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Journal:	ChemComm
Manuscript ID	CC-COM-04-2024-001666.R1
Article Type:	Communication



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

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Received 00th January 20xx, Accepted 00th January 20xx DOI: 10.1039/x0xx00000x

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 (A) Bioactive isothiocyanates





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

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.

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 rearrangement¹⁸ 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 inevitable to obtain alkenyl isothiocyanates. In 1979, α -bromination of alkyl isothiocyanate under photo-irradiation conditions was reported.²¹ Although a few examples of obtaining N- β -brominated alkenyl isothiocyanate are shown in this paper, it remains uncommon and lacks synthetic utility. In 1983, Toshimitsu and coworkers reported the preceding alkenyl isothiocyanate synthesis from alkyl isothiocyanates.²² They synthesized β-(phenylseleno)alkyl

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

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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).²³ (Scheme 2C) The resulting electron-rich olefins are stabilized by the bromo group. Fortunately, the reaction proceeds with high Zstereoselectivity. 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.

(A) Synthesis of alkenyl isothiocyanates



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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 1phenylethyl 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 Page 2 of 4

comparable yield under a gram-scale conditions. Notably, the reactions using *N*-iodosuccinimide or *N*-chlorosuccinimide failed.

Subsequently, we investigate the substrate scope of this reaction. (Scheme 3) The reaction afforded the corresponding isothiocyanates from *p*-substituted phenylethyl alkenvl 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-withdrawing groups such as CN and CF₃ 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 21 and 2m in 64% and 55% yields, respectively. Gratifyingly, the generation of internal olefins was accomplished with the Although dehydrogenation with bromination. stilbene isothiocyanate 2n was obtained in 84% yield, the stereoselectivity was diminished. Furthermore, cyclic isothiocyanates (10, 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 induce a change in fluorescent color or enhance the

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fluorescence intensity. To demonstrate the strategy, we performed the aminothiazolation of alkenyl isothiocyanate 2l with 1-pentamine. Note that the reaction of 2m with 1pentamine proceeded sluggishly, and there was scarcely any noticeable increase in fluorescence observed in the solution. As a result, the corresponding coumarin-conjugated aminothiazole was obtained in 31% yield. Although the fluorescence of alkenyl isothiocyanate 2I 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 2I 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.²⁴ 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 coumarinconjugated alkenyl isothiocyanate could be used as a turn-on fluorescent probe.²⁵ 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,²⁶ and attempted to label it using compound **2I**. 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 2I showed clear emission along their edge, while those without 21 did not. In addition, highresolution MALDI-TOF mass spectrometry revealed the presence of the molecular ion peak of the fluorophoreconjugated PE 7 (see SI). These results indicated that 2I 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.

This work was supported by the Japan Science and Technology Agency (JST) PRESTO Grant Number JPMJPR20D8 (K.M.), the Asahi Glass Foundation (K.M.), 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%), PPh₃ (10 mol%), NaHCO₃ (3.0 equiv.), Toluene/EtOH/H₂O, 80 °C, 7 h. (iii) phenylacetylene (2.0 equiv.), Pd(PPh₃)₄ (5.0 mol%), PPh₃ (20 mol%), Cul (10 mol%), K₂CO₃ (2.0 equiv.), Dioxane, 60 °C, 16 h.

(A) Strategy of an amine sensor



Change the electronic state (B) Fluorophore conjugated N-β-brominated alkenyl isothiocyanate



(C) Fluorescence spectra and fluorescence quantum yields



(D) Fluorescent labeling of phosphatidylethanolamine (PE)





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 2I and 6. (D) Fluorescent labelling of phosphatidylethanol amine (PE).

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