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Halohydroxylation of alkylidenecyclopropanes using *N*-halosuccinimide (NXS) as the halogen source: an efficient synthesis of halocyclopropylmethanol and 3-halobut-3-en-1-ol derivatives

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ABSTRACT

A variety of halocyclopropyl-methanol and 3-halo-but-3-en-1-ol derivatives were prepared in moderate to excellent yields via the simple halohydroxylation reaction of alkylidenecyclopropanes with convenient and mild sources of electrophilic halogen NXS (X = I, Br, Cl, F) and H_2O. A plausible mechanism for the halohydroxylation has been proposed.

Difunctional olefins and cyclopropanes are ubiquitous and essential structural constituents as they are widespread, ranging from many biologically active compounds to useful building blocks in organic molecules.[1] During the last decade, a variety of novel methods have been developed to synthesize difunctional olefins and cyclopropanes.[2] Among these reactions, halohydroxylation of the C=C double bond is an efficient access to the synthesis of β-halogen-substituted alcohols, introducing halogen and hydroxyl groups into substrates by a single step.[3]

Alkylidenecyclopropanes (ACPs) are highly strained but readily available molecules that have served as useful building blocks in organic synthesis.[1g–h,4] So far, increasing attention has been paid to the transition metal-catalyzed reactions of unsubstituted methylenecyclopropanes, which have been employed for the construction of complex organic molecules.[5–7] Recently, we have investigated a novel iodohydroxylation of ACPs **1** with iodine and water that gave iodine-substituted allylic alcohols or iodine-substituted cyclopropylic alcohols.[3j] In order to enlarge its applications and overcome some inherent limitations such as inconvenience in using and environmental toxicity, we wished to explore the use of *N*-halosuccinimides, NXS (i.e., NFS, NCS, NBS and NIS) as more convenient, mild, and variable sources of electrophilic halogen,[8] providing more efficient and green method for the synthesis of various halogen-substituted allylic alcohols and halogen-substituted cyclopropylic alcohols which are potentially very useful synthetic intermediates (Scheme 1).

The reaction of ACP **1a** with 2.0 equiv of *N*-bromosuccinimide (NBS) was initially performed in aqueous acetone at room temperature for 3 h, giving the (1-bromocyclopropyl) methanol **2a** in 91% yield. With this result in hand, various ACPs 1 were examined with *N*-halosuccinimide (NXS) under the identified conditions. The results are summarized in Table 1. When aryl-substituted ACPs **1** reacted with NBS and NIS, the corresponding products **2** were obtained smoothly in good yields (Table 1, entries 1–4).[10] For alkyl-substituted substrate **1g**, the corresponding product was obtained only in 31% yield (Table 1, entry 10). Moreover, for NCS, the reactions proceeded very slowly and the corresponding products **2e–f** were obtained in moderate yields (Table 1, entries 5–6). Even when the weaker electrophile NFS was employed, the expected products were obtained in moderate yields as well (Table 1, entries 7–9). It should be noted that fluorinated organic compounds are of current interest owing to the rapidly increasing number of examples of these compounds with attractive and useful biological activity.[9] Herein we provided a facile approach for the synthesis of these interesting fluorinated compounds.

Furthermore, we have also explored halohydroxylation of alkylidenecyclopropanes with *N*-halosuccinimides (NXS) as sources of electrophilic halogen to give the ring-opening 3-halo-but-3-en-1-ol derivatives.[11] In the presence of 2.0 equiv of NBS in DMSO/H_2O, **1a** was consumed after 24 h at 100 °C to afford **3a** as a major product in 93% yield (Table 2, entry 1). We next examined the reaction of various ACPs **1** with *N*-halosuccinimides (NXS) under identical conditions. As indicated in Table 2, a wide variety of ACPs **1** reacted with NBS and NIS in DMSO/H_2O, giving the expected products efficiently (Table 2, entries 1–8). However, when the weaker electrophiles NCS and NFS were employed as the sources of electrophilic halogen, the desired products were not observed (Table 2, entries 9–10).

A possible mechanistic pathway for the formation of **2–3** is shown in Scheme 2.[3a] First, electrophilic addition of X^+ to the C-1 position of the double bond provides the cyclopropylcarbinyl

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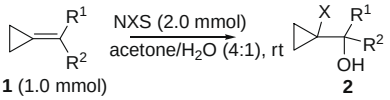
Table 1
Halohydroxylation of ACPs in aqueous acetone[a]

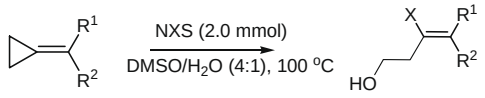


1 (1.0 mmol) **2**

Entry	ACP 1 (R^1/R^2)	NXS	Time (h)	Yield of **2**[b] (%)
1	C_6H_5/C_6H_5(**1a**)	NBS	3	**2a**, 91
2	*p*-ClC_6H_4/*p*-ClC_6H_4(**1b**)	NBS	3	**2b**, 89
3	*p*-FC_6H_4/*p*-FC_6H_4(**1c**)	NBS	3	**2c**, 95
4	**1b**	NIS	24	**2d**, 87
5	**1a**	NCS	60	**2e**, 48
6	**1b**	NCS	60	**2f**, 52
7	**1a**	NFS	60	**2g**, 63
8	*p*-$MeOC_6H_4$/*p*-$MeOC_6H_4$(**1e**)	NFS	48	**2h**, 44
9	*p*-*i*-$PrOC_6H_4$/*p*-*i*-$PrOC_6H_4$(**1f**)	NFS	48	**2i**, 64
10	$R_1,R_2 = CH_2CH_2CHPhCH_2CH_2$(**1g**)	NIS	2	**2j**, 31

[a] Unless otherwise specified, the reaction was carried out using **1** (1.0 mmol) and NXS (2.0 mmol) in aqueous acetone.
[b] Isolated yields and the reaction time are determined by TLC on the basis of consumption of the starting materials **1**.

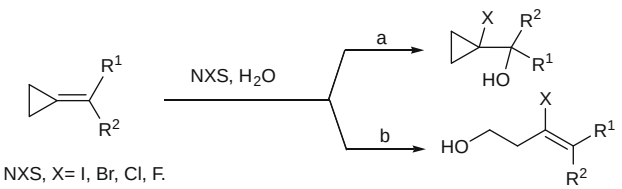
Table 2
Halohydroxylation of ACPs in aqueous DMSO[a]



1 (1.0 mmol) **3**

Entry	ACP **1** (R^1/R^2)	NXS	Time (h)	Yield of **3**[b] (%)
1	**1a**	NBS	24	**3a**, 93
2	**1b**	NBS	24	**3b**, 75
3	**1c**	NBS	24	**3c**, 65
4	*p*-MeC_6H_4/*p*-MeC_6H_4(**1g**)	NBS	24	**3d**, 72
5	*p*-*i*-$BuOC_6H_4$/*p*-*i*-$BuOC_6H_4$(**1h**)	NBS	48	**3e**, 89
6	*p*-*i*-$PrOC_6H_4$/*p*-*i*-$PrOC_6H_4$(**1i**)	NBS	24	**3f**, 94
7	**1b**	NIS	24	**3g**, 68
8	**1h**	NIS	36	**3h**, 85
9	**1a**	NCS	72	**3i**, –[c]
10	**1b**	NFS	72	**3k**, –[c]

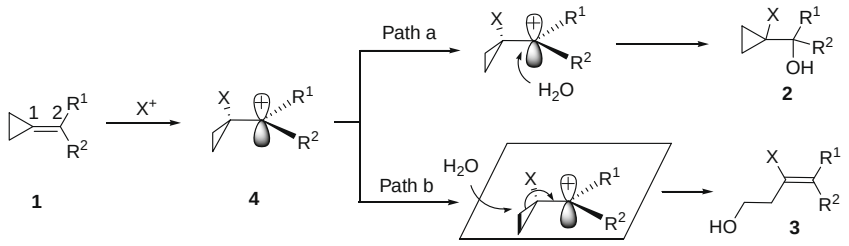
[a] Unless otherwise specified, the reaction was carried out using **1** (1.0 mmol) and NXS (2.0 mmol) in DMSO/H_2O.
[b] Isolated yields.
[c] No desired product was observed.



Scheme 1. Halohydroxylation of ACPs **1**.

cation **4**. Subsequently one molecule of water attacks the C-2 position of **4,** affording the product **2** (Scheme 2, path a). Apparently, product **3** is also derived from the cation **4** (Scheme 2, path b). In this case, strain release is more favorably accomplished by ring opening of the intermediate and bond migration owning to the higher temperature. Nucleophilic attack of the H_2O produces the ring-opened products **3**.

In conclusion, we have developed a halohydroxylation of methlenecyclopropanes using inexpensive and easily handled



Scheme 2. A plausible mechanism for the halohydroxylation of ACPs 1.

N-halosuccinimide (NXS) as the halogen source, providing ready access to a variety of halocyclopropyl-methanol and 3-halo-but-3-en-1-ol derivatives. These convenient available products bearing two functional groups –X and –OH may be converted to other interesting and useful structural units in organic synthesis.[12] In addition, different solvents can lead to selective synthesis of diverse products, which have been the highlight of methylenecyclopropane chemistry. Further studies to expand the scope and synthetic utility of the method are underway.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.07.146.

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10. *Preparation of (1-halo-cyclopropyl)-diphenyl-methanol* (**2**): To a solution of ACP **1a** (1.0 mmol) in 8 mL of acetone was added 2 mL of H_2O. Then NXS (2.0 mmol) was subsequently added. The progress of the reaction was monitored by TLC, and the mixture was stirred until the starting material disappeared. The mixture was extracted with ether (25 mL × 2) and dried over $MgSO_4$. Evaporation and column chromatography on silica gel afforded **2**.
11. *Preparation of 3-halo-4,4-diphenyl-but-3-en-1-ol* (**3**): To a solution of ACP **1a** (1.0 mmol) in 8 mL of DMSO was added 2 mL of H_2O. Then NXS (2.0 mmol) was subsequently added. The reaction mixture was then heated to 100 °C for the required time. The course of the reaction was monitored by TLC. The mixture was extracted with ether (25 mL × 2) and dried over $MgSO_4$. Evaporation and column chromatography on silica afforded **3**.
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