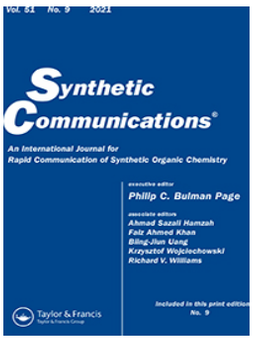


Taylor & Francis
Taylor & Francis Group

Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/lsyc20

Synthesis of thiazolidinimines/thiazinan-2-imines via three-component coupling of amines, *vic*-dihalides and isothiocyanates under metal-free conditions

Rahul Kumar, Abhisek Joshi, Deepa Rawat & Subbarayappa Adimurthy

To cite this article: Rahul Kumar, Abhisek Joshi, Deepa Rawat & Subbarayappa Adimurthy (2021) Synthesis of thiazolidinimines/thiazinan-2-imines via three-component coupling of amines, *vic*-dihalides and isothiocyanates under metal-free conditions, Synthetic Communications, 51:9, 1340-1352, DOI: 10.1080/00397911.2021.1880594

To link to this article: https://doi.org/10.1080/00397911.2021.1880594

SYNTHETIC COMMUNICATIONS®
2021, VOL. 51, NO. 9, 1340–1352
https://doi.org/10.1080/00397911.2021.1880594

Taylor & Francis
Taylor & Francis Group

Synthesis of thiazolidinimines/thiazinan-2-imines via three-component coupling of amines, *vic*-dihalides and isothiocyanates under metal-free conditions

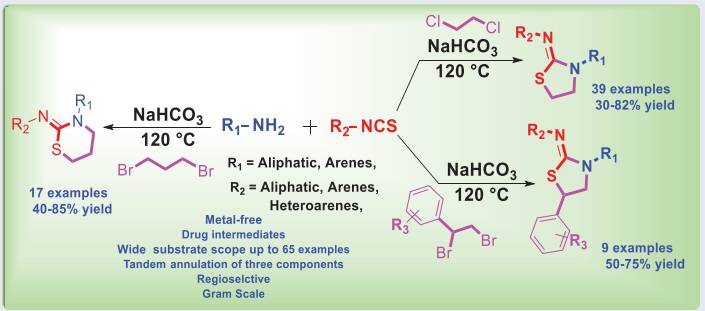
Rahul Kumar[a,b], Abhisek Joshi[a,b], Deepa Rawat[a,b], and Subbarayappa Adimurthy[a,b]

[a]Academy of Scientific and Innovative Research, Ghaziabad, India; [b]CSIR–Central Salt and Marine Chemicals Research Institute, Bhavnagar, India

ABSTRACT

An expeditious approach for the synthesis of thiazolidin-2-imines and 1,3-thiazinan-2-imines through three-components coupling (TCC) of amines, isothiocynates and dihalides under metal-free conditions has been described. Dichloroethane (DCE) employed as two carbon (C2) source for the annulation and obtained saturated five membered heterocycles.With 1,3-dibromopropane, six membered heterocycles were obtained in good yields. The metal-free, broad substrate scope, functional group tolerance and applicability at gram scale synthesis are the advantages of the present protocol.

GRAPHICAL ABSTRACT



ARTICLE HISTORY
Received 10 August 2020

KEYWORDS
Amines; dihalides; isothiocyanates; thiazinan-2-imines; thiazolidinimines

Non-aromatic nitrogen and sulfur-containing heterocycles are privileged scaffolds found in a wide range of pharmaceutical drugs and natural products.[1,2] The pharmaceutical industry continues to require methodologies that address the key synthetic challenges such as synthesis of small aliphatic heterocycles and the installation of desired moiety through late stage functionalization.[3] The concept of introducing a functional handle to the aliphatic heterocyclic system is a powerful way of synthesizing molecules with increased biological activity or suitable for subsequent derivatization. thiazolidin-2-imines/1,3-thiazinan-2-imines moieties are found in several biologically active compounds[4] and exhibit antiviral,[5] anticancer,[6–7] anti-tubercular,[8] and antimicrobial[9]

CONTACT Subbarayappa Adimurthy adimurthy@csmcri.res.in CSIR–Central Salt and Marine Chemicals Research Institute, Bhavnagar, Gujarat 364002, India.

Supplemental data for this article can be accessed on the publisher's website.

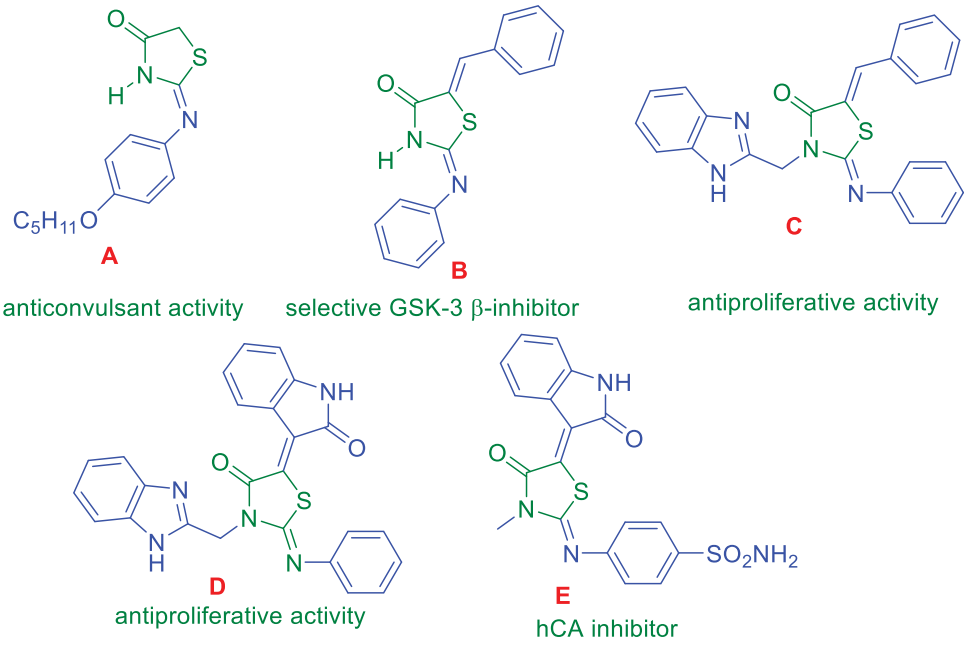


Figure 1. Representative biologically active molecules containing 2-iminothiazolidin motifs.

activities. For example, molecule A (Figure 1) known to exhibit pronounced anticonvulsant activity,[10] molecules B is a selective GSK-3β inhibitor,[11] molecules C and D exhibited antiproliferative activity,[12] and molecule E as hCA inhibitor (Figure 1).[13]

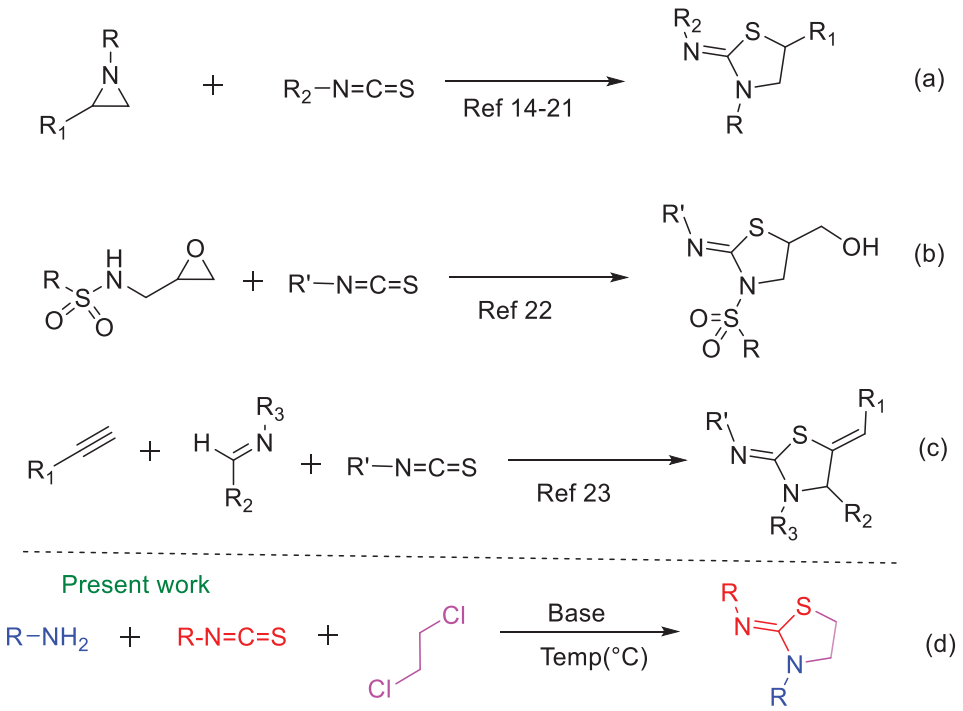
Due to the synthetic and bio-importance of 5-membered heterocycles such as thiazolidin-2-imines and their analogues, much attention has been paid on the development of related methodologies.

A well-established route to access substituted thiazolidin-2-imines are through the ring opening of aziridines,[14–21] epoxides[22] and others[23] using a wide range of catalytic systems. Despite the significance of these methods, it is desirable to develop new methods to access thiazolidin-2-imines for late stage functionalization, hence it is a challenging task to the synthetic chemists.

To our knowledge, 1,2-dichloroethane has rarely been utilized as two carbon source in the synthesis of thiazolidin-2-imines.[24,25] Herein we describe a protocol for the highly selective one pot synthesis of 2- thiazolidinimines from readily available amines, isothiocyanates and 1,2-dichloroethane as C_2 source under transition metal-free conditions (Scheme 1d). Furthermore, this synthetic protocol was successfully extended to 1,3-thiazinan-2-imine to obtain six membered analogues.

Results and discussion

Our initial efforts were focused on the optimization of the reaction conditions with aniline **1a** and phenyl isothiocyanate **2a** as model substrates. When these substrates were reacted using 0.5 equivalents of sodium hydroxide in 1,2- dichloroethane DCE **(3a)** at 120 °C in a sealed tube for 24 hours, 36% yield of the desired product **4a** was obtained (Table 1, entry 1). The structure of product **4a** was further confirmed by the single

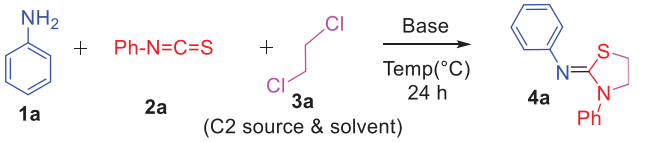


Scheme 1. Representative strategies on the synthesis of thiazolidin-2-imines

crystal XRD analysis. In this reaction DCE plays a dual role, as two carbon source and as a solvent. The coupling reaction proceeded at a marginal improvement in yield with NaOt-Bu and KO*t*-Bu as bases under the same conditions (entries 2 and 3). Use of other bases (CsF, DBU, Et_3N) no improvement in yield was observed (entries 4–6). A significant enhancement in yield (51–75%) was observed by conducting the reaction with carbonates ($CaCO_3$, K_2CO_3, Cs_2CO_3, Na_2CO_3) and KF as base (entries 7–11). Further improvement in yield (82%) was observed with $NaHCO_3$ as base (entry 12). A comparable yield (74%) of **4a** was obtained with 1,2-dibromoethane **(3 b)** as two carbon sources instead of DCE (entry 13), Further attempts to improve the yield, the amount of $NaHCO_3$ and phenyl isothiocyanate **2a** were increased (entries 14–18), but no enhancement in yield was observed. While reducing the reaction temperature (from 120 °C to r.t.) and time, the yield of **4a** was dropped (entries 19–22), and no reaction was observed without base (entry 23). To check the effect of KI as facilitating agent, the reaction was carries out by the addition of KI (0.5 mmol), the desired product yield was declined to 70% (entry 24). Hence the optimum conditions were set as entry 12, Table 1, to study the further scope with both aromatic and aliphatic amines and as well as different isothiocyanates.

The one-pot three-component procedure was ratified to be very general in preparing various thiazolidin-2-imines products. First, phenyl isothiocyanate **2a** was reacted with various aromatic anilines (Scheme 2). Anilines having electron donating groups such as methoxy, isopropyl, t-butyl, substituents reacted well with **2a** and **3a** under the optimized conditions and afford the desired products (**4b–4d**) in moderate to good yields.

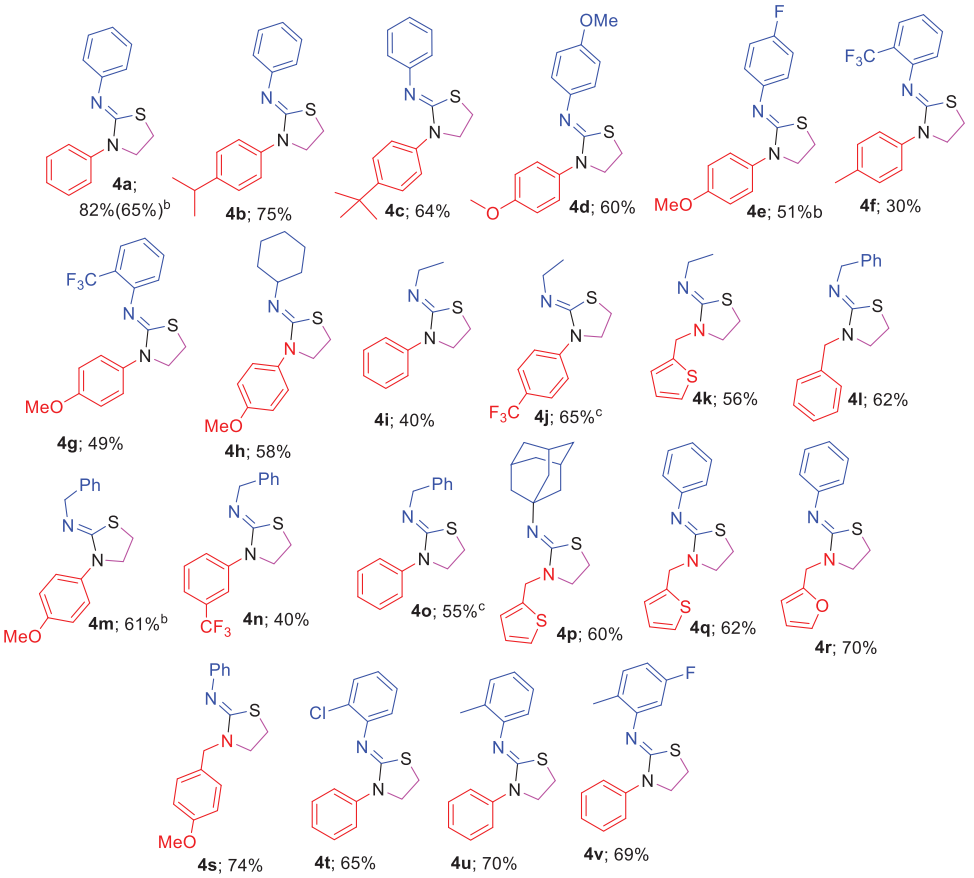
Table 1. Optimization of the reaction conditions.[a]



entry	2a (mmol)	base (mmol)	temp(°C)	solvent	4a (%)[b]
1	1.0	NaOH (0.5)	120	DCE(**3a**)	36
2	1.0	*t*-BuONa (0.5)	120	DCE	38
3	1.0	*t*-BuOK (0.5)	120	DCE	36
4	1.0	CsF (0.5)	120	DCE	30
5	1.0	DBU (0.5)	120	DCE	30
6	1.0	Et_3N (0.5)	120	DCE	36
7	1.0	$CaCO_3$ (0.5)	120	DCE	51
8	1.0	Na_2CO_3(0.5)	120	DCE	58
9	1.0	K_2CO_3 (0.5)	120	DCE	60
10	1.0	KF(0.5)	120	DCE	65
11	1.0	Cs_2CO_3 (0.5)	120	DCE	75
12	**1.0**	**$NaHCO_3$ (0.5)**	**120**	**DCE**	**82**
13	1.0	$NaHCO_3$ 0.5)	120	$BrCH_2CH_2Br$(**3b**)	74
14	1.0	$NaHCO_3$ (1.0)	120	DCE	71
15	1.0	$NaHCO_3$ (1.5)	120	DCE	64
16	1.0	$NaHCO_3$ (2.0)	120	DCE	56
17	1.5	$NaHCO_3$ (0.5)	120	DCE	66
18	2.0	$NaHCO_3$ (0.5)	120	DCE	63
19	1.0	$NaHCO_3$ (0.5)	100	DCE	61
20	1.0	$NaHCO_3$(0.5)	60	DCE	40
21	1.0	$NaHCO_3$(0.5)	RT	DCE	trace
22[c]	1.0	$NaHCO_3$ (2.0)	120	DCE	trace
23	0.5	--	120	DCE	nr
24[d]	1.0	$NaHCO_3$ (0.5)	120	DCE	70

[a]Reaction conditions: **1a** (1 mmol) and **2a** (1 mmol) base (0.5 mmol), solvent (1.0 mL), 24 h. [b]Yield of the isolated product. [c]Reaction time 12 h. [d]Reaction with addition of KI (0.5 mmol). nr: no reaction.

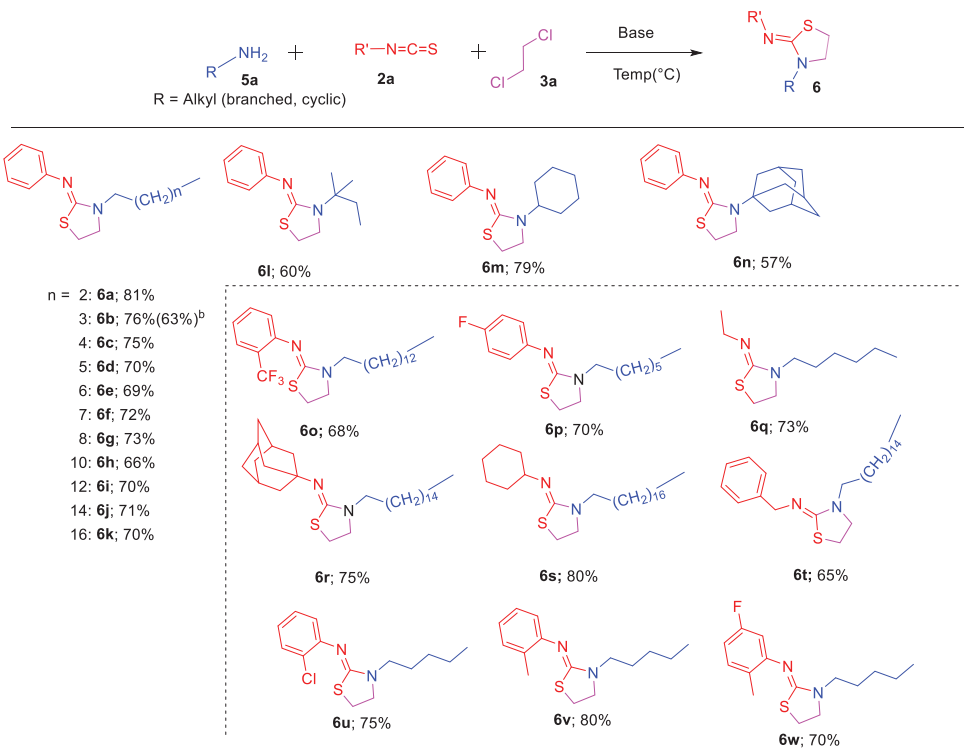
The reaction of fluoro and trifluoromethyl substituted phenyl isothiocyanates with different anilines were well tolerated under the optimal reaction conditions and yield the desired products (**4e–4g**) in moderate yields. Notably, aliphatic isothiocyanates such as cyclohexylisothiocyanate, ethylisothiocyanate, benzylisothiocyanate, and 1-adamantyl isothiocyanate were reacted smoothly with various substituted anilines as well as thiophen-2-ylmethanamine under these conditions and afforded moderate yields (40–65%) of desired products **4h–4p**. Further thiophen-2-ylmethanamine, furan-2-ylmethanamine and methoxy benzyl amines were reacted with arylisothiocyanate and obtained moderate to good yields (62–74%) of corresponding products **4q–4s**. Further the reaction of ortho substituted phenyl isothiocyanates having electron withdrawing and electron donating groups (chloro, methyl) reacted well with aniline and afford the desired products **4t** and



Scheme 2. Scope of isothiocyanate with anilines and benzylamines[a]. [a]Reaction conditions: **1a** (1 mmol) and **2a** (1 mmol), $NaHCO_3$ (0.5 mmol) in **3a** (1 mL), at 120 °C, 24 h, yield of the isolated product. [b]Yield with 1.023 g scale (11.0 mmol). [c]Yields obtained from 1,2-dibromoethane.

4u in moderate to good yields (65% and 70%). Reaction of phenyl isothiocyanates which contain both methyl and floro groups with aniline also gave the desired product (**4v**) in 69% yield.

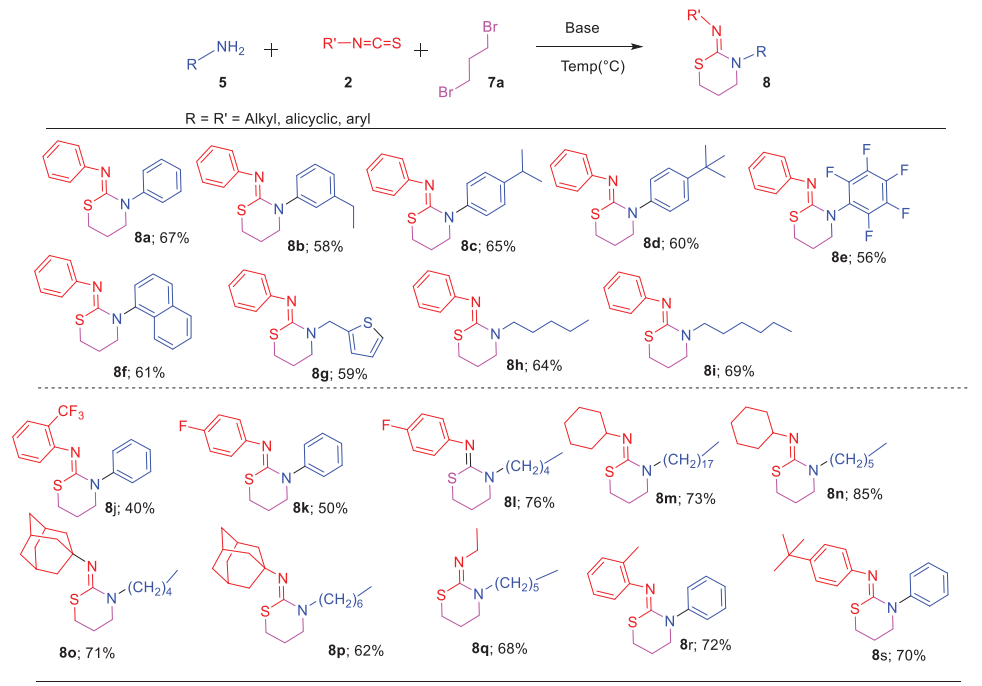
The successful transformation on the synthesis of various thiazolidin-2-imines under metal-free conditions prompted us to further investigate the generality of the method toward aliphatic amine substrates. Thus, different alkyl amines **5** were reacted with different isothiocyanates for the syntheses of alkyl-aryl thiazolidin-2-imines **6** (Scheme 3). Reaction of phenyl isothiocyanate **2a** with aliphatic amines such as long chain (up to C18), branched, cyclic, and bicyclic amines in 1,2-dichloroethane DCE **(3a)** were performed under the optimized conditions and the desired (*Z*)-*N*-phenyl-3-alkylthiazolidin-2-imine products **6a–6k** were obtained in good yields (66–81%). It is important to note that, aryl, alkyl and cyclic isothiocyanates were also reactive with different aliphatic amines under the optimized conditions and produced the corresponding products **6l–6t** in good yields (80%). Further the reaction of ortho substituted phenyl isothiocyanates having electron withdrawing and electron donating groups (chloro, methyl) reacted



Scheme 3. Scope of aliphatic amines[a]. [a]Reaction conditions: **5a** (1 mmol) and **2a** (1 mmol), $NaHCO_3$ (0.5 mmol), **3a** 1.0 mL at 120 °C, 24 h, yield of the isolated product. [b]Yield with 0.957 g scale (11.0 mmol).

with pentylamine and afford the desired products(**6u–6w**) in moderate to good yields (70%— 80%).

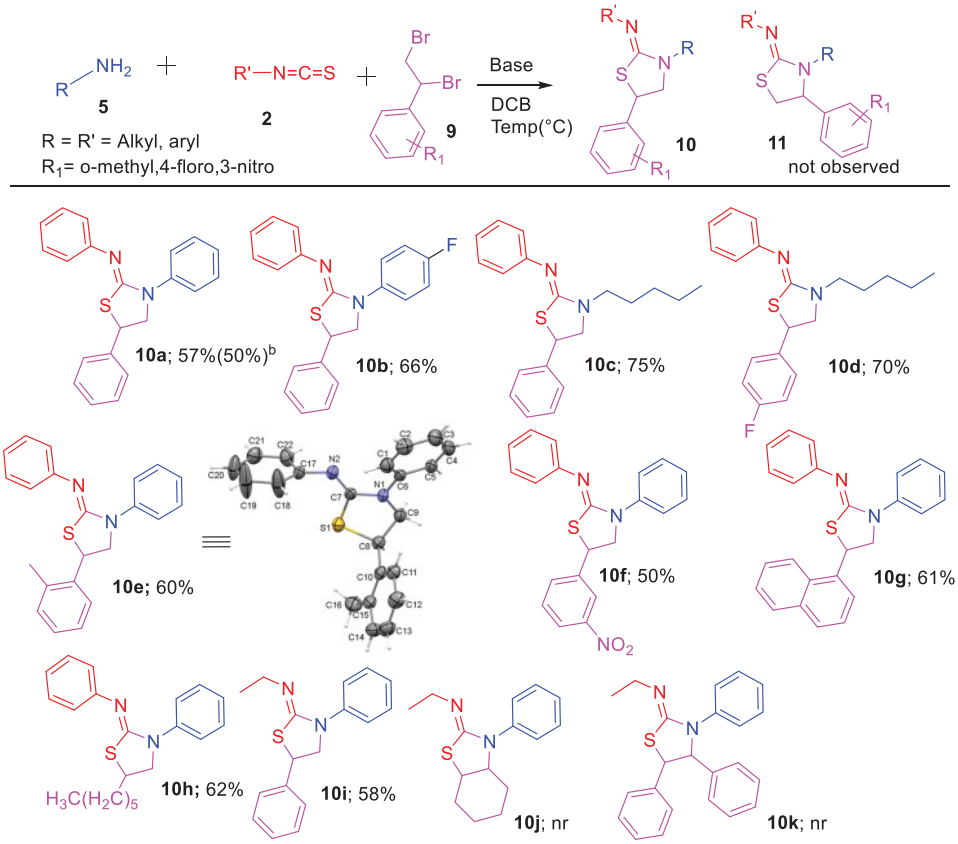
This method is not limited to the use of 1,2-dichloroethane as two carbon sources (products of Schemes 1 and 2); 1,3-dibromo propane **7a** also participates in the three-component coupling reactions, providing very good yields of the desired 1,3-thiazinan-2-imines (Scheme 4). We have examined the reactivity of **7a** with phenyl isothiocyanate **2a** and different amines under the set of optimized conditions. Anilines having various electron donating groups (ethyl, isopropyl and *tert*-butyl) proceeded smoothly and afford the desired diaryl-1,3-thiazinan-2-imines **8a—d** in good yields (58–67%). Pentafluoro aniline gave the desired product **8e** in moderate (56%) yield. Naphthalen-1-amine was also reactive and gave (*Z*)-3-(naphthalen-1-yl)-*N*-phenyl-1,3-thiazinan-2-imine **8f** in 61% yield. The reaction of **7a** and **2a** was also compatible with thiophen-2- ylmethanamine and aliphatic amines under the optimized conditions and provided the corresponding products **8g–8i** in 59–69% yields. The reaction of trifluoromethyl phenylisothiocyanates with aniline under the optimal reaction conditions also provided the desired product (**8j**) in moderate yields. Good yields of desired products **8k** and **8l** were obtained by the reaction of 1-fluoro-4-isothiocyanatobenzene with both aniline as well as pentylamine. Similarly, various aliphatic isothiocyanates (such as cyclic, bicyclic and ethyl) reacted well with a range of aliphatic amines (C_5–C_{18}) and afforded the corresponding products **8m–8q** in good yields (62–85%). Also



Scheme 4. Synthesis and scope of 1,3-thiazinan-2-imines[a]. [a]Reaction conditions: **5a** (1 mmol) and **2a** (1 mmol), $NaHCO_3$ (0.5 mmol) in **7a** 1 mL solvent at 120 °C, 24 h.

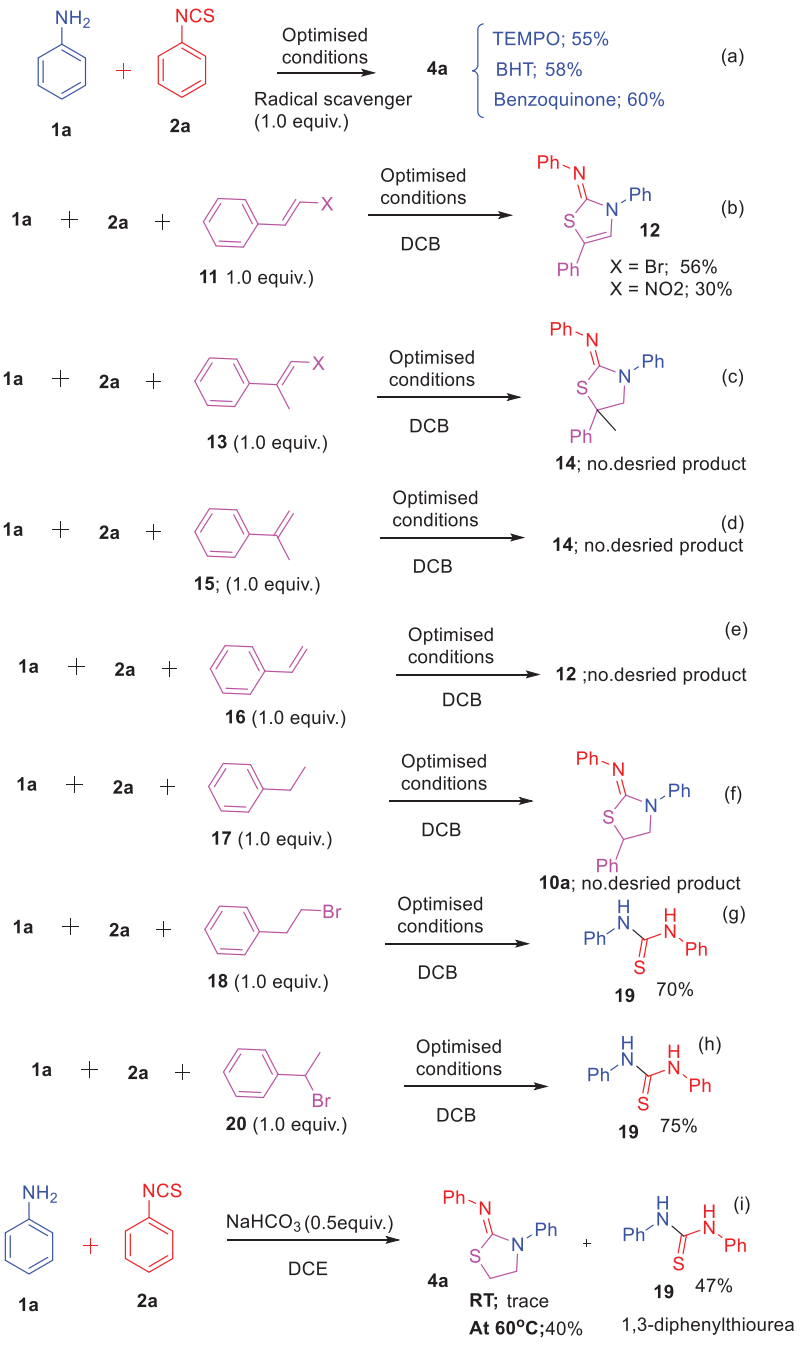
isothiocyanates having activating groups (methyl and *tert*-butyl) proceeded smoothly and afford the desired products **8r** and **8s** in 70% and 72% yields. To further expand the scope of the present three-component strategy, we tested (1,2-dibromoethyl)benzenes **9** as the dihalide source in dichlorobenzene as solvent under the optimized conditions, surprisingly we observed the regioselective annulated product **10** over the other product **11** (Scheme 5). Aniline as well as aliphatic amines 5 and phenylisothiocyanate **2a** were reacted smoothly with 1,2-dibromoethyl)benzene derivatives 9 and afford the desired products **10a−f** in moderate to good yield (50–75%). The regioselective annulation of dibromo styrenes under the present conditions has been further confirmed by XRD analysis of the product **10e**. The reaction of **1a** and **2a** with 1-(1,2-dibromoethyl) naphthalene and 1,2-dibromooctane under the same conditions gave the desired products **10g** and **10h** in 61% and 62% yields respectively. Also, the reaction was performed with ethyl isothiocyanate with aniline and 1,2-dibromoethyl) benzene, the desired annulated product **10i** was obtained in 58% yield. However, the present conditions are not suitable to yield the desired products (**10j** and **10k**) when cyclic and internal dibromo derivatives were employed.

To gain insights into the reaction mechanism, selective control experiments were performed (Scheme 6). The reaction of **1a** and **2a** was subjected to the optimized conditions along with radical scavengers (TEMPO, BHT, and benzoquinone) to know the reaction pathway. Under these conditions, the desired product **4a** was isolated in 55%, 58% and 60% yield "respectively" (Scheme 6a). These reactions suggest that, the present transformation may proceed through the ionic path. The reaction of **1a** and **2a** was



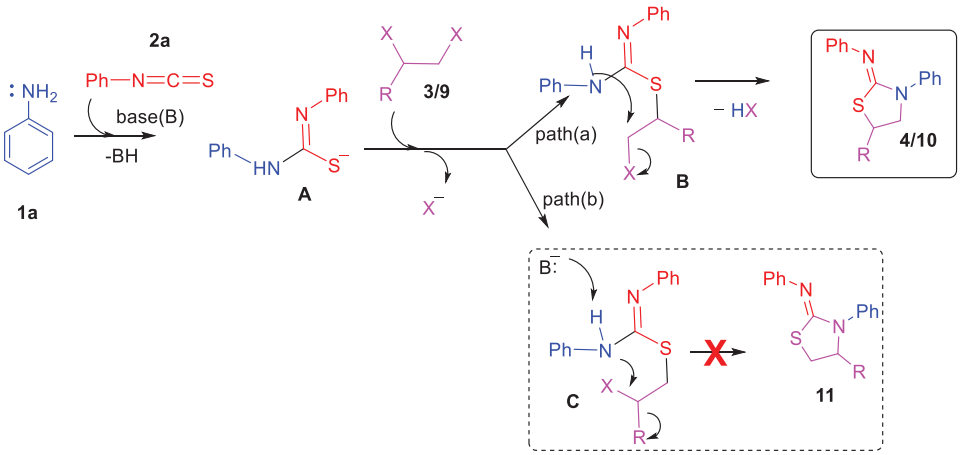
Scheme 5. Synthesis and scope of 1,3-thiazinan-2-imines[a]. [a]Reaction conditions: **5** (1 mmol) and **2** (1 mmol), $NaHCO_3$ (0.5 mmol), **9** (1.0 mmol), 1,2-dichlorobenzene (1.0 mL) at 120 °C, 24 h, yield of the isolated product. [b]Yield with 1.023 g scale (11.0 mmol). CCDC for **10e**: 1959624.

subjected with *β*-bromo/nitro styrene **11** under the optimized conditions in 1,2-dichlorobenzene, and obtained the product (*Z*)-*N*,3,5-triphenylthiazol-2(3H)-imine **12** in 56% and 30% yield (Scheme 6b). Further **1a** and **2a** was subjected with α-substituted styrene **13**, **15** and styrene and **16** with the above conditions, in these cases no reaction was observed (Scheme 6c–e). These reactions indicate that *β*-substituted styrenes react with **1a** and **2a**, but α-substituted styrenes do not react under these conditions. No reaction was observed with ethylbenzene **17** under the same conditions (Scheme 6f). Also the reaction was performed with (2-bromoethyl)benzene **18** and (1-bromoethyl)benzene **20** there were no desired products were obtained only 1,3-diphenylthiourea **19** products was observed (Scheme 6g–h) with yield (70-75%). From the above reactions it suggests that it is essential to have the leaving group at *β*-position and hydride at α-position of styrenes for the cyclization to yield the expected products. When the reaction was performed at room temperature and at 60 °C, the desired product was obtained in trace at r.t, and 40% yield at 60 °C along with 47% yield of undesired product 1,3-diphenylthiourea **19** was observed (Scheme 6i).



Scheme 6. Control experiments.

Based on the control experiments and the literature reports [16,17] plausible reaction mechanism has been proposed for the present transformation (Scheme 7). Initially, the reaction of aniline **1a** with phenylisothiocyanate **2a** in presence of base generates thiourea sulphonium ion intermediate **A.** The nucleophilic attack of **A** on



Scheme 7. Plausible mechanism.

the secondary carbon of **3/9** generates more stable intermediate **B** (path a). The dehydrohalogenation of **B** and followed by cyclization afford the desired product **4/10**. On the other hand, the attack of **A** on the primary carbon of **3/9** (path b), to generate the intermediate **C**, and its subsequent dehydrohalogenation to yield the product **11** was not observed.

Conclusions

In summary, we have developed a convenient method for the synthesis of thiazolidin-2-imines/1,3-thiazinan-2-imines via three-component annulation reactions under metal-free conditions. We have employed both dichloroethane, 1,2-dibromo-octane and (1,2-dibromoethyl) benzenes as two carbon sources for the annulation reactions and obtained the corresponding saturated five-membered heterocycles. Under the same conditions, with 1,3-dibromopropane as dihalide source, the corresponding saturated six membered heterocycles were obtained in good yields. These aliphatic heterocycles enhance the drug discovery process through late stage functionalization. The method works well with broad substrate scope with respect to both isothiocyanates (such as aromatic, aliphatic, cyclic) and amines such as aromatic, aliphatic, cyclic, adamantine including thiophen-2-ylmethanamine and furan-2-ylmethanamine. To validate the feasibility of the process for commercial applications, four products were synthesized at 11.0 mmol scale under the optimized conditions.

Experimental section

General

All commercially available chemicals and reagents were used without any further purification unless otherwise indicated. ^{1}H and ^{13}C NMR spectra were recorded at 600, 500, 200 and 150, 125, 50 MHz, respectively. The spectra were recorded in $CDCl_3$ as solvent. Multiplicity was indicated as follows: s (singlet); d (doublet); t (triplet); m (multiplet);

dd (doublet of doublets), etc. and coupling constants (J) were given in Hz. Chemical shifts are reported in ppm relative to TMS as an internal standard. The peaks around delta values of ^{1}H NMR (7.2), and ^{13}C NMR (77.0) are correspond to deuterated solvent chloroform respectively. Mass spectra were obtained using electron impact (EI) ionization method. Progress of the reactions was monitored by thin layer chromatography (TLC). All products were purified through column chromatography using silica gel 100–200 mesh size using hexane/ethyl acetate as eluent unless otherwise indicated.

General procedure for 4a

A clean washed boiling tube equipped with a magnetic stir bar was charged with aniline **1a** (0.0930 g, 1 mmol), phenyl isothiocyanates **2a** (0.1350 g, 1 mmol), 0.5 mmol of $NaHCO_3$ and dichloroethane (1 mL), the above mixture was stirred for 24 h at 120 °C temperature. After completion of the reaction, the mixture was poured into 10 mL of $NaHCO_3$ solution. The product was extracted with ethyl acetate (10 mL × 3) and dried with anhydrous Na_2SO_4. Removal of the solvent under reduced pressure, the left-out residue was purified through column chromatography using silica gel (20% EtOAc/hexane) to obtained (*Z*)-*N*,3-diphenylthiazolidin-2-imine **4a** in 82% yield (0.2082 g).

Copies of NMR spectra for all compounds, HRMS spectra for new compounds and melting points of solid compounds. This material is available free of charge via the internet at Crystallographic data for compounds **4a** (CCDC-1959623) and **10e** (CCDC-1959624) can be obtained free of charge from the Cam-bridge Crystallographic Data Center via mail-to: www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgments

Authors are thankful to the "Analytical Discipline and Centralized Instrumental Facilities" for providing instrumentation facilities.

Funding

CSIR-CSMCRI communication [No. 140/2019]. R. K is to AcSIR for his Ph.D. enrolment and UGC, New Delhi for Senior Research Fellowship. S. A. is thankful to DST, Govt. India [EMR/2016/000010] for the research grants and CSIR-CSMCRI [MLP-027] for partial financial support.

References

[1] Majumdar, K. C.; Chattopadhyay, S. K. *Heterocycles in Natural Product Synthesis*; Wiley-VCH: Weinheim, 2011; p 658.

[2] For an overview of the synthetic routes and best-selling drugs containing 5 and 6-membered heterocycles, (a) Baumann, M.; Baxendale, I. R.; Ley, S. V.; Nikbin, N. An Overview of the Key Routes to the Best Selling 5-Membered Ring Heterocyclic Pharmaceuticals. *Beilstein, J. Org. Chem.* **2011**, 7,442–495. DOI: 10.3762/bjoc.7.57. (b) Baumann, M.; Baxendale, I. R. An Overview of the Synthetic Routes to the Best Selling Drugs Containing 6-Membered Heterocycles.*Beilstein J. Org. Chem.* **2013**, *9*, 2265–2319. DOI: 10.3762/bjoc.9.265.

[3] (a) Liskey, C. W.; Hartwig, J. F. Iridium-Catalyzed C-H Borylation of Cyclopropanes. *J. Am. Chem. Soc.* **2013**, *135*, 3375–3378. DOI: 10.1021/ja400103p. (b) Cernak, T.;

Dykstra, K. D.; Tyagarajan, S.; Vachal, P.; Krska, S. W. The Medicinal Chemist's Toolbox for Late Stage Functionalization of Drug-Like Molecules. *Chem. Soc. Rev*. **2016**, *45*, 546–576. DOI: 10.1039/c5cs00628g.(c) Durak, L. J.; Payne, J. T.; Lewis, J. C. Late-Stage Diversification of Biologically Active Molecules via Chemoenzymatic C-H Functionalization. *ACS Catal.* **2016**, *6*, 1451–1454. DOI: 10.1021/acscatal.5b02558.

[4] Vicini, P.; Geronikaki, A.; Anastasia, K.; Incerti, M.; Zani, F. Synthesis and Antimicrobial Activity of Novel 2-Thiazolylimino-5-Arylidene-4-Thiazolidinones. *Bioorganic Med. Chem.* **2006**, *14*, 3859–3864. DOI: 10.1016/j.bmc.2006.01.043.

[5] Küçükgüzel, G.; Kocatepe, A.; De Clercq, E.; Sahin, F.; Güllüce, M. Synthesis and Biological Activity of 4-Thiazolidinones, Thiosemicarbazides Derived from Diflunisal Hydrazide. *Eur. J. Med. Chem*. **2006**, *41*, 353–359. DOI: 10.1016/j.ejmech.2005.11.005.

[6] Fuloria, N. K.; Singh, V.; Shaharyar, M.; Ali, M. Synthesis and Antimicrobial Evaluation of Some New Oxadiazoles Derived from Phenylpropionohydrazides. *Molecules* **2009**, *14*, 1898–1903. DOI: 10.3390/molecules14051898.

[7] Fuloria, N. K.; Singh, V.; Shaharyar, M.; Ali, M. Synthesis, Characterization and Biological Studies of Novel Imines and Azetidinones Derivatives of Haloaryloxy Moiety. *Asian J. Chem*. **2008**, *20*, 4891–4900.

[8] Küçükgüzel, S. G.; Oruç, E. E.; Rollas, S.; Sahin, F.; Ozbek, A. Synthesis, Characterisation and Biological Activity of Novel 4-Thiazolidinones, 1,3,4-Oxadiazoles and Some Related Compounds. *Eur. J. Med. Chem*. **2002**, *37*, 197–206. DOI: 10.1016/s0223-5234(01)01326-5.

[9] (a) Sekhar, K. V. G. C.; Rao, V. S.; Reddy, A. S.; Sunandini, R.; Satuluri, V. S. A. K. Solvent Free Microwave Accelerated Synthesis of Heterocyclic Thiazolidin-4-Ones as Antimicrobial and Antifungal Agents. *Bull. Korean Chem. Soc*. **2010**, *31*, 1219–1222. DOI: 10.5012/bkcs.2010.31.5.1219. (b) Gurupadayya, B.; Gopal, M.; Padmashali, B.; Manohara, Y. Synthesis and Pharmacological Evaluation of Azetidin-2-Ones and Thiazolidin-4-Ones Encompassing Benzothiazole. *Indian J. Pharm. Sci.* **2008**, *70*, 572–577. DOI: 10.4103/0250-474X.45393.(c) Singh, N.; Sharma, U. S.; Sutar, N.; Kumar, S.; Sharma, U. K. Synthesis and Antimicrobial Activity of Some Novel 2-Amino Thiazole Derivatives. *J. Chem. Pharm. Res.* **2010**, *2*, 691–698.(d) Taylor, E. C.; Patel, H. H. Synthesis of Pyrazolo 3,4-Dpyrimidine Analogues of the Potent Agent N-4-2-2-Amino-4 3H-Oxo-7H-Pyrrolo 2,3-Dpyrimidin-5-Yl Ethylbenzoyl-L-Glutamic Acid (LY231514). *Tetrahedron* **1992**, *48*, 8089–8100. DOI: 10.1016/S0040-4020(01)80479-8.

[10] Gong, G.-H.; Wang, D.; Zhang, J.-F.; Wei, C.-X.; Quan, Z.-S. Anticonvulsant Activity of 2-(Substituted-Imino)Thiazolidin-4-Ones. *Drug Res.* **2014**, *64*, 5–9. DOI: 10.1055/s-0033-1349095.

[11] Arfeen, M.; Bhagat, S.; Patel, R.; Prasad, S.; Roy, I.; Chakraborti, A. K.; Bharatam, P. V. D. Design, Synthesis and Biological Evaluation of 5-Benzylidene-2-Iminothiazolidin-4-Ones as Selective GSK-3β Inhibitors. *Eur. J. Med. Chem*. **2016**, *121*, 727–736. DOI: 10.1016/j.ejmech.2016.04.075.

[12] Huber-Villaume, S.; Revelant, G.; Sibille, E.; Philippot, S.; Morabito, A.; Dunand, S.; Chaimbault, P.; Bagrel, D.; Kirsch, G.; Hesse, S.; Schohn, H. 2-(Thienothiazolylimino)-1,3-Thiazolidin-4-Ones Inhibit Cell Division Cycle 25 a Phosphatase. *Bioorg. Med. Chem.* **2016**, *24*, 2920–2928. DOI: 10.1016/j.bmc.2016.04.063.

[13] Bianco, G.; Meleddu, R.; Distinto, S.; Cottiglia, F.; Gaspari, M.; Melis, C.; Corona, A.; Angius, R.; Angeli, A.; Taverna, D.; et al. N-Acylbenzenesulfonamide Dihydro-1,3,4-Oxadiazole Hybrids: Seeking Selectivity toward Carbonic Anhydrase Isoforms. *ACS Med. Chem. Lett.* **2017**, *8*, 792–796. DOI: 10.1021/acsmedchemlett.7b00205.

[14] Dahiya, A.; Ali, W.; Patel, B. K. Catalyst and Solvent Free Domino Ring Opening Cyclization: A Greener and Atom Economic Route to 2-Iminothiazolidines. *ACS Sustainable Chem. Eng.* **2018**, *6*, 4272–4281. DOI: 10.1021/acssuschemeng.7b04723.

[15] Bhattacharyya, A.; Kavitha, C. V.; Ghorai, M. K. Stereospecific Synthesis of 2-Iminothiazolidines via Domino Ring-Opening Cyclization of Activated Aziridines with Aryl- and Alkyl Isothiocyanates. *J. Org. Chem*. **2016**, *81*, 6433–6443. DOI: 10.1021/acs.joc.6b01551.

[16] Sengoden, M.; Irie, R.; Punniyamurthy, T. Enantiospecific Aluminum-Catalyzed (3 + 2) Cycloaddition of Unactivated Aziridines with Isothiocyanates. *J. Org. Chem.* **2016**, *81*, 11508–11513. DOI: 10.1021/acs.joc.6b02190.

[17] Sengoden, M.; Punniyamurthy, T. "On Water": Efficient Iron-Catalyzed Cycloaddition of Aziridines with Heterocumulenes. *Angew. Chem. Int. Ed. Engl.* **2013**, *52*, 572–575. DOI: 10.1002/anie.201207746.

[18] Gao, L.; Fu, K.; Zheng, G. Quickly $FeCl_3$-Catalyzed Highly Chemo- and Stereo-Selective [3 + 2] Dipolar Cycloaddition of Aziridines with Isothiocyanates. *RSC Adv.* **2016**, *6*, 47192–47195. DOI: 10.1039/C6RA04923K.

[19] Sengoden, M.; Vijay, M.; Balakumar, E.; Punniyamurthy, T. Efficient Pyrrolidine Catalyzed Cycloaddition of Aziridines with Isothiocyanates, Isoselenocyanates and Carbon Disulfide "On Water". *RSC Adv.* **2014**, *4*, 54149–54157. DOI: 10.1039/C4RA08902B.

[20] Wu, J.-Y.; Luo, Z.-B.; Dai, L.-X.; Hou, X.-L. Tributylphosphine-Catalyzed Cycloaddition of Aziridines with Carbon Disulfide and Isothiocyanate. *J. Org. Chem.* **2008**, *73*, 9137–9139. DOI: 10.1021/jo801703h.

[21] Craig, R. A.; O'Connor, N. R.; Goldberg, A. F. G.; Stoltz, B. M. Stereoselective Lewis Acid Mediated (3 + 2) Cycloadditions of N-H- and N-Sulfonylaziridines with Heterocumulenes. *Chemistry* **2014**, *20*, 4806–4813. DOI: 10.1002/chem.201303699.

[22] Anitha, M.; Swamy, K. C. K. Synthesis of Thiazolidine-Thiones, Imino-Thiazolidines and Oxazolidines via the Base Promoted Cyclisation of Epoxy-Sulfonamides and Heterocumulenes. *Org. Biomol. Chem.* **2018**, *16*, 402–413. DOI: 10.1039/c7ob02915b.

[23] Ranjan, A.; Mandal, A.; Yerande, S. G.; Dethe, D. H. An Asymmetric Alkynylation/Hydrothiolation Cascade: An Enantioselective Synthesis of Thiazolidine-2-Imines from Imines, Acetylenes and Isothiocyanates. *Chem. Commun. (Camb.)* **2015**, *51*, 14215–14218. DOI: 10.1039/c5cc05549k.

[24] Zhang, Y. H.; Shi, B. F.; Yu, J. Q. Palladium(II)-Catalyzed Ortho Alkylation of Benzoic Acids with Alkyl Halides. *Angew. Chem. Int. Ed. Engl.* **2009**, *48*, 6097–6100. DOI: 10.1002/anie.200902262.

[25] (a) Rao, W. H.; Jiang, L. L.; Zhao, J. X.; Jiang, X.; Zou, G. D.; Zhou, Y. Q.; Tang, L. Selective O-Cyclization of N-Methoxy Aryl Amides with CH2Br2 or 1,2-DCE via Palladium-Catalyzed C-H Activation. *Org. Lett.* **2018**, *20*, 6198–6201. DOI: 10.1021/acs.orglett.8b02678. (b) Kidwai, M.; Venkataraman, R.; Dave, B. Solventless Synthesis of Thiohydantoins over K_2CO_3. *Green Chem.* **2001**, *3*, 278–279. DOI: 10.1039/b106034c.(c) Yella, R.; Ghosh, H.; Patel, B. K. It is "2-Imino-4-Thiazolidinones" and Not Thiohydantoins as the Reaction Product of 1,3-Disubstituted Thioureas and Chloroacetylchloride. *Green Chem.* **2008**, *10*, 1307–1312. DOI: 10.1039/b807775d.

[26] Jade, M. N.; Katiya, M. M.; Deotale, V. D.; Sontakke, M. M.; Dhonde, M. G.; Berad, B. N. Synthesis of Thiazol, Thiazinan, Thiadiazin, Thiazolidin, Triazine, Thioxo-Pyrimidin and Thioxo-Imidazolidine by Inter-Intra Molecular Cyclization. *Indian J. Chem.* **2018**, *57*, 1493–1500.