Organic & Biomolecular Chemistry

ROYAL SOCIETY OF CHEMISTRY

COMMUNICATION

View Article Online
View Journal | View Issue



Cite this: *Org. Biomol. Chem.*, 2023, **21**, 1143

Received 21st November 2022,
Accepted 11th January 2023

DOI: 10.1039/d2ob02115c

rsc.li/obc



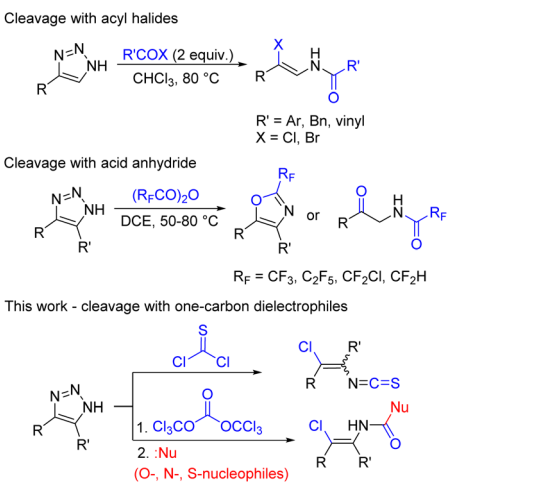
# Synthesis of *N*-vinyl isothiocyanates and carbamates by the cleavage of NH-1,2,3-triazoles with one-carbon electrophiles†

Vladimir Motornov * and Petr Beier *

**Metal-free cascade reaction of NH-1,2,3-triazoles with one-carbon electrophiles, such as thiophosgene and triphosgene, led to *N*-vinylated ring cleavage products. Using this approach the synthesis of *N*-vinylisothiocyanates from NH-triazoles and thiophosgene was achieved. A variety of multifunctional compounds, such as *N*-vinylcarbamates, unsymmetrical vinylureas, carbamothioates, *etc*. was prepared by a one-pot method from NH-triazoles, triphosgene and nucleophiles.**

1,2,3-Triazoles are versatile building blocks for the synthesis of functionalized heterocycles.[1] For example, metal-catalyzed transannulation of *N*-sulfonyl[2] and *N*-fluoroalkyl-[3] 1,2,3-triazoles is a useful and well-established methodology, providing access to various, often bioactive, nitrogen-containing heterocycles and carbocycles. Furthermore, cleavage of *N*-substituted 1,2,3-triazoles with Brønsted[4] and Lewis[5] acids was studied as an alternative to metal-catalyzed transformations. However, much less attention was devoted to the ring cleavage chemistry of NH-1,2,3-triazoles.[6] In comparison to *N*-sulfonyl and *N*-fluoroalkyl triazoles, which require multiple synthetic steps, NH-1,2,3-triazoles are easily accessible in one step from simple azide sources ($NaN_3$ or $TMSN_3$) and commercial alkynes,[7] or aldehydes and nitroalkanes.[8] It is known that the ring cleavage of 1,2,3-triazole is synthetically useful in the presence of an electron-withdrawing group at N1,[2] fused triazole derivatives[9] and specific substrates with more reactive centres.[10] Thus, for a long time NH-1,2,3-triazoles were not considered as building blocks in ring cleavage chemistry. Only very recently, NH-1,2,3-triazoles were successfully used in ring transformations, which was made possible by *N*-acylation followed by *in situ* cleavage of unstable *N*-acyltriazoles.[11,12] Cleavage of NH-1,2,3-triazoles with acyl halides led to β-haloenamides,[11] while reactions with fluoroalkylated acid anhydrides provides routes to fluoroalkylated oxazoles or 2-acylaminoketones (Scheme 1).[12] Thus, utilization of NH-1,2,3-triazoles as building blocks is a highly promising area in organic chemistry.

*N*-Alkenyl compounds are attractive synthetic targets, which are widely used in polymer chemistry, including the synthesis of biocompatible copolymers used in pharmaceutical industry.[13] While unsubstituted vinylamides can be prepared by direct vinylation of amides with acetylene,[14] the synthesis of substituted vinylamides and more complex *N*-vinyl compounds (vinyl carbamates, vinylureas, vinylazoles) is a more challenging task. In the recent two decades, the most common methods to access complex *N*-alkenyl compounds were based on Ru-catalyzed addition of amides to alkynes,[15] as well as Cu-[16] and Pd-catalyzed[17] cross-coupling reactions. Among the variety of *N*-alkenyl compounds, vinyl isothiocyanates deserve a special attention.[18] The vinyl isothiocyanate moiety is present in natural products, such as in Sinapigladioside, which exhibits high antifungal and antibacterial activity (Fig. 1).[18,19] Despite very promising biological activities, vinyl




**Scheme 1** Ring cleavage transformations of NH-1,2,3-triazoles.

*Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Flemingovo nám. 2, 166 10 Prague, Czech Republic.*
*E-mail: vladimir.motornov@uochb.cas.cz, beier@uochb.cas.cz*

† Electronic supplementary information (ESI) available. See DOI: https://doi.org/10.1039/d2ob02115c

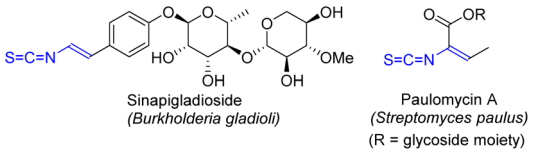
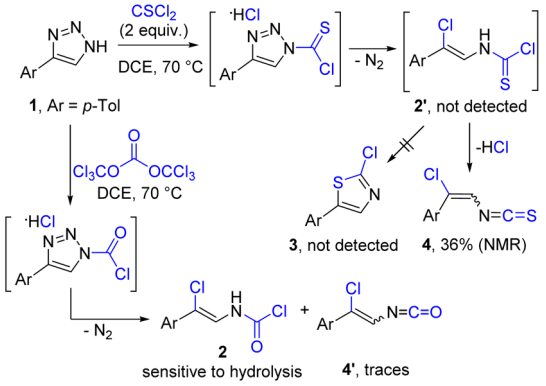



**Fig. 1** Vinyl isothiocyanates in natural products.

isothiocyanates are difficult to obtain synthetically. While reactions of amines and anilines with thiophosgene is an established route to prepare alkyl and aryl isothiocyanates, analogous synthesis of vinyl isothiocyanates is apparently limited.[20] Thus, a new method to access complex *N*-alkenyl compounds, including isothiocyanates, is highly desirable. Herein, we report the metal-free synthesis of vinyl isothiocyanates and other *N*-alkenyl compounds from NH-1,2,3-triazoles and easily available one-carbon electrophiles, such as thiophosgene and triphosgene.

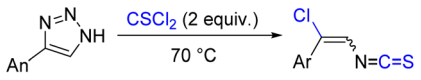
Our study was initiated by the investigation of reactions between NH-1,2,3-triazoles and one-carbon dielectrophiles such as triphosgene and thiophosgene (Scheme 2). We envisioned the formation of *N*-vinylcarbamoyl chloride **2** or *N*-vinylthiocarbamoyl chloride **2′** *via* acylated triazole intermediates and further transformations. In the case of **2′** we expected the formation of 2-chlorothiazole **3** due to a high nucleophilicity of the sulfur atom, which could facilitate intramolecular cyclization. To our surprise, heating the mixture of model NH-1,2,3-triazole **1** and thiophosgene at 70 °C led to the formation of vinyl isothiocyanate **4** in moderate yield as *E*/*Z* mixture, while no intermediate **2′** or cyclization product **3** were detected. In contrast to the reaction with thiophosgene, the application of triphosgene led to the exclusive formation of *N*-vinylcarbamoyl chloride **2** with small amount (<10%) of vinyl isocyanate **4′**.

Screening of reaction conditions for the synthesis of vinyl isothiocyanate **4a** was performed (Table 1). We found that the reaction proceeds more efficiently with electron-rich triazoles, thus, 4-methoxyphenyl-substituted triazole **1a** was chosen as a model substrate. Survey of solvents revealed that non-polar toluene (entry 2) afforded slower reaction than chlorinated sol-




**Scheme 2** Initial findings in reactions of NH-1,2,3-triazole.

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

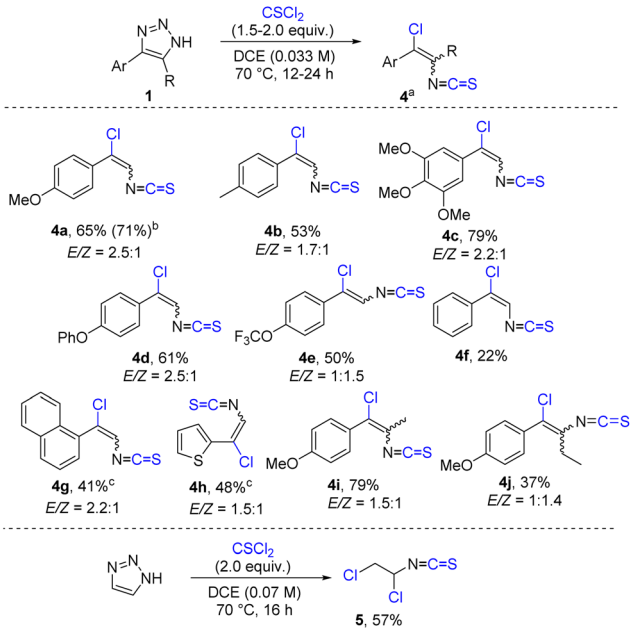



| Entry | Solvent | Conc. (M) | Time (h) | Yield of **4a**[b] (%) |
|---|---|---|---|---|
| 1 | DCE | 0.1 | 12 | 46 |
| 2 | $CHCl_3$ | 0.1 | 12 | 45 |
| 3 | PhMe | 0.1 | 42 | 45 |
| 4 | MeCN | 0.1 | 0.5 | 40 |
| 5[c] | DCE | 0.1 | 12 | 52 |
| 6[d] | DCE | 0.1 | 12 | 41 |
| 7[e] | DCE | 0.1 | 18 | 34 |
| 8 | DCE | 0.05 | 12 | 51 |
| 9 | DCE | 0.2 | 12 | 42 |
| 10 | DCE | 0.033 | 12 | 70 |
| 11[c] | DCE | 0.033 | 18 | 70 (65)[f] |
| 12[g] | DCE | 0.033 | 30 | 49 |
| 13[h] | DCE | 0.033 | 5 | 61 |

[a] Reaction conditions: **1a** (0.1 mmol) and $CSCl_2$ (0.2 mmol) in solvent heated to 70 °C. [b] Yields were determined by $^1$H NMR with methyl 4-nitrobenzoate as an internal standard. [c] $CSCl_2$ (1.5 equiv.). [d] $CSCl_2$ (3 equiv.). [e] $CSCl_2$ (1.0 equiv.). [f] Isolated yield in parentheses. [g] 50 °C. [h] 80 °C.

vents DCE and $CHCl_3$ (entries 1 and 3). On the contrary, the reaction proceeded quickly in more polar acetonitrile (entry 4). The yields in different solvents were similar. Decrease of $CSCl_2$ amount to 1.5 equiv. led to slight improvement of the yield (entry 5), while increase to 3 equiv. afforded lower yield (entry 6). However, further decrease of $CSCl_2$ amount to 1.0 equiv. resulted in drop of yield (entry 7). Studying the effect of concentration revealed that in more diluted (0.05 M) solution the yield was increased (entry 8), while in more concentrated (0.2 M) solution the reaction was less efficient (entry 9). Further dilution to 0.033 M afforded good 70% NMR yield of the target isothiocyanate **4a** (entry 10). Thus, performing the reaction in diluted solution with 1.5 equiv. of $CSCl_2$ was considered optimal (entry 11). Neither reducing nor increasing the temperature did not improve the yield (entries 12 and 13).

Next, the reaction scope was investigated applying optimized conditions (Scheme 3). 4-Substituted triazoles with various aryl groups were tested. Importantly, the reaction proceeded efficiently with triazoles bearing electron-donating groups. Thus, good yields were obtained for 4-methoxyphenyl- (**4a**), 3,4,5-trimethoxyphenyl (**4c**) and 4-phenoxyphenyl- (**4d**) substituted isothiocyanates. In the case of alkyl-substituted aromatic ring, moderate yield of **4b** was obtained. Trifluoromethoxy-substituted triazole also afforded the product **4e** in moderate yield. However, in the case of phenyl group without electron-donating substituents, only 22% yield of isothiocyanate was obtained. This is attributed to the formation of side-products, arising from low stability of vinyl isothiocyanates without electron-rich groups on the aryl ring. Moderate yields could be obtained for sterically demanding α-naphthyl- (**4g**) and 2-thienyl-substituted examples (**4h**), when milder conditions (45 °C, 24 h) were applied to avoid side reac-

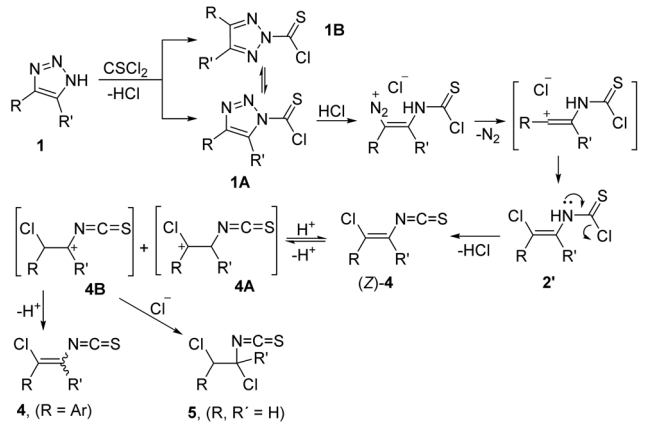



**Scheme 3** The scope of vinyl isothiocyanate synthesis from NH-1,2,3-triazoles. Reaction conditions: **1** (0.2 mmol), $CSCl_2$ (0.3–0.4 mmol), DCE (6 ml), 70 °C, 12–24 h. [a]Isolated yields. [b]Yield on 1 mmol scale. [c]Heating at 45 °C for 24 h.

tions. Apart from monosubstituted 1,2,3-NH-triazoles, 4,5-disubstituted substrates bearing one electron-rich aryl group and alkyl group were also found applicable for isothiocyanate synthesis. High yield was obtained for methyl-substituted product **4i**, while the reaction was less efficient for ethyl-substituted **4j**. Unfortunately, triazoles with electron-deficient aryl substituents were not applicable for this transformation due to their low reactivity under reaction conditions and propensity of forming products of side reactions. Unsubstituted 1,2,3-NH-triazole underwent cleavage with $CSCl_2$ to form 1,2-dichloroethyl isothiocyanate **5** in good yield. Compound **5** is clearly a product of HCl addition to intermediately formed vinyl isothiocyanate.

The developed method was found to be easily scalable as exemplified by the synthesis of isothiocyanate **4a** on 1 mmol (175 mg) scale in 71% yield (Scheme 3). The investigation of reactivity of vinyl isothiocyanates, as well as biological activity and applications are attractive future tasks for organic and medicinal chemists.

According to $^1H$–$^1H$ ROESY NMR analysis, products **4** were obtained as mixtures of *E*- and *Z*-isomers, with the preference for *E*-isomers. This contrasts with literature reports on 1,2,3-triazole cleavage with Brønsted and Lewis acids,[4,5] where the stereoselective formation of *Z*-isomers was confirmed. To explain the above-mentioned observations, the following mechanism of $CSCl_2$-mediated triazole ring cleavage was proposed (Scheme 4). Thioacylation of 1,2,3-NH-triazole with $CSCl_2$ can lead to both N1- and N2-thioacyl triazoles. Reversible interconversion between regioisomers is possible in the presence of acid, which can explain successful ring clea-



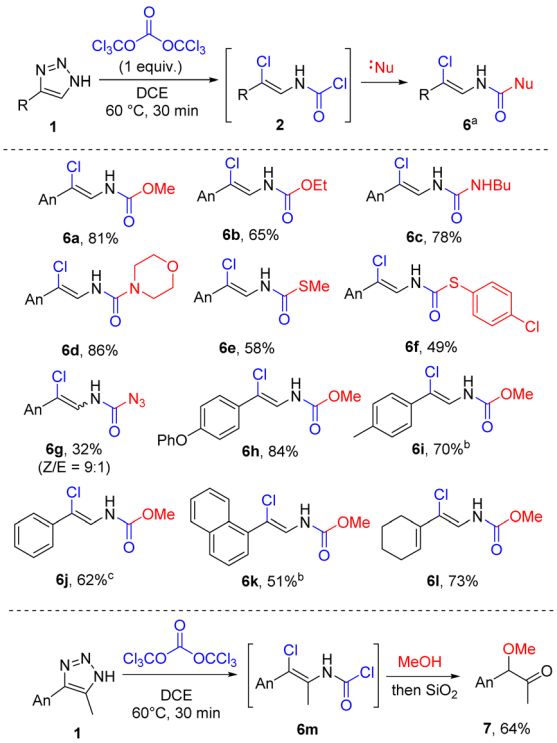

**Scheme 4** Proposed mechanism of $CSCl_2$-mediated triazole ring cleavage.

vage reactions even for 4,5-disubstituted triazoles. N1-Thioacyl-1,2,3-triazole **1A** undergoes ring cleavage in the presence of HCl to form diazo compound followed by nitrogen elimination to vinyl cation, which recombines with chloride anion to form thiocarbamoyl chloride **2′**. It undergoes elimination of HCl to *Z*-isomer of vinyl isothiocyanate **4**. However, in the presence of HCl protonation of the double bond can take place to form cations **4A** and **4B**. Their deprotonation (for R = Ar) leads to isomeric mixtures of vinyl isothiocyanates **4**, while recombination of cation **4B** with chloride anion affords 1,2-dichloroethyl isothiocyanate **5**.

Next, cleavage of NH-1,2,3-triazoles with triphosgene was investigated. Since almost quantitative formation of *N*-vinylcarbamoyl chloride **2** was obtained under similar conditions (60 °C, 30 min), further transformations of **2** were studied without optimization of the first step. Moreover, preliminary results revealed the reaction with triphosgene to be insensitive to concentration, in comparison to synthesis of vinyl isothiocyanates. Thus, 0.2 M concentration was used. Despite low stability of *N*-vinylcarbamoyl chlorides **2**, their electrophilic nature makes them attractive precursors of *N*-vinylated compounds by the treatment with various nucleophiles. Thus, a one-pot synthesis of *N*-vinyl compounds starting directly from NH-triazoles and triphosgene was developed (Scheme 5).

Firstly, when methanol or ethanol were used as nucleophiles, *N*-vinylcarbamates **6a–6b** were obtained in good yields. Using butylamine unsymmetrical vinylurea **6c** was prepared. The method also worked efficiently for a secondary amine (morpholine) as the nucleophile, leading to product **6d** in high yield. Sulfur nucleophiles, such as methanthiolate and 4-chlorothiophenol, proved to be competent in this transformation to give carbamothioates **6e** and **6f**, respectively. In the case of sodium azide the corresponding carbamoyl azide **6g** was prepared, albeit in 32% yield, probably, due to its low stability and propensity to decomposition *via* carbamoyl nitrene.

Regarding the scope of 1,2,3-triazoles, the triphosgene method was successfully applied to 4-phenoxysubstituted triazole, as well as to 4-tolyl, phenyl and 1-naphthyl-substituted

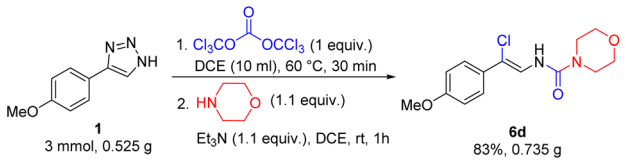



**Scheme 5** One-pot three-component assembly of *N*-alkenyl compounds from NH-1,2,3-triazoles, triphosgene, and nucleophiles. Reaction conditions: **1** (0.1 mmol), triphosgene (0.1 mmol), DCE (0.5 ml), 60 °C, 30 min, then nucleophile was added (see ESI† for detailed procedures). An = 4-methoxyphenyl. [a]Isolated yields. [b]70 °C, 30 min for the first step. [c]70 °C, 20 h for the first step.

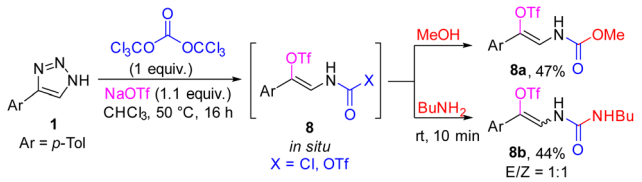
triazoles to afford products **6h–6k**. Importantly, alkenyl-substituted moiety on the triazole part was also tolerated to give product **6l** in 73% yield. For 4,5-disubstituted triazole (Scheme 5, bottom) alcoholysis and hydrolysis of C–N bond rather than only C–Cl bond took place, which led to known α-methoxyketone **7**. Importantly, in the case of triphosgene, intermediates vinylcarbamoyl chlorides **2** did not undergo HCl elimination, thus, their treatment with nucleophiles resulted in complete retention of *Z*-configuration in compounds **6** with the only exception of carbamoyl azide **6g**.

To investigate the scalability of the three-component synthesis of *N*-alkenyl compounds **5**, a 3 mmol scale reaction to synthesize vinylurea **5d** was attempted. Indeed, the process was found to be easily scalable as the product was obtained without significant loss of the yield (Scheme 6). Inexpensive triethylamine was used as a sacrificial base to remove HCl demonstrating that using excess of nucleophile is not necessary. Thus, complex *N*-vinylated compounds can be accessed with high atom-economy.

When sodium triflate was added to the reaction mixture in the first step, the present methodology allowed a one-pot four-component assembly of carbamate **8a** or unsymmetrical vinylurea **8b** with the triflate group (Scheme 7). Changing the solvent to chloroform was crucial for efficient transformation. It is interesting to note that the compound **8b** was obtained as




**Scheme 6** 3 mmol scale three-component synthesis of *N*-chlorovinylurea **6d**.




**Scheme 7** Four-component synthesis of functionalized β-enamido triflates.

1 : 1 mixture of *E*- and *Z*-isomers, in contrast to stereoselective formation of *Z*-isomer of carbamoyl triflate **8a**. This difference in configurational stability might be caused by lower double bond isomerization barrier for more electron-rich vinylurea derivative, which makes spontaneous isomerization possible. Since β-enamido triflates are bench stable and synthetically useful building blocks amenable to cross-coupling reactions,[21] the development of new routes for their synthesis is sought after.

In conclusion, *N*-vinyl isothiocyanates were prepared by the cleavage of NH-1,2,3-triazoles with thiophosgene. A one-pot method to access multifunctionalized *N*-alkenyl compounds from NH-1,2,3-triazoles, triphosgene and various nucleophiles was developed. The main advantages of the methodology are readily available starting materials, atom economy and short reaction times. The methods can be useful for the preparation of natural products with vinyl isothiocyanate moieties, as well as for the synthesis of complex and multifunctional *N*-alkenyl compounds.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

This work was supported by the Czech Academy of Sciences (RVO: 61388963) and by the Ministry of Education, Youth and Sports of the Czech Republic (LTAUSA18037). The authors thank Radek Pohl (IOCB Prague) for measurement of $^{1}H$–$^{1}H$ ROESY NMR spectra.

## References

1 (*a*) M. Akter, K. Rupa and P. Anbarasan, *Chem. Rev.*, 2022, **122**, 13108; (*b*) B. Chattopadhyay and V. Gevorgyan, *Angew. Chem., Int. Ed.*, 2012, **51**, 862; (*c*) M. Zibinsky and V. V. Fokin, *Org. Lett.*, 2011, **13**, 4870.

2 (*a*) H. M. Davies and J. S. Alford, *Chem. Soc. Rev.*, 2014, **43**, 5151; (*b*) *Chemistry of 1,2,3-triazoles, in Topics in Heterocyclic Chemistry*, ed. W. Dehaen and V. A. Bakulev (eds), vol. 40, Springer, 2015.

3 (*a*) V. Motornov, A. Markos and P. Beier, *Chem. Commun.*, 2018, **54**, 3258; (*b*) V. Motornov and P. Beier, *J. Org. Chem.*, 2018, **83**, 15195; (*c*) V. Motornov, V. Košťál, A. Markos, D. Taffner and P. Beier, *Org. Chem. Front.*, 2019, **6**, 3776; (*d*) O. Bakhanovich, V. Khutorianskyi, V. Motornov and P. Beier, *Beilstein J. Org. Chem.*, 2021, **17**, 504.

4 A. Markos, S. Voltrová, V. Motornov, D. Tichý, B. Klepetářová and P. Beier, *Chem. – Eur. J.*, 2019, **25**, 7640.

5 (*a*) A. Markos, L. Janecký, T. Chvojka, T. Martinek, H. Martinez-Seara, B. Klepetářová and P. Beier, *Adv. Synth. Catal.*, 2021, **363**, 3258; (*b*) Z.-F. Xu, H. C. Dai, L. H. Shan and C.-Y. Li, *Org. Lett.*, 2018, **20**, 1054; (*c*) D. Yang, L. Shan, Z.-F. Xu and C.-Y. Li, *Org. Biomol. Chem.*, 2018, **16**, 1461.

6 T. Opsomer and W. Dehaen, *Chem. Commun.*, 2021, **57**, 1568.

7 (*a*) D. Jankovic, M. Virant and M. Gazvoda, *J. Org. Chem.*, 2022, **87**, 4018; (*b*) T. Jin, S. Kamijo and Y. Yamamoto, *Eur. J. Org. Chem.*, 2004, 3789; (*c*) S. Payra, A. Saha and S. Banerjee, *ChemCatChem*, 2018, **10**, 5468.

8 (*a*) R. Hui, M. Zhao, M. Chen, Z. Ren and Z. Guan, *Chin. J. Chem.*, 2017, **35**, 1808; (*b*) L. Wu, X. Wang, Y. Chen, Q. Huang, Q. Lin and M. Wu, *Synlett*, 2016, **27**, 437; (*c*) Q. Hu, Y. Liu, X. Deng, Y. Li and Y. Chen, *Adv. Synth. Catal.*, 2016, **358**, 1689; (*d*) C. P. Parambil, S. P. Veethil and W. Dehaen, *Synthesis*, 2022, **54**, 910; (*e*) V. A. Motornov, S. L. Ioffe and A. A. Tabolin, *Targets Heterocycl. Syst.*, 2019, **23**, 237.

9 (*a*) D. Yadagiri, M. Rivas and V. Gevorgyan, *J. Org. Chem.*, 2020, **85**, 11030; (*b*) V. Helan, A. V. Gulevich and V. Gevorgyan, *Chem. Sci.*, 2015, **6**, 1928; (*c*) Y. Shi and V. Gevorgyan, *Chem. Commun.*, 2015, **51**, 17166; (*d*) Z. Zhang and V. Gevorgyan, *Org. Lett.*, 2020, **22**, 8500; (*e*) A. Joshi, C. Chandra Mohan and S. Adimurthy, *Org. Lett.*, 2016, **18**, 464.

10 (*a*) Yu. N. Kotovshchikov, G. V. Latyshev, M. A. Navasardyan, D. A. Erzunov, I. P. Beletskaya and N. V. Lukashev, *Org. Lett.*, 2018, **20**, 4467; (*b*) Yu. N. Kotovshchikov, G. V. Latyshev, E. A. Kirillova, U. D. Moskalenko, N. V. Lukashev and I. P. Beletskaya, *J. Org. Chem.*, 2020, **85**, 9015; (*c*) V. A. Voloshkin, Yu. N. Kotovshchikov, G. V. Latyshev, N. V. Lukashev and I. P. Beletskaya, *J. Org. Chem.*, 2022, **87**, 7064.

11 (*a*) T. Wang, Z. Tang, H. Luo, Y. Tian, M. Xu, Q. Lu and B. Li, *Org. Lett.*, 2021, **23**, 6293; (*b*) M. Xu, L. Liu, T. Wang, H. Luo, M. Hou, L. Du, X. Xin, Q. Lu and B. Li, *Org. Chem. Front.*, 2022, **9**, 1065.

12 (*a*) V. Motornov and P. Beier, *Org. Lett.*, 2022, **24**, 1958; (*b*) V. Motornov and P. Beier, *New J. Chem.*, 2022, **46**, 14318.

13 (*a*) L. B. Huang, M. Arndt, K. Goossen, H. Heydt and L. J. Goossen, *Chem. Rev.*, 2015, **115**, 2596; (*b*) N. A. Cortez-Lemus and A. Licea-Claverie, *Prog. Polym. Sci.*, 2016, **53**, 1.

14 (*a*) E. Semina, P. Tuzina, F. Bienewald, A. S. K. Hashmi and T. Schaub, *Chem. Commun.*, 2020, **56**, 5977; (*b*) K. S. Rodygin, A. S. Bogachenkov and V. P. Ananikov, *Molecules*, 2018, **23**, 648.

15 (*a*) L. Gooßen, K. S. M. Salih and M. Blanchot, *Angew. Chem., Int. Ed.*, 2008, **47**, 8492; (*b*) L. Gooßen, J. E. Rauhaus and G. Deng, *Angew. Chem., Int. Ed.*, 2005, **44**, 4042; (*c*) M. Arndt, K. S. M. Salih, A. Fromm, L. J. Goossen, F. Menges and G. Niedner-Schatteburg, *J. Am. Chem. Soc.*, 2011, **133**, 7428.

16 (*a*) Y. Bolshan and R. A. Batey, *Angew. Chem., Int. Ed.*, 2008, **47**, 2109; (*b*) Y. Bolshan and R. A. Batey, *Tetrahedron*, 2010, **66**, 5283; (*c*) R. A. Bohmann and C. Bolm, *Org. Lett.*, 2013, **15**, 4277; (*d*) V. Motornov, G. V. Latyshev, Yu. N. Kotovschikov, N. V. Lukashev and I. P. Beletskaya, *Adv. Synth. Catal.*, 2019, **361**, 3306.

17 J. P. Dalvadi, P. K. Patel and K. H. Chikhalia, *RSC Adv.*, 2013, **3**, 22972.

18 (*a*) J. Li, Z. Xie, M. Wang, G. Ai and Y. Chen, *PLoS One*, 2015, **10**, e0120542; (*b*) A. D. Argoudelis, T. A. Brinkley, T. F. Brodasky, J. A. Buege, H. F. Meyer and S. A. Mizsak, *J. Antibiot.*, 1982, **35**, 285; (*c*) L. V. Flórez and M. Kaltenpoth, *Environ. Microbiol.*, 2017, **19**, 3674; (*d*) L. V. Flórez, K. Scherlach, P. Gaube, C. Ross, E. Sitte, C. Hermes, A. Rodrigues, C. Hertweck and M. Kaltenpoth, *Nat. Commun.*, 2017, **8**, 15172; (*e*) L. V. Flórez, K. Scherlach, I. J. Miller, A. Rodrigues, J. C. Kwan, C. Hertweck and M. Kaltenpoth, *Nat. Commun.*, 2018, **9**, 2478.

19 B. Dose, S. P. Niehs, K. Scherlach, S. Shahda, L. V. Flórez, M. Kaltenpoth and C. Hertweck, *ChemBioChem*, 2021, **22**, 1920.

20 For rare examples of vinyl isothiocyanate synthesis, see: (*a*) N. A. Nedolya, B. A. Trofimov and A. Senning, *Sulfur Rep.*, 1996, **17**, 183; (*b*) Z. Rappoport and A. Topol, *J. Am. Chem. Soc.*, 1980, **102**, 406; (*c*) M.-W. Ding, B.-Q. Fu and L. Cheng, *Synthesis*, 2004, 1067.

21 (*a*) T. Chvojka, A. Markos, S. Voltrová, R. Pohl and P. Beier, *Beilstein J. Org. Chem.*, 2021, **17**, 2657; (*b*) Q. Lu, T. Wang, Q. Wu, L. Cheng, H. Luo, L. Liu, G. Chu, L. Wang and B. Li, *Green Chem.*, 2022, **24**, 4399.