CH_2Cl_2 in the absence of silver catalyst. For example, under N_2 atmosphere, 0.5 mmol of phenylacetylene reacted with 0.5 mmol of *N*,*N*-dimethylaniline and 0.5 mmol CH_2Br_2 at 120 °C for 12 h, the product (1-bromovinyl)benzene **2a** was produced in 10% yield (Table 1, entry 1). To improve the yield, amounts of *N*,*N*-dimethylaniline and CH_2Br_2 were screened (Table 1, entries 2–4). When 0.5 mmol of phenylacetylene, 1.5 mmol of *N*,*N*-dimethylaniline, and 2.5 mmol of CH_2Br_2 were loaded, the yield and regioselectivity increased to 91% and 92%, respectively. Interestingly, under air atmosphere, the reaction also gave similar results, indicating that air did not affect the reaction (Table 1, entry 5). Further control experiments showed that this hydrobromination was sensitive to temperature. For example, under similar conditions,

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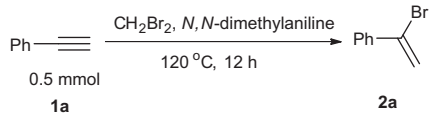
0040-4039/

Table 1
Optimization of reaction conditions[a]



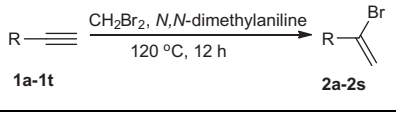
Entry	Amine (mmol)	CH_2Br_2 (mmol)	Yield[b] (%)
1	0.5	0.5	12 (82)
2	1.0	1.0	40 (88)
3	1.5	1.5	60 (90)
4	1.5	2.5	91 (92)
5[c]	1.5	2.5	90 (92)
6[d]	1.5	2.5	85 (90)
7[e]	1.5	2.5	60 (90)
8[f]	1.5	2.5	49 (83)
9[g]	1.5	2.5	60 (85)
10	—	2.5	—

[a] Reaction conditions: phenylacetylene (0.5 mmol), *N*,*N*-dimethylaniline (0.5–1.5 mmol), CH_2Br_2 (0.5–2.5 mmol), N_2 atmosphere, 120 °C, 12 h, 10 mL schlenk tube.
[b] GC yield (α-selectivity based on GC in parentheses).
[c] Under air atmosphere.
[d] 130 °C.
[e] 100 °C.
[f] DMF as solvent.
[g] Dioxane as solvent.

2a was generated in 72% yield at 130 °C and 60% yield at 100 °C, respectively (Table 1, entries 6 and 7). The addition of solvents did not improve the efficiency of the hydrobromination, instead leading to lower conversion and yield (Table 1, entries 4, 8 and 9). It should be noted that aromatic amine was essential, and the hydrobromination of alkynes did not take place at all in the absence of *N*,*N*-dimethylaniline (Table 1, entry 10).

Then, the scope of substrates was extended to various alkynes under the optimized reaction conditions and the results are compiled in Table 2. Both aromatic terminal alkynes and aliphatic terminal alkynes were active in this reaction, giving the corresponding Markovnikov-type vinyl bromides in high yields with high regioselectivity. It is noted that this hydrobromination of alkynes features high functional group tolerance and lots of valuable functional groups such as hydroxy (Table 2, entry 6), ester (Table 2, entry 7), bromo (Table 2, entry 9), chloro (Table 2, entry 10), and nitro (Table 2, entry 11) were all compatible in the present reaction system. Aromatic alkynes bearing electron-donating groups served as efficient substrates under the present reaction condition and the corresponding products vinyl bromines were produced with high regioselectivity (Table 2, entries 2–7). Especially, the aromatic alkyne bearing a hydroxyl group, which would be a potential organic intermediate for medicine,[4j–l] also underwent bromination smoothly with the in-situ 'HBr' to give the corresponding Markovnikov-type product **2f** in high yield (Table 2, entry 6). However, the reaction of 4-ethynylaniline **1h** with the combination of CH_2Br_2/*N*,*N*-dimethylaniline does not take place under similar reaction conditions, which perhaps is ascribed to the strong alkalinity of the amino group (Table 2, entry 8). Electron-withdrawing substituted aromatic alkynes were also easily converted to the corresponding Markovnikov products under the present conditions (Table 2, entries 9–11). In addition to aromatic alkynes, hydrobromination of the aliphatic alkynes **1l**–**1q** also took place under similar reaction conditions, providing the corresponding Markovnikov-type adducts in good yields (Table 2, entries 12–17). When the aliphatic alkyne ethynylcyclohexane **1o** was used as substrate, the hydrobromination took place smoothly, giving the corresponding derivative **2n** in good yield (Table 2, entry 15). Moreover, ester was well-tolerated

Table 2
Substrate scope of alkyne[a]



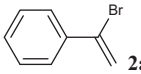
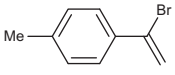
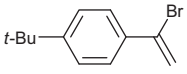
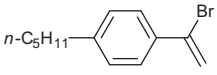
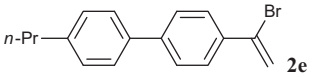
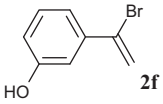
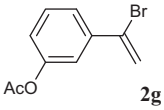
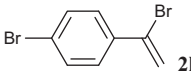
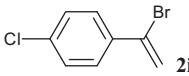
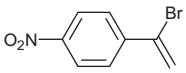
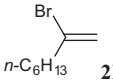
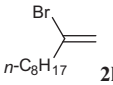
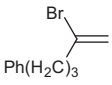
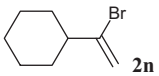
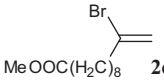
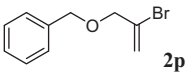
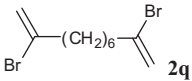
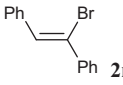
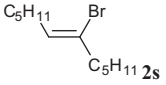
Entry	Alkyne	Product	Yield[b] (%)
1	**1a**	 **2a**	85 (92)
2	**1b**	 **2b**	83 (94)
3	**1c**	 **2c**	88 (95)
4	**1d**	 **2d**	88 (98)
5	**1e**	 **2e**	79 (88)
6	**1f**	 **2f**	82 (95)
7	**1g**	 **2g**	81 (93)
8	**1h**	—	—
9	**1i**	 **2h**	75 (86)
10	**1j**	 **2i**	76 (86)
11	**1k**	 **2j**	76 (83)
12	**1l**	 **2k**	83 (90)
13	**1m**	 **2l**	85 (91)
14	**1n**	 **2m**	81 (91)
15	**1o**	 **2n**	80 (90)
16	**1p**	 **2o**	82 (91)
17	**1q**	 **2p**	71(90)
18	**1r**	 **2q**	86 (92)
19	**1s**	 **2r**	96 (>99)

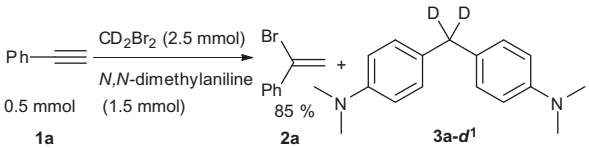
Table 2 (*continued*)

Entry	Alkyne	Product	Yield[b] (%)
20	**1t**	 **2s**	95 (>99)

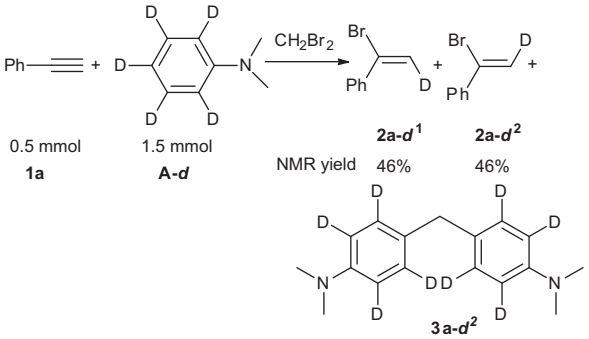
[a] Reaction conditions: alkyne (0.5 mmol), CH_2Br_2 (2.5 mmol), *N*,*N*-dimethylaniline (1.5 mmol), air atmosphere, 120 °C, 12 h.
[b] Isolated yield (α-selectivity based on GC in parentheses).

in this reaction system exemplified by terminal alkynes **1p**, which were readily converted to the corresponding Markovnikov-type **2o** (Table 2, entry 16). The reaction of benzyl propargyl ether **1q** with the combination of CH_2Br_2 and *N*,*N*-dimethylaniline also took place smoothly to furnish the desired product **2p** in 71% yield (Table 2, entry 17). Interestingly, two bromides could be introduced into alkyne one pot in the present system. For example, using diynes **1r** as substrate, the corresponding divinylbromides **2q** were generated efficiently (Table 2, entry 18). Besides, internal alkynes were good substrates for this hydrobromination. When diphenylacetylene and 6-dodecyne were loaded, thermodynamically stable (*Z*)-(1-bromoethene-1,2-diyl)dibenzene **2r** and (*Z*)-6-bromododec-6-ene **2s** were obtained quantitatively and stereoselectively (Table 2, entries 19 and 20).

In an effort to gain some information on the mechanism for this hydrobromination of alkynes, especially for the 'HBr' source, several control reactions were performed. At first, phenylacetylene was allowed to react with CD_2Br_2 and *N*,*N*-dimethylaniline, ^1H NMR measurement clearly showed that CD_2 unit was incorporated into 4,4′-deuteriomethylenebis (*N*,*N*-dimethylaniline) **3a**–***d*¹** (Eq. 2) (more information see SI) and deuterated **2a** was not detected at all.[11] This result suggested that vinyl protons in the vinyl bromide molecules did not originate from CD_2Br_2. Meanwhile, the reaction of phenylacetylene with CH_2Br_2 and fully phenyl-deuterated *N*,*N*-dimethylaniline was carried out. As followed by the NMR technique, the deuterated vinyl bromides **2a**–***d*¹** and **2a**–***d*²** were generated in 85% yields with almost 1:1 ratio, and the deuterated compounds **3a**–***d*²** were produced quantitatively (Eq. 3). Thus, the vinyl protons in the vinyl bromide molecules would derive from *N*,*N*-dimethylaniline other than dibromomethane. Besides, the reaction can be blocked by the addition of radical scavenger 2,2,6,6-tetramethylpiperidinyloxy (TEMPO), indicating that the hydrobromination reaction perhaps involves a radical reaction pathway.



(2)

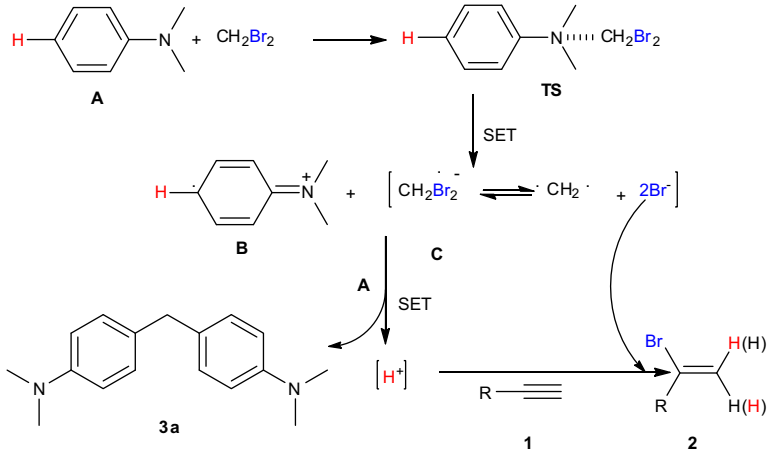


(3)

Based on the present results and the reported literatures,[12] a possible mechanism for the hydrobromination of alkynes is proposed (Scheme 1). *N*,*N*-dimethylaniline **A** firstly coordinates with CH_2Br_2 to generate active transition state **TS**, in which the *para*-sp^2 C—H bond of the amino group is activated. Subsequently, radicals **B** and **C** are formed from active transition state **TS** through single electron transfer (SET).[12] Then bromine anion is produced via C—Br bond cleavage of radical **C**. Followed by another SET and deprotonation process, the coupling product **3a** is produced (the mechanism for the synthesis of **3a** see SI). The released proton and bromine anion are trapped by alkynes **1**, leading to the formation of Markovnikov-type vinyl bromides **2**.

Conclusions

In summary, we have developed a novel regioselective hydrobromination of alkynes to give Markovnikov-type vinyl bromides in good yields. This method provides a simple way to prepare useful vinyl bromides, and represents an elegant example of the activation of both sp^2 C—H bond and C—Br bond in one pot, in which 'HBr' is generated in situ and transferred under metal-free conditions. It also has many advantages in terms of convenient operation, inexpensive and commercially available material, safe, and lowly toxic Br source.



Scheme 1. Plausible mechanism for the hydrobromination of alkynes with *N*,*N*-dimethylaniline and CH_2Br_2.

Experimental section

Typical procedure: Terminal alkynes (0.5 mmol), dibromomethane (2.5 mmol), and *N*,*N*-dimethylaniline (1.5 mmol) were placed in 10 mL Schlenk tube, then stirred at 120 °C for 12 h. After completion of the reaction, the mixture was cooled to room temperature, washed with saturated Na_2CO_3 solution. The crude product extracted three times with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel and eluted with petroleum ether to afford the analytically pure products.

Acknowledgments

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.06.070.

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