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A convenient procedure for the synthesis of β -haloketones via the tandem halogenation/semipinacol rearrangement of allyl alcohols with NaX.

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An economical, convenient and eco-friendly procedure for the one-pot synthesis of β -haloketones with a α -quaternary carbon center via the tandem halogenation/semipinacol rearrangement of allyl alcohols with NaX (X= Cl, Br, I) in H₂O under open-air conditions has been demonstrated. The catalyst-free process affords various halogenated products in moderate to excellent yields (up to 98%). The features of this procedure include catalystfree, aqueous medium, low-cost sodium halide, open to air, excellent yield and gram scalable preparation.

Introduction

Attentions on the green and sustainable chemistry have driven chemists to adopt environmentally benign reactions and conditions. One of the important influential factors in a reaction is solvent effect, and the organic solvents are widely used in the organic synthesis, but many of them are harmful to the ecosystems or human body¹. Thus, organic reactions in water² have drawn increasing attention of researchers³.

Organohalogen compounds⁴ such as β -haloketones, especially containing an all-carbon α -quaternary carbon center, have showed important synthetic utility⁵ and bioactivity⁶, especially in the context of total synthesis⁷. Thus, great efforts have been made in the construction of these ketones by chemists in the past years. Among these methods, reactions involving semipinacol rearrangement⁸ showed to be a valuable strategy. The general process involves allyl alcohols substrates, electrophilic halogenating reagents in organic solvent with catalysts and/or additive to obtain the β haloketones (Scheme 1, route a). For instance, in 1973, Johnson⁹ reported allyl alcohols reacted with t-BuOCl to give β-chloroketones via semipinacol rearrangement. Such strategy

researchers¹⁰. It is worth mentioning that the group of Martín-Matute¹¹ reported the Ir-catalyzed redox isomerization/halogenation of allylic alcohols. It showed transition metal catalysis may also play a vital role in this field. A breakthrough in this field inducing enantioselectivity on the final products with organocatalysts was developed by Tu¹². The group reported а wonderful enantioselective bromination/semipinacol rearrangement of allylic alcohols by using $(DHQD)_2PYDZ$ and NBS for the construction of chiral β bromoketones with excellent yields and ee value. Afterwards, many great works were reported in the organocatalytic asymmetric synthesis of β -haloketones.¹³ However, these methods suffered some disadvantages

with electrophilic halogen resource was also reported by other

including expensive electrophilic halogenation reagents or catalysts, usage of great amounts of toxic or volatile organic solvents, large excess of additives like strong base or acid, obnoxious smelling reagents, stirring under an inert atmosphere and symmetric α , α -diaryl or dialkyl allylic alcohols substrates. Therefore, a more economical, convenient and eco-friendly procedure for the construction of β -haloketones is still in great demand. What's more, to the best of our knowledge, there exists no example of tandem halogenation/semipinacol rearrangement of allyl alcohol in water, and nucleophilic¹⁴ halogenation reagent for the construction of β -haloketones by semipinacol rearrangement of allyl alcohol was few reported.

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⁺Electronic Supplementary Information (ESI) available: details of the experimental procedure, data, and NMR spectra of all compoundws. See DOI: 10.1039/x0xx000 00x

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Driven by our previous work on the halogenation of aryl compounds,¹⁵ we envisaged that sodium halide/oxidant combination may induce the semipinacol rearrangement of allyl alcohol. And considering the solubility of sodium halide in the reaction process, water may be a good choice.

Herein, we reported such a synthesis of α -quaternary carbon center β -haloketones via tandem halogenation / semipinacol rearrangement of allyl alcohols with sodium halide and PIDA in water without any catalyst.

Results and discussion

Allyl alcohol 1a as a model substrate was used in our beginning investigation. 1a with NaBr and PIDA in 1mL water was stirred at room temperature under N₂, to our great delight, the reaction could procced smoothly to give the desired β -haloketone **3ab** in 75 % yield (Table 1, entry 1). Then several other oxidants were tested in the process, unfortunately, none of them could promote the reaction (Table 1, entries 2-5). To investigate the effect of the reaction atmosphere, the process was performed under the air, and the air almost had no effect on the reaction (Table 1, entry 6). Then we attempted to increase the yield by raising the temperature to 40 $^{\circ}$ C, gratifyingly, the yield could improve to 89 % (Table 1, entry 7). However, the yield was kept when further raising the temperature (Table 1, entry 8). Evaluation of the solvent effect was subsequently carried out, all the tested solvent failed to increase the yield (Table 1, entries 9-13). The main disadvantages of this procedure is related with the use of an external oxidant PIDA in a two-fold excess. When the amount of PIDA was reduced to 1.0 equiv., the yield was reduced greatly from 89% to 70% (Table 1. entry 7 vs entry 14). In order to rich the bromide source of the reaction, we also tried other bromides like KBr or CuBr. The reaction went smoothly to deliver the product in 86% and 80% yield respectively.

| Me | Ph —Ph + H | [O] + Na | Br <u> </u> Sol | <mark>→</mark> vent, T | Br Ph Me Ph |
|------------------------|-----------------------|------------------|-----------------|------------------------|------------------------|
| 1a | | | | | 3ab |
| Entry | [0] | Sol. | T (°C) | Atm. | Yield ^b (%) |
| 1 | PIDA | H ₂ O | RT^{c} | N ₂ | 75 |
| 2 | O ₂ in Air | H ₂ O | RT | Air | NR ^d |
| 3 | tBuO₂H | H ₂ O | RT | N ₂ | NR |
| 4 | H_2O_2 | H ₂ O | RT | N ₂ | NR |
| 5 | $K_2S_2O_8$ | H ₂ O | RT | N ₂ | NR |
| 6 | PIDA | H ₂ O | RT | Air | 75 |
| 7 | PIDA | H ₂ O | 40 | Air | 89 |
| 8 | PIDA | H ₂ O | 50 | Air | 89 |
| 9 | PIDA | THF | 40 | Air | trace |
| 10 | PIDA | DCM | 40 | Air | 70 |
| 11 | PIDA | MeCN | 40 | Air | 63 |
| 12 | PIDA | MeOH | 40 | Air | 73 |
| 13 | PIDA | PhMe | 40 | Air | 66 |
| 14 | PIDA ^e | H ₂ 0 | 40 | Air | 70 |
| 15 ⁷ | PIDA | H ₂ O | 40 | Air | 86 |
| 16 ^{<i>g</i>} | PIDA | H ₂ O | 40 | Air | 80 |

Table 1 Optimization of the reaction conditions.^a

^{*a*} Unless otherwise noted, the reaction was carried out on 0.1 mmol scale in 1 mL solvent with the ratio of **1a** /**[O]/NaBr** = 1.0: 2.0: 4.0 under N₂ or air for 24h. ^{*b*} Isolated yield. ^{*c*} Room temperature. ^{*d*} No reaction. ^{*e*} 1.0 equiv PIDA. ^{*f*} KBr was used a bromide source.

With the aforementioned results in hand, we explored whether NaCl or NaI would procced smoothly in the process. Fortunately, the prospective products were obtained in 78% and 81%, respectively (Table 2). Encouraged by the satisfactory results, we next subjected other symmetric $\alpha \alpha$ diaryl allylic alcohols (1b-d) under the optimized conditions. All the substrates with either electron-deficient or electron-rich aryl groups performed well and give the desired β -haloketones (3ba-3dc) in moderate to excellent yields. Moreover, when cyclic allylic alcohol 1e was tested, it showed excellent tolerance to the process to afford the halogenated products 3ea, 3eb and 3ec in 95%, 98% and 94%, respectively). For unsymmetrical α, α -diaryl allylic alcohol **1f**, it performed well for chlorination and bromination to give 3fa and 3fb in good yields of 83% and 88%, while the iodization gave a complex mixture. Similarly, for substrates 1h and 1i, the brominating products 3hb and 3ib were obtained with 65% and 54% yields, respectively. However, the chlorinating and iodinating products of 1h and 1i were two kinds of rearrangement products. Another kind unsymmetrical allylic alcohol 1g with an aryl and an alkyl substituent, the desired products 3gb and 3gc with exclusive migration of aryl group, was obtained in 89% and 77% yields, respectively. And the non-terminal olefin 1j went smoothly in the bromination to give 3jb with 85% yield, but complex mixture in the chlorination and no reaction in the iodization were observed. In addition, the Et-group substitutional allylic alcohol 1k performed well in the standard condition, the 3ka, 3kb and 3kc were achieved in 82%, 94% and 65% yield, respectively. In generally, as can be seen from Published on 24 April 2018. Downloaded by Fudan University on 24/04/2018 03:42:30.

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our investigation, the bromination/semipinacol rearrangement usually gave better yield than the corresponding chlorination or iodination.

Table 2 Synthesis of β -haloketones from **1** and sodium halide.^{*a*}



^{*a*}Reaction condition: Allyl alcohol **1** (0.1 mmol, 1.0 equiv), PIDA (0.2 mmol, 2.0 equiv), NaX (0.4 mmol, 4.0 equiv), water (1 mL), 40° C, under air. ^{*b*} Isolated yield.

To test the practicality of this strategy, a gram-scale reaction was employed (**Scheme 2**). The target product **3ab** could be obtained in 88% yield (89%, 0.1 mmol).



The synthetic potential and utility of this process was further demonstrated through several transformations by the product **3ab (Scheme 3)**. The substitution of the bromine atom with sodium azide could achieve the product **4** in 75% yield. Similarly, when treated with 4-methylthiophenol, it could generate the product **6** with 88% yield. In addition, it also could be reduced by NaBH₄ to give alcohol **5** in 95 % yield.



Next, we tentatively speculated a mechanism similar to those reported in the literature (Scheme 4).^{13b,13g} The allylic alcohol **1a** would react with the active PhI(X)₂ which is formed from the PhI(OAc)₂ and sodium halide to give the halonium ion intermediate **A** with the concomitant 1,2-migration of the migrating group. Subsequently, the formation of the β -haloketone is accompanied by deprotonation.



Experimental

General procedure for the synthesis of β-haloketones 3

To a 10 mL round-bottom flask equipped with a magnetic stirrer bar, were added **1** (0.1 mmol, 1.0 equiv), PIDA (0.2 mmol, 2.0 equiv) and NaBr (0.4 mmol, 4.0 equiv). Then water (1 mL) was added, and the mixture was then stirred at 40° C. Then the reaction was monitored by TLC and till **1** was consumed up. Afterwards, the reaction mixture was cooled down, quenched with saturated NaHCO₃ (10 mL), followed by extraction with ethyl acetate (3 x 5 mL) and washed with brine, dried over Na₂SO₄, filtered and then concentrated in vacuum. The residue was then purified by column chromatography on silica gel (PE/EA, ~300 mL) to afford the desired product **3**.

Conclusions

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In summary, we have described a low-cost, simple and efficient approach for the construction of β -haloketones containing a α -quaternary carbon center via the halogenation/semipinacol rearrangement of allyl alcohols with NaX (X= Cl, Br, I) in H₂O under open to air without any catalyst or additive. The process afforded the desired β -haloketones in moderate to excellent yields with several advantages including: (1) catalyst- and additive-free; (2) aqueous medium; (3) low cost; (4) open to air. In addition, the synthetic utility of the method could be demonstrated by the gram-scale reaction and multifarious transformations of the product.

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