Multiple Halogenation of Aliphatic C-H Bonds within the Hofmann-Löffler Manifold

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Abstract: An innovative approach to position-selective polyhalogenation of aliphatic hydrocarbon bonds is presented. The reaction proceeds within the Hofmann-Löffler manifold with amidyl radicals as the sole mediators to induce selective 1,5- and 1,6-hydrogen atom transfer followed by halogenation. Multiple halogenation events of up to four innate C-H bond functionalizations have been accomplished. The broad applicability of this new entry into polyhalogenation and the resulting synthetic possibilities are demonstrated for a total of 27 different examples including mixed halogenations.

Polyhalogenated aliphatic compounds represent fascinating molecules with important properties that have triggered significant interest from various fields of the chemical sciences. Nature has made use of this particular motif to a large extent with the family of polyhalogenated natural products, which have emerged as an important class of natural marine toxins.^[1] As a result, recent synthetic efforts have elaborated on the polyhalogenation theme. Apart from conventional functional group transformation, commonly employed elegant approaches to this class of compounds rely on allylic and olefinic halogenation strategies.^[2,3] An attractive alternative would consist of direct halogenation of ubiquitous aliphatic C-H bonds. While attempts toward such challenging endeavors have been undertaken for monohalogenation,^[4] the synthetic concept of predictable multiple C-H halogenation has remained notably unaddressed so far. A possible synthetic realization may derive from the application of suitable functional groups to direct the C-H halogenation event. Within this aim, radical processes appear particularly promising.^[5] Amidyl radicals^[6] are known to promote such C-H halogenation as the key step in photochemically initiated Hofmann-Löffler reactions.^[7] Recent improvements by several groups have provided mild reaction conditions based on the stoichiometric use of electrophilic halide sources.^[7,8] Our recent efforts to develop new protocols for the Hofmann-Löffler reaction have identified manifolds that are catalytic in halogen.^[9] Their most important

feature is the accelerated final C-N bond formation in order to regenerate the halide catalyst. To accomplish with the aim of multiple halogenation, the NH group must remain intact in order to re-engage in the C-H halogenation. Unlike mono-functionalization, the anticipated multiple C-H functionalization needs to address several challenges (Figure 1). At the outset, the required N-halogenation of the substrate proceeds with an external halogenating agent [N]X. The photochemically generated amidyl radical provides the required selectivity through intramolecular selection of accessible C-H bonds guided by 1,5-^[8] or 1,6-hydrogen atom transfer^[10] (HAT). In Hofmann-Löffler reactions, the initial C-H halogenation is usually followed by nucleophilic amination to the heterocyclic product, which is commonly a pyrrolidine. Provided that another N-H halogenation will kinetically outperform the nucleophilic amination, multiple aliphatic C-H bond decoration including the depicted vicinal (from sequential 1,5- and 1,6-HAT) and geminal (from two-fold 1,5- or 1,6-HAT) dihalogenation become available. Additional structural motifs arise from branched or cyclic hydrocarbon substrates. As to an additional challenge, a potential background reaction arising from competing amidyl radicals from the halogenating agent itself must be avoided, since the resulting non-guided C-H functionalization process will result in unselective halogenation.

Figure 1. Strategy for multiple carbon-halogen bond formation via consecutive Hofmann-Löffler reaction. [N]X = halogenating agent. Representative hydrogens depicted for each methylene group.

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As a result, multiple C-H halogenation appears challenging at the outset, since only pertinent kinetic dominance of the guided pathway from Figure 1 will ensure the required selectivity. Based on these considerations we screened possible conditions for multiple halogenation reactions and chose the 2-adamantane derivatives **1a-e** as substrates targeting tertiary C-H bonds (Scheme 1). Halogenated hydantoin **2a-c** were chosen as halogenating agents.^[11,12] Under photochemical initiation, in situ formed N-halogenated derivatives engaged cleanly in the expected C-H halogenation reactions for X = I, Br.

Scheme 1. Multiple directed halogenation at the adamantane core: reaction scope. ^[a] With **2a** as reagent. ^[b] i) **2c**, CH₂Cl₂, ii) C₆H₆, black LEDs, iii) **2a-b**, CH₂Cl₂, visible light. Yields refer to the overall 3-step-process.

The reaction outcome depends on the length of the alkyl chain spacer. For ethylenylamides clean diiodination products **3a,b** were observed.^[13] The position-selective C-H halogenation draws its origin from innate 1,5-HAT via N-centered radicals of the Hofmann-Löffler pathway. In contrast, the homologous propylenylamides provide a sufficiently fast cyclization after the initial iodination leading to selective formation of the pyrrolidine products **3c,d**. Such a cyclization should be disfavored for the less reactive bromination products. Indeed, the corresponding

mesylamides generated the expected brominated products, which were isolated as dibromide **3e** and tribromide **3f**. The former is generated through the common 1,5-HAT, while the latter is formed via sequential 1,5- and 1,6-HAT. Potentially competing non-guided bromination of the remaining tertiary C-H bonds via free radical halogenation directly through reagents **2a,b** was never observed indicating the exclusive involvement of innate Hofmann-Löffler pathways.^[14] These reactions provide the selectivity proof of principle for the kinetic dominance of innate amidyl-radical guided multiple C-H halogenation.

In a related manner, recently introduced N-alkyl sulfamate groups^[10] could be employed for this purpose (Scheme 1). While halogenation with N-alkyl sulfamates have been reported,^[10] their use in polyhalogenation is again entirely without precedence. These groups promote the expected preferential 1,6-HAT with visible light as the only initiator and, consequently, substrate **1e** provided the selectively diiodinated and dibrominated products **3g** and **3h**. Applying sequential halogenation reactions with (i) **2c** and (ii) **2a** or **2b** allowed for the introduction of two different halide groups as demonstrated for **3i** and **3j**. To the best of our knowledge, these are the first examples of defined mixed dihalogenation from Hofmann-Löffler reaction conditions.

Scheme 2. Additional halogenation at the adamantane core. ^[a] Yields refer to the overall 2-step-process from **1a**.

Attempts to generate such compounds through alternative halogen exchange reactions did not materialize. For example, treatment of crude **3a** with hydantoin **2b,c** lead to exclusive formation of the chlorinated and brominated pyrrolidines **4a,b** (Scheme 2). A control experiment with the *N*-methylated

derivative of **3a** provided halogen exchange as well, indicating that the potential involvement of a sulfonamide amidyl radical is not the case.^[15] Instead, iodine oxidation^[16] to iodine(III) **A** should be involved in these transformations. This would generate an iodine leaving group for pyrrolidine formation to **B**, as previously demonstrated^[9a] and corroborated with a control experiment with PhICl_2 .^[15] Oxidation of the remaining iodine with liberated $\text{IX}^{[17]}$ would initiate iodide extrusion to cationic **C** and subsequent nucleophilic halogenation^[16a,b,18] thus provides the halogenated pyrrolidines **4a,b** within a unique oxidatively induced transformation of a diiodide.

Interestingly, the corresponding unsaturated substrate **1f** undergoes unprecedented diiodination with **2a** to the corresponding product **3k**. Mechanistically, an unprecedented sequence of two Hofmann-Löffler reactions may be involved. After the initial iodination, non-bonded interactions should initiate the known double bond isomerization^[19] under the present reaction conditions followed by a second Hofmann-Löffler iodination.^[15] Alternative allylic functionalization events appear less plausible due to the lack of stabilization of the putative allylic radical since the rigid adamantyl core would induce orthogonality between the radical and the alkene π -system. With an excess of hydantoin, double bond oxidation takes place leading to the formation of the triiodinated aziridine **3l**. The selective aziridine formation over the azetidine is believed to originate from steric preferences. In fact, chlorination of **1f** leads to clean four-membered ring formation.

Given the observed higher stability in the cases of the brominated adamantyl derivatives and the general interest in brominated organic compounds as important synthons,^[20] polybromination was investigated further for additional alicyclic substrates (Scheme 3). For indane-derived substrates **5a-c**, the 2-ethylenylamides induce selective 1,5-HAT at the benzylic positions demonstrating that dual halogenation is also possible involving methylene groups. Concomitant cyclization takes place to provide the annelated pyrrolidines **6a-c** as single diastereoisomers. The same occurs for the related tetrahydronaphthalene substrates, which display additional selective C-H bromination from 1,5- and 1,6-HAT, products **6e,f**, which are again formed in a completely diastereoselective manner. In case of a higher excess of hydantoin **2b**, dibrominated ketone **6d** is obtained as a single diastereomer, in which the carbonyl is formed from hydrolysis of the geminal dibromination product.^[8d,21] Use of a longer propyl spacer provided the tribrominated products **6g,h** without cyclization. Control experiments indicate again that free non-guided radical bromination^[22c-e] is not competitive with the Hofmann-Löffler reactions in the cases for **6a-h**.^[15] While all products **6a-h** form in high yields, their tendency for decomposition reduced the isolated yields.

In view of the interesting formation of **6d**, we next sought to stabilize the geminal dibromination motif and to this end decided to choose a more flexible cycloheptane ring system (Scheme 4). For mesylated and tosylated derivatives **7a,b** the expected selective tribromination at the homobenzylic position was obtained. This outcome corresponds to three independent 1,5-HAT processes and exemplifies the potential of sequential Hofmann-Löffler reactions. For the first time, this process has thus been employed for the formation of a geminal dihalogenation motif.^[23] In contrast, lesser stabilized triflamide and

trifluoroacetamide amidyl radicals^[6b] do not promote halogenation via the amidyl pathway and due to free radical benzylic bromination only low yields are obtained for products **8c,d**. The outcome for **8a,b** suggests that loss of rigidity in the substrate favors multiple halogenation.

Scheme 3. Multiple halogenation of cyclic aliphatic C-H bonds. ^[a] With 5 equiv. **2b**.

Scheme 4. Selectivity in multiple C-H amination. Hofmann-Löffler vs. free radical pathways.

To further explore this context, acyclic substrates were investigated. In contrast to cyclic aliphatic substrates, their acyclic counterparts perform less efficiently for sulfonamides. An exception was encountered for acyclic sulfonamide **9**, which under reported conditions^[23] underwent dihalogenation followed by amination at the more activated benzylic position to diastereomerically pure piperidine **10** (Scheme 5). Importantly, N-methyl sulfamates **11a-d** could be applied for amidyl radical-promoted sequential di- and tribromination within a Hofmann-Löffler pathway. These reactions again rely on their common 1,6-HAT,^[10] and provide selective dibromination for symmetric **11a** and for terpene derivative **11b**. For the latter, the remote tertiary

C-H bond remains intact due to the absence of any free radical pathway. The reaction is not restricted to tertiary C-H bonds, and provides exclusive double bromination at the benzylic and tertiary positions of **11c**, respectively. Furthermore, in the presence of an excess of hydantoin **2b**, multiple bromination of **11d** accesses tribrominated **12d** with a geminal dibromination motif.

Scheme 5. Multiple halogenation of acyclic aliphatic C-H bonds. ^[a] With 4 equiv. **2b**.

In summary, we have pioneered conditions that allow for multiple position-selective C-H halogenation reactions within the Hofmann-Löffler manifold. These reactions provide access to various new structures, which derive from unprecedented mixed dihalogenation and polyhalogenation of up to four selective C-H oxidation events and geminal dihalogenation. These results render amidyl radicals important tools for sequential innate C-H halogenation and overall streamline C-H halogenation strategy.

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More than one at a time! Multiple site-selective C-H halogenation events can be accomplished as an innovative variant of the classic Hofmann-Löffler reaction using halogenated hydantoins as oxidants and halide source. The scope includes cyclic and linear hydrocarbons, as well as vicinal and geminal halogenation.

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