Tetrahedron Letters xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of thiazolidin-4-ones via [3+2] cycloaddition of in situ generated aza-oxyallylic cations with isothiocyanates

Gangqiang Wang [a,1], Sen Zhao [a,1], Rongxing Chen [a], Liangfeng Yang [a], Jian Wang [a], Haibing Guo [a], Minghu Wu [a], Justin Domena [b], Yalan Xing [b,*], Shaofa Sun [a,*]

[a] Non-power Nuclear Technology Collaborative Innovation Center, School of Nuclear Technology and Chemistry & Biology, Hubei University of Science and Technology, Xianning 437100, China
[b] Department of Chemistry, William Paterson University of New Jersey, 300 Pompton Road, Wayne, NJ 07470, United States

ARTICLE INFO

Article history:
Received 25 August 2017
Accepted 2 October 2017
Available online xxxx

Keywords:
Cycloaddition
Aza-oxyallylic cation
One-pot
Heterocycles
Isothiocyanates

ABSTRACT

A highly efficient one-pot synthesis of thiazolidin-4-ones via [3+2] cycloaddition of aza-oxyallylic cations with isothiocyanates is developed. The aza-oxyallyic cations were generated in situ in the present of a base. This cycloaddition reaction allows the rapid access to a variety of thiazolidin-4-one derivatives in mild conditions, good yield, and excellent functional group compatibility.

Introduction

Thiazolidin-4-ones are unique heterocyclic structural motifs which have been identified with a wide range of biological activities, such as cardiovascular,[1] hypnotic,[2] and anticancer activities[3] (Fig. 1). These important biological activities and intriguing heterocyclic structures attracted noticeable attention from the synthetic community, which led to the development of efficient methods for the synthesis of thiazolidin-4-one derivatives.[4]

During our continuous effort of developing efficient syntheses of bio-active heterocyclic compounds, we decided to take advantage of the [3+2] cycloaddition reaction of aza-oxyallylic cations to access thiazolidin-4-ones. After Jeffrey first reported the application of the aza-oxyallylic cation in [4+3] cycloaddition reactions, many research groups began to utilize aza-oxyallylic cations as the unique synthon for cycloaddition reactions in order to prepare heterocyclic molecules (Scheme 1). For instance, Lin and co-workers described a [3+3] cycloaddition of aza-oxyallylic cations with 2-alkenylindoles for the preparation of carbolinones.[5] In 2016, Jeffrey reported a synthesis of 4-oxazolidinone by [3+2] cycloaddition of aza-oxyallylic cations with carbonyl compounds.[6] Very recently, we communicated an efficient one-pot synthesis of 1,3-dihydro-2H-pyrrol-2-one derivatives via [3+2] cycloaddition of aza-oxyallylic cations and alkynes.[7] On the other hand, isothiocyanates have been extensively used in the [3+2] cycloaddition of aziridines for the synthesis of heterocycles.[8] Thiazolidin-4-ones derivatives have been prepared by [3+2] cycloaddition reaction previously[9] While we are preparing our manuscript, a report of base-promoted [3+2] cycloaddtion of azaoxyallyl cations with isothiocyanates appeared in the literature using hexafluoro-2-propyl alcohol (HFIP) as the solvent.[10] Herein, we present our study on the [3+2] cycloaddition of in situ generated aza-oxyallylic cations and isothiocyanates for the synthesis of thiazolidine-4-one derivatives. It is worth to mention that our work illustrated many examples with mono-substituted haloamides while the previous publications focus on germinal dimethyl-substituted haloamides.

Results/Discussion

We started our investigation for the optimal reaction conditions by choosing α-Bromoamide **1a** and isothiocyanatobenzene **2a** as the model substrate (Table 1). First, Na_2CO_3 was utilized as the base to produce aza-oxyallylic cations from α-Bromoamide **1a**. The corresponding aza-oxyallylic cation was expected to react with **2a** for the [3+2] cycloaddition. To our delight, CH_3CN was identified to be the best solvent (entry 1) which gave 93% yield of the desired [3+2] cycloaddition product **3a**. Other solvents including Toluene, Hexafluoroisopropanol (HFIP), CH_2Cl_2, DMF, CH_3OH, and THF all

* Corresponding authors.
E-mail address: xingy@wpunj.edu (Y. Xing).
[1] These authors contributed equally to this work

https://doi.org/10.1016/j.tetlet.2017.10.004
0040-4039/

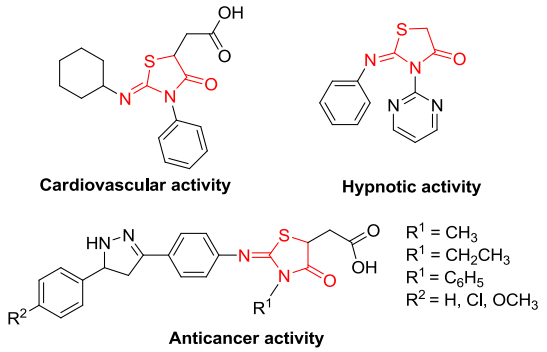
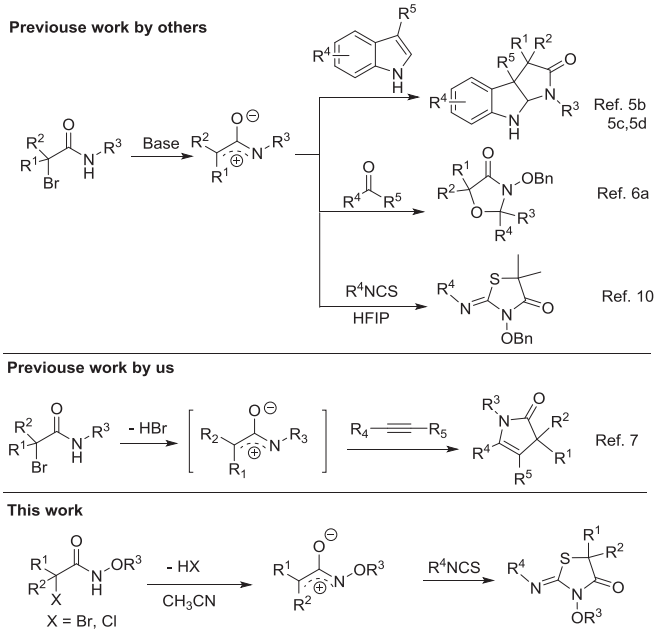


Fig. 1. Bioactive thiazolidin-4-ones.

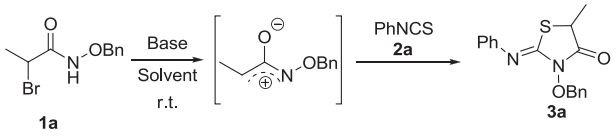


Scheme 1. Previous work.

gave less yields (entries 2–7). Next, different bases such as Cs_2CO_3, triethylamine, K_2CO_3, NaOAc, NaOH were screened. It was found that all other bases gave less yield than Na_2CO_3 (entries 8–12) in the presence of the optical solvent CH_3CN. This efficient cycloaddition reaction was conducted at a mild condition at room temperature within short reaction time (4 h).

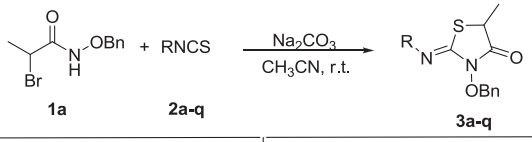
With the optimal conditions in hand, we began our study on the substrate scope and limitations of this reaction. As shown in Scheme 2, α-Bromoamide **1a** was utilized as the aza-oxyallylic cation donor. Concurrently, a variety of substituted aromatic and aliphatic thiocyanates were tested under the optimal [3+2] cycloaddition reaction conditions. Substituted isothiocyanatobenzene bearing either electron withdrawing or electron donating groups on the phenyl ring all gave good to excellent yields (entries **3a**–**l**). It is noticeable that strong electron withdrawing groups on the phenyl ring slightly decrease the yields of this reaction (entry **3j** and **3k**). Steric effect were also observed toinfluence the yields of the reaction. For example, *ortho*-substituted isothiocyanatobenzenes (entries **3b** and **3c**) showed lower yields than the corresponding *meta*- or *para*-substituted ones (entries **3b**, **3e**, **3h**, **3c**, **3d**, and **3f**). Additionally, the [3+2] cycloaddition reaction of thiocyanate with heteroaromatic substitute pyridine (entry **3m**) proceeded in good yield (89%). Several alkyl substituted thiocyanates

Table 1
Optimization of reaction conditions.[a]



Entry	Base	Solvent	T/h	T/°C	Yield[b]
1	Na_2CO_3	CH_3CN	4	r.t.	93%
2	Na_2CO_3	Tol	4	r.t.	<5%
3	Na_2CO_3	HFIP	4	r.t.	65%
4	Na_2CO_3	DCM	4	r.t.	<5%
5	Na_2CO_3	DMF	4	r.t.	67%
6	Na_2CO_3	CH_3OH	4	r.t.	15%
7	Na_2CO_3	THF	4	r.t.	13%
8	Cs_2CO_3	CH_3CN	4	r.t.	76%
9	TEA	CH_3CN	4	r.t.	73%
10	K_2CO_3	CH_3CN	4	r.t.	81%
11	NaOAc	CH_3CN	4	r.t.	11%
12	NaOH	CH_3CN	4	r.t.	43%

[a] Reaction condition: 1a (1.0 mmol), 2a (1.0 mmol), base (2.0 equiv.) in solvent (2 mL) for 4 h at room temperature.
[b] Isolated yields.



Entry	R	Yield(%)	Entry	R	Yield(%)
3a		93	3i	MeO	85
3b	Cl	81	3j	NC	79
3c	Me	78	3k	O_2N, Me	76
3d	Me	90	3l	Cl, Cl	86
3e	Cl	91	3m	N	89
3f	Me	85	3n	Ph	90
3g	F	90	3o	Ph	70
			3p		78
3h	Cl	89	3q		87

Scheme 2. Substrate scope of isothiocyanates.

were also found to generate the [3+2] cycloaddition products in good yields (entries **3n**–**q**).

To confirm the structure of the thiazolidin-4-one product of this [3+2] cycloaddition reaction, we successfully obtained the X-ray

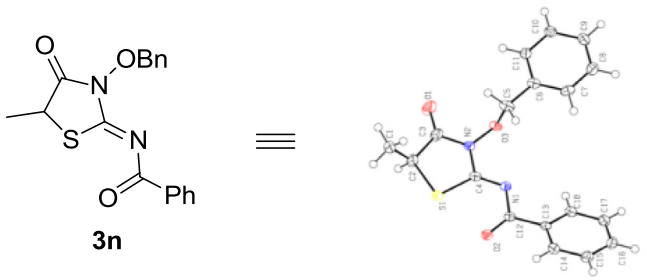
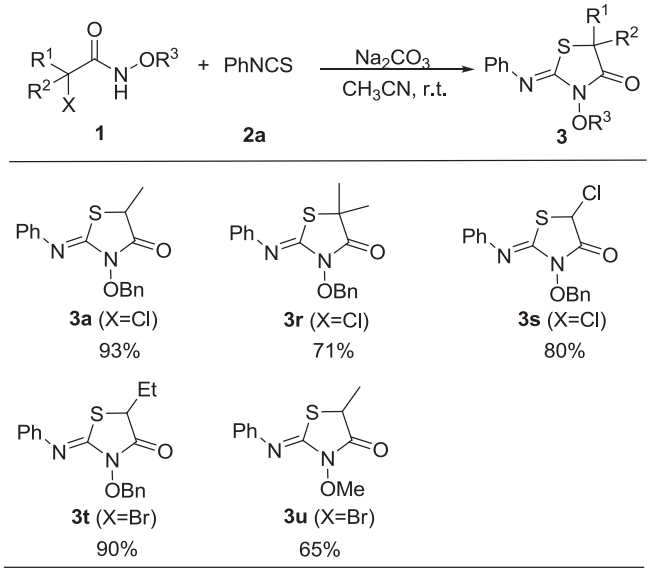
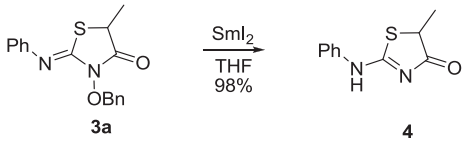


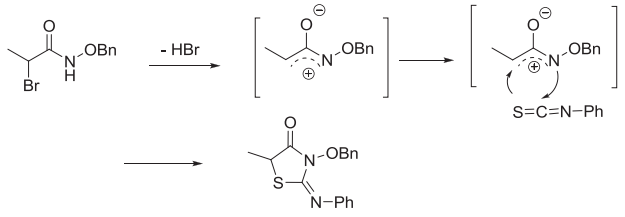
Fig. 2. X-ray structure of 3n.



Scheme 3. Substrate scope of α-haloamide.



Scheme 4. N—O bond cleavage.



Scheme 5. Proposed reaction mechanism.

crystallography of **3n** which clearly indicated the thiazolidin-4-one core structure (Fig. 2).[11]

Next, we turned our attention to the study of substrate scopes and limitation of the aza-oxyallylic cations which were in situ generated from α-haloamides. We found that both α-chloroamides and α-bromoamides can be utilized for the aza-oxyallylic cation formation for the cycloaddition reaction. α-Chloroamides with methyl, di-methyl, and chloro substitutions participated in this cycloaddition reaction smoothly and produced the desired products in good to excellent yields (Scheme 3, **3a**, **3r**, and **3s**). When α-bromoamide with ethyl substitution was employed, cycloaddition products were also obtained in 90% yield (**3t**). However, the reaction yield dropped to 65% when *N*-substitution was changed from OBn to OMe group (**3u**).

To demonstrate the broad application of this reaction in heterocyclic structure syntheses, we explored the N—O bond cleavage to remove the OBn group. Based on a literature procedure,[6] the N—OBn bond of **3a** was cleaved by SmI_2 to provide 2-aminothiazolone derivative **4** in good yield (Scheme 4). 2-Aminothiazolone core structure, which exhibits a wide range of biological activities,[12] is a well exploited pharmacophore in medicinal chemistry.[13] Our [3+2] cycloaddition followed by SmI_2 deprotection can serve as an efficient method to access these 2-aminothiazolone derivatives.

A plausible mechanism was proposed for this interesting [3+2] cycloaddition (Scheme 5). First, when a base was used, the aza-oxyallylic cation was generated. The dipolarphile thiocyanate reacts with the azaoxyllyic cation to produce the [3+2] cycloaddition product. The excellent regioselectivity of this reaction can be explained by the electronic property of isothiocyanates.[8] The nucleophilicity of sulphur and electrophilicity of carbon of isothicyantate determined the regioselectivity of this [3+2] cycloaddition.

Conclusion

In conclusion, we have developed an efficient and facile synthesis of thiazolidin-4-ones from [3+2] cycloaddition of in situ generated aza-oxyallylic cations and isothiocyanates. This one-pot reaction offers a unique approach to access bio-active thiazoidine-4-ones motifs in both good yield and mild conditions.

Acknowledgments

This work was supported by University and Education Department of Hubei Province Science and Technology Research Project (Nos. Q20162803). The authors are also grateful to National Natural Science Foundation (21602053). This research was supported by a grant from the Center for Research, College of Science and Health, William Paterson University of New Jersey. The authors are also grateful to the ART program, College of Science and Health, and Chemistry Department of William Paterson.

A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetlet.2017.10.004.

References

1. Nagar S, Singh HH, Sinha JN, Parmar SS. *J Med Chem*. 1973;16:178–180.
2. (a) Chaudhari SK, Verma M, Chaturvedi AK, Parmar SS. *J Pharm Sci*. 1975;64:614–617;
   (b) Chaudhary M, Parmar SS, Chaudhary SK, Chaturvedi AK, Rama Sastry BVJ. *Pharm Sci*. 1976;65:443–446.
3. Abdullah JH, Yahya THA, Al-ghorafi MAH, Yassin SH. *Der Pharma Chem*. 2014;6:203–210.
4. (a) Pankova AS, Samartsev MA, Shulgin LA, Goluvev PR, Avdontceva MS, Kuznetsov MA. *RSC Adv*. 2014;4:51780–51786;
   (b) Sathiskhkumar M, Nagarajan S, Shanmugavelan P, Dinesh M, Ponnuswamy A. *Beilstein J Org Chem*. 2013;9:689–697;
   (c) Abdel-Aziz HA, EI-Zahabi HSA, Dawood KM. *Eur J Med Chem*. 2010;45:2427–2432;
   (d) Mamaghani M, Loghmanifar A, Taati MRU. *Ultrason Sonochem*. 2011;18:45–48;
   (e) Urbano M, Guerrero M, Velaparthi S, et al. *Bioorg Med Chem Lett*. 2011;21:6739–6745;
   (f) Arfeen M, Bhagat S, Patel R, et al. *Eur J Med Chem*. 2016;121:727–736.
5. (a) Lin's work: Zhang K, Xu X, Zheng J, Yao H, Huang Y, Lin A. *Org Lett*. 2017;19:2596–2599;

(b) . Other's work:DiPoto MC, Hughes RP, Wu J. *J Am Chem Soc*. 2015;137:14861–14864;
(c) Acharya A, Anumandla D, Jeffrey CS. *J Am Chem Soc*. 2015;137:14858–14860;
(d) Ji WZ, Yao LC, Liao XB. *Org Lett*. 2016;18:628–630.
6. (a) Jeffrey's work: Acharya A, Montes K, Jeffrey CS. *Org Lett*. 2016;18:6082–6085;
(b) . Other's work:Zhang K, Yang C, Yao H, Lin A. *Org Lett*. 2016;18:4618–4621;
(c) Jia QF, Du ZY, Zhang K, Wang J. *Org Chem Front*. 2017;4:91–94.
7. Wang GQ, Chen RX, Wu MH, et al. *Tetrahedron Lett*. 2017;58:847–850.
8. (a) Sengoden M, Irie R, Punniyamurthy T. *J Org Chem*. 2016;81:11508–11513;
(b) Nadir UK, Basu N. *J Org Chem*. 1995;60:1458–1460;
(c) Wu J-Y, Luo Z-B, Dai L-X, Hou X-L. *J Org Chem*. 2008;73:9137–9139;
(d) Sengoden M, Vijay M, Balakumar E, Punniyamurthy T. *RSC Adv*. 2014;4:54149–54157;
(e) Sengoden M, Punniyamurthy T. *Angew Chem Int Ed*. 2013;52:572–575.
9. (a) Revelant G, Hesse S, Kirsch G. *Synthesis*. 2010;19:3319–3324;
(b) Bolli MH, Abele S, Binkert C, et al. *J Med Chem*. 2010;53:4198–4211;
(c) Revelant G, Huber-Villaume S, Dunand S, Kirsch G, Schohn H, Hesse S. *Eur J Org Chem*. 2015;94:102–112;
(d) Cai M-G, Wu Y, Chang J. *Bioorg Med Chem Lett*. 2016;26:2517–2520.
10. Zhao H-W, Zhao Y-D, Liu Y-Y, et al. *Eur J Org Chem*. 2017;3466–3472.
11. Crystallographic data for 3n has been deposited with the Cambridge Crystallographic Data Centre as deposition no. CCDC 1565744. Detailed information can be found in the Supporting Information.
12. (a) Teraishi F, Wu S, Zhang L, et al. *Cancer Res*. 2005;65:6380–6387;
(b) Dayam R, Aiello F, Deng J, et al. *J Med Chem*. 2006;49:4526–4534;
(c) Suzuki M, Morita K, Yukioka H, Miki N, Mizutani AJ. *Pesticide Sci*. 2003;28:37–43.
13. (a) Pulici M, Quartieri F. *Tetrahedron Lett*. 2005;46:2387–2391;
(b) Caile S, Bercot EA, Cui S, Faul MM. *J Org Chem*. 2008;73:2003–2006.