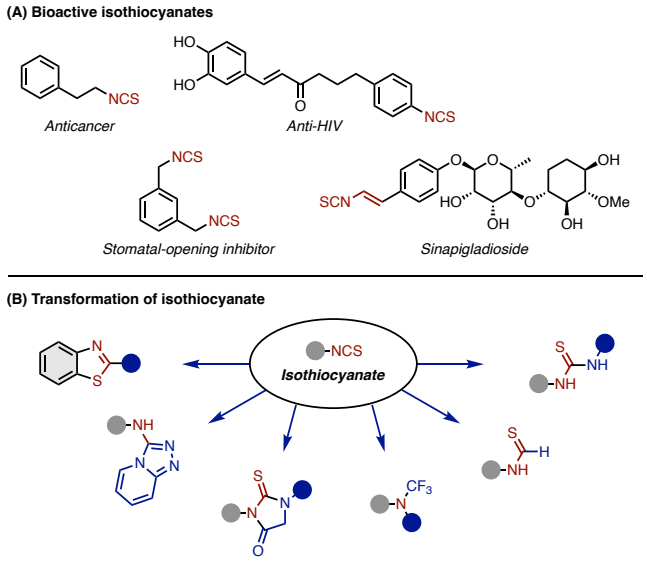
Please do not adjust margins

# Synthesis of *N*-β-brominated alkenyl isothiocyanates via dehydrogenation of alkyl isothiocyanates

Bumpei Maeda,[a] Ryohei Akiyoshi,[a] Daisuke Tanaka,[a] Kohei Sato,[a] Kei Murakami*[a,b]

**This study presents a new dehydrogenative synthesis of alkenyl isothiocyanates, providing compounds with bromo and isothiocyanate groups. These reactive functionalities offer versatility for further transformations. Application in an amine sensor utilizing a coumarin-attached product demonstrates practical utility. This streamlined approach facilitates access to alkenyl isothiocyanates, valuable tools for biological studies.**

Isothiocyanates are expected as promising candidates for pharmaceutical applications because they exhibit diverse biological activities such as antioxidant,[1] anti-inflammatory,[2] anticancer,[3] and anti-HIV virus.[4] (Scheme 1A) Isothiocyanates are derived as metabolites synthesized from glucosinolates by the members of the Brassicales family,[5] and they are recognized as defensive chemicals against herbivorous insects,[6] bacteria,[7] and fungi.[8] Recently, we identified benzyl isothiocyanates on stomatal opening inhibitors, and they act as drought tolerance-conferring agrochemicals.[9] Moreover, phenyl isothiocyanate is used in the sequencing of amino acids in peptides (Edman degradation).[10] Furthermore, isothiocyanates have been extensively used in organic synthesis, and various transformations into many nitrogen-containing functional groups have been developed.[11] (Scheme 1B) Notably, isothiocyanates are frequently employed as pivotal starting materials for the synthesis of thioureas,[12] which are utilized as chiral catalysts.[13] Additionally, utilizing isothiocyanates in the synthesis of numerous synthetic methods of heterocyclic compounds has been extensively reported.[14] Hence, isothiocyanates play crucial roles in both chemical biology and organic chemistry.



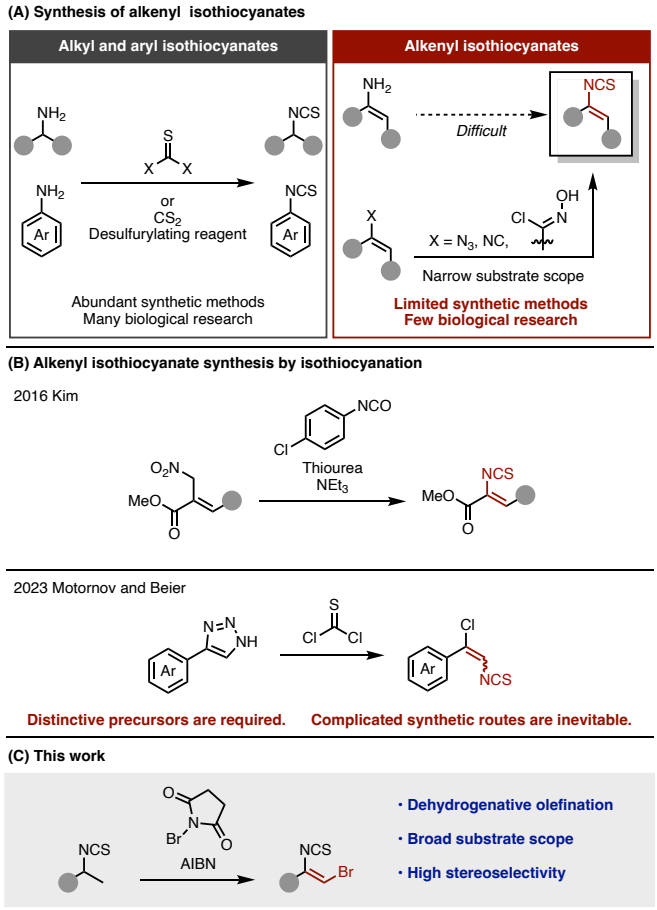

**Scheme 1.** (A) The examples of bioactive isothiocyanates. (B) The examples of transformation of isothiocyanate moiety.

Although many synthetic methods of aryl or alkyl isothiocyanates have been established,[15] the development of synthetic approaches to alkenyl isothiocyanates is not sufficient. Accordingly, there are a few examples for the study of their reactivities and bioactivities. (Scheme 2A) There are two synthetic routes have been explored for the synthesis of alkenyl isothiocyanates (i) isothiocyanation of alkenyl compounds and (ii) dehydrogenation of alkyl isothiocyanates. Several methods for the isothiocyanation of alkenyl compounds such as sulfur transfer to alkenyl isocyanide,[16] the combination of Staudinger reaction and Aza-Wittig reaction with alkenyl azides,[17] and isothiocyanation via 1,3-dipolar cycloaddition and rearrangement[18] have been reported. Additionally, in 2016, the Kim group accomplished the synthesis of α-isothiocyanato-α,β-unsaturated esters from allyl nitro compounds, which are useful for the synthesis of heterocycles.[19] (Scheme 2B) Recently, one synthetic approach of *N*-vinyl isothiocyanate from triazole utilizing thiophosgene was reported by Motornov and Beier.[20] Although several isothiocyanation methods successfully provide alkenyl isothiocyanates, they require the preparation of alkenyl substrates as isothiocyanate precursors, thus, complicated synthetic routes are

[a] *Department of Chemistry, School of Science, Kwansei Gakuin University, Sanda, Hyogo 669-1330, Japan*
[b] *Japanese Science and Technology Agency (JST)–PRESTO, Chiyoda, Tokyo 102-0076, Japan*

Please do not adjust margins
https://doi.org/10.26434/chemrxiv-2024-42j6j **ORCID:** https://orcid.org/0000-0001-5405-3069 Content not peer-reviewed by ChemRxiv. **License:** CC BY-NC-ND 4.0

inevitable to obtain alkenyl isothiocyanates. In 1983, Toshimitsu and coworkers reported the preceding alkenyl isothiocyanate synthesis from alkyl isothiocyanates.[21] They synthesized β-(phenylseleno)alkyl isothiocyanates from olefins, and following elimination afforded vinylic isothiocyanates. However, the reaction requires toxic $Hg(SCN)_2$ to prepare β-(phenylseleno)alkyl isothiocyanates as intermediates. In this context, an ideal dehydrogenation of isothiocyanates has been required. However, dehydrogenation of isothiocyanates is challenging due to the sensitivity of electron-rich alkenyl isothiocyanates to oxidation conditions. To obtain stable isothiocyanates, the substitution of the electron-withdrawing group is necessary. Herein, we discovered the dehydrogenation with bromination of alkyl isothiocyanates using *N*-bromosuccinimide (NBS).[22] (Scheme 2C) The resulting electron-rich olefins are stabilized by the bromo group. Fortunately, the reaction proceeds with high *Z*-stereoselectivity. The products, containing reactive isothiocyanate and bromo groups, are applicable to a variety of transformations, and they are expected to be used as versatile building blocks in synthetic chemistry.




**Scheme 2.** (A) The comparison of the synthetic methods of alkyl or aryl isothiocyanate and alkenyl isothiocyanate. (B) The examples of previous alkenyl isothiocyanate synthesis. (C) This work.

We conducted the optimization of dehydrogenation with 1-phenylethyl isothiocyanate (**1a**) as a model substrate (see SI). We found that a slight excess amount of NBS improved the yield. Although the reaction could proceed without AIBN in the dark, the yield was notably decreased. To ensure reproducibility, the catalytic amount of AIBN was necessary. As a result of the optimization, *N*-β-brominated alkenyl isothiocyanate **2a** was obtained in 86% yield. To our delight, the reaction provided the desired product in a comparable yield under a glam-scale conditions.

Subsequently, we investigate the substrate scope of this reaction. (Scheme 3) The reaction afforded the corresponding alkenyl isothiocyanates from *p*-substituted phenylethyl isothiocyanates, regardless of their electronic properties (**2b**–**2e**). Notably, electron-donating substituents (Me and MeO) furnished the desired alkenyl isothiocyanates in 57% and 40% yields, respectively (**2b** and **2c**). Also, electron-with-drawing groups such as CN and $CF_3$ did not impede the dehydrogenation (**2d** and **2e**). Additionally, halogenated aromatic substrates were applicable to the reaction, regardless of the substitution position (**2f**–**2j**). In this reaction, the steric effect was not critical for the yields (**2g** and **2j**), however, the stereoselectivities were decreased. Naphthyl ethyl isothiocyanate smoothly reacted to provide **2k** in 86% yield, and the structure was confirmed by X-ray crystallography. Furthermore, the reaction tolerated α,β-unsaturated esters, consequently, we successfully obtained a coumarin scaffold containing alkenyl isothiocyanates **2l** and **2m** in 64% and 55% yields, respectively. Gratifyingly, the generation of internal olefins was accomplished with the dehydrogenation with bromination. Although stilbene isothiocyanate **2n** was obtained in 84% yield, the stereoselectivity was diminished. Furthermore, cyclic isothiocyanates (**1o**, **1p**) also afforded the desired products respectively, however, under the standard conditions, overoxidation was observed. To circumvent the overoxidation, employing excess starting material, the desired products were obtained in moderate to low yields. In addition to the benzylic isothiocyanates, non-benzylic isothiocyanates could also be efficiently converted through the reaction, the bulky adamantyl isothiocyanate compound could also be employed (**2q**). These results indicated that this dehydrogenation has broader substrate scope including non-benzylic compounds.

We next turned our attention to exploring the reactivity of *N*-β-brominated alkenyl isothiocyanate. (Scheme 4) As previously mentioned, isothiocyanate can transform into various functional groups and heterocycles. As a representative transformation, the synthesis of thioureas by amine addition has been conducted. The treatment of alkenyl isothiocyanate **2a** with morpholine rapidly afforded aminothiazole **3** in 32% yield. It is noteworthy that the reaction furnished aminothiazole instead of the expected thiourea. Moreover, we considered that the cross-coupling reaction would enable the modification of *N*-β-brominated alkenyl isothiocyanate. Initially, the Suzuki–Miyaura cross-coupling reaction was performed with **2a**, consequently, the desired *E*-stilbene isothiocyanate **4** was obtained. Additionally, Sonogashira cross-coupling afforded enyne alkenyl isothiocyanate **5** in 30% yield.

We were inspired by the formation of aminothiazole from the *N*-β-brominated alkenyl isothiocyanate and amine, we envisioned that *N*-β-brominated alkenyl isothiocyanate could be used as an amine sensor. (Scheme 5) In this concept, a fluorophore-conjugated alkenyl isothiocyanate reacts with amine, subsequently, afforded aminothiazole. We hypothesized that the switch of the π-systems and electro-properties would


https://doi.org/10.26434/chemrxiv-2024-42j6j ORCID: https://orcid.org/0000-0001-5405-3069 Content not peer-reviewed by ChemRxiv. License: CC BY-NC-ND 4.0

induce a change in fluorescent color or enhance the fluorescence intensity. To demonstrate the strategy, we performed the aminothiazolation of alkenyl isothiocyanate **2l** with 1-pentamine. As a result, the corresponding coumarin-conjugated aminothiazole was obtained in 31% yield. Although the fluorescence of alkenyl isothiocyanate **2l** was not confirmed under 365 nm irradiation, the appearance of the solution was changed after amine addition and exhibited blue fluorescence under 365 nm irradiation. (Scheme 5B) The fluorescence quantum yields of both compounds were measured, compound **2l** was 2.7%, while compound **6** exhibited a significantly higher quantum yield of 57%. (Scheme 5C) The photoelectric properties of coumarin could be tuned by the introduction of substituents, thus the fluorescent property could be easily adjusted.[23] These results indicated that a *N*-β-brominated alkenyl isothiocyanate is applicable to the amine sensor. Furthermore, the coumarin structure has also been frequently investigated in its bioactivities, therefore, there is a possibility that coumarin-conjugated alkenyl isothiocyanate could be used as a turn-on fluorescent probe.[24] In this context, we investigated the ability to sense amine groups present on the biomembrane surface. For this purpose, we prepared giant unilamellar vesicles (GUVs) as cell models containing phosphatidylethanolamine (**PE**), a phospholipid known for its abundance in brain and neuronal cell membranes,[25] and attempted to label it using compound **2l**. As shown in Scheme 5D, phase contrast micrographs visualized the successful formation of GUVs regardless of the presence of **2l**. Strikingly, the corresponding fluorescence micrographs showed a distinct difference: GUVs with **2l** showed clear emission along their edge, while those without **2l** did not. In addition, high-resolution MALDI-TOF mass spectrometry revealed the presence of the molecular ion peak of the fluorophore-conjugated **PE 7** (see SI). These results indicated that **2l** successfully labeled **PE** within biomembranes and enabled its visualization by microscopy technique, demonstrating its promising applicability in biological studies.

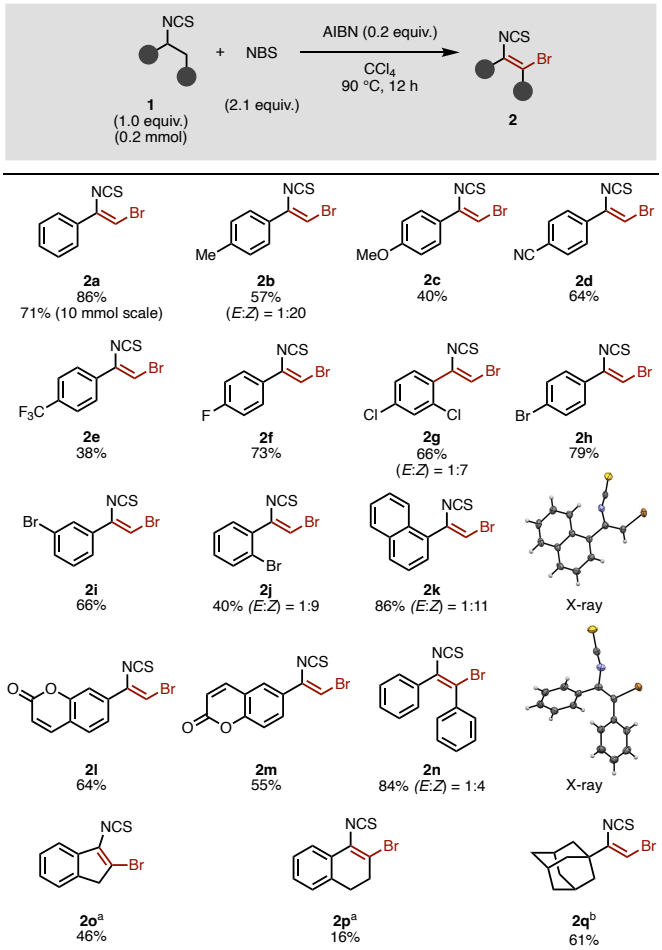
In conclusion, we developed dehydrogenation of alkyl isothiocyanates with *N*-bromosuccinimide. The resulting *N*-β-brominated alkenyl isothiocyanate has readily convertible isothiocyanate and bromo groups. Thus, they are applicable to various transformations. Additionally, coumarin-attached alkenyl isothiocyanate was applied to an amine sensor.

## Conflicts of interest

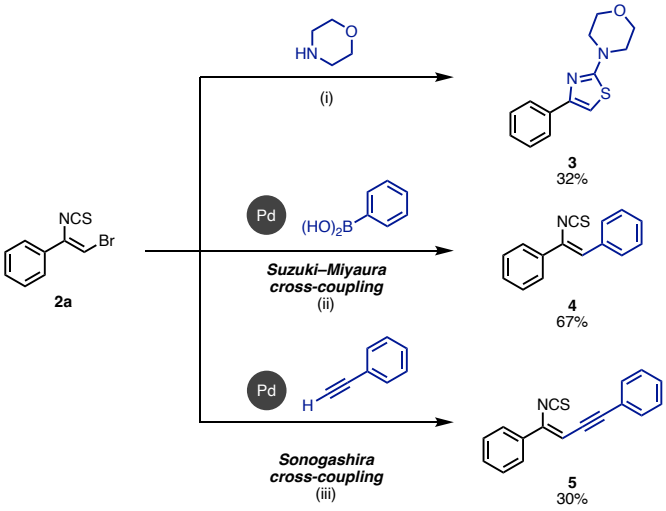
The authors declare no competing financial interest.

## Acknowledgements

This work was supported by the Japan Science and Technology Agency (JST) PRESTO Grant Number JPMJPR20D8 and JSPS KAKENHI Grant 23KJ2119 (B.M.). We acknowledge the support of Profs. Ryo Inoue and Yasuhiro Morisaki (Kwansei Gakuin University) for the quantum yield measurements.

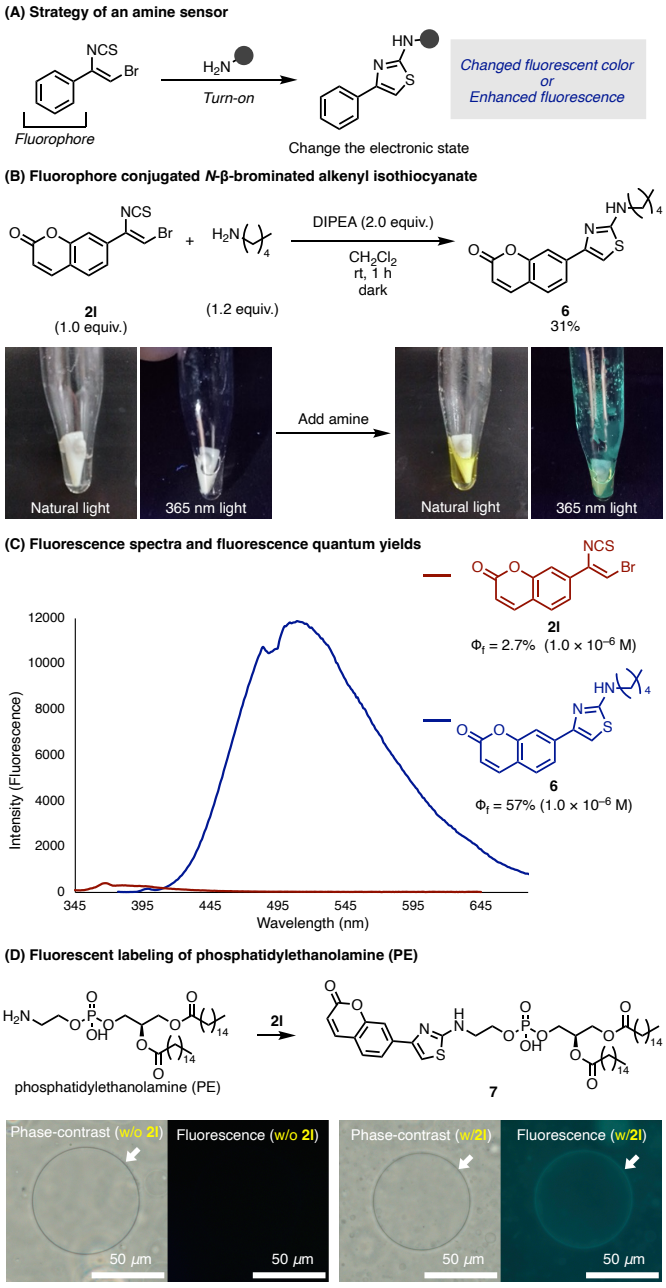



**Scheme 3.** The substrate scope of *N*-β-brominated alkenyl isothiocyanate synthesis. [a] Substrate (3.0 equiv.), NBS (1.0 equiv.) and AIBN (0.2 equiv.) were used. [b] Benzene was used as a solvent.




**Scheme 4.** Transformation of *N*-β-brominated alkenyl isothiocyanate. (i) morpholine (1.0 equiv.), DIPEA (2.0 equiv.), MeCN, rt, 10 min. (ii) phenylboronic acid (1.5 equiv.), $Pd(dba)_2$ (5.0 mol%), $PPh_3$ (10 mol%), $NaHCO_3$ (3.0 equiv.), Toluene/EtOH/$H_2O$, 80 °C, 7 h. (iii) phenylacetylene (2.0 equiv.), $Pd(PPh_3)_4$ (5.0 mol%), $PPh_3$ (20 mol%), CuI (10 mol%), $K_2CO_3$ (2.0 equiv.), Dioxane, 60 °C, 16 h.


https://doi.org/10.26434/chemrxiv-2024-42j6j **ORCID:** https://orcid.org/0000-0001-5405-3069 Content not peer-reviewed by ChemRxiv. **License:** CC BY-NC-ND 4.0




**Scheme 5.** (A) The strategy of an amine sensor. (B) The synthesis of an amine sensor and the change of the appearance of the reaction solution. (C) Fluorescence spectra and fluorescence quantum yields of **2l** and **6**. (D) Fluorescent labelling of phosphatidylethanol amine (PE).

## Notes and references


1 J. W. Fahey, A. T. Zalcmann and P. Talalay, *Phytochemistry,* 2001, **56**, 5–51.

2 (a) S. Giacoppo, M. Galuppo, G. R. De Nicola, R. Iori, P. Bramanti and E. Mazzon, *Bioorg. Med. Chem.,* 2015, **23**, 80–88. (b) C. Waterman, D. M. Cheng, P. Rojas-Silva, A. Poulev, J. Dreifus, M. A. Lila and I. Raskin, *Phytochemistry*, 2014, **103**, 114–122. (c) M. Galuppo, S. Giacoppo, G. R. De Nicola, R. Iori, M. Navarra, G. E. Lombardo, P. Bramanti and E. Mazzon, *Fitoterapia*, 2014, **95**, 160–174. (d) T. Uto, D.-X. Hou, O. Morinaga and Y. Shoyama, *Adv. Pharmacol. Sci.*, 2012, **61**, 4046. (e) J. V. Cross, J. M. Rady, F. W. Foss, C. E. Lyons, T. L. Macdonald and D. J. Templeton, *Biochem. J.*, 2009, **423**, 315–321.

3 (a) D. K. D. Priya, R. Gayathri, G. R. Gunassekaran, S. Murugan and D. Sakthisekaran, *Pharm. Biol.*, 2013, **51**, 621–628. (b) C. Fimognar i, M. Lenzi and P. Hrelia, *Curr. Med. Chem.,* 2008, **15**, 440–447. (c) Y. Nakamura and N. Miyoshi, *Biosci. Biotechnol. Biochem.*, 2010, **74**, 242–255. (d) S. V. Singh and K. Singh, *Carcinogenesis,* 2012, **33**, 1833–1842. (e) C. Ioannides and N. Konsue, *Drug Metab. Rev.*, 2015, **47**, 356–373.

4 X. Zhang, N. Neamati, Y. K. Lee, A. Orr, R. D. Brown, N. Whitaker, Y. Pommier and T. R. Burke, *Bioorg. Med. Chem.*, 2001, **9**, 1649–1657.

5 I. Blažević, S. Montaut, F. Burčul, C. E. Olsen, M. Burow, P. Rollin and N. Agerbirk, *Phytochemistry*, 2020, **169**, 112100.

6 R. N. Bennett and R. M. Wallsgrove, *New Phytol.*, 1994, **127**, 617–633.

7 V. Dufour, M. Stahl and C. Baysse, *Microbiology*, 2015, **161**, 229–243.

8 T. Plaszkó, Z. Szűcs, G. Vasas and S. J. Gonda, *Fungi*, 2021, **7**, 539.

9 Y. Aihara, B. Maeda, K. Goto, K. Takahashi, M. Nomoto, S. Toh, W. Ye, Y. Toda, M. Uchida, E. Asai, Y. Tada, K. Itami, A. Sato, K. Murakami and T. Kinoshita, *Nat. Commun.*, 2023, **14**, 2665.

10 P. Edman, *Acta. Chem. Scand.*, 1950, **4**, 283–293.

11 (a) C.-G. Cho and G. H. Posner, *Tetrahedron Lett.*, 1992, **33**, 3599–3602. (b) C.-Y. Chen, F. F. Wong, J.-J. Huang, S.-K. Lin and M.-Y. Yeh, *Tetrahedron Lett.*, 2008, **49**, 6505–6507. (c) K. de la Vega-Hernandez, R. Senatore, M. Miele, E. Urban, W. Holzer and V. Pace, *Org. Biomol. Chem.*, 2019, **17**, 1970–1978. (d) R. Senatore, M. Malik, T. Langer, W. Holzer and V. Pace, *Angew. Chem., Int. Ed.*, 2021, **60**, 24854–24858. (e) T. B. Nguyen and P. Retailleau, *Org. Lett.*, 2021, **23**, 5344–5348. (f) W. Guo, G. Liu, L. Deng, W. Mei, X. Zou, Y. Zhong, X. Zhuo, X. Fan and L. Zheng, *J. Org. Chem.*, 2021, **86**, 17986–18003. (g) Z. Dong, M.-Y. Ma, J. Xu and Z. Yang, *Chem. Commun.*, 2022, **58**, 7980–7983. (h) Y. Hu, L. Chen, C. Zou, J. He, L. Feng, J.-Q. Wu, W.-H. Chen and J. Hu, *Org. Lett.*, 2022, **24**, 5137–5142.

12 (a) D. C. Schroeder, *Chem. Rev.*, 1995, **55**, 181–228. (b) U. Zahra, A. Saeed, T. A. Fattah, U. Flörke and M. F. Erben, *RSC Adv.*, 2022, **12**, 12710–12745.

13 T. Parvin, R. Yadav and L. H. Choudhury, *Org. Biomol. Chem.*, 2020, **18**, 5513–5532.

14 A. K. Mukerjee and R. Ashare, *Chem. Rev.*, 1991, **91**, 1–24.

15 (a) K. Eschliman and S. H. Bossmann, *Synthesis*, 2019, **51**, 1746–1752. (b) B. Maeda and K. Murakami, *Chem. Commun.*, 2024, **60**, 2839–2864.

16 W. Adam, R. M. Bargon, S. G. Bosio, W. A. Schenk and D. Stalke, *J. Org. Chem.*, 2002, **67**, 7037–7041.

17 L.-P. Gao, M.-W. Ding and Y. Sun, *Synth. Commun.*, 2006, **36**, 1185–1191.

18 M. Baumann and I. R. Baxendale, *Beilstein J. Org. Chem.*, 2013, **9**, 1613–1619.

19 K. H. Kim, S. Y. Kim, J. Lee and J. N. Kim, *Bull. Korean Chem. Soc.*, 2016, **37**, 592–595.

20 V. Motornov and P. Beier, *Org. Biomol. Chem.*, 2023, **21**, 1143–1147.

21 A. Toshimitsu, S. Uemura and M. Okano, *J, Org. Chem.*, 1983, **48**, 5246–5251.

22 X. Li, Z. Cheng, J. Liu, Z. Zhang, S. Song and N. Jiao, *Chem. Sci.*, 2022, **13**, 9056–9061.

23 D. Cao, Z. Liu, P. Verwilst, S. Koo, P. Jangili, J. S. Kim and W. Lin, *Chem. Rev.,* 2019, **119**, 10403–10519.

24 F. Annunziata, C. Pinna, S. Dallavalle, L. Tamborini and A. Pinto, *Int. J. Mol. Sci.*, 2020, **21**, 4618.

25 J. E. Vance, G. Tasseva, *Biochim. Biophys. Acta*, 2013, **1831**, 543–554.



https://doi.org/10.26434/chemrxiv-2024-42j6j **ORCID:** https://orcid.org/0000-0001-5405-3069 Content not peer-reviewed by ChemRxiv. **License:** CC BY-NC-ND 4.0