Halogenation Reagents Initiating Ring Opening of Vinylidenecyclopropanes: Easy Access to Halogenated Tetrahydropyrans

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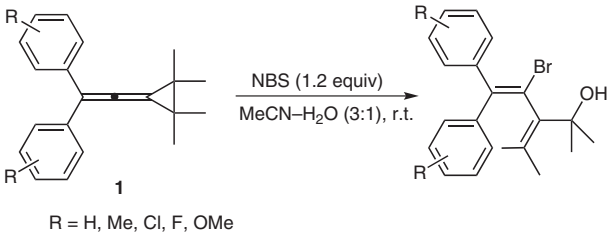
Abstract: A novel synthetic protocol that uses halogenation reagents (NBS, NIS and selectfluor) to initiate intramolecular ring-opening reactions of diarylvinylidenecyclopropanes (VDCPs) connected to alcohol-bearing chains has been developed. The approach provides a variety of halogenated tetrahydropyran derivatives in moderate to good yields under mild conditions. Plausible reaction mechanisms are proposed on the basis of previous literature and the substrate scope has been carefully examined.

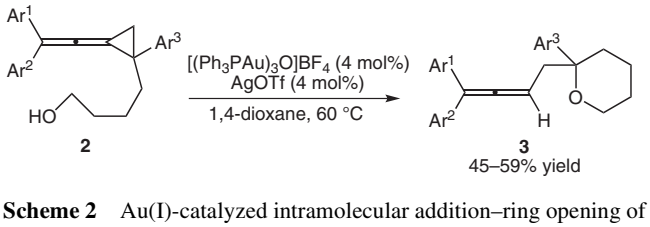
Key words: vinylidenecyclopropanes, halogenation, hydroxyl group, ring opening, tetrahydropyrans

Tetrahydropyrans are found widely in a variety of naturally occurring and biologically active compounds, and synthetic methodologies for producing tetrahydropyrans and their derivatives have attracted much attention. As a result, many useful synthetic methods have been explored.[1,2] For example, it has been reported that tetrahydropyrans could be formed from intermolecular/intramolecular nucleophilic attack of a pre-nucleophile containing a hydroxyl group on an alkyne under the catalysis of transition metals,[3] or from allylic ethers through 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) mediated oxocarbenium ion formation with subsequent intramolecular nucleophilic addition in a highly diastereocontrolled way,[4] or by a cross-metathesis of common alkenes containing a hydroxyl group, followed by iodocyclization.[5] However, to the best of our knowledge, examples of synthetic methods that generate tetrahydropyran rings by means of ring-opening reactions of highly strained small rings are rare.[3c] Therefore, to extend the synthetic approach to tetrahydropyran rings, we attempted to establish a new general method to access this interesting structural motif under mild conditions through ring-opening reactions of highly strained small rings, such as vinylidenecyclopropanes (VDCPs) with an attached alcohol moiety.

Over the past several years, we and others have been studying the chemical transformations of VDCPs, which are highly strained small rings that are readily accessible.[6] For example, previously, we have reported the hydrobromination of vinylidenecyclopropanes **1** by *N*-bromosuccinimide (NBS) and water in acetonitrile to afford hydrobromination products in good yields (Scheme 1).[7] More recently, we have found an efficient intramolecular ring-opening reaction of VDCPs **2** tethered to alcohol-bearing chains under gold catalysis that gives the corresponding functionalized tetrahydropyran derivatives **3** in moderate to good yields (Scheme 2).[3c] Herein, we wish to report a novel use of halogenation reagents such as NBS or NIS to initiate ring-opening reactions of **2** under mild conditions, affording halogenated tetrahydropyran derivatives in moderate to good yields.



Scheme 1 Hydrobromination of vinylidenecyclopropanes **1** by NBS and water in acetonitrile



Scheme 2 Au(I)-catalyzed intramolecular addition–ring opening of VDCPs **2**

Initial experiments on the intramolecular ring-opening reactions of VDCPs **2** were performed by exposing VDCP **2a** (0.2 mmol) to NBS (1.2 equiv) in CH_2Cl_2 (2.0 mL) at room temperature (20 °C). To our delight, it was found that, under these conditions, the corresponding brominated tetrahydropyran derivative **4a**[8] was obtained in 20% yield after three hours (Table 1, entry 1). We then attempted to optimize the reaction by adjusting the conditions; the results of these experiments are shown in Table 1. Changing the solvent to acetonitrile improved the yield of **4a** to 61% after three hours (Table 1, entry 2). Other solvents, such as tetrahydrofuran (THF), toluene or *N*,*N*-dimethylformamide (DMF) did not facilitate the formation of **4a** (Table 1, entries 3–5). Moreover, we found that increas-

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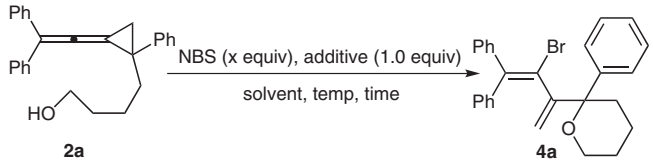
Table 1 Optimizing the Reaction Conditions[a]



2a 4a

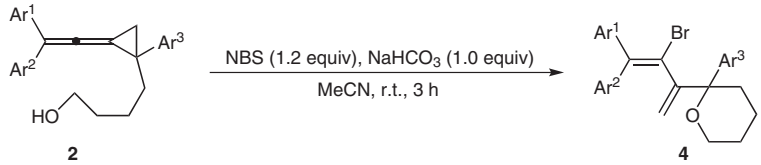
Entry	x	Solvent	Temp (°C)	Time (h)	Additive	Yield of **4a** (%)[b]
1	1.2	CH_2Cl_2	r.t.	3	–	20
2	1.2	MeCN	r.t.	3	–	61
3	1.2	THF	r.t.	3	–	trace
4	1.2	toluene	r.t.	3	–	3
5	1.2	DMF	r.t.	3	–	5
6	1.5	MeCN	r.t.	3	–	42
7	1.8	MeCN	r.t.	3	–	40
8	1.2	MeCN	r.t.	3	$NaHCO_3$	70
9	1.2	MeCN	r.t.	3	Et_3N	32
10	1.2	MeCN	r.t.	1	$NaHCO_3$	53
11	1.2	MeCN	r.t.	2	$NaHCO_3$	65
12	1.2	MeCN	30	3	$NaHCO_3$	43

[a] *Reagents and conditions:* **2a** (0.2 mmol), NBS (x equiv) and additive (1.0 equiv) were added into a flask under argon, then solvent (2.0 mL) was added into the flask via syringe.
[b] Isolated yield.

ing the amount of NBS employed also did not favor the formation of **4a** (Table 1, entries 6 and 7). When $NaHCO_3$ was included as an additive, it was found that **4a** could be obtained in 70% yield (Table 1, entry 8), although using triethylamine (Et_3N) as an additive failed to improve the yield of **4a** (Table 1, entry 9). Examination of the reaction time and the reaction temperature revealed that this NBS-initiated reaction was best carried out at room temperature (20 °C) for three hours; shortening the reaction time or raising the reaction temperature did not improve the yields of **4a** (Table 1, entries 10–12). Ultimately, it was found that the ring-opening product **4a** was obtained in 70% yield when VDCP **2a** (0.2 mmol) tethered to an alcohol-bearing chain was used to react with NBS (1.2 equiv) in MeCN (2.0 mL) within three hours at room temperature (20 °C), using $NaHCO_3$ (1.0 equiv) as an additive; these conditions were thus established as the optimal reaction conditions for this transformation.

Under these optimal reaction conditions, we then examined the substrate scope of this novel ring-opening reaction by employing a variety of VDCPs **2**; the results of these experiments are outlined in Table 2. As can be seen from Table 2, all the VDCPs examined reacted smoothly with NBS to yield the corresponding tetrahydropyran derivatives **4** in moderate to good yields. For diphenylvinylidenecyclopropanes **2b–g**, bearing electron-withdrawing or electron-donating groups on the aromatic rings of Ar^3, the corresponding products **4b–g** were obtained in 44–61% yields (Table 2, entries 2–7). In the case of VDCP **2g**, the corresponding product **4g** was obtained in 44% yield, presumably due to the steric hindrance of the *meta*-substituent Br atom on the aromatic ring (Ar^3). Similarly, introducing electron-donating or moderately electron-withdrawing groups onto the aromatic rings of Ar^1 and Ar^2 also afforded the corresponding tetrahydropyran derivatives **4h–j** in moderate to good yields (Table 2, entries 8–10). For unsymmetrical diarylvinylidenecyclopropane **2k**, the corresponding tetrahydropyran derivative **4k** was obtained as a pair of diastereoisomers with a ratio of 1:1 in 52% total yield under identical conditions (Table 2, entry 11).

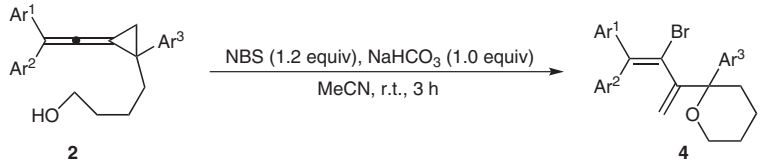
Table 2 Intramolecular Ring-Opening Reactions of VDCPs **2** with NBS[a]



2 4

Entry	Ar^1	Ar^2	Ar^3	Starting material	Yield of **4** (%)[b]
1	Ph	Ph	Ph	**2a**	70
2	Ph	Ph	4-MeC_6H_4	**2b**	56
3	Ph	Ph	4-$MeOC_6H_4$	**2c**	61
4	Ph	Ph	4-FC_6H_4	**2d**	59
5	Ph	Ph	4-ClC_6H_4	**2e**	59
6	Ph	Ph	4-BrC_6H_4	**2f**	52
7	Ph	Ph	3-BrC_6H_4	**2g**	44

Table 2 Intramolecular Ring-Opening Reactions of VDCPs **2** with NBS[a] (continued)

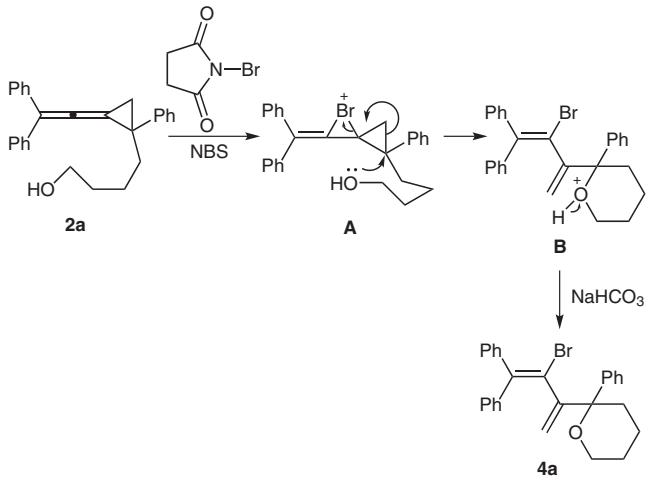


2 4

Entry	Ar^1	Ar^2	Ar^3	Starting material	Yield of **4** (%)[b]
8	4-MeC_6H_4	4-MeC_6H_4	Ph	**2h**	63
9	4-$MeOC_6H_4$	4-$MeOC_6H_4$	Ph	**2i**	43
10	4-ClC_6H_4	4-ClC_6H_4	Ph	**2j**	39
11	4-ClC_6H_4	Ph	Ph	**2k**	52[c]

[a] *Reagents and conditions:* **2** (0.2 mmol), NBS (1.2 equiv), $NaHCO_3$ (1.0 equiv), Ar, MeCN (2.0 mL), r.t., 3 h.
[b] Isolated yield.
[c] *E*/*Z* isomeric mixture (ratio 1:1).

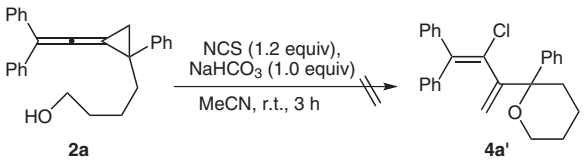
A mechanistic explanation for the intramolecular ring opening of VDCP **2a** in the presence of NBS is proposed in Scheme 3 using **2a** as a model. Firstly, a three-membered cyclic bromonium ion **A** is formed by the electrophilic addition of a Br^+ ion (generated in situ from NBS) onto **2a**,[9] which undergoes intramolecular nucleophilic addition of the hydroxyl group onto the cyclopropane, accompanied by a ring-opening process to afford the corresponding cationic intermediate **B**. Deprotonation of **B** with $NaHCO_3$ furnishes the corresponding vinyltetrahydropyran derivative **4a** (Scheme 1).



2a A B 4a

Scheme 3 A plausible mechanism for the intramolecular ring opening of VDCP **2a** with NBS

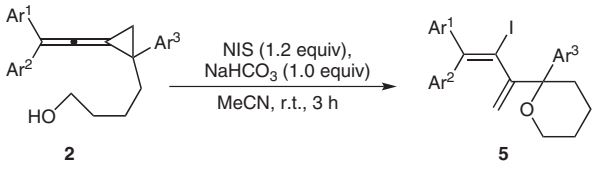
These results also stimulated us to investigate the reaction of VDCPs **2** with other halogenation reagents. Thus, we utilized *N*-chlorosuccinimide (NCS) to replace NBS in the ring-opening reaction of VDCP **2a**, but found that no reaction occurred under identical conditions, presumably due to the fact that NBS is more reactive than NCS (Scheme 4). Using *N*-iodosuccinimide (NIS) to replace NBS afforded the corresponding iodinated product **5a** in 80% yield, together with traces of unidentified byproducts. As shown in Table 3, VDCPs **2b** and **2c** were also suitable substrates for this reaction under the standard conditions, giving the iodinated tetrahydropyran derivatives **5b** and **5c** in 70–81% yields, respectively (Table 3, entries 2 and 3).



2a 4a'

Scheme 4 The reaction of VDCP **2a** with NCS

Table 3 Intramolecular Ring-Opening Reactions of VDCPs **2** with NIS[a]



2 5

Entry	Ar^1	Ar^2	Ar^3	Starting material	Product	Yield of **5** (%)[b]
1	Ph	Ph	Ph	**2a**	**5a**	80
2	Ph	Ph	4-FC_6H_4	**2b**	**5b**	70
3	Ph	Ph	4-MeC_6H_4	**2c**	**5c**	81

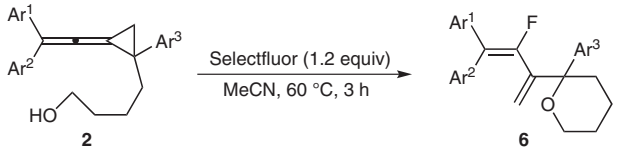
[a] *Reagents and conditions:* **2** (0.2 mmol), NIS (1.2 equiv), $NaHCO_3$ (1.0 equiv), Ar, MeCN (2.0 mL), r.t., 3 h.
[b] Isolated yield.

In our previous work, we investigated the details of the reaction between VDCPs **1** and *N*-fluorodibenzenesulfonimide (NFSI).[9] Therefore, we also examined the reaction of VDCPs **2** with NFSI under the standard conditions. However, we found that the reaction was rather sluggish and complex product mixtures were formed. We then utilized 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo-

[2.2.2]octane bis(tetrafluoroborate) (Selectfluor) as the fluorination reagent in this reaction and found that the reaction proceeded efficiently in MeCN at 60 °C within three hours, affording the expected fluorinated product **6a** in 72% yield (Table 4, entry 1). Examination of substrate scope of this interesting fluorination reaction revealed that, as for diphenylvinylidenecyclopropanes **2b–d** bearing electron-withdrawing or electron-donating groups on their aromatic rings of Ar^3, the corresponding fluorinated products **6b–d** could be obtained in 43–72% yields (Table 4, entries 2–4). Similarly, introducing moderately electron-donating or electron-withdrawing groups onto the aromatic rings of Ar^1 and Ar^2 also afforded the corresponding fluorinated tetrahydropyran derivatives **6e** and **6f** in moderate to good yields (Table 4, entries 5 and 6).

A plausible mechanism for the intramolecular ring opening of VDCPs **2** with Selectfluor is shown in Scheme 5 using **2a** as a model. The fluoric cation F^+ is first generated from Selectfluor under the standard reaction conditions,[11] which adds to a double bond of **2a** to give the corresponding three-membered cationic intermediate **C**.[10] Intramolecular nucleophilic addition of the hydroxyl group onto the cyclopropane combined with a ring-opening process, affords the corresponding cationic intermediate **D**, which undergoes deprotonation to furnish the corresponding fluorinated vinyltetrahydropyran derivative **6a** (Scheme 5).

Table 4 Intramolecular Ring-Opening Reactions of VDCPs **2** with Selectfluor[a]

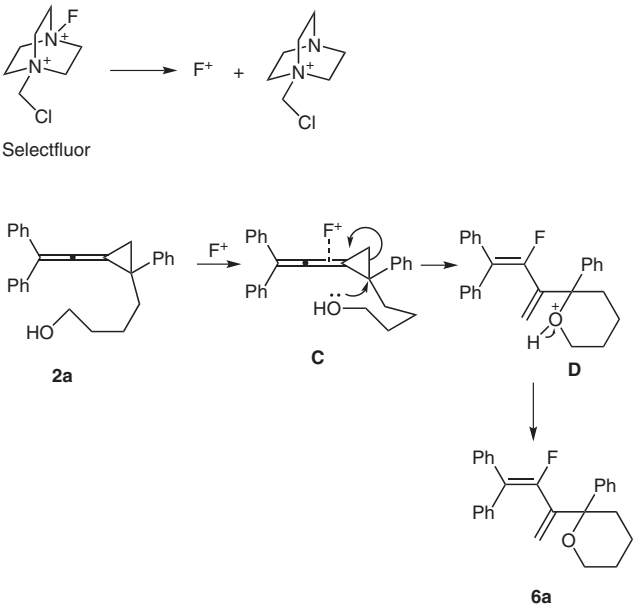


2 6

Entry	Ar^1	Ar^2	Ar^3	Starting material	Yield of **6** (%)[b]
1	Ph	Ph	Ph	**2a**	72
2	Ph	Ph	4-ClC_6H_4	**2b**	72
3	Ph	Ph	4-BrC_6H_4	**2c**	63
4	Ph	Ph	4-$MeOC_6H_4$	**2d**	43
5	4-ClC_6H_4	4-ClC_6H_4	Ph	**2e**	47
6	4-MeC_6H_4	4-MeC_6H_4	Ph	**2f**	64

[a] *Reagents and conditions:* **1** (0.2 mmol), Selectfluor (1.2 equiv), Ar, MeCN (2.0 mL), 60 °C, 3 h.
[b] Isolated yield.

In conclusion, we have developed a novel application of halogenation reagents such as NBS, NIS, and Selectfluor that initiates intramolecular ring-opening reactions of diarylvinylidenecyclopropanes (VDCPs) **2** tethered to alcohol-bearing chains, to give a variety of halogenated tetrahydropyran derivatives in moderate to good yields under mild conditions.[12] Plausible reaction mechanisms have been proposed on the basis of previous investigations and literature data, and the substrate scope has been carefully examined. These reactions provide an alternative synthetic approach to functionalized tetrahydropyran derivatives from easily available highly strained small rings. Efforts are in progress to further elucidate the mechanistic details of this reaction and to determine its scope and limitations.



Scheme 5 A plausible mechanism of the intramolecular ring opening of VDCPs **2a** with Selectfluor

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

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(12) G eneral procedure for the intramolecular ring-opening reaction of diarylvinylidenecyclopropanes **2** with NBS. VDCP **2** (0.2 mmol), NBS (1.2 equiv), and $NaHCO_3$ (1.0 equiv) were added into a tube under argon, then MeCN (2.0 mL, 0.1 M of **2** in MeCN) was added into the tube via syringe. The mixture was stirred for 3 h at r.t., then the solvent was removed in vacuo and the residue was purified by flash column chromatography on silica gel column (petroleum ether–EtOAc, 20:1) to give **4** in moderate to good yields.