EurJOC
European Journal of Organic Chemistry

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Metal-free C−S bond cleavage to access N-substituted acrylamide and β-aminopropanamide

Authors: Ke Yang, Yi Li, Zhiyan Ma, Long Tang, Yue Yin, Hao Zhang, Zhengyi Li, and Xiaoqiang Sun

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201900960

Link to VoR: http://dx.doi.org/10.1002/ejoc.201900960

Supported by
ACES Asian Chemical Editorial Society

WILEY-VCH

10.1002/ejoc.201900960

WILEY-VCH

Metal-free C−S bond cleavage to access *N*-substituted acrylamide and β-aminopropanamide

Ke Yang,*[a] Yi Li,[a] Zhiyan Ma,[a] Long Tang,[a] Yue Yin,[a] Hao Zhang,[a] Zhengyi Li*[a] and Xiaoqiang Sun*[a]

Abstract: Metal-free and Selectfluor-mediated C−S bond cleavage is decscribed. This novel strategy provides a facile and efficient method to access important *N*-substituted acrylamide and β-aminopropanamide derivatives with good functional groups tolerance and yields.

Introduction

The activation and transformations of organic chemical bonds are fundamental scientific issues. Recently, C−S bond cleavages and their transformations for the construction of C−C bonds and C−heteroatom bonds have received tremendous attention in the organic and petroleum chemistry.[1] Among them, thioether compounds have great potential to undergo C−S bond cleavages to construct various important skeletons in many natural products and pharmaceuticals.[2] The most developed one in this area relies on the insertion of a transition-metal catalyst into the C−S bond, which leads to the corresponding C−S bond cleavage.[2a-g] Although significant progress have been made in the past decades, the development of a facile and efficient metal-free C−S bond cleavage process is still a challenging issue.

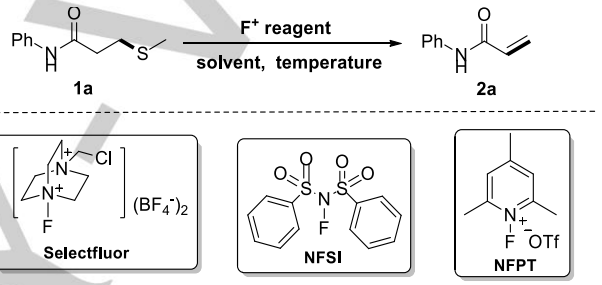
Selectfluor [1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)], as one of the important electrophilic fluorinating reagents, has attracted much attention due to its significant improvement in the fluorination.[3] Besides, Selectfluor can also be used as an oxidant or Lewis acid in some other organic transformations.[4] Very recently, our group demonstrated the metal-free intramolecular N-S bond formation to construct benzoisothiazol-3-ones.[5] In our continuing studies, we found the selective C−S bond cleavage of *N*-substituted 3-methylthiopropanamides could produce *N*-substituted acrylamides in the presence of Selectfluor. Inspired by this investigation, we believe that Selectfluor can also promote the construction of important biologically active β-aminopropanamides via an intermolecular metal-free C−S bond cleavage and C−N formation process. Herein, we report our results on the direct synthesis of *N*-substituted acrylamide and β-aminopropanamide derivatives in the presence of Selectfluor.

[a] Dr. Ke Yang, Yi Li, Zhiyan Ma, Long Tang, Yue Yin, Hao Zhang, Prof. Dr. Zhengyi Li, and Prof. Dr. Xiaoqiang Sun
Jiangsu Key Laboratory of Advanced Catalytic Materials & Technology
School of Petrochemical Engineering
Changzhou University
1 Gehu Road, Changzhou, Jiangsu 213164, China
E-mail: keyang@cczu.edu.cn
Homepage: http://che.cczu.edu.cn/2019/0304/c2960a200740/page.htm

Supporting information for this article is given via a link at the end of the document.

Results and Discussion

Table 1. Optimization of reaction conditions for *N*-substituted acrylamide. [a]

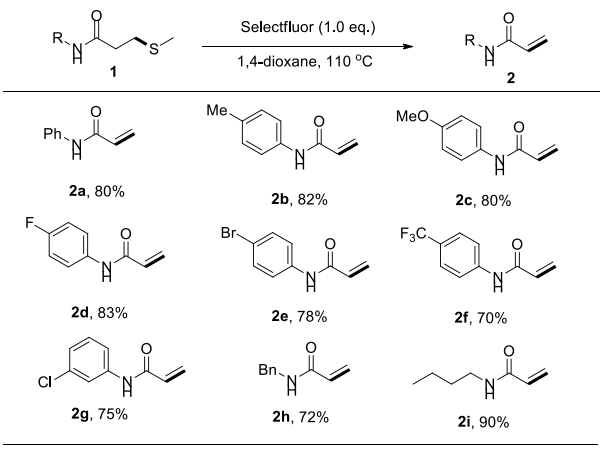


Entry	F+ reagent	Solvent	Temperature	Yield [b]
1	Selectfluor (1.0 eq.)	MeCN	110 °C	28%
2	Selectfluor (1.0 eq.)	MeOH	110 °C	62%
3	Selectfluor (1.0 eq.)	THF	110 °C	21%
4	Selectfluor (1.0 eq.)	Acetone	110 °C	57%
5	Selectfluor (1.0 eq.)	1,4-dioxane	110 °C	80%
6	Selectfluor (1.0 eq.)	1,4-dioxane	100 °C	69%
7	Selectfluor (1.0 eq.)	1,4-dioxane	120 °C	62%
8	Selectfluor (0.5 eq.)	1,4-dioxane	110 °C	31%
9	Selectfluor (1.5 eq.)	1,4-dioxane	110 °C	46%
10	NFSI (1.0 eq.)	1,4-dioxane	110 °C	62%
11	NFPT (1.0 eq.)	1,4-dioxane	110 °C	40%

[a] Reaction conditions: **1a** (0.2 mmol), F+ reagent, solvent (2.5 mL), 12 h. [b] Isolated yields. NFSI = *N*-Fluorobenzenesulfonimide. NFPT = 1-Fluoro-2,4,6-trimethylpyridinium triflate.

Our initial investigation began with the reaction of 3-(methylthio)-*N*-phenylpropanamide **1a** in the presence of a stoichiometric amount of Selectfluor in MeCN at 110 °C, *N*-phenylacrylamide **2a** was detected in 28% yield (Table 1, entry 1). To our delight, the subsequent examination of other solvents revealed that this process can be smoothly carried out in the solvent of 1,4-dioxane in 80% yield (entries 1-5). However, the yield of **2a** could not be improved any more by increasing or decreasing the reaction temperature or amounts of Selectfluor

(entries 6-9). Finally, the screening of fluorinating reagents revealed that a low yield was detected with *N*-fluorobenzenesulfonimide (NFSI) or 1-fluoro-2,4,6-trimethylpyridinium triflate (NFPT) (entries 10-11). With the optimized reaction conditions in hand, the substrate scope for *N*-substituted acrylamide was carried out. As shown in Scheme 1, various *N*-substituted 3-methylthiopropanamides were well tolerated and provided the desired *N*-substituted acrylamides (**2a-i)** in good yields.



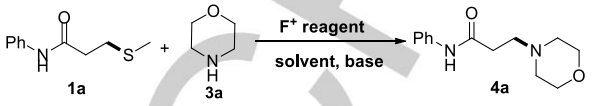
Scheme 1. Substrate scope for *N*-substituted acrylamide. Reaction conditions: **1** (0.2 mmol), Selectfluor (0.2 mmol), 1,4-dioxane (2.5 mL), 110 °C, 12 h. Isolated yields.

Based on the above results, we explored the reactions of *N*-substituted 3-methylthiopropanamides and amines for the one-pot synthesis of *N*-substituted β-aminopropanamides in the presence of Selectfluor (Table 2). However, only trace desired product **4a** was obtained in the reaction of substrate **1a** and morpholine **3a** under the standard conditions. After rescreening of the reaction conditions, the results indicated that the reaction of **1a** and morpholine **3a** using a stoichiometric amount of Selectfluor and K_2CO_3 in the solvent of MeOH gave the desired product **4a** in 70% isolated yield.

As shown in Scheme 2, different *N*-aryl substituted 3-methylthiopropanamides including electron-donating groups (Me and MeO) and electron-withdrawing groups (F, Cl, Br and CF_3) were investigated, and the desired *N*-substituted β-aminopropanamides (**4a**-**g**) were isolated in moderate to good yields. Notably, the well-tolerated halogens could provide further manipulations of the initial products. Furthermore, *N*-benzyl substituted substrate **1h** afforded the desired product **4h** in 68% isolated yield. Next, the scope study of amine was also tested in this system. The simple diethylamine **3b** could be used to construct the corresponding product **2g** in 75% yield. Moreover, both linear and branched aliphatic amines were tolerated and gave the desired *N*-substituted β-aminopropanamides (**4j**-**l)** in moderate yields.

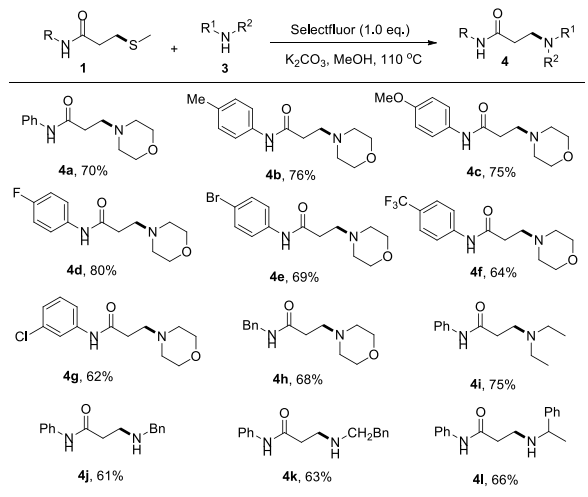
Proposed mechanistic pathways have been proposed in Scheme 3. Substrate **1a** produces fluorosulfonium salt **A** in the presence of Selectfluor,[5-6] then salt **A** can be converted to the corresponding thionium intermediate **B** and its isomer **C**.[7] Next, the intermolecular elimination of intermediate **C** provides the acrylamide **2a**.[8] Finally, in the presence of base and morpholine, the desired product **4a** is formed through a Michael addition process (path a).[9] On the other hand, substrate **1a** can be oxidized to the corresponding sulfoxide **D** in the presence of Selectfluor, which is further transformed into acrylamide **2a**. Moreover, product **4a** can also be prepared through the amine substitution of sulfoxide **D** (path b, see Scheme S2 in Supporting Information).[5,10]

Table 2. Optimization of reaction conditions for *N*-substituted β-aminopropanamide.[a]

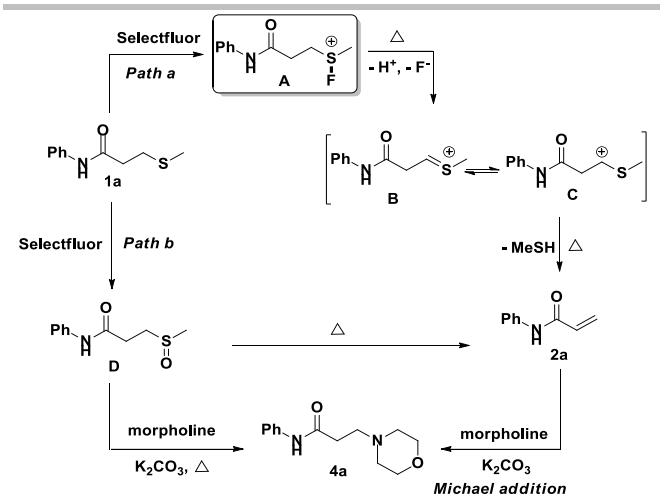


Entry	F+ reagent	Solvent	Base	Yield[b]
1	Selectfluor (1.0 eq.)	1,4-dioxane	-	trace
2	Selectfluor (1.0 eq.)	MeCN	-	5%
3	Selectfluor (1.0 eq.)	MeOH	-	21%
4	Selectfluor (1.0 eq.)	THF	-	9%
5	Selectfluor (1.0 eq.)	Acetone	-	10%
6	Selectfluor (1.0 eq.)	MeOH	K_2CO_3	70%
7	Selectfluor (1.0 eq.)	MeOH	Na_2CO_3	60%
8	Selectfluor (1.0 eq.)	MeOH	KOAc	35%
9	Selectfluor (0.5 eq.)	MeOH	K_2CO_3	23%
10	Selectfluor (1.5 eq.)	MeOH	K_2CO_3	62%
11	NFSI (1.0 eq.)	MeOH	K_2CO_3	20%
12	NFPT (1.0 eq.)	MeOH	K_2CO_3	34%

[a] Reaction conditions: **1a** (0.2 mmol), **3a** (0.2 mmol), F+ reagent, base (0.2 mmol), solvent (2.5 mL), 110 °C,12 h. [b] Isolated yields. NFSI = *N*-Fluorobenzenesulfonimide. NFPT = 1-Fluoro-2,4,6-trimethylpyridinium triflate.



Scheme 2. Substrate scope for *N*-substituted β-aminopropanamide. Reaction conditions: **1** (0.2 mmol), **3** (0.2 mmol), Selectfluor (0.2 mmol), K_2CO_3 (0.2 mmol), MeOH (2.5 mL), 110 °C, 12 h. Isolated yields.



Scheme 3. The plausible reaction mechanism.

Conclusions

In summary, an efficient Selectfluor-promoted C−S bond cleavage process has been developed to access different important *N*-substituted β-aminopropanamide and acrylamide derivatives by using *N*-substituted 3-methylthiopropanamides as the starting materials. This metal-free protocol is featured with good functional group compatibility and board substrate scope. Moreover, the study on its application is ongoing in our laboratories.

Experimental Section

General procedures for the synthesis of product 2. A 25 mL Schlenk tube was charged with 3-methylthiopropanamide **1** (0.2 mmol), Selectfluor (70.85 mg, 0.2 mmol) and 1,4-dioxane (2.5 mL). The tube was then sealed and stirred vigorously at 110 ˚C for 12 h. After cooling to room temperature, the reaction mixture was diluted with EtOAc (20 mL), filtered through a pad of Celite, and the filtrate was then concentrated in vacuo. The residue was purified by flash chromatography on silica gel to yield the desired product **2**.

General procedures for the synthesis of product 4. A 25 mL Schlenk tube was charged with 3-methylthiopropanamide **1** (0.2 mmol), amine **3** (0.2 mmol), Selectfluor (70.85 mg, 0.2 mmol), K_2CO_3 (27.64 mg, 0.2 mmol) and MeOH (2.5 mL). The tube was then sealed and stirred vigorously at 110 ˚C for 12 h. After cooling to room temperature, the reaction mixture was diluted with EtOAc (20 mL), filtered through a pad of Celite, and the filtrate was then concentrated in vacuo. The residue was purified by flash chromatography on silica gel to yield the desired product **4**.

Acknowledgments

We gratefully acknowledge the financial support from the National Natural Science Foundation of China (21572026, 21702019) and Advanced Catalysis and Green Manufacturing Collaborative Innovation Center, Changzhou University.

Keywords: Selectfluor • C-S bond cleavage • Metal-free • β-Aminopropanamide • Organic synthesis

[1] For selected reviews, see: (a) S. Otsuka, K. Nogi, H. Yorimitsu, *Top. Curr. Chem.* **2018**, *376*, 1. (b) L. Zhang, J. Dong, X. Xu, Q. Liu, *Chem. Rev.* **2016**, *116*, 287. (c) F. Pan, Z.-J. Shi, *ACS Catal.* **2014**, *4*, 280. (d) S. G. Modha, V. P. Mehta, E. V. Van der Eycken, *Chem. Soc. Rev.* **2013**, *42*, 5042. (e) L. D. Wang, W. He, Z.-K. Yu, *Chem. Soc. Rev.* **2013**, *42*, 599.

[2] For selected examples, see: (a) H. Minami, K. Nogi, H. Yorimitsu, *Org. Lett.* **2019**, *21*, 2518. (b) Y. Ma, J. Cammarata, J. Cornella, *J. Am. Chem. Soc.* **2019**, *141*, 1918. (c) H. Minami, S. Otsuka, K. Nogi, H. Yorimitsu, *ACS Catal*. **2018**, *8*, 579. (d) Z. Lian, B. N. Bhawal, P. Yu, B. Morandi, *Science* **2017**, *356*,1059. (e) M. Iwasaki, N. Topolovčan, H. Hu, Y. G. Nishimura, Y. G. Gagnot, R. Nanakorn, R. Yuvacharaskul, K. Nakajima, Y. Nishihara, *Org. Lett.* **2016**, *18*, 1642. (f) Y. Uetake, T. Niwa, T. Hosoya, *Org. Lett.* **2016**, *18*, 2758. (g) I. Burkhardt, L. Lauterbach, N. L. Brock, J. S. Dickschat, *Org. Biomol. Chem.* **2017**, *15*, 4432. (h) N. George, M. Bekkaye, A. Alix, J. Zhu, G. Masson, *Chem. Eur. J.* **2014**, *20*, 3621. (i) N. George, M. Bekkaye, G. Masson, J. Zhu, *Eur. J. Org. Chem.* **201**1, *2011*, 3695

[3] For selected reviews, see: (a) P. A. Champagne, J. Desroches, J.-D. Hamel, M. Vandamme, Paquin, J.-F. *Chem. Rev.* **2015**, *115*, 9073. (b) X. Yang, T. Wu, R. J. Phipps, F. D. Toste, *Chem. Rev.* **2015**, *115*, 826. (c) M. G. Campbell, T. Ritter, *Chem. Rev.* **2015**, *115*, 612. (d) V. Bizet, T. Besset, J.-A. Ma, D. Cahard, *Curr. Top. Med. Chem.* **2014**, *14*, 901. (e) S. Stavber, M. Zupan, *Adv. Org. Synth.* **2006**, *2*, 213. (f) P. T. Nyffeler, S. G. Duron, M. D. Burkart, S. P. Vincent, C.-H. Wong, *Angew. Chem., Int. Ed.* **2005**, *44*, 192.

[4] (a) S. Stavber, *Molecules* **2011**, *16*, 6432. (b) H. Bao, Z. Xu, D. Wu, H. Zhang, H. Jin, Y. Liu, *J. Org. Chem.* **2017**, *82*, 109. (c) J. Zhang, D. Shi, H. Zhang, Z. Xu, H. Bao, H. Jin, Y. Liu, *Tetrahedron* **2017**, *73*, 154. (d) J. Zhang, H. Zhang, D. Shi, H. Jin, Y. Liu, *Eur. J. Org. Chem.* **2016**, *2016*, 5545. (e) D. Liang, X. Li, Q. Lan, W. Huang, L. Yuan, Y. Ma, *Tetrahedron Lett.* **2016**, *57*, 2207. (f) J. Zhang, H. Wang, S. Ren, W. Zhang, Y. Liu, *Org. Lett.* **2015**, *17*, 2920. (g) H. Wang, S. Ren, J. Zhang, W. Zhang, Y. Liu, *J. Org. Chem.* **2015**, *80*, 6856. (h) S. Ren, J. Zhang, J.-H. Zhang, H. Wang, W. Zhang, Y. Liu, M. Liu, *Eur. J. Org. Chem.* **2015**, *2015*, 5381. (i) K. K. Laali, G. C. Nandi, S. D. Bunge, *Tetrahedron Lett.* **2014**, *55*, 2401. (j) A. M. Jadhav, S. A. Gawade, D. Vasu, R. B. Dateer, R.-S. Liu, *Chem. Eur. J.* **2014**, *20*, 1813. (k) J. Zhang, D. Wu, X. Chen, Y. Liu, Z. Xu, *J. Org. Chem.* **2014**, *79*, 4799. (l) D. Wu, J. Zhang, H. Wang, J.-H. Zhang, Y. Liu, M. Liu, *Asian J. Org. Chem.* **2014**, *3*, 1163. (m) W. Zhang, J. Zhang, Y. Liu, Z. Xu, *Synlett* **2013**, *24*, 2709.

[5] K. Yang, H. Zhang, B. Niu, T. Tang, H. Ge, *Eur. J. Org. Chem.* **2018**, *2018*, 5520.

[6] (a) G. S. Lal, *J. Org. Chem.* **1993**, *58*, 2791. (b) S. P. Vincent, M. D. Burkart, C.-Y. Tsai, Z. Zhang, C.-H. Wong, *J. Org. Chem.* 1**999**, *64*, 5264.

[7] Z. Li, H. Li, X. Guo, L. Cao, R. Yu, H. Li and S. Pan, *Org. Lett.,* **2008**, *10*, 803-805.

[8] (a) Y. F. Liu, X. Zhan, P. Y. Ji, J. W. Xu, Q. Liu, W. P. Luo, T. Q. Chen, C. C. Guo, *Chem. Commun.* **2017**, *53*, 5346. (b) Y.-F. Liu, P.-Y. Ji, J.-W. Xu, Y.-Q. Hu, Q. Liu, W.-P. Luo, C.-C. Guo, *J. Org. Chem.* **2017**, *82*, 7159.

[9] K. C. Bharadwaj, *ChemistrySelect*, **2017**, *2*, 5384.

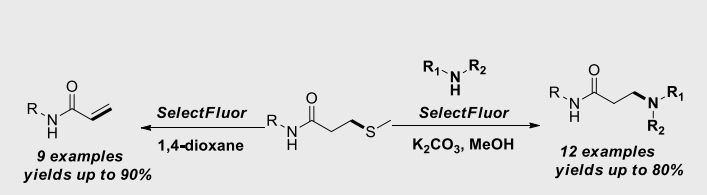
[10] S. Nagashima, M. Yokota, E. Nakai, S. Kuromitsu, K. Ohga, M. Takeuchi, S. Tsukamoto, M. Ohta, *Bioorg. Med. Chem.* **2007**, *15*, 1044.

10.1002/ejoc.201900960

WILEY-VCH

Entry for the Table of Contents (Please choose one layout)

COMMUNICATION



The metal-free C−S bond cleavege process has been established to construct *N*-substituted acrylamide and β-aminopropanamide derivatives in the presence of Selectfluor.

Selectfluor-Mediated Reactions

Ke Yang, Yi Li, Zhiyan Ma, Long Tang, Yue Yin, Hao Zhang, Zhengyi Li* and Xiaoqiang Sun**

Page No. – Page No.

Metal-free C−S bond cleavage to access *N*-substituted acrylamide and β-aminopropanamide