Organic LETTERS

Letter

pubs.acs.org/OrgLett

N-Iodosuccinimide-Promoted Hofmann−Löffler Reactions of Sulfonimides under Visible Light

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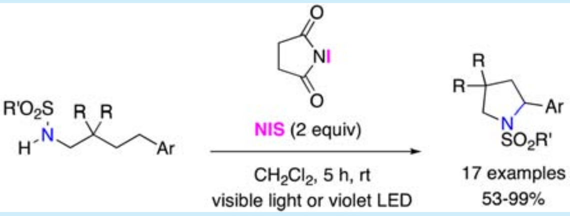
Ⓢ *Supporting Information*

ABSTRACT: Conditions for an attractive and productive protocol for the position-selective intramolecular C−H amination of aliphatic groups (Hofmann−Löffler reaction) are reported employing sulfonimides as nitrogen sources. *N*-Iodosuccinimide is the only required promoter for this transformation, which is conveniently initiated by visible light. The overall transformation provides pyrrolidines under mild and selective conditions as demonstrated for 17 different substrates.



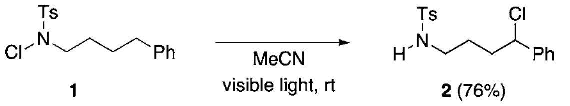
The intramolecular C−H amination of aliphatic groups has recently attracted significant interest from the synthetic community. Major work has focused on the identification of suitable transition-metal catalysts to provide the aforementioned transformation.[1] Directed evolution of metalloproteins has recently emerged as a complementary approach.[2] An alternative consists of the use of small organocatalysts[3] as nonmetallic promoters, which, due to their capability to avoid metal contamination, is of major importance to fields such as biological and medicinal synthesis.

From a historical perspective, the halide-mediated C−N bond formation at nonactivated hydrocarbons was discovered over a century ago and is well established as the Hofmann−Löffler reaction.[4] The general conditions call for preformation of a halogenated amine, which upon irradiation in the presence of strong acid promotes C−H halogenation, which is usually followed by base-mediated pyrrolidine formation. A useful modification providing significantly milder reaction conditions was introduced by Suárez,[5] who reported that Hofmann−Löffler-type cyclization reactions can be conducted in the presence of a mixture of molecular iodine and a hypervalent iodine reagent of the general structure $ArI(O_2CR)_2$.[6] This protocol was employed by Fan, who demonstrated its compatibility with sulfonamides as nitrogen sources.[7]

We have recently demonstrated that this reaction can be conducted with catalytic amounts of iodine and the use of a single equivalent of hypervalent iodine(III) as the terminal oxidant.[8] This accomplishment has demonstrated that iodine catalysis is indeed feasible within the borders of the Hofmann−Löffler reaction, provided that the iodine concentration is maintained at a sufficient level to perpetuate the two intertwined catalytic cycles. However, the permanent requirement of using a hypervalent iodine reagent as a terminal oxidant[9] has triggered interest in whether the reaction could also be conducted with just a single amount of halide reagent as a stoichiometric promoter. Such a reaction would serve as an important addition to the existing protocols for Hofmann−Löffler reactions.

Our investigation on a halide-mediated Hofmann−Löffler transformation commenced from the corresponding *N*-chlorinated compound **1**. In agreement with a recent literature report,[10] we observed the expected chemoselective chlorination of the benzylic position, which proceeded readily even in the absence of the photocatalyst that was previously deemed indispensable (Scheme 1). Still, the requirement of an individual treatment of **2** with base rendered the reaction less attractive from a synthetic point of view. In addition, attempts to develop an in situ formation of **1** using *N*-chlorosuccinimide as chlorinating agent resulted in no conversion.[11] In order to arrive at a direct pyrrolidine formation, we turned to the use of N−Br derivatives (Table 1).

Scheme 1. Chloride-Mediated Intramolecular C−H Functionalization

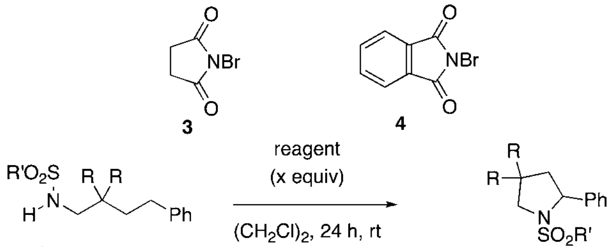


We initially investigated the application of our earlier $KBr/NaClO_2$ protocol from intramolecular diamination of alkenes.[12] For the two selected starting materials **5a** and **5b**, no conversion could be obtained under these conditions (entries 1 and 2). In contrast, use of conventional brominating reagents such as *N*-bromosuccinimide (**3**) and *N*-bromophthalimide (**4**) led to a clean pyrrolidine formation. Initially, substrate **5a** could be cyclized to **6a** in 40% yield using a single equivalent of **3**

Received: December 7, 2015
Published: January 19, 2016

DOI: 10.1021/acs.orglett.5b03476
Org. Lett. 2016, 18, 436−439

Table 1. NBS/NBP-Promoted Hofmann–Löffler Reaction

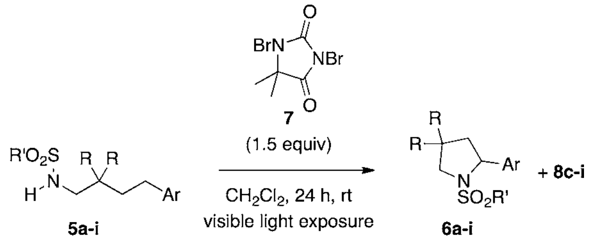


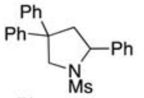
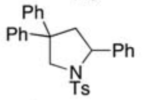
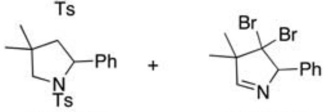
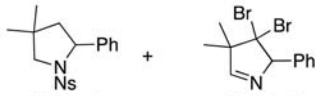
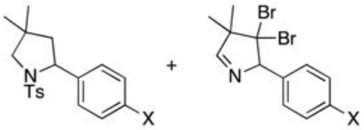
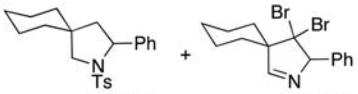
5a (R = Me, R' = Tol) **6a**
5b (R = Ph, R' = Me) **6b**

entry	substrate	reagent	*x*	conv (%)
1	**5a**	$KBr/NaClO_2$	0.1/2	
2	**5b**	$KBr/NaClO_2$	0.1/2	
3	**5a**	**3**	1	40
4	**5a**	**3**	2	52
5[a]	**5a**	**3**	2	56
6	**5a**	**4**	2	55
7[a]	**5a**	**4**	2	55
8	**5b**	**4**	2	47
9	**5a**	**4**	3	66
10	**5b**	**4**	3	81

[a] Under irradiation (400 nm monochromatic wavelength).

Table 2. Oxidation of Alkylsulfonamides 5 with Reagent 7



entry	products (yields)		
1	 **6b** (74%)		
2	 **6c** (29%, 99%[a])		
3		**6a** (39%)	**8a** (47%)
4		**6d** (35%)	**8d** (59%)
			
5	X = F:	**6e** (32%)	**8e** (54%)
6	X = Cl:	**6f** (26%)	**8f** (62%)
7	X = Me:	**6g** (24%)	**8g** (50%)
8	X = OMe:	**6h** (48%)	**8h** (40%)
9		**6i** (16%)	**8i** (76%)

[a] Based on recovered starting material.

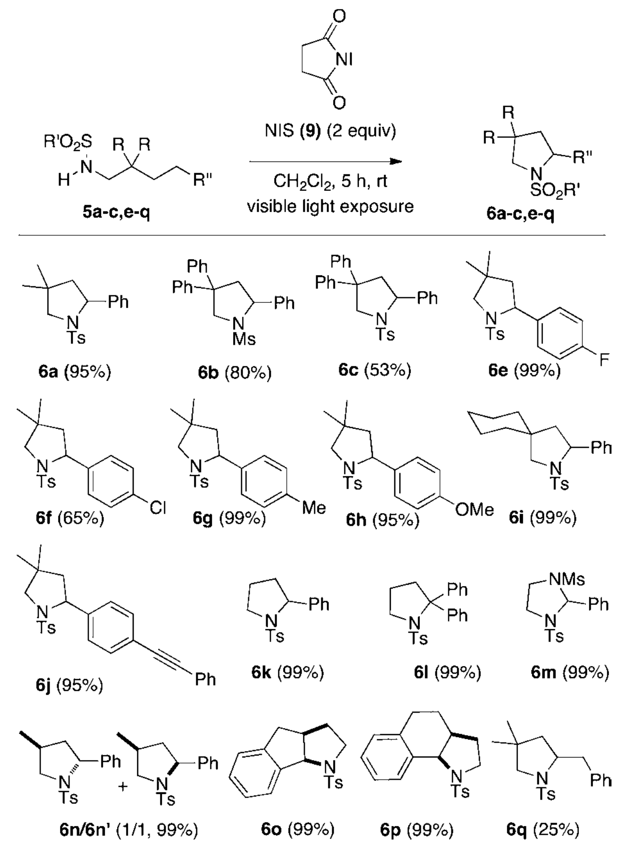
(entry 3). Increasing the amount of **3** to 2 equiv gave a slightly increased yield (52%, entry 4). Changing visible light for monochromatic light of 400 nm had little effect (entry 5). With **4** as bromine source, a comparable result was obtained (entry 7). Changing to mesylated substrate **5b**, a less efficient transformation was observed (47%, entry 8). A further increase of **4** to 3 equiv only had a minor beneficial effect for formation of **5a** (66% yield, entry 9), while for **5b** a significantly improved yield of **6b** was obtained (entry 10). It is noteworthy that the reaction proceeds with complete chemoselectivity and that even in the presence of an excess of reagents **3** and **4**, there are no products other than **6a,b** formed. These are the first successful examples of a Hofmann–Löffler variant starting from in situ generated *N*-brominated tosylamides.

In another series of experiments (Table 2), the dibrominated hydantoin **7** was employed as the halide promoter in order to attempt to lower the amount of halide promoter. While the initial work with the mesylated derivative **5b** gave a very good yield of 74% (entry 1), the tosylated derivative **5c** resulted in low conversion (entry 2). Unexpectedly, the applicability of these conditions for a general process with other substrates **5a,d–i** was hampered by the occurrence of unexpected dibrominated imine products **8a,d–i**, which in all cases but one (**6h**/**8h**) constituted the main reaction product (entries 3–9). For all these transformations, the two products constituted the only oxidation products detected in the crude reaction mixture, the remaining material being unreacted starting material. Employing higher amounts of reagent **7** only increased the relative formation of products **8**.

Control experiments suggest that formation of dibrominated imines **8** occurs after the pyrrolidine cyclization. For isolated products **6e** and **6i**, treatment with dibromo hydantoin **7** led to formation of compounds **8e** and **8i**, respectively, upon complete consumption of starting materials. Pyrrolidines **6** and dibromo imines **8** could be separated by column chromatography and isolated in pure form. The formation of the latter is unexpected, but has some relation to an overoxidation reaction in the corresponding Hofmann–Löffler reactions under the Suárez conditions.[13] In any case, compounds **8a,d–i** may be interesting synthons for future organic transformations.

We then finally turned to *N*-iodosuccinimide (NIS, **9**) as the halogen promoter. This reagent enabled completely selective transformations of all investigated tosylamides **5** into the corresponding pyrrolidines **6** (Scheme 2). The reactions proceed readily in the presence of visible light and at room temperature. Isolated yields are in the range of 53–99%, with several of the reactions yielding quantitative product formation. In the latter cases, products are obtained in analytically pure form directly after workup. Examples include tolerance of common substituents as in **6e–h** and **6j**. The reaction works equally well for nonsubstituted chain (**6k**), for cyclization at the dibenzylic position as in product **6l**, and for aminal synthesis (**6m**). In agreement with a radical process, acyclic stereocontrol was not successful resulting in the formation of a 1:1-mixture of diastereoisomers for **6n**/**6n′**. In contrast, annelation led to quantitative yields of single diastereomeric products **6o** and **6p**, respectively. In contrast to benzylic C–H amination, related aliphatic positions led to conversion at a reduced rate and

Scheme 2. NIS-Promoted Hofmann−Löffler Reaction: Scope



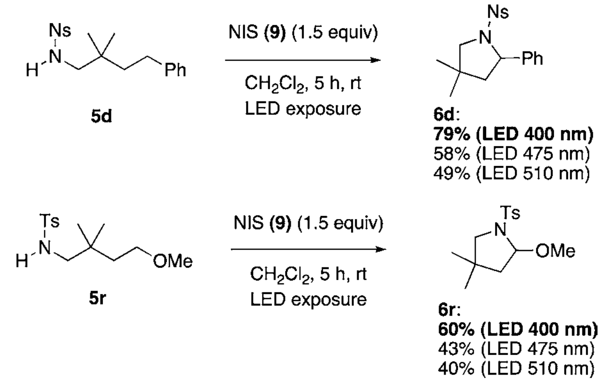
resulted in lower yields as demonstrated for the homobenzylic amination in **6q** (25%, 99% based on recovered starting material). Given the commercial availability of NIS and its rather economical price, this reagent appears as an optimum promoter for the iodine-mediated Hofmann−Löffler reaction under neutral conditions and with visible light as the only initiator being required. It is noteworthy that for the reactions with quantitative product formation, aqueous workup led to complete removal of succinimide and thus provided products **6** in pure form without any requirement for further purification. All reactions are characterized by complete chemoselectivity leading to pyrrolidine formation without any overoxidation/iodination being observed in any case.

The corresponding 1,3-diiodo 2,2-dimethylhydantoin **10** was also successful in the transformation of **5e** and **5p** into **6e** and **6p**, respectively. However, as it represents a significantly more expensive approach it was not investigated further in detail.

In cases with less effective cyclization under visible light conditions, exposure of the reaction mixture to LED irradiation results in significantly better reaction yields. This was demonstrated for the two cyclization reactions of products **6d**,**r** (Scheme 3). In line with the previous determination of an optimum irradiation at 410 nm wavelength, conducting the reaction in the presence of violet LED offered the best reaction conditions.

The mechanism is depicted in Figure 1 with **5a** as the representative substrate and is reminiscent of our earlier catalytic transformation.[8] It relies on the formation of the key intermediate **A** that is generated from the starting material **5a** by iodination with NIS under concomitant release of succinimide.

Scheme 3. LED-Initiated Hofmann−Löffler Reaction



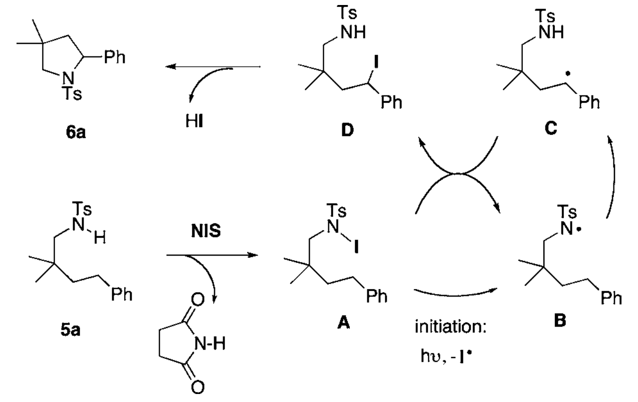
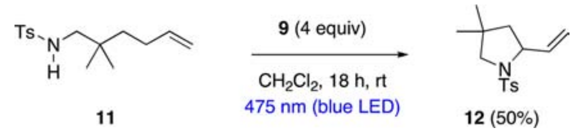


Figure 1. Mechanistic scenario for NIS-promoted Hofmann−Löffler reaction.

Visible light-induced homolytic cleavage initiates a radical chain reaction comprising nitrogen and carbon centered radical stages **B** and **C** that ultimately generates the benzylic iodine **D**. Nucleophilic substitution generates the final pyrrolidine product **6a**. Since the radical chain reaction is identical to the one involved in the related catalytic variant, it requires the same optimum wavelength of 410 nm or violet LED. No conversion is observed in the absence of light (dark laboratory).[11]

Finally, the prospects of the present reaction may go beyond the common C−H amination. For compound **11**, conditions could be developed that allow promoting an allylic amination reaction[14] to proceed without consumption of the free double bond (Scheme 4). Mechanistically, this transformation should generate an allylic radical comparable to the benzylic one from intermediate **A** followed by amination of the subsequent allylic iodide. Interestingly, blue LEDs provided the best irradiation conditions for the present transformation.

Scheme 4. NIS-Promoted Allylic Amination



In summary, we have developed convenient synthetic conditions for an iodine-mediated Hofmann−Löffler reaction. The scope compares well with alternative protocols. The employed iodine reagent NIS is significantly more economic than related reagent combinations that include the requirement for hypervalent iodine reagents.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03476.

Full experimental details and characterization data for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Financial support for this project was provided from the Spanish Ministry for Economy and Competitiveness (CTQ2011-25027 and CTQ2013-50105-EXP grants to K.M. and Severo Ochoa Excellence Accreditation 2014-2018 to ICIQ, SEV-2013-0319), the ICIQ Summer Fellow Programme (grants to C.Q.O'B. and P.F.) and Cellex-ICIQ Program (fellowship to C.M.).

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