Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: F. Zeng, L. Zhang, X. Shao, Z. Li and X. Xu, *Org. Biomol. Chem.*, 2018, DOI: 10.1039/C7OB02924A.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/obc

View Article Online
DOI: 10.1039/C7OB02924A

Catalyst-free synthesis of thiazolidines *via* sequential hydrolysis/rearrangement reactions of 5-arylidenethiazolidin-4-ones at room temperature

Fanxun Zeng [a], Letian Zhang [a], Xusheng Shao [a], Zhong Li [a, b], Xiaoyong Xu * [a, b]

[a] *Shanghai Key Laboratory of Chemical Biology, School of Pharmacy, East China University of Science and Technology, 130 Meilong Road, Shanghai 200237, China*

[b] *Shanghai Collaborative Innovation Center for Biomanufacturing Technology, 130 Meilong Road, Shanghai 200237, China*

* *Corresponding author. Tel.: +86-21-64252945; fax: +86-21-64252603. E-mail: xyxu@ecust.edu.cn.*

Abstract

A catalyst-free sequential reaction involving hydrolysis and intramolecular aza-Michael addition was developed for synthesizing functionalized thiazolidines from 5-arylidenethiazolidin-4-ones at room temperature. A series of thiazolidine-5-carboxylic acids were prepared in good to excellent yields (up to 97% yield) and excellent diastereoselectivities (up to >20:1 dr). This methodology was applicable to the construction of derivatives of thiacloprid and flutianil with good yields.

Introduction

Thiazolidines are important N and S-heterocycles due to their diverse biological activities,[1] practical synthetic values[2] and extensive applications in peptide synthesis.[3] In particular, the thiazolidine scaffold is the key structural component of many natural products[4] and marketed products including insecticide,[5] fungicide[6] and antibiotics.[7] Four representative examples are shown in Fig. 1. Latrunculin A and its analogs, marine toxins purified from the red sea sponge *Latrunculia magnifica*, have been found to disrupt microfilament organization and inhibit actin polymerization.[8] Thiacloprid is one of neonicotinoid insecticides, whose discovery has been regarded as a milestone in the past three decades.[5,9] Flutianil is a fungicide mainly used for grapevine and ornamental crops protection.[6, 10] The clinical success of penicillin G prompted the development of antibiotics, which is recognized as one of the most significant advances in modern medicine.[11]

View Article Online
DOI: 10.1039/C7OB02924A

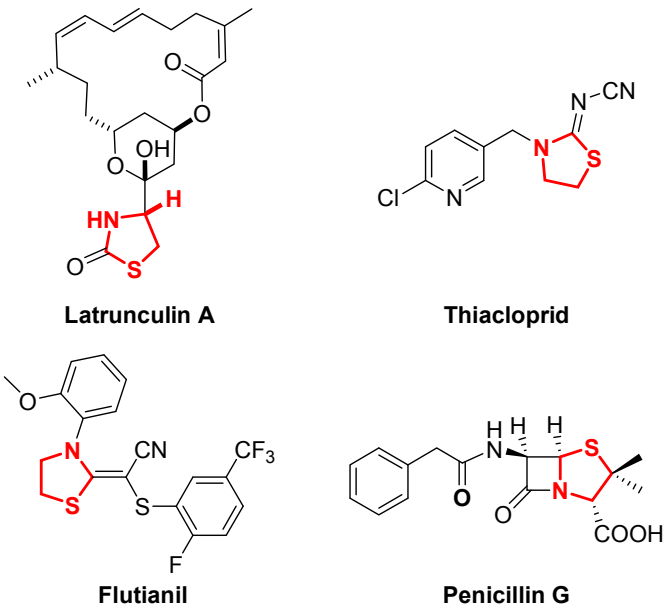
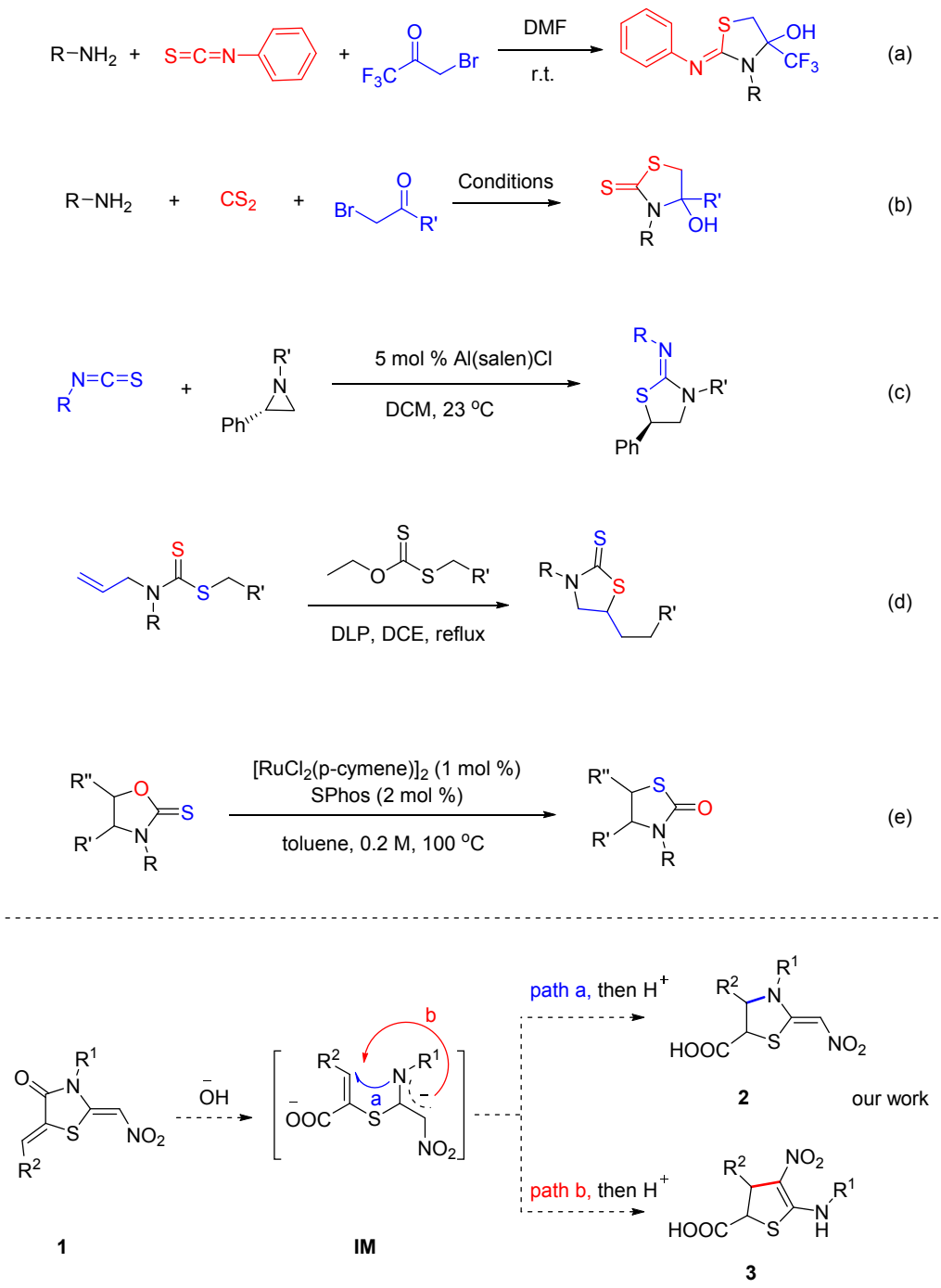


Fig. 1 Representative thiazolidines.

The synthesis of thiazolidine-containing compounds is a focus of research.[12] For example, the synthesis of 2-imino-4-(trifluoromethyl) thiazolidin-4-ol derivatives by one-pot, three-component reactions of primary amines, aryl isothiocyanates, and 3-bromo-1,1,1-trifluoro-propanone has been disclosed by Kumbhare and co-workers (Scheme 1a).[13] Efficient constructions of thiazolidines by the reactions of primary amines, carbon disulphide and α-bromides have been demonstrated by Yavari and Sun groups (Scheme 1b).[14] Recently, Al-catalyzed (3+2) cycloaddition of inactivated chiral aziridines with isothiocyanates to prepare 2-iminothiazolidines has been reported (Scheme 1c).[15] The generation of thiazolidines from alkyl allyl(alkyl/aryl)-dithiocarbamates *via* radical cyclization with the corresponding S-alkyl O-ethyl xanthates as the adscititious radical precursors has also been developed by Xu *et al* (Scheme 1d).[16] In particular, Frost and co-workers have reported ruthenium-catalyzed O- to S-alkyl migration to prepare thiazolidine derivatives (Scheme 1e).[17] Most of these methodologies, however, suffered from drawbacks such as harsh conditions, limited substrate scopes or the use of catalysts. Consequently, exploring practical and novel reaction types to prepare functionalized thiazolidines are still greatly in demand.

Since the intermolecular conjugate addition of stabilized carbanions to electron-deficient olefins was discovered by Arthur Michael in 1887, Michael reactions have emerged as powerful synthetic tools for mild constructions of carbon-carbon or carbon-heteroatom bonds.[18] Our research program focusing on thiazolidin-4-ones indicated that this scaffold was unstable under alkaline condition.[19] We envisioned that compounds **1** could be converted to intermediates **IM** and then turned to the corresponding thiazolidines **2** *via* intramolecular aza-Michael addition reactions (path a, Scheme 1) or 2,3-dihydrothiophenes **3** *via* intramolecular conjugate addition reactions (path b, Scheme 1) under basic conditions. The obtained products were finally proved to be thiazolidines **2.** Herein, we report a novel hydrolysis/aza-Michael addition reaction cascade for the synthesis of thiazolidines from 5-arylidenethiazolidin-4-ones.

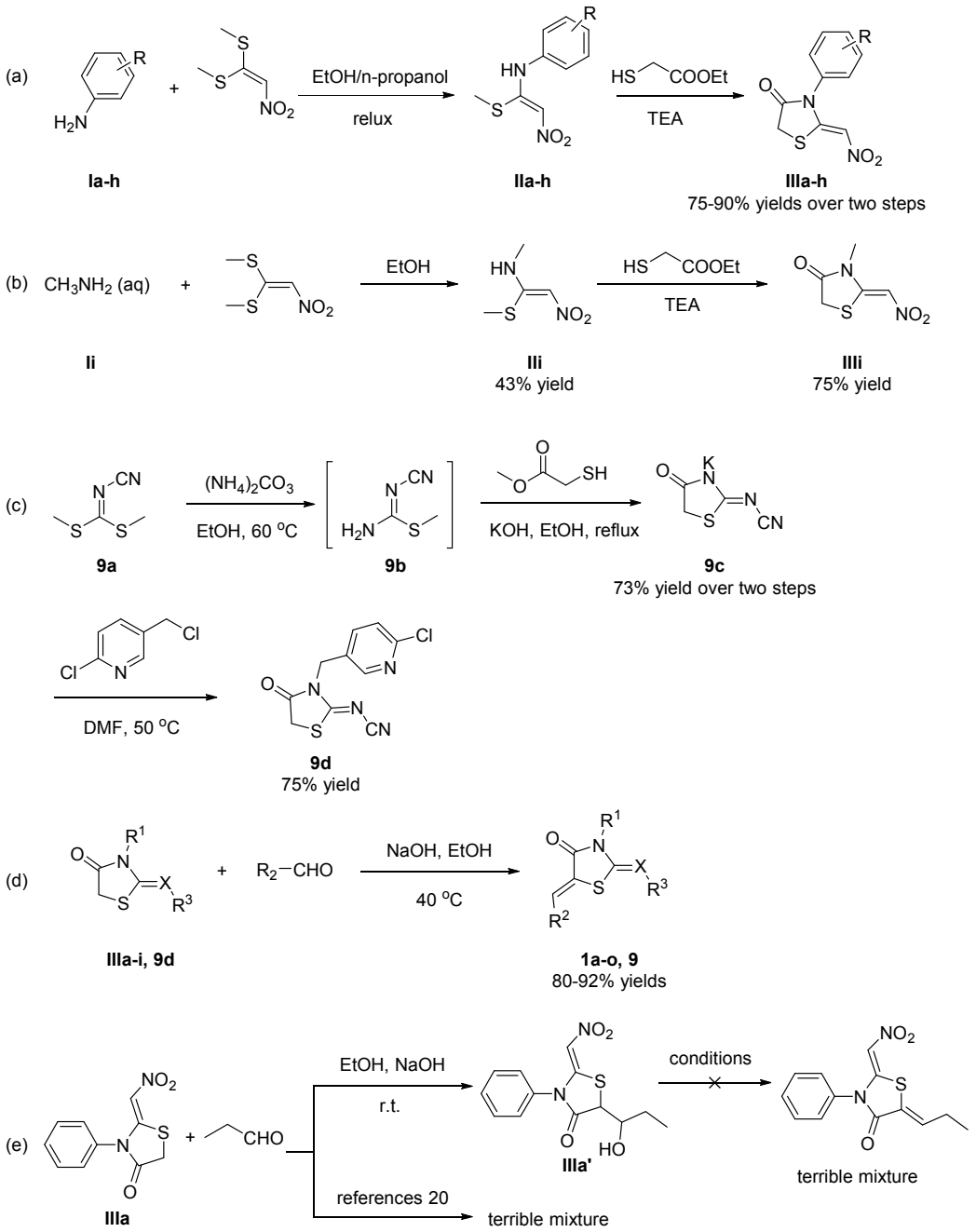
View Article Online
DOI: 10.1039/C7OB02924A



Scheme 1 Selected examples of thiazolidinones synthesis and the diagram of our work.

Results and discussion

View Article Online
DOI: 10.1039/C7OB02924A



Scheme 2 Preparation of starting materials 5-arylidenethiazolidin-4-ones and the example of synthesis of alkyl-substituted starting material.

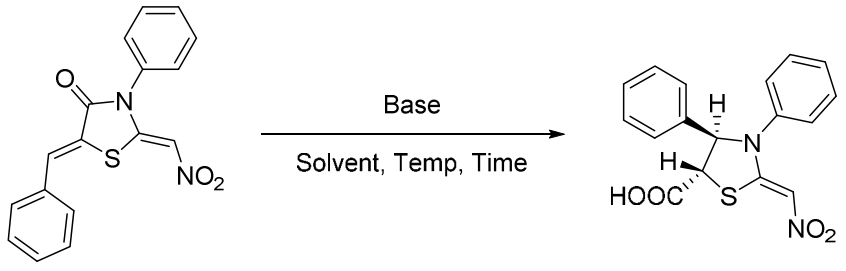
Starting materials 5-arylidenethiazolidin-4-ones **1a-o** and **9** were easily prepared by Knoevenagel condensations of commercially available aromatic aldehydes with thiazolidin-4-ones **IIIa-i** and **9d** in 80-92% yields (Scheme 2). Thiazolidin-4-ones **IIIa-i** were synthesized by one-pot method. Nucleophilic substitutions of (2-nitroethene-1,1-diyl)bis(methylsulfane) with arylamines **Ia–h** gave intermediates **IIa-h**, which were further reacted with ethyl 2-mercaptoacetate to give key precursors **IIIa-h**. Compound **IIIi** was obtained through cyclization reaction of ethyl 2-mercaptoacetate and compound **IIi**, which was prepared by nucleophilic substitution reaction of

View Article Online
DOI: 10.1039/C7OB02924A

(2-nitroethene-1,1-diyl)bis(methylsulfane) with methylamine. Pyridine derivative **9d** was synthesized by the reaction of 2-chloro-5-(chloromethyl)pyridine and intermediate **9c**, which was obtained by the one-pot reaction of dimethyl cyanocarbonimidodithioate, ammonium carbonate and methyl 2-mercaptoacetate. The overall yields were generally high and the isolation was typically simple.

5-Benzylidene-3-phenylthiazolidin-4-one **1a** was selected as the model substrate to optimize the reaction conditions. Initially, a variety of solvents were explored using NaOH as a base (Table 1, entries 1–8). No product was detected even under reflux with water as initial solvent, which may be due to the poor solubility of **1a** (Table 1, entry 1). Moreover, no desired product was observed when SDS was added (Table 1, entry 2). Then the above experiments were performed in several polar solvents in combination with 10 equivalents of water (Table 1, entries 3–8). To our delight, product **2a** with an excellent yield was obtained in ethanol at room temperature (Table 1, entry 7). The yield of product **2a** was further raised to 98% in methanol (Table 1, entry 8). The influence of temperature was also investigated (Table 1, entries 9–11). Only yield of 7% was obtained even if extended reaction time was consumed when the reaction was carried out at 0 ^{o}C (Table 1, entry 9). When this experiment was conducted at 40 ^{o}C or under reflux conditions, less time was needed with slightly lower yields provided (Table 1, entry 8 vs. entries 10 and 11). Furthermore, the reactions were tried using different bases (Table 1, entries 12–15). Similar result was observed when KOH was used (Table 1, entry 8 vs. entry 12). Weaker bases led to lower yields and prolonged reaction time (Table 1, entries 13 and 14). And no product was observed when TEA was introduced (Table 1, entry 15). It was noticed that the amount of NaOH played a key role in the reaction (Table 1, entries 8 and entries 16–18). Furthermore, the effect of the amount of water was carefully studied (Table 1, entries 19–26). It was found that adding a litter bit of water slightly increased the yield and further increasing the proportion of water decreased the yield of **2a**. From the above experimental conditions, it may conclude that the base of NaOH (1.5 equiv.) in methanol combining with water (7.5 equiv.) at room temperature are the optimal reaction conditions suited for this conversion (Table 1, entry 23).

Table 1 Optimization of reaction conditions [a]



1a **2a**

Enty	Base (equiv.)	Solvent	Temp (ºC)	Time (h)	Yield[c] (%)
1	NaOH (1.5)	H_2O	reflux	12	trace
2[b]	NaOH (1.5)	H_2O	reflux	12	trace
3	NaOH (1.5)	10 equiv. H_2O + dioxane	r.t.	12	trace
4	NaOH (1.5)	10 equiv. H_2O + ACN	r.t.	12	trace
5	NaOH (1.5)	10 equiv. H_2O + DMF	r.t.	12	2

View Article Online
DOI: 10.1039/C7OB02924A

6	NaOH (1.5)	10 equiv. H_2O + DMSO	r.t.	12	2
7	NaOH (1.5)	10 equiv. H_2O + EtOH	r.t.	8	83
8	NaOH (1.5)	10 equiv. H_2O + MeOH	r.t.	8	98
9	NaOH (1.5)	10 equiv. H_2O + MeOH	0	48	7
10	NaOH (1.5)	10 equiv. H_2O + MeOH	40	2.5	91
11	NaOH (1.5)	10 equiv. H_2O + MeOH	reflux	1	92
12	KOH (1.5)	10 equiv. H_2O + MeOH	r.t.	8	97
13	LiOH (1.5)	10 equiv. H_2O + MeOH	r.t.	20	78
14	K_2CO_3 (1.5)	10 equiv. H_2O + MeOH	r.t.	20	22
15	TEA (1.5)	10 equiv. H_2O + MeOH	r.t.	48	0
16	NaOH (0.8)	10 equiv. H_2O + MeOH	r.t.	20	75
17	NaOH (1.0)	10 equiv. H_2O + MeOH	r.t.	20	93
18	NaOH (1.2)	10 equiv. H_2O + MeOH	r.t.	20	97
19	NaOH (1.5)	absolute MeOH	r.t.	8	89
20	NaOH (1.5)	1 equiv. H_2O + MeOH	r.t.	8	93
21	NaOH (1.5)	2 equiv. H_2O + MeOH	r.t.	8	92
22	NaOH (1.5)	5 equiv. H_2O + MeOH	r.t.	8	97
23	**NaOH (1.5)**	**7.5 equiv. H_2O + MeOH**	**r.t.**	**8**	**99(95[d])**
24	NaOH (1.5)	20 equiv. H_2O + MeOH	r.t.	10	96
25	NaOH (1.5)	0.1 mL H_2O + 0.9 mL MeOH	r.t.	15	87
26	NaOH (1.5)	0.2 mL H_2O + 0.8 mL MeOH	r.t.	20	80

[a] Reaction conditions: substrate **1a** (0.2 mmol), slovent (1 mL). [b] 0.04 mmol SDS was added. [c] Yield was determined by UPLC (ultra performance liquid chromatography). [d] Isolated yield.

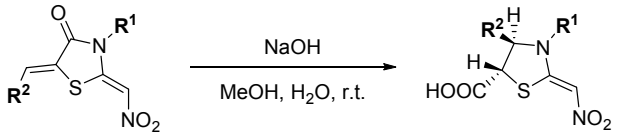
With the optimal conditions in hand, the substrate scope was explored (Table 2). The optimized reaction conditions could be easily adapted to a variety of substituted thiazolidinones. As shown in Table 2, diversified 5-arylidenethiazolidin-4-ones were transformed to the corresponding thiazolidines in good to excellent yields. We explored the effect of substituents on the nitrogen atoms. Substrates with phenyl and phenyl groups bearing electron-withdrawing groups (Cl, CF_3) or electron-donating groups (Me, OMe) at their *para*, *meta* or *ortho*-positions were used under the optimized conditions, affording the corresponding products **2a**-**2h** in excellent yields of over 95%. Substituted groups and positions showed no obvious influence on the yields. However, the substrates **1c** and **1d** with electron-withdrawing groups had higher reaction rates. And the reactivity was slightly decreased when the substrates **1f** and **1h** containing strong electron-donating groups were used. The reaction of the methyl-substituted **1i** gave **2i** in relatively low yield of 61%, and several by-products were observed. To further study the generalization of the transformation, then we investigated the effect of the R_2 group. Both electron-deficient and electron-rich phenyl groups were well tolerated, with the corresponding products **2j**–**2n** being formed in high yields of 70–96%. In the case of a 4-nitrophenyl-substituted substrate, a less reaction time was required and only 70% yields was obtained. The substrates **1l** and **1n** with strong electron-donating substituent methoxy group also worked well but with a prolonged reaction time. Finally, the furan-containing substrate was carried out under the optimized reaction conditions. Product **2o** was successfully obtained in 82% yield. In most cases, products could be

View Article Online
DOI: 10.1039/C7OB02924A

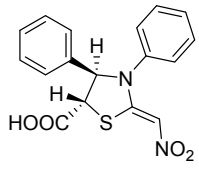
easily purified by simple operation rather than column chromatography.

Unfortunately, we cannot verify whether this methodology would be applied to the preparation of alkyl-substituted derivatives (R^2 = alkyl) because we failed to prepare corresponding starting materials effectively. Some efforts to prepare the alkyl-substituted raw materials using our general method or according to literature methods were unsuccessful,[20] with only terrible mixture was obtained and very little target product formed which can be detected by LC-MS (Scheme 2e).

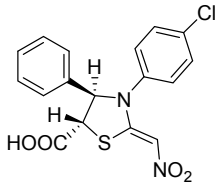
Table 2 Substrate scope of the thiazolidines synthesis[a,b]



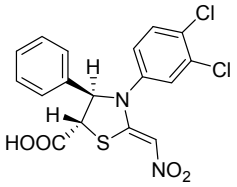
1 **2**



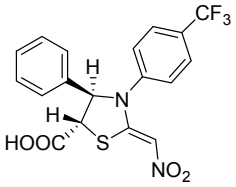
2a
8 h, 95%, >20:1 dr



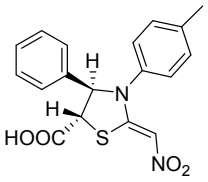
2b
8 h, 96%, >20:1 dr



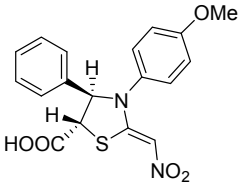
2c
5 h, 95%, >20:1 dr



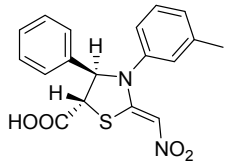
2d
3 h, 96%, >20:1 dr



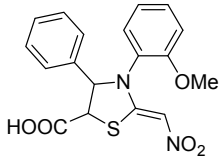
2e
8 h, 97%, >20:1 dr



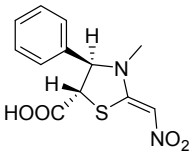
2f
24 h, 96%, >20:1 dr



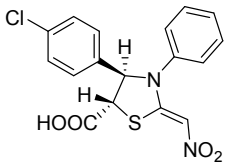
2g
8 h, 95%, >20:1 dr



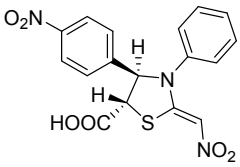
2h
20 h, 97%, 1.7:1 dr



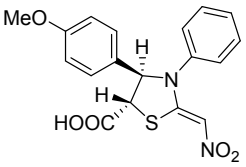
2i
8 h, 61%[c], >20:1 dr



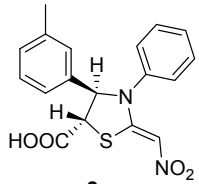
2j
8 h, 96%, >20:1 dr



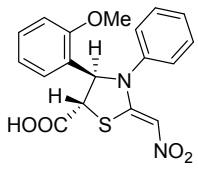
2k
0.5 h, 70%, >20:1 dr



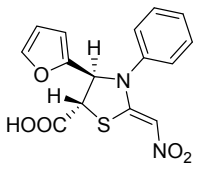
2l
36 h, 93%, >20:1 dr



2m
10 h, 95%, >20:1 dr



2n
48 h, 95%, >20:1 dr



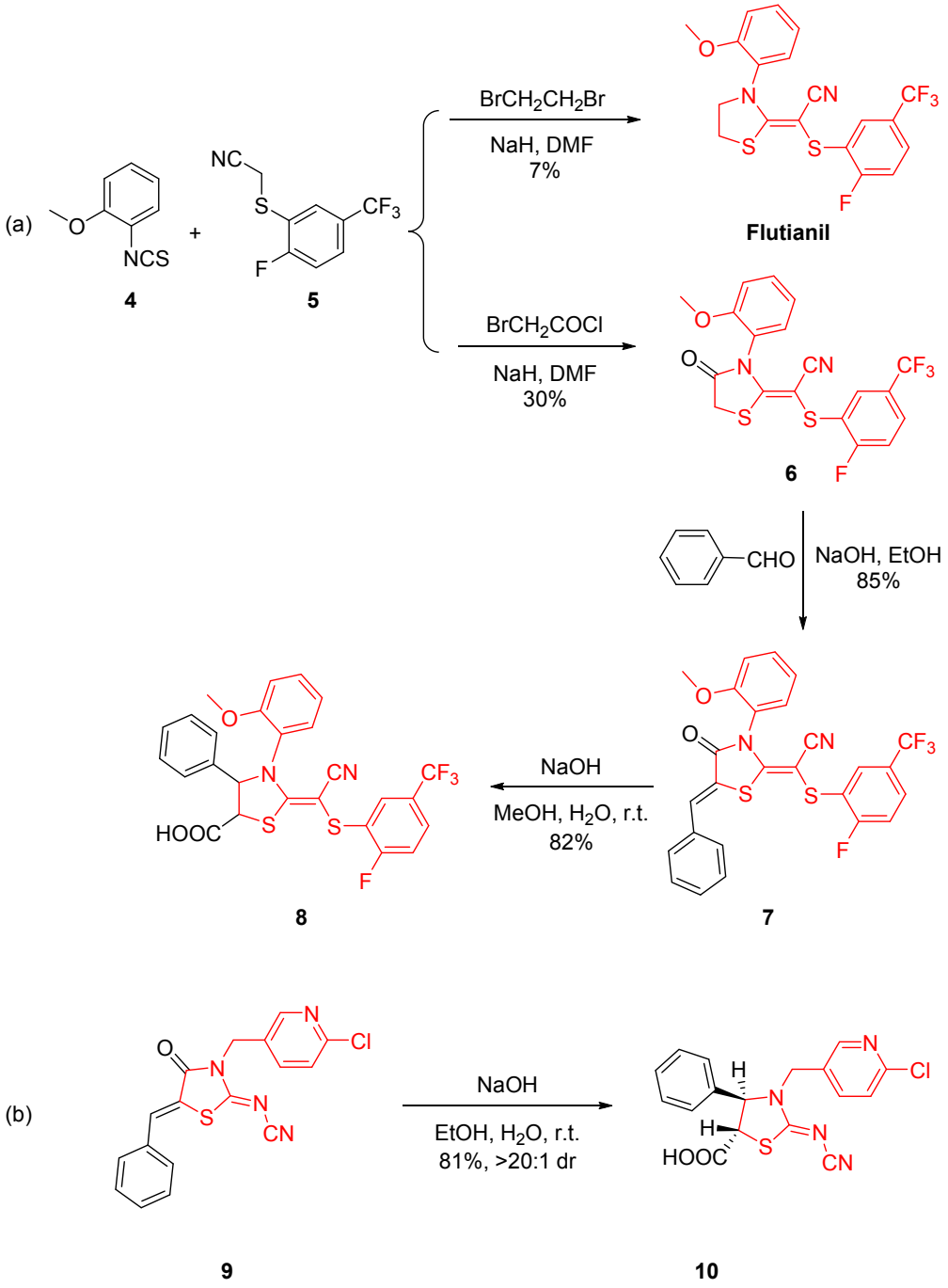
2o
24 h, 82%, >20:1 dr

[a] Reaction conditions: All reactions were performed with 0.5 mmol of **1**, 1.5 equiv. of NaOH, 7.5 equiv. of H_2O, and 2.5 mL of MeOH at r.t. for 0.5-48 h. [b] Isolated yield. [c] The solvent was

View Article Online
DOI: 10.1039/C7OB02924A

changed to EtOH.

In order to illustrate the potential synthetic utility of this methodology, the reactions of **7** and **9** were carried out to prepare the derivatives of thiacloprid and flutianil (Scheme 3). Flutianil was synthesized by the reaction of compounds **4**, **5** and 1,2-dibromoethane in yield of only 7%.[10a] In this study, compound **8**, the derivative of flutianil, was obtained from the same starting materials **4** and **5** in a total yield of about 21% over 3 steps (Scheme 3a), which is three times of that of flutianil. Compound **10**, the derivative of thiacloprid, could be smoothly obtained in yield of 81% from compound **9** (Scheme 3b).



View Article Online
DOI: 10.1039/C7OB02924A

Scheme 3 Synthesis of the derivatives of thiacloprid and flutianil.

Moreover, the stereochemistry of the products was also preliminary investigated. The diasteromeric ratio of **2a** was determined to be >20:1 *anti*/*syn* by the analysis of the ^{1}H NMR spectrum and single-crystal X-ray diffraction structure of **2a** (Fig. 2). The major stereoisomer formed was trans-isomer owing to steric hindrance. Compounds **2b-2g**, **2i-2o** and **10** were also obtained with excellent diastereoselectivities (>20:1 dr). But 2-methoxy substituted derivatives **2h** and **8** were obtained with poor dr values of 1.7:1 and 1.17:1.

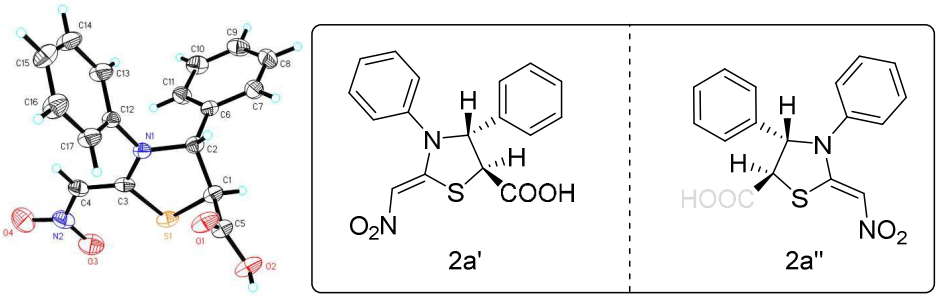


Fig. 2 Single-crystal X-ray diffraction structure and trans-isomers of **2a**.

Conclusions

In summary, we developed the general and operationally simple rearrangement reactions of 5-arylidenethiazolidin-4-ones, affording functionalized thiazolidines. The reactions were carried out with high yields and excellent diastereoselectivities at room temperature without any catalyst, additive or ligand. These advantages illustrated the potential using of this reaction in industrial production. The synthetic utility of this protocol was further demonstrated by efficient synthesis of the derivatives of thiacloprid and flutianil.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was financial supported by National Key Research Program of China (2017YFD0200505, 2016YFD0300709-02) and National Natural Science Foundation of China (21272071). This work was also partly supported by the Shanghai Foundation of Science and Technology (15431902100) and Fundamental Research Funds for the Central Universities (222201718004).

Notes and references

1. (a) N. L. Subasinghe, R. J. Bontems, E. McIntee, R. K. Mishra and R. L. Johnson, *J. Med. Chem.,* 1993, **36**, 2356; (b) C. G. Bonde and N. J. Gaikwad, *Biorg. Med. Chem.,* 2004, **12**, 2151; (c) A. Bodtke, W.-D. Pfeiffer, N. Ahrens and P. Langer, *Bioorg. Med. Chem. Lett.,*

View Article Online
DOI: 10.1039/C7OB02924A

2004, **14**, 1509; (d) M. D'Hooghe, A. Waterinckx and N. De Kimpe, *J. Org. Chem.,* 2005, **70**, 227; (e) Q. Zhang, H. Zhou, S. Zhai and B. Yan, *Curr. Pharm. Des.,* 2010, **16**, 1826; (f) R. S Bahare, S. Ganguly, R. Agrawal and S. N Dikshit, *Cent. Nerv. Syst. Agents Med. Chem.,* 2017, **17**, 26.

2. (a) L. Munive, V. M. Rivas, A. Ortiz and H. F. Olivo, *Org. Lett.,* 2012, **14**, 3514; (b) S. C. Kennington, J. M. Romo, P. Romea and F. Urpi, *Org. Lett.,* 2016, **18**, 3018.
3. (a) J. Shao and J. P. Tam, *J. Am. Chem. Soc.,* 1995, **117**, 3893; (b) D. Kern, M. Schutkowski and T. Drakenberg, *J. Am. Chem. Soc.,* 1997, **119**, 8403; (c) R. S. Roy, A. M. Gehring, J. C. Milne, P. J. Belshaw and C. T. Walsh, *Nat. Prod. Rep.,* 1999, **16**, 249; (d) D. Forget, D. Boturyn, E. Defrancq, J. Lhomme and P. Dumy, *Chem. Eur. J.,* 2001, **7**, 3976; (e) J. R. Falsey, M. Renil, S. Park, S. Li and K. S. Lam, *Bioconjug. Chem.,* 2001, **12**, 346.
4. Y. Kashman, A. Groweiss and U. Shmueli, *Tetrahedron Lett.,* 1980, **21**, 3629.
5. M. Tomizawa and J. E. Casida, *Annu. Rev. Entomol.,* 2003, **48**, 339.
6. M. H. Lee, H. K. Lee, P. H. Cho, Y. S. Kim, S. K. Cho, S. E. Kim, H. Chun, H. G. Kim, S. W. Kim and Y. S. Lee, *Res. Plant Dis.,* 2015, **21**, 94.
7. S. M. Drawz and R. A. Bonomo, *Clin. Microbiol. Rev.,* 2010, **23**, 160.
8. (a) I. Spector, N. R. Shochet, Y. Kashman and A. Groweiss, *Science,* 1983, **219**, 493; (b) M. Coué, S. L. Brenner, I. Spector and E. D. Korn, *FEBS Lett.,* 1987, **213**, 316.
9. (a) M. Tomizawa and J. E. Casida, *Annu. Rev. Pharmacol. Toxicol.,* 2005, **45**, 247; (b) A. Elbert, M. Haas, B. Springer, W. Thielert and R. Nauen, *Pest Manag. Sci.,* 2008, **64**, 1099; (c) S. Kagabu, *J. Agric. Food Chem.,* 2010, **59**, 2887; (d) J. E. Casida, *J. Agric. Food Chem.,* 2010, **59**, 2923.
10. (a) M. Hayashi, Y. Endo and T. Komura, WO0147902[P], 2001; (b) J.-E. Kwon, J.-A. Do, H. Park, J.-Y. Lee, Y.-J. Cho, J.-H. Oh, G.-S. Rhee, S.-J. Lee and M.-I. Chang, *Korean J. Food Sci. Technol.,* 2014, **46**, 7; (c) A. Leadbeater, *Plant Prot. Sci.,* 2015, **51**, 163.
11. (a) J. F. Fisher, S. O. Meroueh and S. Mobashery, *Chem. Rev.,* 2005, **105**, 395; (b) A. L. Demain and S. Sanchez, *J. Antibiot.,* 2009, **62**, 5.
12. (a) M. D'hooghe and N. De Kimpe, *Tetrahedron,* 2006, **62**, 513; (b) U. Albrecht, I. Freifeld, H. Reinke and P. Langer, *Tetrahedron,* 2006, **62**, 5775; (c) M. Sengoden, M. Vijay, E. Balakumar and T. Punniyamurthy, *RSC Adv.,* 2014, **4**, 54149; (d) S. V. Kumar, S. Muthusubramanian and S. Perumal, *RSC Adv.,* 2015, **5**, 90451.
13. T. Dalmal, K. Appalanaidu, U. B. Kosurkar, N. Jagadeesh Babu and R. M. Kumbhare, *Eur. J. Org. Chem.,* 2014, **12**, 2468.
14. (a) I. Yavari, S. Seyfi, Z. Hossaini, M. Sabbaghan and F. Shirgahi-Talari, *Monatsh. Chem.,* 2008, **139**, 1479; (b) S.-F. Gan, J.-P. Wan, Y.-J. Pan and C.-R. Sun, *Synlett,* 2010, **6**, 973.
15. M. Sengoden, R. Irie and T. Punniyamurthy, *J. Org. Chem.,* 2016, **81**, 11508.
16. S. Gao, Y. Zhang, J. Dong, N. Chen and J. Xu, *Org. Biomol. Chem.,* 2016, **14**, 1002.
17. W. Mahy, P. Plucinski, J. Jover and C. G. Frost, *Angew. Chem. Int. Ed. Engl.,* 2015, **54**, 10944.
18. (a) B. D. Mather, K. Viswanathan, K. M. Miller and T. E. Long, *Prog. Polym. Sci.,* 2006, **31**, 487; (b) D. Enders, A. Saint□Dizier, M. I. Lannou and A. Lenzen, *Eur. J. Org. Chem.*, 2006, 29; (c) J. Wang, P. Li, P. Y. Choy, A. S. Chan and F. Y. Kwong, *ChemCatChem*, 2012, **4**, 917; (d) D. P. Nair, M. Podgórski, S. Chatani, T. Gong, W. Xi, C. R. Fenoli and C. N. Bowman, *Chem. Mater.*, 2013, **26**, 724; (e) R. Miyaji, K. Asano and S. Matsubara, *Org. Lett.,*

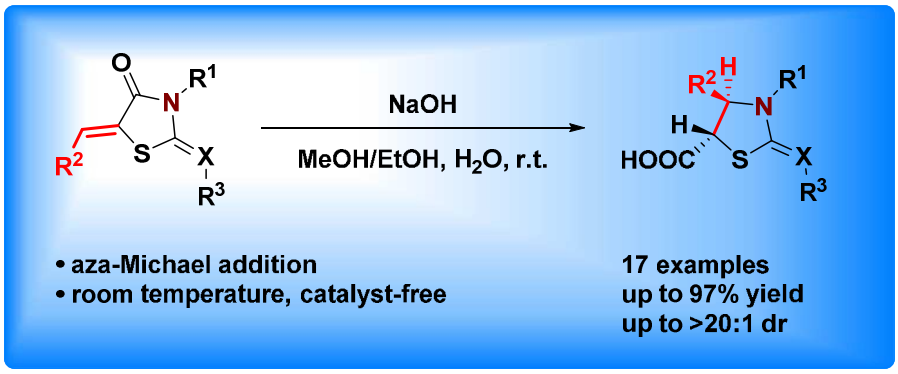
View Article Online
DOI: 10.1039/C7OB02924A

2013, **15**, 3658; (f) C. Le Guen, M. L. Tran Do, A. Chardon, C. Lebargy, J. F. Lohier, E. Pfund and T. Lequeux *J. Org. Chem.,* 2016, **81**, 6714.

19. (a) F. Zeng, P. Liu, X. Shao, Z. Li and X. Xu, *RSC Adv.,* 2016, **6**, 59808; (b) F. Zeng, T. Qi, C. Li, T. Li, H. Li, S. Li, L. Zhu and X. Xu, *Med. Chem. Commun.,* 2017, **8**, 1297.
20. (a) M. Joshi, C. Vargas, P. Boisguerin, A. Diehl, G. Krause, P. Schmieder, K. Moelling, V. Hagen, M. Schade and H. Oschkinat, *Angew. Chem. Int. Ed. Engl.,* 2006, **45**, 3790; (b) S. Wu, Y. Zhang, X. He, X. Che, S. Wang, Y. Liu, Y. Jiang, N. Liu, G. Dong and J. Yao, *Med. Chem. Commun.,* 2014, **9,** 2639; (c) A. Bugarin, K. D. Jones and B. T. Connell, *Chem. Commun.,* 2010, **46**, 1715; (d) D. Klein, B. Fink, B. Arold, W. Eisenreich and W. Schwab, *J. Agric. Food Chem.,* 2007, **55**, 6705.

View Article Online
DOI: 10.1039/C7OB02924A

Table of Contents Entry



Functionalized thiazolidines were obtained *via* the rearrangement reactions of 5-arylidenethiazolidin-4-ones at room temperature.