Reductive Halogenation Reactions: Selective Synthesis of Unsymmetrical α-Haloketones

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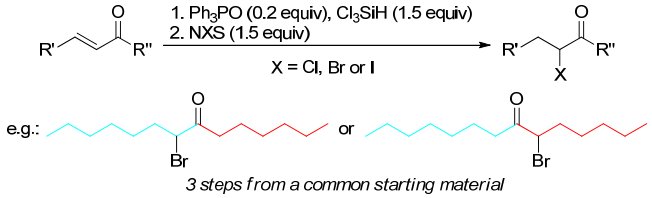
Supporting Information Placeholder

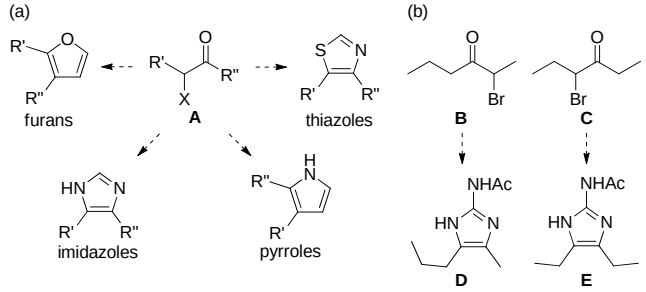


ABSTRACT: A method for the selective synthesis of unsymmetrical α-haloketones has been developed. The key transformation is a triphenylphosphine oxide-catalyzed reductive halogenation of a α,β-unsaturated ketone in which trichlorosilane is the reducing reagent and an *N*-halosuccinimide is the electrophilic halogen source. This method allows for a halogen atom to be installed selectively at either of two very similarly substituted sites adjacent to a ketone group.

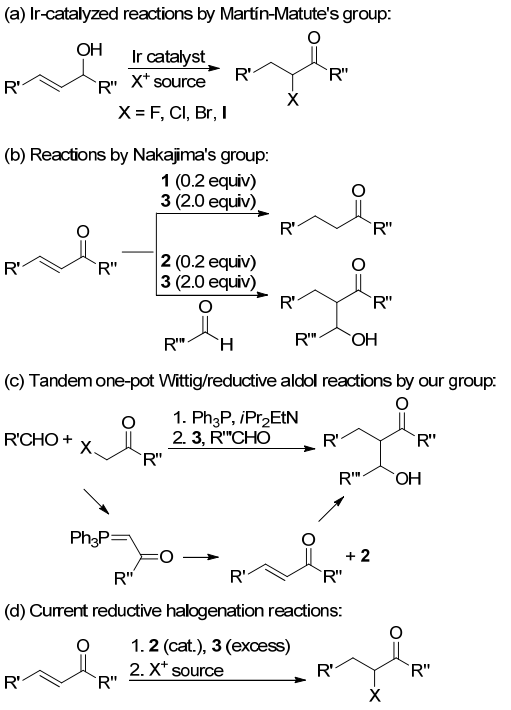
α-Haloketones are versatile building blocks that are useful for the synthesis of a wide range of heterocyclic compounds.[1] For example compounds such as **A** can be converted into furans,[2] imidazoles,[3] pyrroles,[4] thiazoles,[5] and many other structures (Scheme 1a). However, a survey of the literature reveals that in virtually all cases the α-haloketones used for such purposes are derived from ketones that are either symmetrical, such as acetone, or that can only form a enol to one side of the ketone group, such as acetophenone. It seems that the use of α-haloketones derived from unsymmetrical ketones that can tautomerize to form enols on both sides of the ketone group is somewhat rare. This lack of structural diversity of the α-haloketones used severely impacts the range of compounds that can be synthesized from them, and thus medicinal chemistry in general, since many heterocyclic compounds have interesting biological activities. For example, access to either **B** or **C** would allow for the selective synthesis of **D** or **E** (Scheme 1b), both of which have not been previously reported in the literature,[6] despite their rather simple structures. One of the reasons for the current situation could be a lack of simple and general methods for the selective synthesis of unsymmetrical α-haloketones with two enolizable α-positions.[7,8] In this regard, perhaps the Ir-catalyzed isomerization/halogenation reactions of allylic alcohols reported by Martín-Matute and co-workers represents the best such method for the synthesis of these compounds (Scheme 2a), and this has been described in a series of publications only relatively recently.[9]

Against this backdrop, we have been inspired by the work of Nakajima and co-workers who showed that Lewis bases such as hexamethylphosphoramide (HMPA, **1**) and triphenylphosphine oxide (**2**) can catalyse conjugate reduction and reductive aldol reactions of enones using Cl_3SiH (**3**) as the reducing reagent (Scheme 2b).[10] We subsequently built upon this reactivity by using one-pot Wittig reactions, in which a phosphorane was generated in situ, to produce the enone substrates, and used the waste **2** formed in the Wittig reaction directly as the catalyst for the reductive aldol reactions (Scheme 2c).[11] Herein we wish to report an extension of this research where we replaced the aldehyde electrophile of the reductive aldol reactions with an electrophilic halogen source to develop what is to our knowledge the first reductive halogenation method that directly converts α,β–unsaturated ketones into unsymmetrical α-haloketones (Scheme 2d). It should be noted that up to now it seems the concept of reductive halogenation has only been used in the organic chemistry literature to describe the conversion of epoxides[12] and carbonyl functional groups[13] into corresponding alkyl halides. In describing our work, we are using this phrase in a context that is analogous to reductive aldol reactions.[14,15]

Scheme 1. Synthesis of heterocyclic compounds from α-haloketones

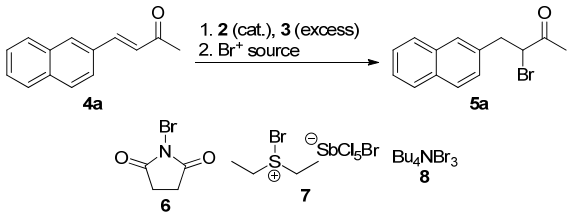


Scheme 2. Literature precedent and reductive halogenation for the synthesis of unsymmetrical α-haloketones



In order to test our hypothesis that an electrophilic halogen source, such as *N*-bromosuccinimide (NBS, **6**), could replace an aldehyde in reductive aldol-like reactions we chose enone **4a**[16] as a test substrate with the aim of converting it into α-bromoketone **5a** (Table 1).[17] Based on our previous research regarding reductive aldol reactions involving the catalyst/reagent combination of **2** and **3** we started our studies using 0.2 equivalents of **2** with 2.0 equivalents of **3** in dry CH_2Cl_2. After 4 hours **6** (1.5 equivalents) was added and the reaction was stirred for 16 hours more. Gratifyingly these reaction conditions afforded the desired product **5a** in very high isolated yield (entry 1). Reducing the amount of **3** to 1.5 equivalents did not affect the obtained yield, but lowering it further resulted in lower yield (entries 2 and 3). Reducing the loading of **2** to 0.1 equivalents also resulted in lower yield (entry 4), so 0.2 equivalents of **2** were used for all future reactions. Replacing **6** with Snyder's reagent **7**[18] did not improve the yield of **5a**, and using **8** resulted in no formation of **5a** (entries 5 and 6). Thus, since **6** is relatively inexpensive, widely available and an easy to dispense solid at room temperature, as are *N*-chlorosuccinimide (NCS, **9**) and *N*-iodosuccinimide (NIS, **10**), we chose to use **6** for further studies. Finally, we assessed the scalability of our method by performing the reductive bromination of **4a** on a 1.0 g (5.1 mmol) scale using the optimized reaction conditions. Gratifyingly **5a** was isolated in 62% yield from this reaction (entry 7).

Table 1. Triphenylphosphine oxide (2)-catalyzed reductive bromination of enone 4a to produce α-bromoketone 5a[a]



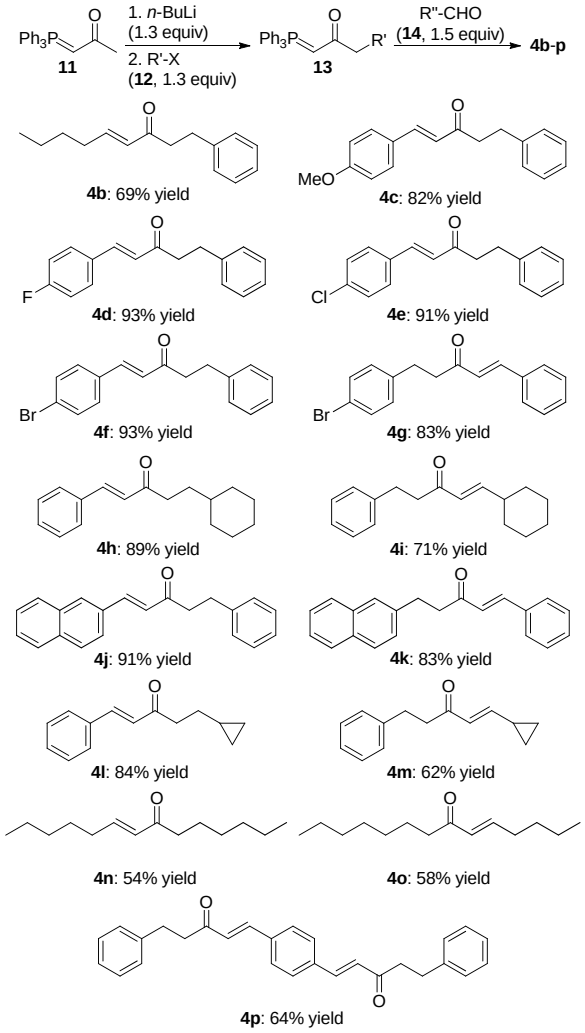
entry	2	3	X+ source	yield[b] (%)
1	0.2 equiv	2.0 equiv	6 (2.0 equiv)	84
2	0.2 equiv	1.5 equiv	6 (1.5 equiv)	85
3	0.2 equiv	1.2 equiv	6 (1.2 equiv)	73
4	0.1 equiv	1.5 equiv	6 (1.5 equiv)	74
5	0.2 equiv	1.5 equiv	7 (1.5 equiv)	67
6	0.2 equiv	1.5 equiv	8 (1.5 equiv)	0
7	0.2 equiv	1.5 equiv	6 (1.5 equiv)	62[c]

[a]Conditions: 2, 3 and 4a (1.0 mmol) in dry CH_2Cl_2 (2 mL) under Ar at rt were stirred for 4 h followed by the addition of 6, 7 or 8 (1.5 mmol) and stirring for 16 h more. [b]Isolated yield. [c]Reaction was performed on a using 5.1 mmol of 4a.

Having validated our hypothesis by showing that reductive bromination of **4a** to form **5a** was possible using a catalyst/reagent combination of **2** and **3** for the reduction and **6** as the electrophilic reagent, we next synthesized enones **4b-p** in two steps from the common starting material **11** (Scheme 3).[17] This was deprotonated, and then alkylated with an alkyl halide (**12**) to generate **13**.[19] Phosphoranes **13** were then reacted in Wittig reactions with aldehydes **14** to generate enones **4b-p**.

Enones **4b-p** were then converted into the corresponding α–bromoketones **5b-p** (Figure 1) using the optimized reaction conditions (Table 1, entry 2). As is readily apparent from the structure of **5b**, when the ketone has two equivalent enolizable α–positions, the bromine substituent can be introduced at one of them selectively, even when the difference between the two sidechains is very minor and remote from the position being functionalized, as in **5c-e**. We even extended this concept by synthesizing pairs of compounds in which the bromine substituent is introduced into either of the similar enolizable α–positions, such as **5f and 5g**, **5h** and **5i**, **5j** and **5k**, **5l** and **5m,** and **5n** and **5o**. In all cases the reductive bromination reaction occurred with high yield (ca. 75-85%). Even a double reductive bromination reaction to produce **5p** was highly efficient. Thus, **5b-p** could all be selectively synthesized in only three steps from phosphorane **11** .

Scheme 3. Synthesis of enone substrates 4b-p



Next we examined the possibility of replacing **6** with **9** and **10** in order to synthesize α–chloroketones **15** and α–iodoketones **16**, respectively (Figure 2). Gratifyingly, we were able to synthesize **15a-d** in high yields, and **16a-b** in moderate yields from the corresponding enones.

Lastly we examined the possibility of performing one-pot, tandem Wittig and reductive halogenation reactions in which the **2** formed as a by-product in the first reaction serves as the catalyst in the second reaction. This concept was first reported by Zhou and co-workers in a range or reactions,[20] and we subsequently extended it to tandem Wittig/reductive aldol reactions (Scheme 2c).[11] Gratifyingly, we were able to generate **4a** in situ by reacting phosphorane **11** with 2-napthaldehyde (**14a**), and converted it directly into either **5a** or **15a** in moderate overall yields in one-pot, three-step reactions (Scheme 4).

With regard to the mechanism of these reductive halogenation reactions, the sum total of our results presented here and including those previously reported regarding reductive aldol reactions[11] and the selective α.β-reduction of conjugated polyunsaturated ketones,[21] supports the idea originally proposed by Nakajima and co-workers[10] that a six-membered cyclic transition state such as **F** may be involved (Scheme 5).

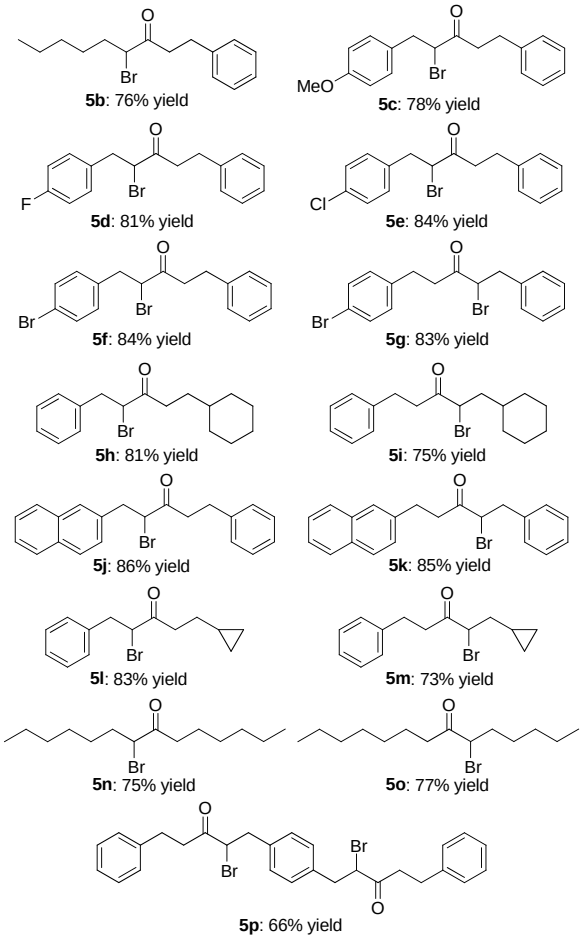


Figure 1. α-Bromoketones synthesized.

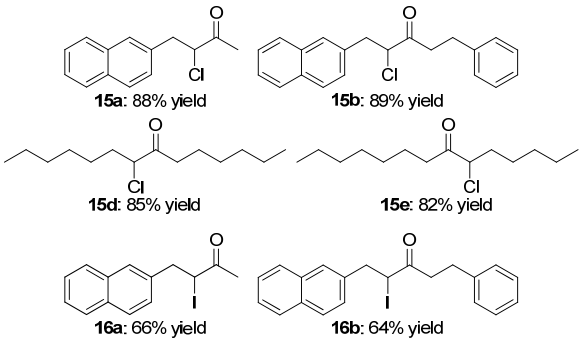
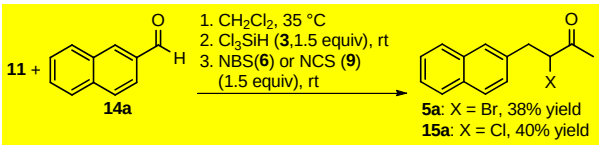
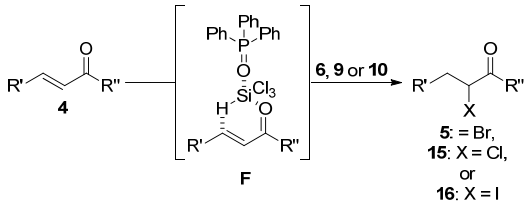


Figure 2. α-Chloro- and α-iodoketones synthesized using NCS (**9**) and NIS (**10**).

Scheme 4. One-pot tandem Wittig/reductive halogenation reactions



Scheme 5. Mechanism of the reductive halogenation reactions



In summary, we have developed a method for the reductive halogenation of enones in reactions that are conceptually akin to reductive aldol reactions and that result in the selective synthesis of unsymmetrical α–haloketones. This method involves a conjugate reduction process involving the catalyst/reagent combination of **2** and **3**. Various electrophilic halogen sources can be used, and α–chloro, α–bromo and α–iodoketones can be synthesized in a few steps from simple building blocks. It is expected that this metal-free method can greatly expand the addressable chemical space of heterocyclic compounds since the products it allows access to are versatile building blocks in this context, and this is the focus of our current efforts. Additionally we are working to identify more efficient catalysts for these reactions that can be used with lower loading levels so as to render this method more amenable for performing large-scale reactions.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Detailed experimental procedures, compound characterization data, NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(6) It is illustrative to note that a Scifinder search of the exact structures of **B** and **C** on July 4, 2019 resulted in only 4 and 6 reports regarding them, respectively. Furthermore, while a search of the exact structures of **D** and **E** resulted in no results found, substructure searches of these same structures resulted in 660 and 339 results found, respectively.

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(17) See Supporting Information for detailed experimental procedures.

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