Chemoselective Intramolecular Functionalization of Methyl Groups in non-Constrained Molecules Promoted by *N*-iodosulfonamides.

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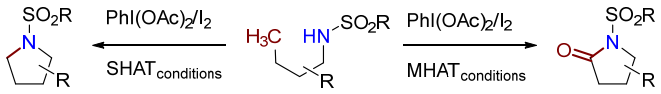
Supporting Information Placeholder

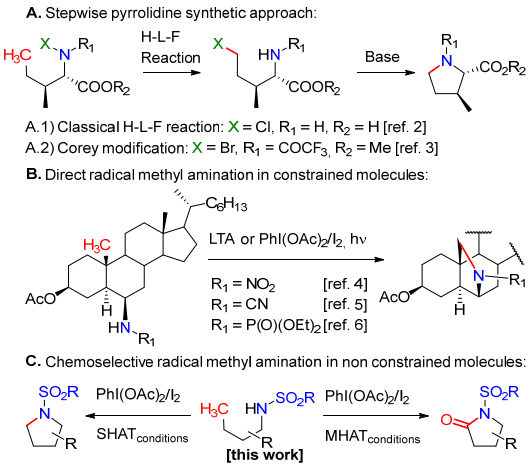


ABSTRACT: Mechanistic evidences observed in Hofmann-Löffler-Freytag type reactions have been crucial to achieve the chemoselective functionalization of methyl groups under mild conditions. Radical mediated methyl-iodination and subsequent oxidative deiodination are the key steps in this functionalization, where iodine chemistry has a pivotal role on the formation of the C–N bond. The concepts of Single Hydrogen Atom Transfer (SHAT) and Multiple Hydrogen Atom Transfer (MHAT) are introduced to describe the observed chemoselectivity.

The functionalization of the ubiquitous C–H bonds in organic molecules is certainly of high importance in the development of the Organic Synthesis and remains currently as one of the most challenging task in this field.[1] In this regard, the C(sp^3)–H bonds of methyl groups that are not directly influenced by other vicinal functional groups by inductive, conjugative or hyperconjugative effects, are of special interest due to their relative low reactivity. Nitrogen centered radicals have appeared in the literature as an intermediate capable to achieve methyl amination. Thus, Lavergne described a multistep procedure based on the original Hofmann-Löffler-Freytag (H-L-F) reaction, employing free amine group as precursor of *N*-radicals under strong acidic conditions (eq A.1).[2] More recently, Corey and coworkers reported a very efficient modification under neutral conditions via methyl bromination, utilizing *N*-trifluoroacetyl derivatives to optimize the intramolecular C–H abstraction pathway (eq A.2).[3] The Suárez modification has also been used to accomplish the direct methyl amination in a one-pot procedure employing *N*-nitroamides,[4] *N*-cyanamides[5] and *N*-phosphoramidates.[6] However, its application has been limited to cyclic systems with restricted geometry (eq B).

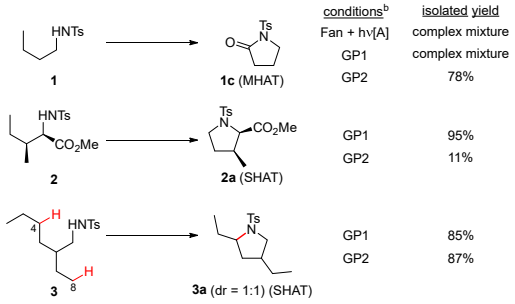
In our ongoing program, we have focused our attention in the direct intramolecular C–H amination of unactivated methyl groups employing nitrogen centered radicals with the idea of developing chemoselective procedures to synthesize pyrrolidines and pyrrolidinones under mild conditions. The strategy is based on the direct sequential transformation C–H → C–I → C–N already proposed in H-L-F type reactions[7] and employing its Suarez modification[8] to generate nitrogen centered radicals (eq C). We attempted to overcome the classical limiting scopes of previously reported methodologies,[9,10] and tackle three major problems: suitable *N*-radical precursors, conformational restrictions and control of the chemoselectivity.

Scheme 1. Intramolecular radical methyl aminations



In this work, we decided to reconsider the employment of sulfonamides as *N*-radical precursors to achieve the proposed functionalization, motivated by the success of Fan and col. in their intramolecular functionalization of methylene groups.[11] Although their optimized conditions were not efficient to obtain the respective pyrrolidine derived from *N*-tosylamide **1**, we repeated the experiment under irradiation with two tungsten lamps (80W) (hν[A]). Complete consumption of starting material and formation of a complex mixture of compounds was observed (Scheme 2). Mono- and poliiodo-containing compounds were detected by mass spectra of the mixture, indicating some functionalizations. After testing many conditions, we found that employing an excess of $PhI(OAc)_2$ (600 mol%), $NaHCO_3$, more diluted conditions and slow addition of a solution of iodine in DCE (keeping low concentrations of I_2), while the reaction mixture was irradiated at rt (denominated as GP2), a clean reaction took place to afford the 2-pyrrolidinone **1c** in 78% yield after purification. Thus, we assumed that the main problem to obtain the expected pyrrolidine does not rely only on the step of the transference of the hydrogen atom from the methyl group to the *N*-radical, but also on the process of cyclization, leading, in this case, to the highly selective formation of an "over-oxidized" product.

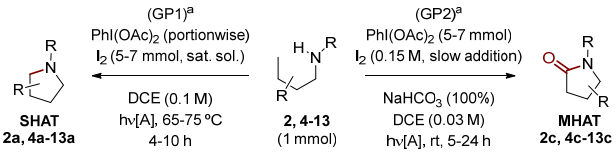
Scheme 2. Structure dependent chemoselective functionalization[a]

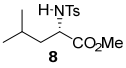
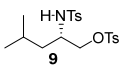
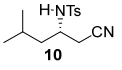
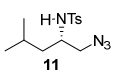
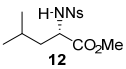
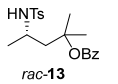


[a] SHAT = Single Hydrogen Atom Transfer, MHAT = Multiple (*triple*) Hydrogen Atom Transfer. [b] For more detailed conditions, see *SI*.

Conversely, when the same procedure GP2 was used with compound **2**, characterized by holding two substituents in α and β position from the amide group respectively, only the corresponding pyrrolidine was obtained, as expected for constrained molecules, with a low conversion (73% of **2** was recovered). This result evidenced that the efficiency of this approach is highly dependent on the shape of each precursor. At this point, we were interested to find general patterns of reactivity, in order to favor the formation of pyrrolidines (N**a**)[12] or 2-pyrrolidinones (N**c**)[12] considering that the cyclization step (highly influenced by the geometry of the molecule) is determinant in the chemoselectivity. In this regard, we found that employing an excess of iodine (saturated solution), more concentrated conditions (0.1 M in DCE) and portionwise addition of $PhI(OAc)_2$ while the reaction mixture was irradiated in a sealed tube allowing to reach 65-75 ºC (named as GP1 conditions), were excellent to convert compound **2** into the corresponding pyrrolidine **2a** in almost quantitative yields and complete chemoselectivity. However, a complex mixture was obtained when GP1 was applied to **1**. This suggests that, due to the entropic penalty to approach the amide group to the mono-iodinated methyl position (Thorpe-Ingold effect),[13] the cyclization step is slow and would enable the competition of other intra- and intermolecular reactions. When compound **3** was submitted to either GP1 or GP2, pyrrolidine **3a** was obtained as the sole product without any stereoselectivity, evidencing that methanediyl group is more reactive than methyl group in both determining steps: First, in the HAT-step due to enthalpic factors [ΔH_{C4-H} = 93.9 Kcal mol^{-1}; ΔH_{C8-H} = 97.5 Kcal mol^{-1}] (see *SI*: DFT calculations) and second, in the cyclization step due to the faster oxidative deiodination of a secondary mono-iodinated carbon versus a primary one.[14] Moreover, the absence of "over-oxidized" product led us to consider the functionalization of methyl groups as a particular matter.

Table 1. Chemoselective functionalization of methyl groups.



entry	Substrate	procedure[a]	SHAT %(*syn*/*anti*)[b]	MHAT %(*syn*/*anti*)[b]
1		GP1	61	7
2	**4**	GP2	-	77
3		GP1	65	-
4	**5**	GP2	-	78
5		GP1	65	-
6	**6**	GP2	-	56
7		GP1	86	-
8		GP2	9	73
9	**7**	GP3[c]	-	83
10		GP1	95	-
11		GP2	11	-
12	**2**	$GP3_{Na2CO3}$[d]	-	81
13		GP1	81(1:1.4)	8(1:0)
14		$GP1_{Zn(OTf)2}$[e]	88(1:1)	-
15		$GP1_{CSA}$[f]	93(1.1:1)	-
16	**8**	GP2	-	72(1.1:1)
17		GP1	72(1:1.7)	5(1:0)
18	**9**	GP2	-	88(2.8:1)
19		GP1	32(1:2.8)	40(4:1)
20		$GP1_{CSA}$[f]	86(1.3:1)	-
21	**10**	GP2	-	72(2.5:1)
22		GP1	52(1.5:1)	15(1:1)
23		$GP1_{CSA}$[f]	36(1:3)	23(4.3:1)
24	**11**	GP2	-	68(2:1)
25		GP1	69.5(1:1.8)	24(2.5:1)
26		$GP1_{CSA}$[f]	82(1:1.2)	-
27	**12**	GP2	-	60(1:1.1)
28		$GP1_{CSA}$	52(1.7:1)	24(1:0)
29	*rac*-**13**	GP2	-	83(7.5:1)

[a] For more details in reaction conditions, see *SI*; [b] Total isolated yield (diastereoisomeric ratio); [c] GP3 same as GP2 but I_2 (1.4 mmol) added in one portion; [d] $GP3_{Na2CO3}$ same as GP2 but I_2 (1.0 mmol) added in one portion and Na_2CO_3 instead of $NaHCO_3$; [e] $GP1_{Zn(OTf)2}$ same as GP1 but I_2 (0.5 mmol) and $Zn(OTf)_2$ (0.6 mmol) were added; [f] $GP1_{CSA}$ same as GP1 but I_2 (0.6 mmol) and CSA (1.0 mmol) were added.

Fortunately, when we used GP1 and GP2, to perform the fuctionalization with other butylamine derivatives (compounds **4**, **5** and **6**, Table 1, entries 1-6), we obtained the corresponding pyrrolidines and 2-pyrrolidinones with good yields and excellent chemoselectivity, indicating that these procedures were reliable.[15] In the same manner, GP1 and GP2 were efficient with the amino acid derivatives **7** and **8** obtaining good yields and chemoselectivities, as well as for the leucinol derivatives **9**, **10** and **11**. Alternatively, we found that the formation of pyrrolidines could be optimized, for some substrates, employing $GP1_{Zn(OTf)2}$ or $GP1_{CSA}$, which combine catalytic amounts of iodine with a Lewis or Brønsted acids such as $Zn(OTf)_2$ or CSA (entries 14, 15, 20 and 26), although these behavior was not general (entry 23). On the other hand, the employment of Na_2CO_3 ($GP3_{Na2CO3}$) instead of $NaHCO_3$ (GP2) was highly efficient to improve the chemoselectivity toward the formation of the 2-pyrrolidinone **2c** (entry 12).

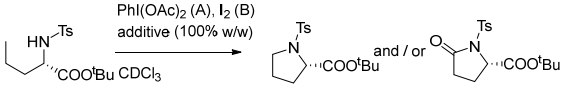
Replacement of the *N*-tosylamidyl group in compound **8** for the *N*-nosylamidyl group (compound **12**) led to very similar reactivity either under GP1, $GP1_{CSA}$ or GP2 conditions. However, poor reactivity was observed when it was replaced by either diphenyl-phosphoramidyl or alkylcarbamate groups. Furthermore, non-reactivity was observed with the trifluoroacetamidyl derivative (see *SI*: tables *S14*, *S15* and *S16*).

Functional groups such as sulfonic esters, nitriles and azides were tolerated by these procedures as shown with substrates **9**, **10** and **11**. Additionally, it was also proved that neither GP1 nor GP2 conditions induced epimerization in compound **7** (see *SI*: Scheme *S14*).

Finally, we evidenced that either GP1 or GP2 can be used to synthesize pyrrolidines and 2-pyrrolidinones with good stereoselectivities (table 1, entries 28 and 29). It is important to notice the chemoselectivity observed in compounds with two methyl groups in γ-position such as **4**, **8**-**13**, where only one of the methyl groups was functionalized, especially under GP2 conditions. This chemoselectivity could be explained on the basis of the C–H DBE for the methyl and the mono- and di-iodinated methyl group (see scheme *S15*).

In order to elucidate the key of the chemoselectivity, we decided to synthesize compounds **14**, **14(I)** and **14(I_2)** and monitor their reactivity by ^{1}H RMN (see *SI*, mechanistic studies section).

Table 2. NMR monitored experiments with 14.

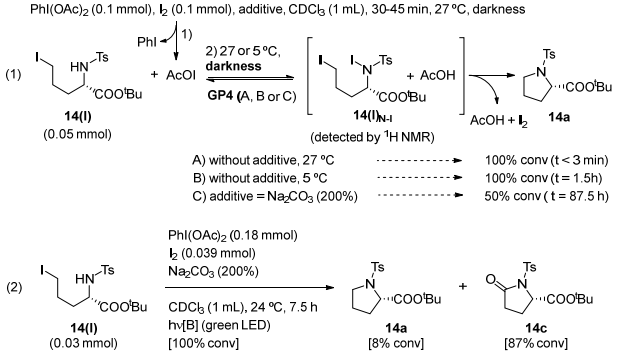


entry	procedure[a]	A, B (mmol)	additive	[c] (M)	hν[b]	t (h)	conv[c] **14a**	conv[c] **14c**
1	GP1	4, 5	-	0.1	[A]	4.5	73	-
2	GP3	6, 1.4	Na_2CO_3	0.03	[A+ f]	6	4	88
3	GP3	2, 2	-	0.05	dark	0.4[d]	-	-
4	GP3	2, 2	Na_2CO_3	0.05	dark	3.6[e]	-	-

[a] GP1: $PhI(OAc)_2$ added portionwise , T = 60-65 ºC; GP3: all reagents added in one portion, T = 26-27 ºC; [b] [A] = tungsten lamps (80W), [A+f] = filtered light (λ>445 nm); [c] calculated by ^{1}H NMR; [d] (**14**/**$14_{N\text{-}I}$**, 1:1.52) after 20 min; [e] (**14**/**$14_{N\text{-}I}$**, 1:0.31) after 3.6 h.

Firstly, we checked that GP1 and $GP3_{Na2CO3}$ were good procedures to obtain **14a** and **14c** with good chemoselectivity also in $CDCl_3$ (Table 2, entries 1, 2). Interestingly, for both procedures, the *N*-iodoamide intermediate (**$14_{N\text{-}I}$**) established an equilibrium with **14** while the reaction is kept in the darkness. This equilibrium was reached much faster and further displaced toward **$14_{N\text{-}I}$** in absence of Na_2CO_3 than in the presence of the base (entries 3 and 4). Additionally, this intermediate **$14_{N\text{-}I}$** did not undergo any reaction in absence of light; however, wavelengths above 445 nm were efficient to initiate the methyl functionalization (entry 2). Noteworthy, no intermediate was detected under conditions of entry 1, while intermediates **14(I)** and **14(I_2)** were detected within the formation of lactam **14c**.

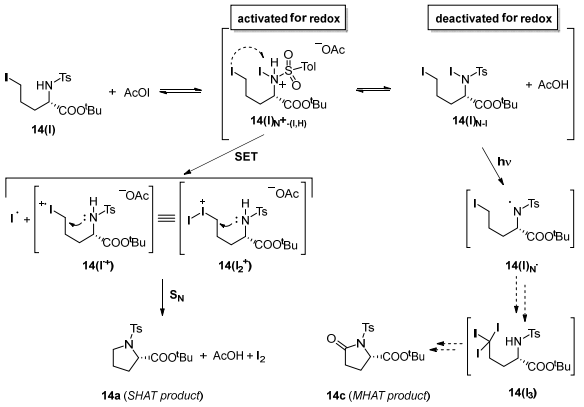
Scheme 3. Evolution of 14(I) toward 14a or 14c.



Secondly, we also found that the cyclization process did not involve a classical intramolecular nucleophilic substitution catalyzed by acids, since the evolution of **14(I)** in the absence of reagent or separately addition of iodine, AcOH, CSA, $Zn(OTf)_2$ or $PhI(OAc)_2$, and either under irradiation with light or in the dark, no considerable evolution toward cyclic compound **14a** was observed (see *SI*: table *S20*, entries 1-7). Nevertheless, when **14(I)** was added to a previously stirred solution of $PhI(OAc)_2$ and I_2 in the dark and absence of Na_2CO_3 (Scheme 3, equation 1), it was completely converted into **14a** in less than 3 minutes. On the contrary, this cyclization was dramatically slowed down when it was carried out in the presence of a slurry of Na_2CO_3 (conditions C), where 87.5 hours were necessary to achieve the 50% of conversion. Fortunately, when the reaction was performed

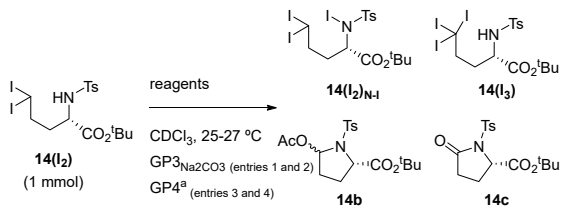
in absence of Na_2CO_3 at 5 ºC (conditions B), it was possible to monitor it by ^1H NMR and plot the concentrations versus time for **14(I)**, **14a** and **14(I)$_{N\text{-}I}$**, providing a graph consistent with a second-order pre-equilibrium first-order reaction, the pathway suggested in equation 1, where **14(I)$_{N\text{-}I}$** is proposed as an intermediate (schemes 4 and *S11*).

Scheme 4. Proposed mechanism for the cyclization step (key of chemoselectivity)



Therewith, we proposed that the cyclization step involved a mechanism of oxidative deiodination, where the protonated *N*-iodoamide group of intermediate **14(I)$_{N\text{-}I}$** is responsible for the oxidative activation of the primary iodoalkane moiety.[16] As a consequence of the inhibition of the cyclization step by the presence of Na_2CO_3, further generation of *N*-radical specie **14(I)$_{N}$•** is favored under irradiation and subsequent intramolecular HAT reactions could take place (scheme 4). As a result, the reaction continues toward the multiple (triple) iodination of the methyl group, leading to the formation of **14c** after cyclization.

Table 3. Monitored experiments with **14(I$_2$)** by ^1H NMR:



entry	reagents (mmol)	hν	t (h)	conv[b]	major product (conv)[b]
1	$PhI(OAc)_2$ (3.5), I_2 (1), Na_2CO_3 (100%)	[A]	2	87	**14c** (78.3)
2	$PhI(OAc)_2$ (10), I_2 (2), Na_2CO_3 (100%)	[A+f]	0.25	95.3	**14(I$_3$)** (87.2)[c]
3	$PhI(OAc)_2$ (4), I_2 (1)	-	3	100	**14b** (>95)
4	$PhI(OAc)_2$ (4), I_2 (1), Na_2CO_3 (200%)	-	3	12	**14b** (7)[d]

[a] GP4: reagents were stirred in the $CDCl_3$ for 24 h previous to the addition of **14(I$_2$)**; [b] calculated by ^1H NMR; [c] **14c** (8.1%) was also detected; [d] **14(I$_2$)$_{N\text{-}I}$** (22%) was also detected.

Furthermore, we observed that **14(I$_2$)** could be efficiently transformed into **14c** employing the $GP3_{Na2CO3}$ (table 6, entry 1) via cyclization of the pseudo-stable intermediate **14(I$_3$)**, which could be detected as the major product when the reaction was monitored in earlier stage (entry 2). **14(I$_2$)** could also be almost quantitatively cyclized into **14b** (entry 3) following an oxidative deiodination mechanism in absence of light. This cyclization is much slower than in the case of **14(I)** toward **14a** and also does not compete with the third methyl-iodination process toward **14(I$_3$)** employing $GP3_{Na2CO3}$ under irradiation (compare entry 2 and entry 4, scheme *S12*). Moreover, we elucidated that neither **14a** nor **14b** are intermediates toward **14c** under our reaction conditions (scheme *S16*). Thus, we defined that the formation of pyrrolidines **Na** involves a single hydrogen Atom Transfer process (SHAT), while the formation of 2-pyrrolidinones requires a Multiple Hydrogen Atom Transfer process (MHAT).

In summary, the herein described tunable reactivity of *N*-iodo sulfonamides as radical precursors as well as oxidant of iodoalkanes can be used to achieve the chemoselective intramolecular functionalization of unactivated methyl groups. Consequently, we present a new methodology to synthesize pyrrolidines (SHAT process) or 2-pyrrolidinones (MHAT process) in a wide range of conformationally non-restricted substrates. It has been useful to define the concept of SHAT/MHAT to refer to single or multiple oxidations at the same carbon center, that has been extended to achieve chemoselective fuctionalizations at unactivated methanediyl-groups. These studies will appear in the literature in due course.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, full characterization of products, DFT calculations, NMR monitored experiments, additional schemes and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org..

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Notes

The authors declare no competing financial interest.

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[12] (**Na**), (**Nb**) or (**Nc**): **N** refers to number of the precursor without any functionalization; **a** refers to pyrrolidine derivatives; **b** refers to 2-acetyl pyrrolidine derivatives; **c** refers to 2-pyrrolidinone derivatives.

[13] Jung, M. E.; Piizzi, G. *Chem. Rev.* **2005**, *105*, 1735.

[14] Recommended ionization energies (IEs; in eV) of halopropanes (R–X → R–X$^{+\bullet}$) taken from S.G. Lias, "Ionization Energy Evaluation" in NIST Chemistry WebBook, NIST Standard Reference Database Number 69, Eds. P.J. Linstrom and W.G. Mallard, National Institute of Standards and Technology, Gaithersburg MD, 20899, http://webbook.nist.gov, (retrieved September 19, 2014): ICH_2–CH_2–CH_3 (9.26); CH_3–CHI–CH_3 (9.19).

[15] The results obtained when other interesting selected conditions were employed, are summarized in the Supporting Information.

[16] For an overview on effective oxidative deiodination, see: (a) Zefirov, N. S.; Zhdankin, V. V.; Koz'min, A. S. *J. Org. Chem.* **1985**, *50*, 1872; (b) Macdonalds, T. L.; Narasimhan, N. *J. Org. Chem.* **1985**, *50*, 5000; (c) Gallos, J.; Varvoglis, A. *J. Chem. Soc. Perkin Trans. I* **1983**, 1999.