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Metal-free hydration of aromatic haloalkynes to α-halomethyl ketones

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ABSTRACT

A highly regioselective and efficient metal-free hydration of aromatic haloalkynes to α-halomethyl ketones using cheap tetrafluoroboric acid as catalyst is described. The protocol is conducted under convenient conditions and affords products in good to excellent yields, with broad substrate scope, including a variety of aromatic alkynyl chlorides, alkynyl bromides, and alkynyl iodides.

α-Halomethyl ketones are one kind of the most important intermediates and versatile building blocks in organic synthesis, and their high reactivity makes them easily convert into various of useful compounds.[1] Moreover, their derivatives are widely represented in many natural products and biologically active molecules.[2] α-Halomethyl ketones are commonly prepared from olefins,[3] ketones, and their derivatives with different halogen-donating agents.[4] However, most of the reactions suffered from one or more drawbacks, such as harsh reactions, hazardous reagents, nonregiospecific reaction, and overhalogenation.

On the other hand, great achievements have been made for the synthesis of ketones through catalyzed hydration of alkynes.[5] In sharp contrast, only few examples have been developed for the hydration of 1-haloalkynes to give α-halomethyl ketones. In a pioneering work, He and co-workers described a gold-catalyzed of 1-bromoalkynes and 1-chloroalkynes to generate the corresponding α-haloketones (Scheme 1, a).[6] In 2014, Chen and Liu reported a AgF/TFA catalyzed hydration of 1-bromoalkynes and 1-chloroalkynes to the α-halomethyl ketones.[7] In 2016, He's group developed a $Cu(OAc)_2$/TFA catalyzed hydration of 1-haloalkynes.[8] In addition, Xiao's group also reported a similar transformation through $In(OAc)_3$/HOAc catalytic system.[9] Obviously, these approaches required transition-metal catalysts with or without acidic solvent, which limited their application (Scheme 1, b). Very recently, Li's group reported a mild protocol for alkyne hydration under metal-free conditions.[10] Inspired by the work and previous transformation, here we present the first Brønsted acid catalyzed hydration of 1-haloalkynes to the corresponding α-halomethyl ketones in trifluoroethanol solvent (Scheme 1, c).

We began our study by screening the reaction between (bromoethynyl)benzene **1h** and water to obtain the optimal reaction conditions. As shown in Table 1, firstly trifluoroethanol was chosen as the reaction solvent, and different acids were tried as catalyst. Both acetic acid and trifluoroacetic acid only gave the product in trace yield (Table 1, entries 1 and 2). We were pleased to find that trifluoromethanesulfonic acid can generate **2h** in 35% yield, a portion of vinyl trifluoromethanesulfinate was detected except the corresponding product and the raw material with GC–MS analysis, this showed that trifluoromethanesulfonic acid can proceed electrophilic addition with haloalkyne (Table 1, entry 3). The yield can be increased to 97% when the reaction time was extended to 24 h, we speculated that it is advantageous for the hydrolysis of the vinyl trifluoromethanesulfinate intermediate (Table 1, entry 4). To our delight, tetrafluoroboric acid can efficiently catalyze the reaction to produce **2h** in 95% isolated yield (Table 1, entry 5). It should be pointed out that tetrafluoroboric acid cannot be added to triple bond of the haloalkyne for the weak nucleophile activation of tetrafluoroborate anion. The control experiment showed that the catalyst was essential for the reaction (Table 1, entry 6). Then a variety of common solvents were

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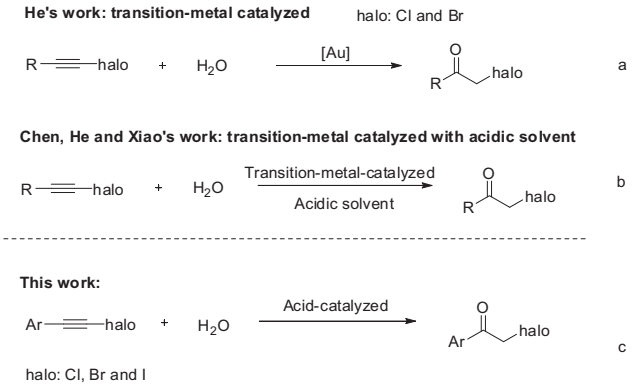


Scheme 1. Catalyzed hydration of 1-haloalkynes.

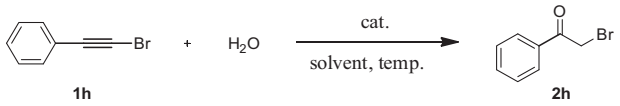
investigated, including polar aprotic and protic solvents, the reaction did not give satisfactory yields (Table 1, entries 7–15). The reaction temperature was essential to the transformation; the yields decreased at lower or higher temperature (Table 1, entries 16 and 17). After some attempts, we considered that the best reaction condition is as follows: **1h** (0.2 mmol), water (1 equiv) with tetrafluoroboric acid (20 mol %, 40% aqueous solution) and 2,2,2-trifluoroethanol (1 mL) at 80 °C for 2 h.

With the optimal reaction conditions in hand, we set out to test the functional group compatibility by utilizing various haloalkynes with different functional groups. As summarized in Table 2, in general aromatic alkynyl chlorides, alkynyl bromides, and alkynyl iodides were all compatible in the standard conditions. Compared to alkynyl bromides and alkynyl iodides, alkynyl chlorides required longer time to finish the transformation. Various aromatic haloalkynes bearing electron-withdrawing or electron-donating groups were all effective for the reaction. For example, alkynyl chlorides bearing the substituents with different nature on the benzene ring afforded the products in good yields (**2a**–**g**). Alkynyl bromides were tolerant with a wide range of functional groups, such as alkyl, methoxy, phenyl, fluoro, chloro, bromo, nitro, cyano, and trifluoromethyl (**2h**–**s**). Thienyl derivative was tolerant in this hydration reaction (**2t**). The haloalkynes bearing a bulky tert-butyl group gave the corresponding α-halomethyl ketones in high yields (**2d**, **2j** and **2w**). The presence of a substituent in the *para* or *meta* position of the phenyl ring does not have a significant effect on the reaction, but the substituents on the *ortho*-positions had some impact on the yields (**2o** and **2z**). It is noteworthy that carbon–halogen bonds were well tolerated and the products containing halogen groups were afforded smoothly. Especially, the aryl chloride or bromide could be further functionalized (**2g**, **2n**–**p** and **3a**). Gratifyingly, the challenging substrates, alkynyl iodides were also suitable in the system (**2u**–**3b**). However, some methyl ketone side products were detected in the transformation which may come from the carbon–iodide bond cleavage of the α-iodomethyl ketone products.

It is well-known that the electrophilic addition of alkynes under acidic conditions usually proceeds vinylic carbocation intermediate. Although the α-chloro vinylic carbocation was used as the model structure for a DFT calculation, the optimized results showed that a allene-type intermediate was rational in the protonation step in our catalytic system (see the Supporting Information). Possible mechanism was proposed and outlined in Scheme 2. First an allene-type intermediate **A** was formed through the electrophilic addition of 1-chloroalkyne **1a** with acid. Then the enol intermediate **B** was generated by successive nucleophilic attack of water and deprotonation process. Finally the α-chloromethyl ketone product **2a** was afforded through keto-enol tautomerism.

In conclusion, we have developed a highly efficient and facile method for the synthesis of α-halomethyl ketones from 1-haloalkynes.[11] The cheap tetrafluoroboric acid was used as catalyst in the transformation, which avoided the precious transition metal as catalyst and strong acid as reaction solvent. A wide range of aromatic alkynyl chlorides, alkynyl bromides and alkynyl iodides were compatible in the standard conditions and afforded the corresponding products in good yields with excellent regioselectivity. The DFT calculation showed that an allene-type intermediate was rational in the protonation step. Further utilization of this procedure and understanding the detailed mechanism will continue in our laboratory.

Table 1
Optimization of reaction conditions for the synthesis of 2-bromo-1-phenylethanone[a]

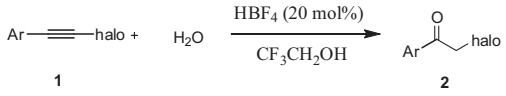


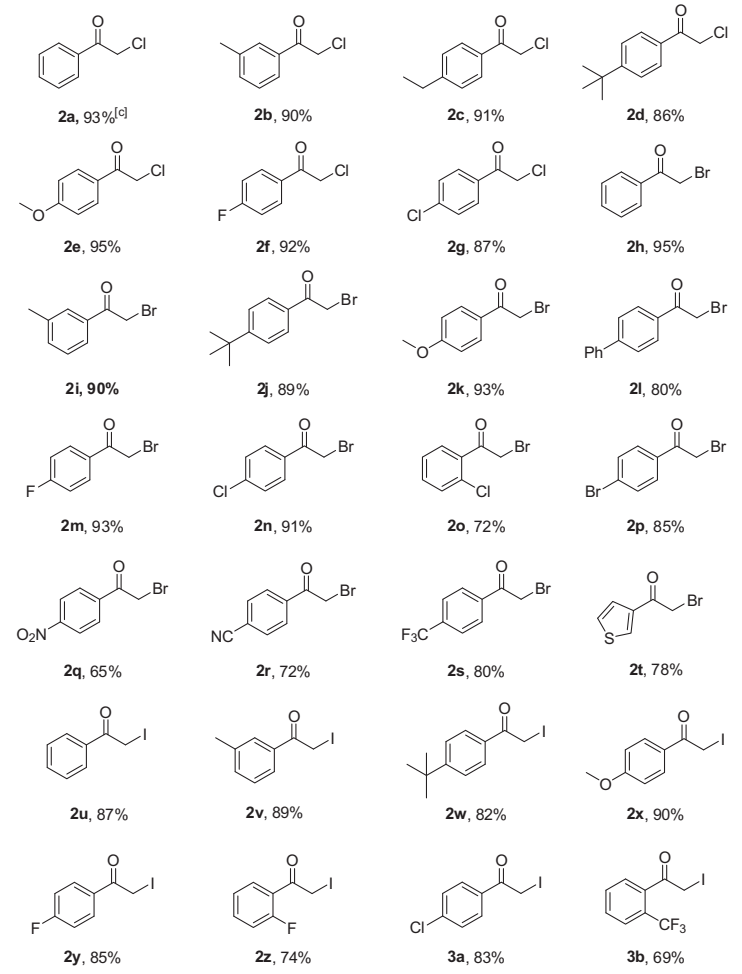
1h **2h**

Entry	Solvent	Acid cat.	Temp	Yield[b] (%)
1	CF_3CH_2OH	CH_3COOH	80	Trace
2	CF_3CH_2OH	CF_3COOH	80	Trace
3	CF_3CH_2OH	CF_3SO_3H	80	35
4[c]	CF_3CH_2OH	CF_3SO_3H	80	97
5	**CF_3CH_2OH**	**HBF_4**	**80**	**98 (95)**
6	CF_3CH_2OH	—	80	n.p.
7	1,4-Dioxane	HBF_4	80	n.p.
8	DMF	HBF_4	80	n.p.
9	DMSO	HBF_4	80	n.p.
10	CH_3CN	HBF_4	80	n.p.
11	PhCl	HBF_4	80	trace
12	Toluene	HBF_4	80	n.p.
13	C_2H_5OH	HBF_4	80	n.p.
14	DCE	HBF_4	80	n.p.
15	THF	HBF_4	80	n.p.
16	CF_3CH_2OH	HBF_4	50	67
17	CF_3CH_2OH	HBF_4	100	86

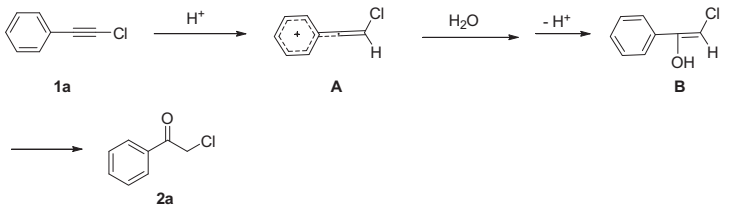
[a] Reactions were carried out using **1h** (0.2 mmol), water (1.0 equiv), solvent (1.0 mL) and catalyst (5 mol %) for 2 h.
[b] Yields were determined by GC analysis with mesitylene as internal standard; isolated yields in brackets.
[c] Reacted for 24 h.

Table 2
Scope of the haloalkyne hydration reaction[a,b]





[c]Reacted for 10 h from **1a**–**1g**.
[a] Reaction conditions: **1** (0.2 mmol), water (1 equiv) tetrafluoroboric acid (20 mol %, 40% aqueous solution) in 2,2,2-trifluoroethanol (1 mL) was stirred at 80 °C for 2 h.
[b] Isolated yield.



Scheme 2. Possible reaction mechanism.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.09.088.

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11. A mixture of haloalkyne (0.2 mmol), tetrafluoroboric acid (20 mol %, 40% aqueous solution) in 2,2,2-trifluoroethanol (1 mL) was stirred at 80 °C for 2 or 10 h. After the reaction was finished, water (5 mL) was added and the solution was extracted with ethyl acetate (3 × 5 mL), the combined extract was dried with anhydrous $MgSO_4$. Solvent was removed, and the residue was separated by column chromatography to give the pure sample.