Organic LETTERS

Letter

pubs.acs.org/OrgLett

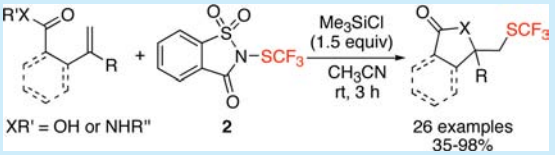
Lewis Acid Mediated Trifluoromethylthio Lactonization/Lactamization

Chunfa Xu and Qilong Shen*

Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, China

Supporting Information

ABSTRACT: A highly selective Lewis acid mediated trifluoromethylthio lactonization/lactamization of olefins is described. The reaction was proposed to proceed via a thiiranium ion intermediate, which was further attacked by the carboxylic acid or amide to generate the corresponding trifluoromethylthiolated lactone/lactam.



Halolactonization, a fundamental reaction that stereoselectively forges two carbon-heteroatom bonds, represents a powerful synthetic transformation that enables the synthetic chemists to build up molecular complexity in a predictable manner.[1] Mechanistically, the reaction was proposed to proceed via a nucleophilic attack of a carboxylic acid to an electrophilic halonium ion that is generated from the reaction of an olefin with an electrophilic halogen reagent.[2] Likewise, sulfenofunctionalization of alkenes using electrophilic sulfur reagents,[3] one of the most vigorous approaches for the introduction of a valuable thio group that allows further manipulations, was proposed to undergo a similar thiiranium ion intermediate.[3b] Because the CF_3S group is generally considered as a pseudohalide,[4] we speculate whether the reaction of an olefin with an electrophilic trifluoromethylthiolating reagent, such as trifluoromethylthiosuccinimide,[5] trifluoromethylthiophthalimide,[6] or trifluoromethylthiosaccharin **2**[7] that was developed in our laboratory recently, could form an analogous trifluoromethyl-substituted thiiranium ion intermediate **A** or **B**. Subsequent nucleophilic attack of the thiiranium ion by the carboxylic acid would generate trifluoromethylthiolated lactone **C** and/or **D** (Figure 1). Thus, the overall process would constitute a new efficient method for the incorporation of the trifluoromethylthio group into small molecules. Currently, development of efficient methods for the incorporation of the trifluoroemthylthio group into small molecules under mild reaction conditions is of great interest due to the beneficial effects of the trifluoromethylthio group for the drug-like molecules, such as enhanced lipophilicity and improved metabolic stability.[8]

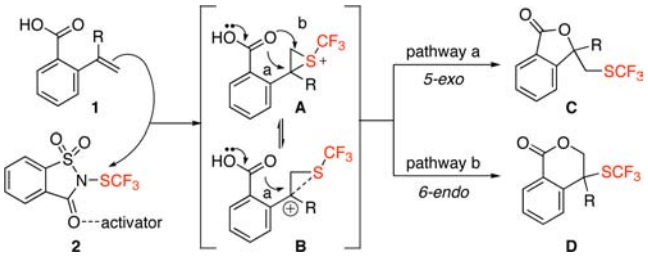


Figure 1. Proposed trifluoromethylthio lactonization reaction.

Herein, we describe a Lewis acid promoted trifluoromethylthio lactonization/lactamization of olefins using trifluoromethylthiosaccharin **2** as the electrophilic trifluoromethylthiolating reagent and 1.5 equiv of Me_3SiCl as the activator. Notably, even though intermolecular trifluoromethylthio functionalization reactions of olefins have been reported previously,[9] to the best of our knowledge, the current method represents the first intramolecular trifluoromethylthio lactonization/lactamization reaction of olefins.

The trifluoromethylthio lactonization of 2-(1-phenylvinyl)-benzoic acid **1** with trifluoromethylthiosaccharin **2** in the presence of different Lewis acids or Brønsted acids as the activator was initially chosen as a model reaction to optimize the reaction conditions. In general, reactions of 2-(1-phenylvinyl)-benzoic acid with trifluoromethylthiosaccharin in the presence of 1.0 equiv of $HCl{\cdot}Et_2O$ or Me_3SiCl[7] occurred smoothly after 2 h at room temperature to give a single product **3a** in 57% and 61%, respectively, as determined by ^{19}F NMR spectroscopy (Scheme 1, entries 3 and 7), while reactions using *p*-toluenesulfonic acid or (*S*)-2-(diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine as the activator occurred in less than 5% yield (Scheme 1, entries 1−2). To probe whether the halogen anion played an important role for the reaction, we further studied the reaction using $n Bu_4NCl$ or $n Bu_4NBr$ as the activator under otherwise identical conditions, and formation of the trifluoromethylthio lactonization product was observed in less than 5% yield (Scheme 1, entries 5−6). These results indicated that the lactonization was promoted by either a Lewis acid or a Brønsted acid. It was further discovered that the amount of the activator is important for the yield of the product. When 1.5 equiv of Me_3SiCl was used as the activator, the desired product was formed in quantitative yield and was isolated in 95% yield (Scheme 1, entry 8). In contrast, the yield of the product was decreased to 51% when 0.5 equiv of Me_3SiCl was used (Scheme 1, entry 9). We further studied the effect of

Received: August 10, 2015
Published: September 9, 2015

DOI: 10.1021/acs.orglett.5b02315
Org. Lett. 2015, 17, 4561−4563

Scheme 1. Optimization of Lewis Acid or Brønsted Acid Mediated Trifluoromethylthio Lactonization[a]

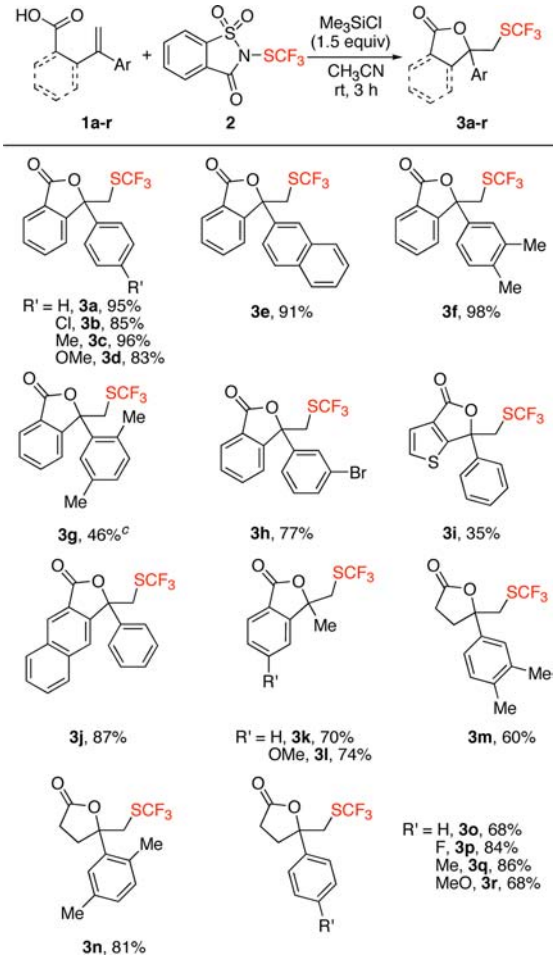
entry	activator	solvent	temp	time	yield (%)[b]
1	TsOH·H_2O	CH_3CN	rt	2 h	< 5[c]
2	Silyl ether [d]	CH_3CN	rt	2 h	< 5
3	HCl·Et_2O	CH_3CN	rt	2 h	57
4	HCl·Et_2O	CH_2Cl_2	rt	2 h	8
5	nBu_4NCl	CH_3CN	rt	2 h	< 5[e]
6	nBu_4NBr	CH_3CN	rt	2 h	< 5[e]
7	TMSCl	CH_3CN	rt	2 h	61
8	TMSCl	CH_3CN	rt	2 h	99(95)[f]
9	TMSCl	CH_3CN	rt	2 h	51[g]
10	TMSCl	CH_2Cl_2	rt	4 h	< 5
11	TMSCl	CH_2Cl_2	60 °C	6 h	75
12	TMSCl	$CHCl_3$	rt	2 h	15
13	TMSCl	toluene	rt	2 h	< 5
14	TMSCl	acetone	rt	2 h	< 5
15	TMSCl	THF	rt	2 h	< 5
16	TMSCl	CH_3CN	rt	2 h	< 5[h]
17	TMSCl	CH_3CN	rt	2 h	< 5[i]

[a]Reaction conditions: 2-(1-phenylvinyl)benzoic acid **1a** (0.05 mmol), electrophilic trifluoromethylthiosaccharin (0.05 mmol), activator (1.0−1.5 equiv) in solvent at room temperature 2−6 h. [b]Yields were determined by ^{19}F NMR analysis of the crude reaction mixture with an internal standard. [c]2-(1-(4-Chlorophenyl)vinyl)benzoic acid was used. [d](*S*)-2-(Diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine. [e]2-(1-(4-Methylphenyl)vinyl)benzoic acid was used. [f]Me_3SiCl (1.5 equiv) was used, isolated yield. [g]Me_3SiCl (0.5 equiv) was used. [h]Trifluoromethylthiosuccinimide was used. [i]Trifluoromethylthiophthalimide was used.

different solvents. Reactions in other solvents such as toluene, acetone, THF, CH_2Cl_2, or $CHCl_3$ were less efficient (Scheme 1, entries 10−15). Furthermore, when trifluoromethylthiosuccinimide or trifluoromethylthiophthalimide was used as the electrophilic trifluoromethylthiolating reagent, formation of the desired product was observed in less than 5% yield (Scheme 1, entries 16−17). These results were in agreement with our previous observation that trifluoromethylthiosaccharin is much more reactive than trifluoromethylthiosuccinimide or trifluoromethylthiophthalimide because of the stronger electron-withdrawing property of the sulfonyl group as compared to that of a carbonyl group.[7] Since compound **D** was not observed under these reaction conditions, it is likely that transition state **B** was the main form of the thiiranium ion intermediate because of two conjugated phenyl groups that could stabilize the tertiary carbon cation (Figure 1). Subsequent nucleophilic attack of the cation by the carboxylic acid through a 5-exo cyclization pathway generates trifluoromethylthiolated lactone **C**. In agreement with this assertion, an inseparable mixture of **C**/**D** (R = H) in a 10:1 ratio was observed to form in 50% yield when 2-vinylbenzoic acid was reacted with reagent **2** after 3 h at room temperature, since the thiiranium ion intermediate was stabilized only by one phenyl group.

Having established the best conditions for highly selective trifluoromethylthiolactonization, we assessed the potential of this reaction for a variety of substituted 2-(1-phenylvinyl)benzoic acids and 4-arylpent-4-enoic acids, as summarized in Scheme 2.

Scheme 2. Scope of Me_3SiCl Mediated Trifluoromethylthio Lactonization[a,b]



[a]Reaction conditions: compound **1a−r** (0.3 mmol), electrophilic trifluoromethylthiosaccharin (0.45 mmol), Me_3SiCl (0.45 mmol) in CH_3CN at room temperature for 3 h. [b]Isolated yields. [c]80 °C.

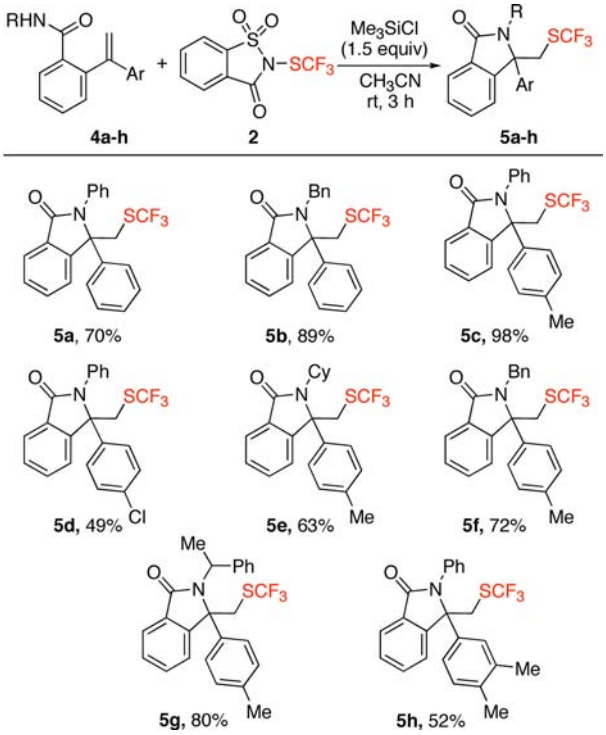
In most cases, the trifluoromethylthio cation induced cyclizations of substrates **1a−r** were completed to give the corresponding lactone products within 3 h at room temperature, except for the reaction of 2-(1-(2,5-dimethylphenyl)vinyl)benzoic acid which required 80 °C. It is likely that the *ortho*-methyl group of the phenyl ring makes the double bond sterically slightly hindered that requires higher activation energy for the electrophilic trifluoromethylthio cation to get close to the double bond. In general, only the five-membered lactones via the exo-cyclization pathway were observed. The structure of compound **3j** was further confirmed by X-ray diffraction of its single crystals (see Supporting Information for details).

The success of trifluoromethylthio lactonization reactions led us to study the reactions of trifluoromethylthiosaccharin with vinyl benzamides. Under the standard reaction conditions, various vinyl benzamides reacted with trifluoromethylthiosaccharin **2** to give the corresponding trifluoromethylthiolactams in high yields (Scheme 3). Likewise, only the *exo*-tirfluoromethylthio lactamization products were observed as determined by ^{19}F NMR spectroscopy.

Since a chiral carbon center was established in the cyclization reaction, it provides an opportunity to explore the asymmetric trifluoromethylthio lactonization/lactamization.[3c] Although we

DOI: 10.1021/acs.orglett.5b02315
Org. Lett. 2015, 17, 4561−4563

Scheme 3. Scope of Me_3SiCl Mediated Trifluoromethylthio Lactamization[a,b]



[a]Reaction conditions: compound **4a–h** (0.3 mmol), electrophilic trifluoromethylthiosaccharin (0.45 mmol), Me_3SiCl (0.45 mmol) in CH_3CN at room temperature for 3 h. [b]Isolated yields.

tried many catalysts derived from different chiral Lewis acids, the best enantioselectivity (23% ee) was observed when a 10 mol % Et_2AlCl/(*S*)-BINOL was used as the catalyst.[10] Clearly, there is still room for improvement of the enatioselectivity of the trifluoromethylthio lactonization/lactamization.

In summary, we have developed a Lewis acid mediated trifluoromethylthio lactonization/lactamization of gem-disubstituted alkenes. The reaction proceeded with excellent selectivity via an exo-cyclization pathway. It was proposed that a thiiranium ion intermediate was initially formed, which was further attacked by the carboxylic acid or amide to generate the corresponding trifluoromeththiolated lactone/lactam. Further investigation of the corresponding asymmetric trifluoromethylthio lactonization/lactamization is ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02315.

All experimental procedures and spectroscopic data of compounds **3a–r** and **5a–h** (PDF)

X-ray crystallography data of **3j** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: shenql@mail.sioc.ac.cn

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank the financial support from National Basic Research Program of China (2012CB821600), National Natural Science Foundation of China (21172245/21172244/21372247/21421002) and sioc.

■ REFERENCES

(1) (a) Dowle, M. D.; Davies, D. I. *Chem. Soc. Rev.* **1979**, *8*, 171. (b) Chen, G.-F.; Ma, S. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 8306. (c) Snyder, S. A.; Treitler, D. S.; Brucks, A. P. *Aldrichimica Acta* **2011**, *44*, 27. (d) Tan, C.-K.; Zhou, L.; Yeung, Y.-Y. *Synlett* **2011**, *10*, 1335. (e) Denmark, S. E.; Kuester, W. E.; Burk, M. T. *Angew. Chem., Int. Ed.* **2012**, *51*, 10938. (f) Nolsoe, J. M. J.; Hansen, T. V. *Eur. J. Org. Chem.* **2014**, *2014*, 3051. (g) Cheng, Y.-A.; Yu, W. Z.; Yeung, Y.-Y. *Org. Biomol. Chem.* **2014**, *12*, 2333. (h) Hennecke, U.; Wilking, M. *Synlett* **2014**, *25*, 1633.

(2) Ingold, C. K. *Structure and Mechanism in Organic Chemistry*; Cornell University Press: Ithaca, 1953; pp 658 − 670.

(3) (a) Capozzi, G.; Modena, G. In *Organic Sulfur Chemistry*; Bernardi, F., Csizmadia, I. G., Mangini, A., Eds.; Elsevier: Amsterdam, 1985; Chapter 5. (b) Smit, V. A.; Zefirov, N. S.; Bodrikov, I. V.; Krimer, M. Z. *Acc. Chem. Res.* **1979**, *12*, 282. (c) Denmark, S. E.; Vogler, T. *Chem. - Eur. J.* **2009**, *15*, 11737.

(4) Yagupol'skii, L. M.; Ilchenko, A. Y.; Kondratenko, N. V. R. *Russ. Chem. Rev.* **1974**, *43*, 32.

(5) (a) Hass, A.; Möller, G. *Chem. Ber.* **1996**, *129*, 1383.

(6) (a) Munavalli, S.; Rohrbaugh, D. K.; Rossman, D. I.; Berg, F. J.; Wagner, G. W.; Durst, H. D. *Synth. Commun.* **2000**, *30*, 2847. (b) Bootwicha, T.; Liu, X.; Pluta, R.; Atodiresei, I.; Rueping, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 12856. (c) Rueping, M.; Liu, X.; Bootwicha, T.; Pluta, R.; Merkens, C. *Chem. Commun.* **2014**, *50*, 2508. (d) Pluta, R.; Nikolaienko, P.; Rueping, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 1650. (e) Kang, K.; Xu, C.-F.; Shen, Q. *Org. Chem. Front.* **2014**, *1*, 294. (f) Yang, T.; Lu, L.; Shen, Q. *Chem. Commun.* **2015**, *51*, 5479.

(7) Xu, C.-F.; Ma, B.-Q.; Shen, Q. *Angew. Chem., Int. Ed.* **2014**, *53*, 9316.

(8) (a) Leroux, F.; Jeschke, P.; Schlosser, M. *Chem. Rev.* **2005**, *105*, 827. (b) Manteau, B.; Pazenok, S.; Vors, J.-P.; Leroux, F. R. *J. Fluorine Chem.* **2010**, *131*, 140. (c) Boiko, V. N. *Beilstein J. Org. Chem.* **2010**, *6*, 880. (d) Manteau, B.; Pazenok, S.; Vor, J.-P.; Leroux, F. R. *J. Fluorine Chem.* **2010**, *131*, 140. (e) Landelle, G.; Panossian, A.; Pazenok, S.; Vors, J.-P.; Leroux, F. R. *Beilstein J. Org. Chem.* **2013**, *9*, 2476. (f) Tlili, A.; Billard, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 6818. (g) Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 8214. (h) He, W.-M.; Weng, Z.-Q. *Prog. Chem.* **2013**, *25*, 1071. (i) Toulgoat, F.; Alazet, S.; Billard, T. *Eur. J. Org. Chem.* **2014**, *2014*, 2415. (j) Xu, X.-H.; Matsuzaki, K.; Shibata, N. *Chem. Rev.* **2015**, *115*, 731. (k) Shao, X.-X.; Xu, C.-F.; Lu, L.; Shen, Q. *Acc. Chem. Res.* **2015**, *48*, 1227.

(9) (a) Ferry, A.; Billard, T.; Langlois, B. R.; Bacque, E. *Angew. Chem., Int. Ed.* **2009**, *48*, 8551. (b) Luo, J.; Zhu, Z.-C.; Liu, Y.-N.; Zhao, X.-D. *Org. Lett.* **2015**, *17*, 3620.

(10) Ishiyama, T.; Ahiko, T.-A.; Miyaura, N. *J. Am. Chem. Soc.* **2002**, *124*, 12414.

DOI: 10.1021/acs.orglett.5b02315
Org. Lett. 2015, 17, 4561−4563