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Reactions of tertiary propargyl alcohols with sodium halides under oxidative conditions

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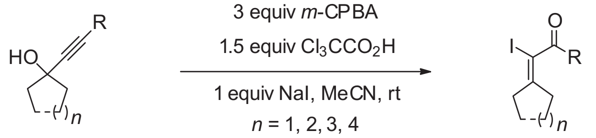
ABSTRACT

The study of the reactions of tertiary propargyl alcohols with sodium halides under oxidative conditions is presented. With sodium iodide, α-iodoenones were formed, however, with sodium bromide or chloride the α-haloenones were only formed in low yields under anhydrous conditions. Conversely, upon addition of water to the reaction mixtures, α,α-dibromoketones and α,α-dichloroketones were formed in good yields, but α,α-diiodoketones were not observed.

A wide range of halogenation reactions can be readily achieved through treatment of the substrate with the elemental halogen, that is iodine, bromine, chlorine, or fluorine,[1] or by addition of reagents such as *N*-iodo-, *N*-bromo-, or *N*-chlorosuccinimide.[2] These reactants work very well in many cases, but each has drawbacks such as toxicity, corrosiveness, ease-of-use, relative high cost, low atom efficiency, or supply issues. Consequently, the ability to use cheap, readily available, and easy-to-handle inorganic halides in electrophilic halogenation reactions is a useful addition to the synthetic tool box and several research groups have reported examples of this recently.[3]

Substituted propargyl alcohols are readily prepared from aldehydes/ketones and terminal alkynes and are useful and versatile synthetic intermediates.[4] We previously reported that tertiary propargyl alcohols **1** undergo rearrangement to α-iodoenones **2** upon treatment with sodium iodide under oxidative conditions (Scheme 1).[5] We postulated that under acidic conditions, hypoiodous acid was generated which induced the rearrangement to occur through iodination of the alkyne.

We were interested in studying whether this rearrangement process would occur with sodium bromide or sodium chloride, in place of sodium iodide, under similar conditions to those we previously identified. Carrying out the reaction with NaI and *m*-chloroperbenzoic acid in the presence of trichloroacetic acid in acetonitrile led to the expected α-iodoenone **2a** in 75% yield (Table 1, entry 1). Replacing NaI with NaBr led to low conversion to the analogous α-bromoenone **3a** and a small amount of another compound, which was subsequently identified as α,α-dibromoketone **4a** (entry 2). Li et al. reported a similar process to form α,α-dihaloketones catalyzed by $FeCl_3$ with either *N*-bromosuccinimide or *N*-chlorosuccinimide as the halogen source.[6] At this point, a systematic study of the reaction conditions was initiated: varying the oxidant identified Oxone to be superior (entry 3), while the use of other oxidants, solvents, and acids led to inferior results (entries 4–15). Unfortunately, a pure sample of **3a** could not be obtained by chromatography as impurities including **4a** could not be fully separated. We envisaged that adventitious water was responsible for the formation of compound **4**, however, all attempts to eliminate water from the reaction mixture to preclude its formation were unsuccessful. Running the reaction in a 1:1 mixture of acetonitrile and water led to a cleaner reaction, but compound **4** became the sole product in 63% yield (entry 16). Repeating the reaction without the acid successfully yielded the product, however, slightly



1 **2**, 61-85%

Scheme 1. Hypoiodous acid induced rearrangement of propargyl alcohols to α-iodoenones.

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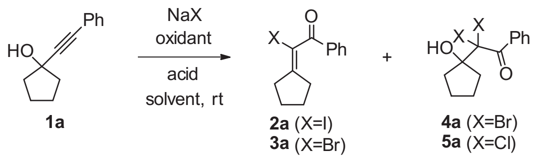
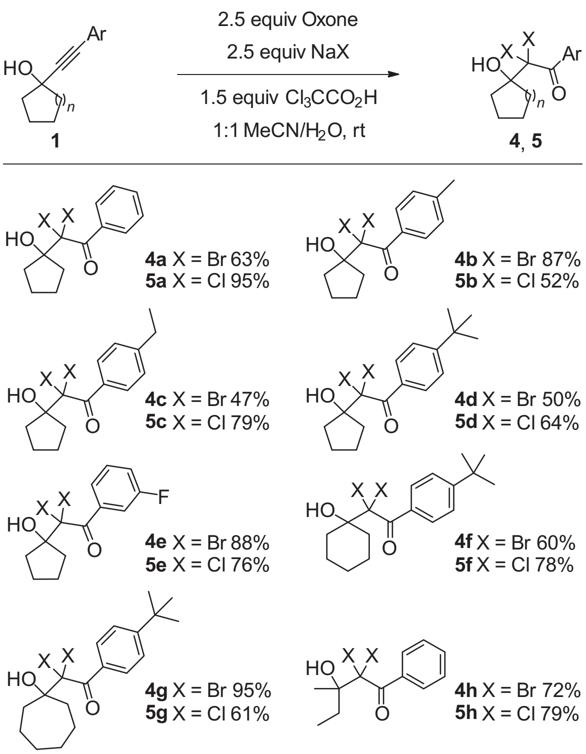
Table 1
Investigation of reaction conditions



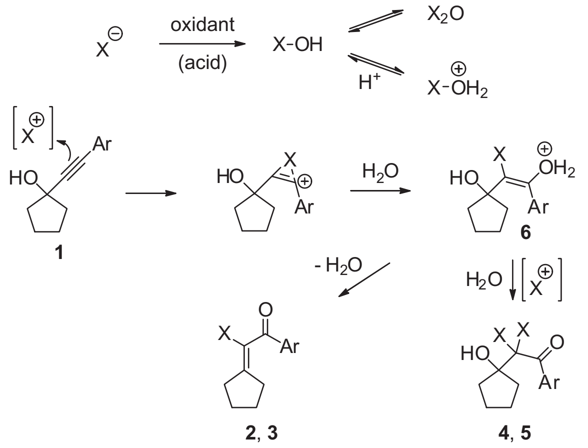
Entry	X	Oxidant	Acid	Solvent	Yield[a] (%)
1	I	*m*CPBA	TCA	MeCN	75 (**2a**)
2	Br	*m*CPBA	TCA	MeCN	22 (**3a**), 9 (**4a**)
3	Br	Oxone	TCA	MeCN	35 (**3a**), 9 (**4a**)
4	Br	KIO_4	TCA	MeCN	0 (**3a**), 0 (**4a**)
5	Br	$PhI(OAc)_2$	TCA	MeCN	18 (**3a**), 3 (**4a**)
6	Br	H_2O_2	TCA	MeCN	—
7	Br	$NaBO_4$	TCA	MeCN	—
8	Br	Oxone	TFA	MeCN	29 (**3a**), 8 (**4a**)
9	Br	Oxone	AcOH	MeCN	—
10	Br	Oxone	—	MeCN	30 (**3a**), 10 (**4a**)
11	Br	Oxone	$TsOH·H_2O$	MeCN	—
12	Br	Oxone	TfOH	MeCN	—
13	Br	Oxone	TCA	MeOH	—
14	Br	Oxone	TCA	CH_2Cl_2	—
15	Br	Oxone	TCA	TFE	—
16	Br	Oxone	TCA	$MeCN/H_2O$	63[b] (**4a**)
17	Br	Oxone	—	$MeCN/H_2O$	65[b] (**4a**)
18	Cl	Oxone	TCA	$MeCN/H_2O$	95[b] (**5a**)
19	I	Oxone	TCA	$MeCN/H_2O$	31 (**2a**)
20	I	*m*CPBA	TCA	$MeCN/H_2O$	14 (**2a**)

[a] Determined by ^1H NMR analysis.

[b] Yield of isolated compound after flash chromatography. TCA = trichloroacetic acid. TFE = 3,3,3-trifluoroethanol.



Scheme 2. Investigation of α,α-dihaloketone formation.



Scheme 3. Postulated mechanism for the halogenations of propargyl alcohols.

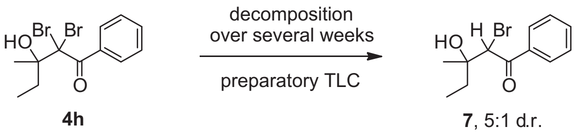
more by-products were formed which made purification more difficult. Consequently, it was decided to continue with trichloroacetic acid as an additive. Repeating the reaction with NaCl instead of NaBr led to conversion into the analogous chloride **5a** in 95% yield (entry 18). However, with NaI, formation of the α,α-diiodoketone was not observed under any of the conditions investigated (entries 19 and 20).

α,α-Dihaloketones are useful compounds for the preparation of, for example, heterocycles,[7] ynol esters,[8] and cyclopropanes.[9] This present method appears to be a valuable route to substituted compounds of this type. Therefore, with the optimized conditions for the formation of α,α-dihaloketones **4** and **5** in hand, a number of substrates were prepared and subjected to these conditions (Scheme 2).[10] The reactions worked in all cases to generate both the chloro and bromo analogs in generally moderate to good yields. The crude products were obtained in reasonable to high purity, which could be purified by flash chromatography in most cases. However, in many cases, attempts to purify the crude reaction mixtures on silica gel led to partial decomposition of the products leading to diminished yields.

During the course of our study, Madabhushi et al. published their findings on the use of similar reaction conditions with terminal alkynes to generate dibromo- and dichloroketones.[11] Interestingly, they were able to prepare the diiodoketones by this method as a 1:1 mixture with the corresponding *trans*-1,2-diiodoalkenes. Neither of these two products was obtained with our propargyl alcohol substrates with NaI.

The mechanism of this reaction is proposed to proceed through oxidation of the halide to generate the corresponding hypohalous acid (Scheme 3). The hypohalous acid can be protonated to form a more reactive halogenating species, or be converted into the corresponding halogen monoxide (X_2O).[12] Subsequent halogenation of the alkyne by one of these species followed by addition of water generates hypothetical intermediate **6**. This species can either eliminate water to generate the α-haloenone, for example **3**, or react with a further equivalent of the halogen species to form an α,α-dihaloketone, for example **4**. In the absence of water as a solvent, the former is the favored pathway, whereas with added water the latter process dominates (apart from for X = I which always favors the former). Formation of the α,α-diiodoketone could be prevented by the large size of the iodine atoms causing unfavorable steric interactions or, because under the reaction conditions, iodine forms different species than bromine and chlorine and alternative pathways are favored. Notably, the NaI procedure requires acidic reaction conditions for efficient conversion, while the NaBr and NaCl methods do not.

Upon standing at room temperature under an air atmosphere for several weeks, compound **4h** had decomposed and compound **7** could be isolated as a 5:1 mixture of diastereomers by preparatory TLC (Scheme 4). There are only two reported methods for



Scheme 4. Decomposition of α,α-dibromoketone **4h**.

the mono-debromination of α,α-dibromoketones that we are aware of.[13]

In conclusion, tertiary propargyl alcohols have been shown to react with sodium bromide and sodium chloride under oxidative conditions to generate α,α-dihaloketones. The presence of water is key to the success of this process as an alternative product, the α-haloenone, is favored under anhydrous conditions.

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Supplementary data

Supplementary data (analytical data and copies of ^{1}H and ^{13}C NMR spectra for novel compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.02.042. These data include MOL files and InChiKeys of the most important compounds described in this article.

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10. *Representative procedure for the synthesis of α,α-haloketones:* 1-(Phenylethynyl)cyclopentanol (**1a**) (50 mg, 0.27 mmol), Oxone (412 mg, 0.67 mmol), NaBr (69 mg, 0.67 mmol), and trichloroacetic acid (66 mg, 0.4 mmol) were dissolved in MeCN (1 mL) at room temperature under a nitrogen atmosphere. H_2O (1 mL) was added dropwise to the mixture, which was stirred overnight. The reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ solution (5 mL) and extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (20:1 petroleum ether/EtOAc) to give the product **4a** as a yellow oil (62 mg, 63%). $\text{IR}_{(\text{neat})}$: 686 (s), 810 (s), 1229 (m), 1665 (m), 2954 (w), 3539 (br) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.71–1.81 (2H, m), 1.88–1.97 (2H, m), 2.03–2.12 (2H, m), 2.37–2.46 (2H, m), 3.56 (1H, s), 7.46 (2H, t, $J = 8.0$ Hz), 7.58 (1H, t, $J = 7.4$ Hz), 8.40 (2H, d, $J = 7.8$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.1 (2C), 39.6 (2C), 74.5, 89.8, 128.2 (2C), 131.8 (2C), 133.3, 134.0, 191.1. MS: m/z (M+23) 383.0. HRMS: m/z calcd for [M+Na] $C_{13}H_{14}Br_2NaO_2$ 382.9252; found 382.9248.
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