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Debromination

Selective Debromination of α,α,α-Tribromomethylketones with HBr–H_2O Reductive Catalytic System

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Abstract: A debromination of α,α,α-tribromomethylketones is developed for chemoselective synthesis of α-mono- and α,α-dibromomethylketones with high selectivity under H_2O–HBr reductive conditions. This method offers an efficient and direct way to synthesize α-mono or α,α-dibromomethylketone compounds in high to excellent yields through the process of HBr self-circulation in water.

Introduction

α-Mono- and α,α-dihalomethylketones are important synthetic intermediates, which are widely applied in the construction of α,β-unsaturated ketones or 1,4-diones,[1] ynols,[2] heterocycles,[3] and other small ring compounds.[4] It is also known that α-mono- and α,α-dihalomethylketone skeletons widely occur in natural products, pharmaceuticals, agrochemicals and exhibit interesting biological activities, for example, antifungal, antibacterial, anti-HIV, and antitumor (Figure 1).[1,5,6] In particular, the α-mono- and α,α-dibromomethylketones are of great interest in designing for new drug candidates and agrochemicals because of its high reactivity and selectivity.

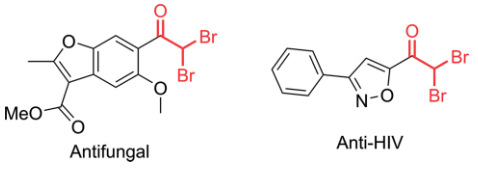
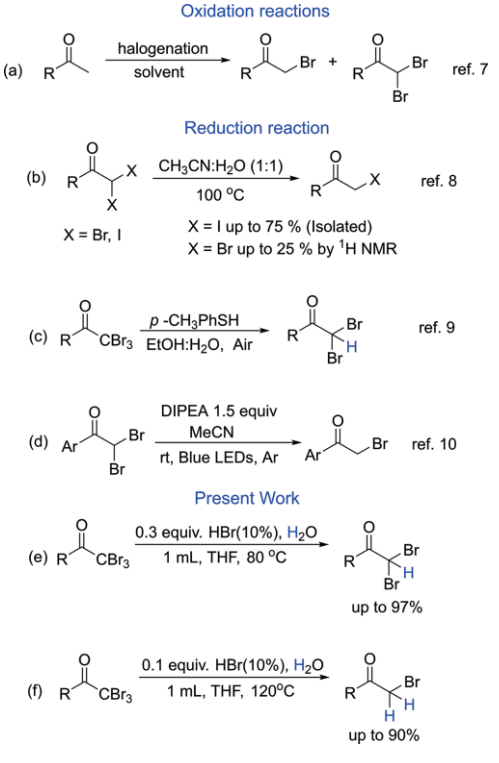


Figure 1. Significant geminal dihalo-compounds.

Traditional preparation of bromides usually induces the bromine atom of molecular bromine, *N*-bromosuccinimide, or other organic bromo-reagents to the substrates (Scheme 1**a**).[7] In contrast, the reductive debromination reactions to obtain monobromo-/dibromo- from tribromo-compounds were less explored. Quite recently, Baire et al. used CH_3CN/H_2O as an unusual reductive system to synthesize α-iodoacetophenone compounds (Scheme 1**b**) from diiodoacetophenones, but the α-bromoacetophenone product was obtained in very low yield in this method.[8] Recently our research group also published related papers (Scheme 1**c**).[9] Oxidative bromination usually resulted in the unselective introduction of one, two or three bromine atoms to the substrates in a single step, causing the subsequent purification difficulties as presented in a lot of synthetic routes. Based on our knowledge, the reductive debromination is also a good method for the preparation of α-mono- and α,α-dibromomethylketones, which can circumvent



Scheme 1. The synthesis of α-mono- or α,α-dibromomethylketones.

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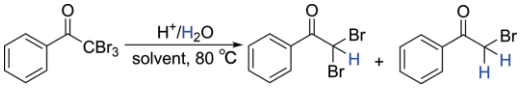
this difficulty and obtain the desired mono- or dibromo compounds with high purity and yield. (Scheme 1**d**).[10] Herein, we report a selective debromination reaction of α,α,α-tribromomethylketones in water with Brønsted acid as a catalyst. In this reaction, α-mono- or α,α-dibromomethylketones can be synthesized selectively in one step by adjusting the amount of HBr and reaction temperature.

Results and Discussion

Our inspiration of debromination of α,α,α-tribromomethylketones originated from the observation of reaction of α,α,α-tribromoacetophenone and acetic acid in acetonitrile. A small amount (5 %, Table 1, entry 3) of compound **2a** was isolated in the reaction. Shifting the acid to benzoic acid, *p*-toluenesulfonic acid, hydrochloric acid did not improve the yield (Table 1, entry 4–6), while diluted sulfuric acid and nitric acid cannot facilitate the occurrence of debromination. Delightedly, hydroiodic acid in acetonitrile improved the yield to 15 % (Table 1, entry 7), while hydrobromic acid in acetonitrile resulted in the selective attainment of α,α-dibromoacetophenone **2a** in a 76 % yield (Table 1, entry 8).Other solvents were also screened for this debromination reaction. It was found that the reaction system also worked smoothly in acetyl acetate, while 1,2-dichloroethane and toluene were detrimental to the reaction (Table 1, entry 9–11). Compound **2a** can be isolated in 55 % yield when the reaction conducted in ethanol (Table 1, entry 12). The optimized yield was achieved when using THF as the solvent (Table 1, entry 13). There were no obviously increases in yield when treated with less amount of HBr (Table 1, entry 14–17). When the catalytic amount of HBr was 10%, the isolated yield reached 82% (Table 1, entry 16), which may immensely reduce the industrial costs and satisfied the mass production. Therefore, from the optimization of the reaction conditions studies, it was observed that the desired product α,α-dibromoacetophenone (**2a**) was obtained in 82 % yield in the presence of 0.3 equivalents 10 % HBr in 1 mL of tetrahydrofuran solvent at 80 °C for 10 h. Furthermore, increasing the reaction temperature while using less amount of hydrobromide, α,α-dibromoacetophenone **2a** would further undergo debromination to be converted into α-bromoacetophenone **3a** (Table 1, entry 18). In the absence of HBr, no reaction occurred (Table 1, entry 20). In a word, by controlling the amount of HBr and reaction temperature, the preparation of dibromoacetophenone or monobromoacetophenone was achieved from the same starting material.

With the optimized conditions in hand, we next investigated the scope of substrates in this reductive systems. This new

Table 1. Optimization of the reaction conditions.[a]

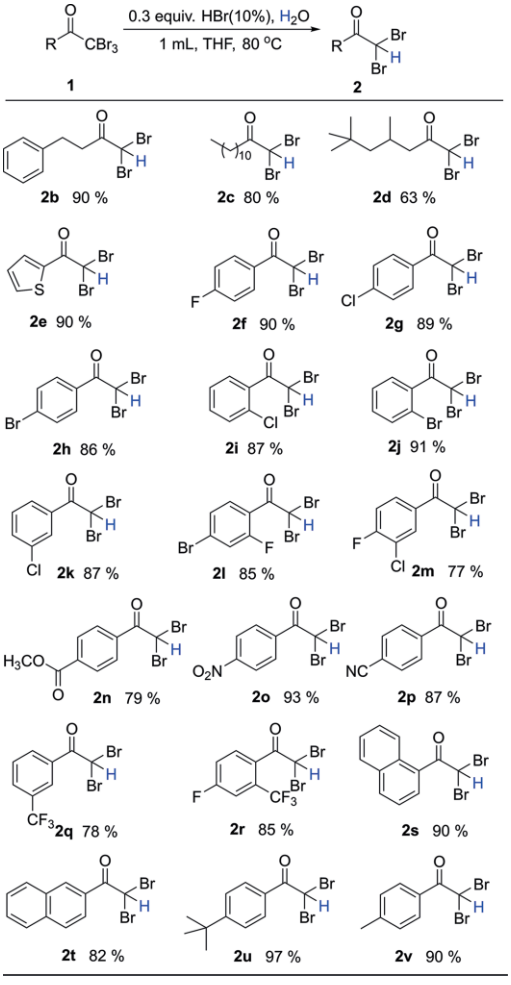


1a **2a** **3a**

Entry	Acid (1 equiv.)	Solvent	**2a** Yield [%][b]	**3a** Yield [%][b]
1	H_2SO_4	CH_3CN	no	no
2	HNO_3	CH_3CN	no	no
3	CH_3COOH	CH_3CN	5	0
4	PhCOOH	CH_3CN	6	0
5	*p*-$CH_3C_6H_4SO_3H$	CH_3CN	5	0
6	HCl	CH_3CN	5	0
7	HI	CH_3CN	15	0
8	HBr	CH_3CN	76	0
9	HBr	AcOEt	82	0
10	HBr	DCE	7	0
11	HBr	toluene	29	0
12	HBr	EtOH	55	0
13	HBr	THF	92	0
14[c]	HBr	THF	81	0
15[d]	HBr	THF	80	0
16[e]	**HBr**	THF	**82**	**0**
17[f]	HBr	THF	70	0
18[g]	**HBr**	THF	**0**	**85**
19[h]	HBr	THF	15	66
20	–	THF	0	0

[a] The reactions of **1a** (0.10 mmol) and H^+ (0.10 mmol) were carried out in 1 mL of solvent at 80 °C for 10 h. [b] Isolated yield. [c] 0.3 equivalents of 40 % HBr. [d] 0.3 equivalents of 20 % HBr. [e] 0.3 equivalents of 10 % HBr. [f] 0.3 equivalents of 5 % HBr. [g] The reaction was stirred at 120 °C for 2 h, 0.1 equivalents of 10 % HBr. [h] The reaction was stirred at 120 °C for 6 h, 0.1 equivalents of 5 % HBr.

Table 2. Synthesis of α,α-dibromomethylkenones from tribromomethylketones.[a,b]



[a] The reactions of **1a** (0.10 mmol) and HBr (0.03 mmol, 10 % HBr) were carried out in 1 mL of THF at 80 °C for 4–12 h. [b] Isolated yield.

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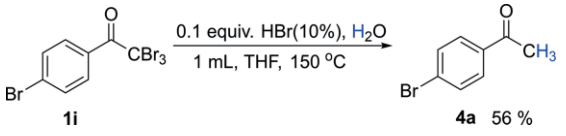
method turned out to be broadly applicable for tribromomethyl ketones, such as aromatic, aliphatic, and heterocyclic ketones, almost all of which could give a good yield (Table 2). Meanwhile, the position of substituent in these substrates usually did not affect the yield.

The electronic and steric effects of different functional groups on the benzene ring of tribromomethylketones **1** were examined (**2a**–**2v**), which revealed that the substituent groups of the benzene in the substrates had no significant effect on the yield of target compounds. In addition, a wide range of functional groups, such as halides (F, Cl, Br), methyl and trifluoromethyl groups, were introduced to different positions of the benzene ring (**2q** and **2v**). Even for strong electron-withdrawing groups on the benzene ring, which could affect the reactive properties of carbonyl groups, this reductive HBr–H_2O route also gave good yields, as observed in the yields of compounds **2f** (90 %), **2j** (91 %), **2s** (90 %), **2u** (97 %) and **2v** (90 %), respectively. Moreover, this method could be applied effectively for aliphatic and heterocyclic substrates, with the good to excellent yields as shown in compounds **2b** (90 %), **2c** (80 %), **2d** (63 %), and **2e** (90 %). Fused aromatic substituted (**2s**–**2t**) substrates could also be transformed into the corresponding products with good yields.

Similar applications to a wide scope of substrates were also observed for α-bromomethylketones (Table 3). The electronic and steric effects of different functional groups on the benzene ring of tribromomethylketones **1** were examined (**3a**–**3p**). Besides, various functional groups, such as halides (F, Cl, Br), cyano, trifluoromethyl, and alkyl groups, were introduced into the benzene ring. This reductive HBr–H_2O route also gave good yields to those substrates, as exampled in the yields of compound **3b** (68 %), **3e** (90 %), **3f** (83 %), **3h** (80 %) and **3p** (90 %), respectively.

In addition, the total debromination of α,α,α-tribromoacetophenone also can be achieved with increased reaction temperature (Scheme 2). It was observed that the target product **4a** (56 %) can be obtained at 150 °C in the presence of 0.1 equivalent 10% HBr.

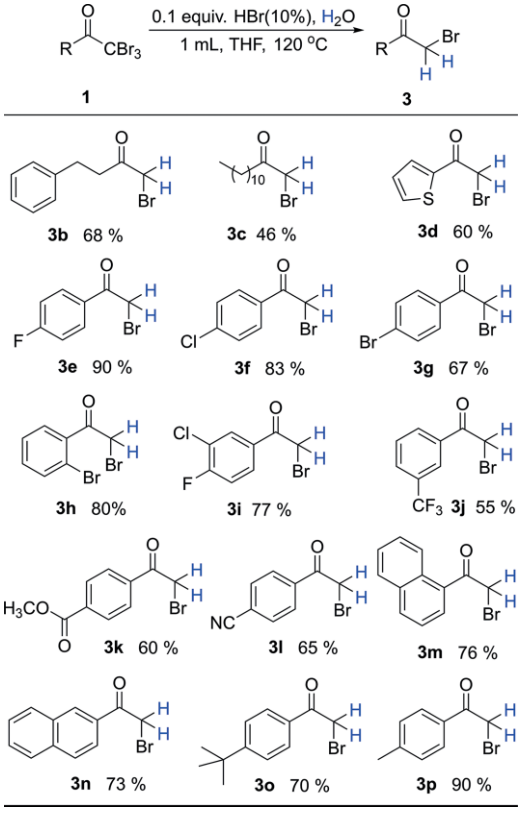


Scheme 2. The total debromination of α,α,α-tribromoacetophenone.

Mechanism

The proposed reaction mechanism is shown in Figure 2. The α,α,α-tribromomethylketone was protonated to provide an intermediate **I** in acidic condition and resulted in a relatively low electron density in α-C. The produced Br^- during the protonation would combine with the bromine atom located in α-C and existed as Br_2, generating an intermediate **II**. The intermediate **II** was isomerized to furnish the target product. It is noteworthy that the Br_2 produced in the reaction system would react well with water to generate HBr, which would be capable of catalyzing another round of reaction. Interestingly, hypobromic acid would also decompose at high temperatures and generate another of HBr, which ensured that a sufficient amount of HBr to support multiple rounds of HBr–H_2O reduction. This hypothesis reaction mechanism also was supported by the deuterated target products which were obtained from a reaction carried out in the presence of DBr/D_2O system (Figure 2), (^{1}H-NMR spectrum of the crude product, see SI).

Table 3. Synthesis of α-monobromomethylkennes from tribromomethylketones.[a,b]



[a] The reactions of **1a** (0.10 mmol) and HBr (0.01 mmol, 10 % HBr) were carried out in 1 mL of THF at 120 °C for 4–12 h. [b] Isolated yield.

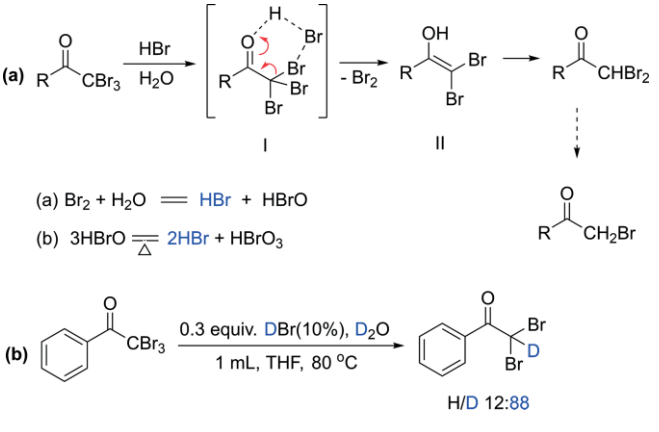


Figure 2. A possible route from α,α,α-tribromomethylketones to α,α-dibromomethylketones.

Conclusion

In summary, in this article, we have developed an efficient debromination reaction of α,α,α-tribromomethylketones with HBr–H_2O as a key reductive catalytic system. In this method, the α-mono or α,α-dibromomethylketones are synthesized selectively by adjusting the amount of HBr and the reaction temperature in one step reaction. This method features easily accessible starting materials, high chemoselectivity, inexpensive reductive reagent, high to excellent yields, and mild reaction conditions.

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Keywords: Debromination · Rational product design · Self-circulation · Green synthesis · Mild reduction

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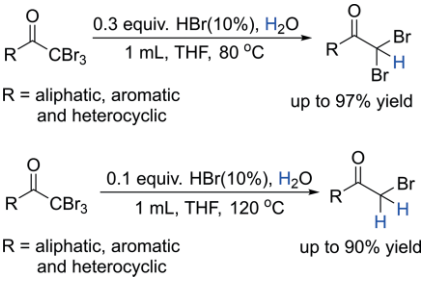

A debrominationreaction to synthesize α-mono- and α,α-dibromomethylketones with high selectivity from α,α,α-tribromomethylketones by the controlling of H_2OHBr reductive conditions was developed.

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