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Dihalogenation of Alkenes Using Combinations of *N*-Halosuccinimides and Alkali Metal Halides

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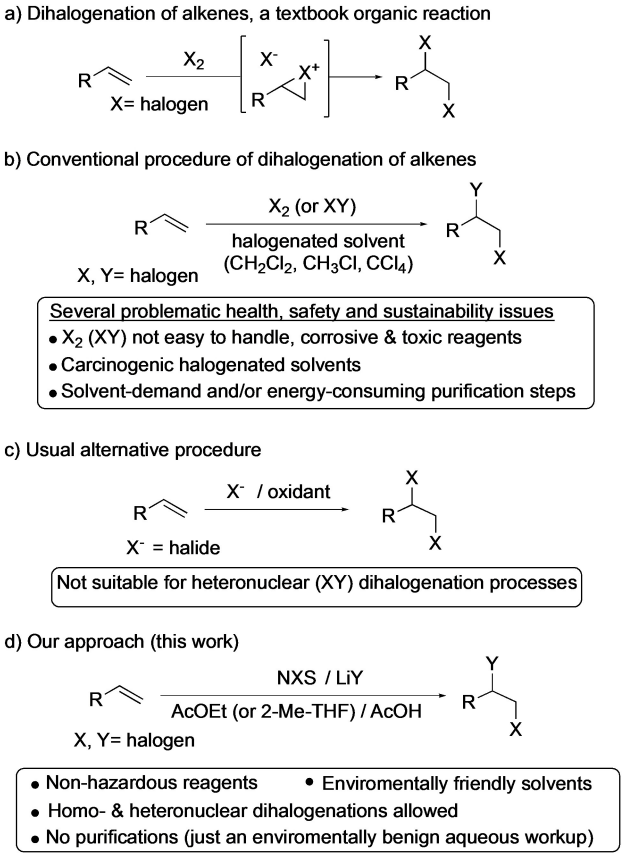
A simple, efficient and eco-friendly method for the vicinal dihalogenation of alkenes is described. The reaction is performed with a combination of a *N*-halosuccinimide and an alkali metal halide using environmentally benign solvents such as acetic acid and ethyl acetate. Purification steps are avoided, and pure products are usually obtained after a simple aqueous workup.

The vicinal dihalogenation of alkenes is one of the fundamental reactions taught in any introductory organic chemistry course (Scheme 1a).[1] This process is a typical example of an electrophilic addition that proceeds through the formation of a halonium ion (haliranium ion) and subsequent ring opening of this intermediate by addition of a halide ion.[2] This reaction is interesting not only from the academic point of view but also from the synthetic and industrial side. In this context, it should be noted that the significance of halogenated compounds is increasing rapidly. These products find application in fields ranging from the manufacture of pharmaceuticals and agrochemicals,[3] the synthesis of natural products,[4] material science and many others.[5] The use of homonuclear elemental halogens (X_2) and heteronuclear diatomic halogens (XY) in (carcinogenic) chlorinated solvents remains, by far, the preferred choice to perform the 1,2-dihalogenation of alkenes (Scheme 1b).[6] The highly corrosive and toxic nature of these reagents, as well as their high reactivity, are important drawbacks for their use in organic synthesis. For these reasons, the development of new strategies to perform electrophilic halogenations under safer conditions or by using alternative halogenating agents has received much attention in the last years.[7] In this context, the utilization of halogens generated in situ from the oxidation of halide ions has become a popular approach (Scheme 1c).[8] Although useful, all these strategies are designed to perform homonuclear dihalogenations. In other words, these methods make use of generated halogens (X_2) or formal equivalents. However, alternative methods to carry out heteronuclear dihalogenation reactions of alkenes avoiding the direct use of diatomic halogens (XY) need to be disclosed.



Scheme 1. Vicinal dihalogenation reaction of alkenes.

A recent research work has revealed that homonuclear and heteronuclear halogens can be easily generated in situ by combining a *N*-halosuccinimide and an alkali metal halide.[9] This simple method was just applied to the vicinal dihalogenation of alkynes. Inspired by this elegant work and motivated by our interest in halogenation reactions,[10] we started a study for the development of a new method for the homo- and heteronuclear dihalogenation of alkenes avoiding the use of toxic, corrosive and not easy to handle halogenating reagents. Details on this investigation are provided herein.

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We started our investigation by attempting the iodochlorination of styrene **1a** (Table 1). In an initial experiment, the alkene (0.5 mmol) was mixed with *N*-iodosuccinimide (1.5 equiv) and lithium chloride (2 equiv) in dichloromethane (1.25 mL) as solvent. After 12 hours at room temperature, we did not observe any kind of transformation (entry 1). In order to activate the *N*-iodosuccinimide and favor the solubility of lithium chloride, we considered the addition of some protic co-solvents. Although the presence of hexafluoroisopropanol (HFIP; 1.25 mL) or trifluoroacetic acid (TFA; 1.25 mL) led to the consumption of the starting material, a complex mixture of unidentified products was obtained even at low temperature (−25 °C; entries 2, 3). Interestingly, when the reaction was performed in a 1:1 mixture of dichloromethane and acetic acid (1.25 mL of each solvent), formation of the desired dihalogenated product **2a** was observed. However, an equimolecular amount of the acetate derivative **3a** was also formed (entry 4). Generation of product **3a** was attributed to the nucleophilic nature of acetic acid. Thus, supposing the formation of a cyclic iodonium intermediate, the subsequent nucleophilic ring opening could be promoted by the chloride anion to give **2a** or by acetic acid to give **3a**.

We observed that the temperature of the reaction had an important impact on the ratio **2a**/**3a**. Thus, by decreasing the temperature to 0 °C, the desired compound **2a** became the major product of the reaction (ratio **2a**/**3a** = 6:1; entry 5). This ratio could be further increased to 20:1 by performing the reaction at −25 °C (entry 6). By decreasing the volume of acetic acid (0.25 mL) the process could be improved to get a >40:1 ratio of **2a**/**3a** (entry 7). Interestingly, the amount of *N*-iodosuccinimide could be reduced to just 1.1 equivalents. Furthermore, under these conditions the desired compound **2a** could be obtained basically as a single product (ratio **2a**/**3a** >40:1; entry 8) without any purification step and just following a simple aqueous workup procedure (washing the final mixture with saturated solutions of sodium thiosulfate and sodium hydroxide; 75% yield). This process could be converted into a more eco-friendly method by changing the solvent. Pleasantly, bio-renewable 2-methyl tetrahydrofuran and ethyl acetate, considered one of the least environmentally harmful solvents, were shown as appropriate (entries 9, 10). As before, it was not necessary to purify compound **2a**. The regioselectivity of this dihalogenation reaction should be remarked upon at this point. In fact, we observed the exclusive formation of **2a** while the alternative product with the halogen atoms at interchanged positions was not detected.

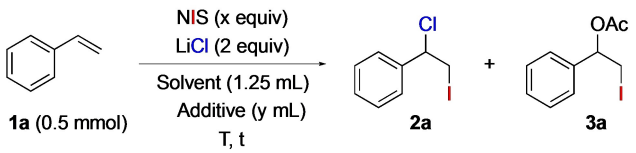
Having identified the conditions shown in Table 1, entry 10 as optimal, we next studied the scope of the transformation.

As shown in Scheme 2, the combination of different *N*-halosuccinimides and alkali metal halides allowed the construction of a diverse library of compounds **2** incorporating two similar or different halogen atoms in their structure. This simple method allowed the access to dihalogenated compounds in a safe way, using easy-to-handle reagents, and so, avoiding the direct use of toxic, dangerous and corrosive halogenation reagents such as ICl, IBr, Br_2 or BrCl.

The reactions were very efficient and selective being products **2** the result of a Markovnikov-type *anti*-addition of the implied halogen atoms to the carbon-carbon double bond of **1**. Mono-, di- and trisubstituted alkenes **1** were used in this study. Alkyl- and aryl-substituted olefins were suitable substrates. Again, it is important to remark that compounds **2** were isolated in pure form after a simple aqueous wash of the reaction mixture with saturated solutions of sodium thiosulfate and sodium hydroxide.[11] To further prove the utility of our methodology, we performed the dihalogenation of natural products such as α-terpineol, (−)-carvone, (−)-β-citronellol and vinylestrone to get products **2an**–**2aq**. Interestingly, the dibromination of (−)-carvone, containing two different alkenes, was chemoselective occurring the reaction on the electron-richer vinyl substituent and leaving the deactivated carbon-carbon double bond of the cyclohexanone skeleton untouched.

Usefully, the iodochlorination reaction of 4-methylstyrene (**1b**) could be performed on a gram scale. Thus, 1.21 grams of

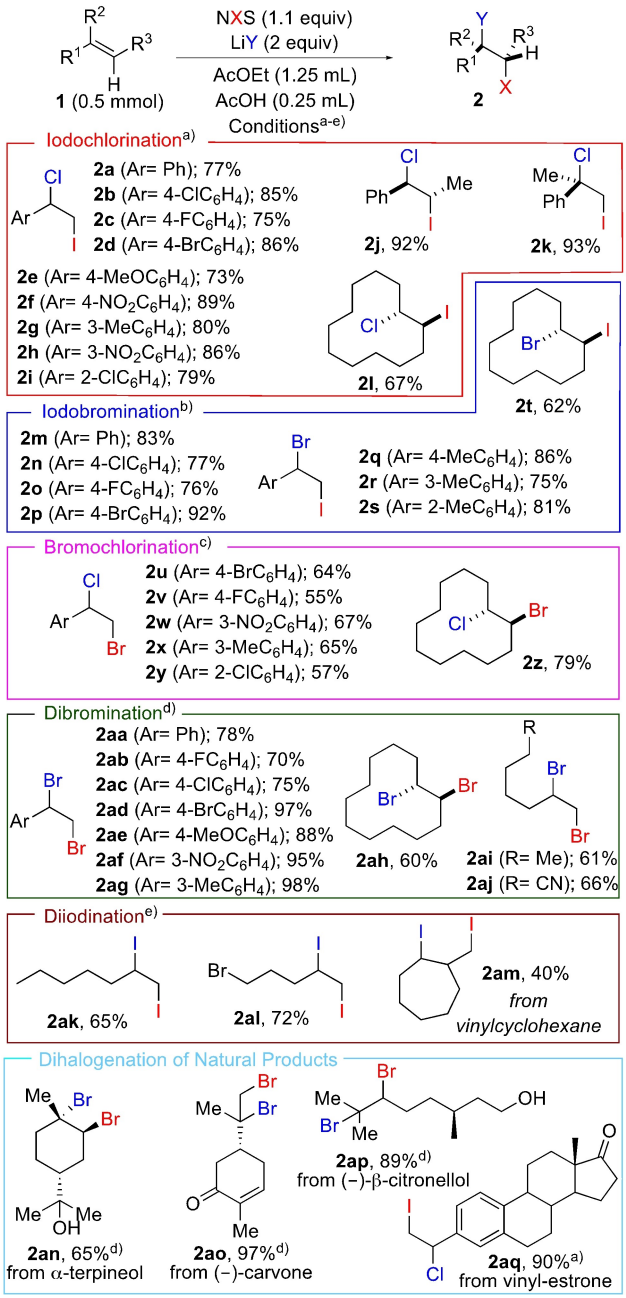
Table 1. Initial experiments. Optimization of the reaction conditions.



1a (0.5 mmol) **2a** **3a**

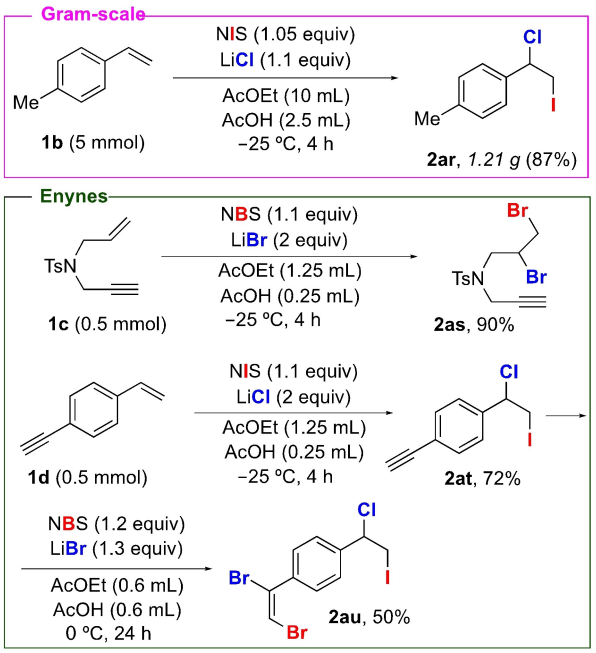
Entry	x (NIS [equiv.])	Solvent	Additive (y [mL])	T [°C]	t [h]	**2a**:**3a**
1	1.5	CH_2Cl_2	–	rt	12	–[a]
2	1.5	CH_2Cl_2	HFIP (1,25 mL)[b]	−25	8	–[c]
3	1.5	CH_2Cl_2	TFA (1.25 mL)[d]	−25	8	–[c]
4	1.5	CH_2Cl_2	AcOH (1.25 mL)	rt	1	1.1:1
5	1.5	CH_2Cl_2	AcOH (1.25 mL)	0	1	6:1
6	1.5	CH_2Cl_2	AcOH (1.25 mL)	−25	2	20:1
7	1.5	CH_2Cl_2	AcOH (0.25 mL)	−25	2	>40:1
8	1.1	CH_2Cl_2	AcOH (0.25 mL)	−25	2	>40:1[e]
9	1.1	2-Me THF	AcOH (0.25 mL)	−25	2	>40:1[f]
10	1.1	AcOEt	AcOH (0.25 mL)	−25	2	>40:1[g]

[a] No reaction. [b] HFIP = hexafluoroisopropanol. [c] Complex mixture of products. [d] TFA = trifluoroacetic acid.[e] **2a** was isolated in 75% yield without any purification step (simple aqueous workup). [f] **2a** was isolated in 74% yield without any purification step (simple aqueous workup). [g] **2a** was isolated in 77% yield without any purification step (simple aqueous workup).



Scheme 2. Scope of the dihalogenation reaction of alkenes. [a] Conditions A: NIS/LiCl; −25 °C, 1–22 h. [b] Conditions B: NIS/LiBr; −45 °C, 2–20 h. [c] Conditions C: NBS/LiCl; −15 °C, 2–24 h. [d] Conditions D: NBS/LiBr; −25 °C, 1–24 h. [e] Conditions E: NIS/KI (instead of LiI); 0 °C, 6–12 h.

1-(1-chloro-2-iodoethyl)-4-methylbenzene (**2 ar**) were easily prepared in one batch and isolated in pure form without purification (Scheme 3). Interestingly, in this gram-scale experiment, the amount of *N*-iodosuccinimide and lithium chloride could be nearly reduced to equimolecular quantities (1.05 and 1.1 equivalents, respectively). This result indicates that the method here presented is an effective, practical and sustainable alternative for the synthesis of dihalogenated compounds from alkenes.

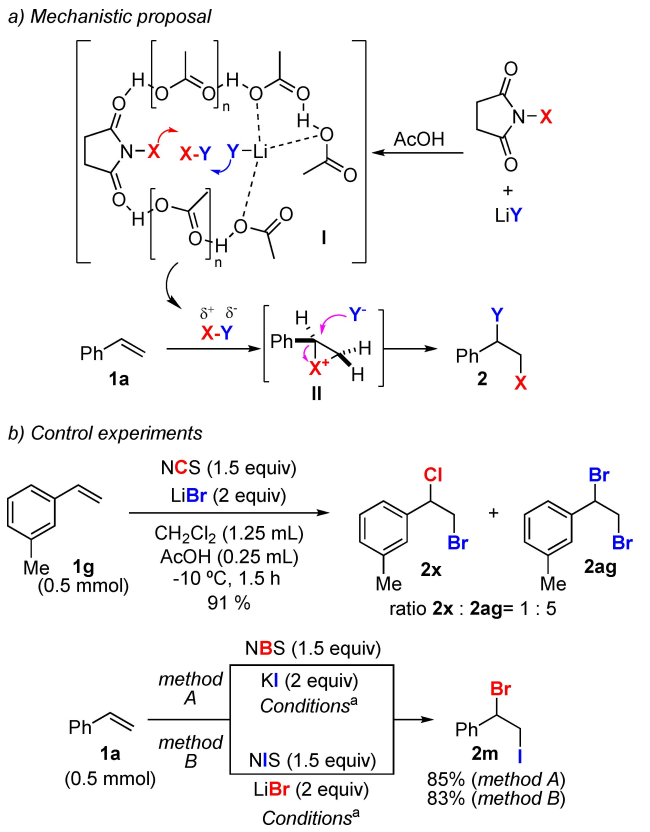


Scheme 3. Gram scale experiment and selectivity studies on enyne derivatives.

Next, we performed some experiments with enyne derivatives **1 c**, **d** (Scheme 3). Interestingly, the dihalogenation reaction was selective and we observed preferential reaction on the alkene moiety to get the alkyne-containing products **2 as** and **2 at**. This chemoselectivity allowed the sequential reaction of the two functional groups (alkene/alkyne) with different halogens. Thus, after isolation of iodochlorinated product **2 at**, the subsequent dibromination reaction of the alkyne led to the polyhalogenated product **2 au** (Scheme 3).

On the basis of our results, a plausible mechanism for the dihalogenation reaction is shown in Scheme 4a. Considering that acetic acid forms linear H-bond aggregates,[12] we propose that the strong interaction of the *N*-halosuccinimide (NXS) with this aggregate and the presence of lithium halide (LiY) favors the formation of the dihalogen species XY (see **I**). The most electropositive center of this species coordinates to the alkene **1 a** to finally form the halonium ion (haliranium ion) intermediate **II**. Nucleophilic attack of the halide (Y^-) to the most electrophilic carbon of the 3-membered ring of **II** leads to the final product **2**.

Support for our mechanistic proposal, and particularly for the in-situ formation of dihalogen species XY, was gained from some control experiments (Scheme 4b). Thus, when alkene **1 g** was treated with *N*-chlorosuccinimide and lithium bromide, we observed the formation of bromochlorinated product **2 x**. This compound is the same that the one previously obtained by using the combination of *N*-bromosuccinimide and lithium chloride (see Scheme 2). Incorporation of the bromine atom at the less substituted position of the alkene indicates the formation of the corresponding bromonium ion intermediate **I**, and ultimately the presence of BrCl in the reaction media (see



Scheme 4. Mechanistic proposal and control experiments. [a]. Conditions: CH_2Cl_2 (1.25 mL), AcOH (0.25 mL); −45 °C, 2 h.

Scheme 4a). In this reaction, we also isolated the dibrominated product **2 ag**. Again, this indicates the formation of the electrophilic bromination species BrCl and subsequent generation of the bromonium ion intermediate that may react with the excess of lithium bromide to yield **2 ag**.[13] Further evidence for the in-situ formation of dihalogen species was found in another set of experiments performed with styrene **1 a** (Scheme 4b). Thus, we observed the exclusive formation of (1-bromo-2-iodoethyl) benzene **2 m** independently of the combination of the *N*-halosuccinimide and alkali metal halide used. Thus, with *N*-bromosuccinimide and potassium iodide we obtained **2 m** in 85 % yield while with *N*-iodosuccinimide and lithium bromide, **2 m** was isolated in 83 % yield.

In summary, we have developed a simple method for the vicinal dihalogenation of alkenes. The procedure consists on the treatment of the alkene with a *N*-halosuccinimide and an alkali metal halide in the presence of acetic acid and using ethyl acetate as an environmentally benign solvent. The dihalogenation reaction here presented supposes and alternative that complements and challenges conventional methods based on the use of toxic, corrosive and not easy to handle reagents such as ICl, IBr, BrCl or Br_2. This method also avoids the use of oxidants typically utilized for the in-situ generation of homonuclear diatomic halogens. In this context, the procedure here described allows not only homonuclear but also heteronuclear dihalogenation processes.

Experimental Section

General Procedure for the Iodochlorination of Alkenes 1

In a 10 mL reaction vessel, LiCl (1 mmol, 2 equiv.), AcOEt (1.25 mL), AcOH (0.25 mL) and NIS (0.55 mmol, 1.1 equiv.) were added and the vessel was sealed with a septum. The mixture was stirred for 1 min at room temperature. Then, the corresponding alkene **1** (0.5 mmol, 1 equiv.) was added dropwise to the stirred mixture at −25 °C. After alkene **1** was consumed (monitored by TLC), the reaction mixture was allowed to warm to room temperature, diluted with Et_2O (20 mL), and washed with sat. aqueous $Na_2S_2O_3$ (10 mL) and 0.5 M aqueous NaOH (2×10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The corresponding iodochlorinated product **2** was obtained in pure form without further purification.

General Procedure for the Iodobromination of Alkenes 1

In a 10 mL reaction vessel, LiBr (1 mmol, 2 equiv.), AcOEt (1.25 mL), propionic acid (1 mL) and NIS (0.55 mmol, 1.1 equiv.) were added and the vessel was sealed with a septum. The mixture was stirred for 1 min at room temperature. Then, the corresponding alkene **1** (0.5 mmol, 1 equiv.) was added dropwise to the stirred mixture at −45 °C. After alkene **1** was consumed (monitored by TLC), the reaction mixture was allowed to warm to room temperature, diluted with Et_2O (20 mL), and washed with sat. aqueous $Na_2S_2O_3$ (10 mL) and 0.5 M aqueous NaOH (2×10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The corresponding iodobrominated product **2** was obtained in pure form without further purification.

General Procedure for the Bromochlorination of Alkenes 1

In a 10 mL reaction vessel, LiCl (1 mmol, 2 equiv.), AcOEt (1.25 mL), AcOH (0.25 mL) and NBS (0.55 mmol, 1.1 equiv.) were added and the vessel was sealed with a septum. The mixture was stirred for 1 min at room temperature. Then, the corresponding alkene **1** (0.5 mmol, 1 equiv.) was added dropwise to the stirred mixture at −15 °C. After alkene **1** was consumed (monitored by TLC), the reaction mixture was allowed to warm to room temperature, diluted with Et_2O (20 mL), and washed with sat. aqueous $Na_2S_2O_3$ (10 mL) and 0.5 M aqueous NaOH (2×10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Unless otherwise stated, the corresponding bromochlorinated product **2** was obtained in pure form without further purification.

General Procedure for the Dibromination of Alkenes 1

In a 10 mL reaction vessel, LiBr (1 mmol, 2 equiv.), AcOEt (1.25 mL), AcOH (0.25 mL) and NBS (0.55 mmol, 1.1 equiv.) were added and the vessel was sealed with a septum. The mixture was stirred for 1 min at room temperature. Then, the corresponding alkene **1** (0.5 mmol, 1 equiv.) was added dropwise to the stirred mixture at −25 °C. After alkene **1** was consumed (monitored by TLC), the reaction mixture was allowed to warm to room temperature, diluted with Et_2O (20 mL), and washed with sat. aqueous $Na_2S_2O_3$ (10 mL) and 0.5 M aqueous NaOH (2×10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The corresponding dibrominated product **2** was obtained in pure form without further purification.

General Procedure for the Diiodination of Alkenes 1

In a 10 mL reaction vessel, KI (1 mmol, 2 equiv.), AcOEt (1.25 mL), AcOH (0.25 mL) and NIS (0.55 mmol, 1.1 equiv.) were added and the vessel was sealed with a septum. The mixture was stirred for 1 min at room temperature. Then, the corresponding alkene **1** (0.5 mmol, 1 equiv.) was added dropwise to the stirred mixture at 0 °C. After alkene **1** was consumed (monitored by TLC), the reaction mixture was allowed to warm to room temperature, diluted with Et_2O (20 mL), and washed with sat. aqueous $Na_2S_2O_3$ (10 mL) and 0.5 M aqueous NaOH (2×10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The corresponding diiodinated product **2** was obtained in pure form without further purification.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Alkenes · Electrophilic additions · Halides · Halogenation · Synthetic methods

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[11] We observed that most of the dihalogenated products **2** decompose to some extension when purified by column chromatography on silica gel. The procedure here described, which avoids such purification step, is in advantageous not only in this sense but also because the amount of solvents required to get the final pure products is reduced.

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[13] These results could also be explained by a halogen interchange between NCS and LiBr to form, under the reaction conditions, NBS and LiCl. However, the analysis of some NMR experiments we performed with a mixture of NCS, LiBr and AcOH in CD_2Cl_2 (reaction conditions) did not show the formation of NBS. Instead, formation of succinimide was observed further supporting our proposal. For details, see the Supporting Information.

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