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Formation of benzo[*c*]thiophen-1-aminium iodide by the reaction of *o*-alkynylbenzothioamide with iodine



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Synthesis of heterocyclic compounds is important to construct natural products, biological active compounds, functional materials, and other materials. Iodine-mediated cyclization reaction is a useful method to give heterocycles.¹ Those compounds possess an iodine atom at the specific position. Further reactions based on the iodine atom are applicable to produce various materials. The reactions are included in the nucleophilic attack of heteroatoms toward the triple bond activated by iodine. The reactions of carboxylic and amide groups are well known respectively as iodolactonization² and iodolactamization.³ Heteroatoms of sp³ such as ether, amine, and thioether as well as sp² atom such as carbonyl and imine are applicable to reactions. Imine nucleophiles reportedly give the corresponding cyclized products such as isoquinolines,⁴ quinolines, indoles, and quinolones.⁵ Oxygen atoms on the carbonyl group are applicable for reactions as nucleophiles. The reaction of 2-propargylated carbonyl compounds with iodine proceeded to form furan derivatives.⁶ The reaction of *o*-alkynylbenzaldehydes to give a pyrilium cation intermediate followed to form various compounds such as isochromenes,⁷ naphthalenes,^{5,8} and α -diketones⁹ through reaction with alcohol, alkene/alkyne, and H₂O, respectively. Reportedly oxygen atoms on sulfoxide also act as nucleophiles toward the triple bond activated by iodine to give the corresponding α -diketone derivatives.¹⁰ sp³ Sulfur atom also has potential as a reactive site.¹¹ Recently, Sashida and co-workers reported the formation of 4-(iodoalkylidene)benzo[d][1,3]thiazines by the attack from sp² sulfur atom of the thiourea group.¹² Specifically regarding the metal-catalyzed reaction, the reactions

ABSTRACT

Reaction of o-alkynylbenzothioamide with molecular iodine was investigated. Unique benzo[c]thiophen-1-aminium iodide was obtained when the tertiary thioamide was used as a reactant. The reaction proceeded efficiently in less polar solvent, whereas the corresponding product was also obtained in a polar solvent. Single crystal X-ray analysis revealed that the benzo[c]thiophen-1-aminium structure possesses a resonance structure in N–C–S bond. Its stabilization shows a clear difference in the result from the reaction of amide analogue with iodine to give no stable compound.

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of triple bond with thioamide in the presence of rhodium¹³ and gold¹⁴ catalysis were reported to give the thiophene and thiopyrylium derivatives. The thermal reaction also gave the 1,3-dihydrobenzo[*c*]thiophenimine derivatives.¹⁵ Nevertheless, no report describes the reaction of thioamide groups as a nucleophile toward the activated triple bond with iodine, although the reaction of amide with iodine gave the corresponding isobenzofuranimines and isochromenimines reported by Opatz and Larock (Chart 1).¹⁶ We herein report the reaction of *o*-alkynylbenzothioamide (1) with iodine to form novel benzo[*c*]thiophen-1-aminium iodide (2). The reaction was able to proceed under ambient conditions. Structural features were revealed by single crystal X-ray analysis.











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Scheme 1. Reaction of precursor of **1a** with Lawesson's reagent (L.R.) to give **3**, and the structures of plausible products (3', 3'', and 3''').

ucts when the amide was treated with Lawesson's reagent at room temperature to give the corresponding thioamide (Scheme 1). The formation of 1,3-dihydrobenzo[c]thiophenimines with Lawesson's reagent under heated conditions was reported by Peng and coworkers.¹⁵ Result of our investigation suggested that the cyclization reaction of the secondary thioamide proceeded under ambient conditions. It is possible to form four types of products (3, 3', 3", and $\mathbf{3}^{\prime\prime\prime}$). 6-Membered cyclic products ($\mathbf{3}^{\prime}$ and $\mathbf{3}^{\prime\prime}$) were excluded by the difference of melting point reported in the literature¹⁷ (obtained compound showed 111-112 °C, whereas 3' and 3" showed 87 °C and 97 °C, respectively). Specific C=N stretching vibration was detected at 1590 cm⁻¹ in the IR spectrum.¹⁷ Furthermore, the peak at 164.5 ppm assigned to an imine carbon was observed in the ¹³C NMR spectrum, although the peaks of thioamide moiety (195-200 ppm) were not detectable. The other spectroscopic data were consistent with the structure as **3** (See Supplementary data). Therefore, we inferred the structure of the obtained compound as 1,3dihydrobenzo[c]thiophenimine.

We specifically examined the reaction of tertiary thioamides that were formed safely by the reaction with Lawesson's reagent. When *N*,*N*-dimethyl-*o*-(2-phenylethynyl)benzothioamide (**1b**) was treated with 1 mol-equivalent of iodine in CH₃CN at room temperature, a pale yellow precipitate was obtained (Scheme 2). That precipitate had low solubility in various organic solvents (CHCl₃, EtOAc, THF, acetone, and DMSO) and in aqueous solutions (water, 1 M aq HCl, and 1 M aq NaOH). However, we were able to measure ¹H NMR spectrum in CDCl₃ despite its low



Scheme 2. Reaction of 1b with iodine, single X-ray structure, and intermediate structure (A).

concentration. A specific peak at 9.45 ppm was observed as a doublet, which suggested that a strong electron-withdrawing character was attached in the benzene ring. The spin-spin coupling relations derived from ortho-substituted benzene (doublet-triplet-triplet-doublet) were detectable between 7.87 and 9.47 ppm. Additionally, two different methyl peaks were found, respectively, at 3.75 and 4.25 ppm. They showed the lower shift against the starting 1b (3.18 and 3.64 ppm), which suggested the increment of the electron deficiency of nitrogen atom. Specifically regarding the C-N bond of thioamide in IR spectrum $(1390-1600 \text{ cm}^{-1})$,¹⁸ the absorption of a longer wavenumber (1586 cm^{-1}) was observed against that of **1b** (1520 cm^{-1}) . It showed that the shortening of the C-N bond would occur in the product. Fortunately, we were able to obtain good crystals from hot water for single crystal X-ray structure analysis.¹⁹ The crystallographic structure was revealed in which the obtained compound (2b) has a benzolclthiophen-1-aminium structure with iodide as a counter anion. The C-N bond length is 1.316 Å, which is shorter than that of general C-N single bond (1.39 Å) and which is longer than that of general C-N double bond (1.28 Å).²⁰ It is a slightly small value compared with a value of C-N bond in the amide group (1.33–1.35 Å).²⁰ Double bond character in C-S bond of 2b (1.712 Å) was revealed because the C-S single bond is measured in 1.82 Å and the C-S double bond of thiourea is obtained as 1.68 Å.²⁰ Therefore, the resonance structure in N-C-S bonds was actually found in 2b. Its stabilization shows a clear difference with the reaction of amide analogues to give no stable compounds.^{16a} The trans alignment between I and S atoms in the external C-C double bond was observed. That configuration is reasonable to infer as related with the reaction mechanism though the activation of the triple bond by coordination of molecular iodine (structure A). Based on the amount of the collected precipitate, the yield of 2b was 37%. And the starting 1b and byproducts was found in mother liquor.

The substituent on nitrogen atom is influenced in both formation and solubility of the benzo[c]thiophen-1-aminium compounds (Table 1). When the reaction was conducted in CHCl₃, **2b** was also obtained as the precipitate with increasing the yield (entry 1).²¹ *N*,*N*-Diethyl derivative (**1c**) formed the precipitate in the reaction to obtain the corresponding 2c with a slight decrease of the yield against 1b. Phenyl-substituted derivative (1d) also gave 2d as the precipitate in 64% yield. When the compounds bearing long alkyl chains (1e and 1f) were treated with iodine in CHCl₃, no precipitation was obtained during the reaction. After quenching with saturated aq. Na₂S₂O₃ to remove residual iodine, the yields of the product were estimated from the integration of ¹H NMR using an internal standard and the sample collected from small amount of the organic extracts. Although higher than 50% yields of benzo[c]thiophen-1-aminium products were obtained, the decrease of the yield was observed after introduction of the long alkyl chain, probably because of the bulkiness around the sulfur nucleophile toward the iodine-activated triple bond. Additionally, unidentified products were also formed. The precipitates were obtained adding EtOAc into the organic extracts to isolate 2e and 2f. The isolation yield of 2f decreased greatly because of its solubility in EtOAc.

Finally, we examined the reaction of **1e** in various solvents (Table 2). Results show that all the examined solvent served **2e** in varying the isolated yield. The polar solvent gave lower yield in both net and isolated ones. For THF and CH_3CN , starting **1e** remained after the reaction for 2 days (entries 3 and 4), which suggests that the reaction proceeded in a less polar solvent efficiently. We were unable to ascertain why such a difference occurred, but we suspected that the nucleophilic attack in the structure **A** depicted in Scheme 2 was inhibited by solvation at either iodonium cation or thioamide moiety (or its resonance structure).

Table 1

Reaction of **1** with iodine



| Entry | Compound | R^1 | R ² | State after reaction | Yield ^a (%) | Isolated yield (%) |
|-------|----------|-------|----------------|-----------------------|------------------------|--------------------|
| 1 | 1b | Me | Me | Precipitate formation | - | 77 |
| 2 | 1c | Et | Et | Precipitate formation | - | 69 |
| 3 | 1d | Me | Ph | Precipitate formation | - | 64 |
| 4 | 1e | Me | Bn | Clear solution | 63 | 63 ^b |
| 5 | 1f | Me | nHex | Clear solution | 57 | 16 ^b |
| | | | | | | |

^a Determined by the integration of ¹H NMR analysis using *m*-dimethoxybenzene as an internal standard toward the concentrate of small amount of organic extracts. ^b Precipitate was obtained by adding EtOAc to organic extracts and collected by the filtration, when the precipitate was not obtained after the reaction proceeded.

Table 2

Reaction of **1e** with iodine in various solvents



^a Determined by the integration of ¹H NMR analysis using *m*-dimethoxybenzene as an internal standard toward the concentration of a small amount of organic layer.

^b Precipitate was obtained by adding EtOAc to the organic layer and collected by filtration when the precipitate was not obtained after the reaction proceeded.

In conclusion, the reaction of tertiary benzothioamide derivatives (1) bearing triple bond at the *ortho* position with iodine gave the corresponding benzo[c]thiophen-1-aminium iodide (2) in good vield. Compared with the reaction of amide analogue, sulfur atom is important to stabilize the ionic structure. The various N-substituted compounds were achieved to form the corresponding benzo[c]thiophen-1-aminium salts. The reaction of 1 in various solvents is applicable to form 2, and some gave a clear solution after the reaction proceeded. Therefore, we infer that this reaction might be applicable to further reactions under solution conditions in a one-pot manner, whereas isolated **2** showed low solubility in various solvents. 2 will show a unique feature based on iodovinyl and benzo[c]thiophen-1-aminium moieties. Therefore, various applications using 2 for the reactivity and material science are possible. The further reaction of 2 in a one-pot manner is still under investigation.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013. 12.094.

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- 19. Crystal data for **2b**: $C_{17}H_{15}I_2NS$, triclinic, P-1, Z = 2, a = 8.0599(8)Å, b = 9.9210(9) Å, c = 11.3687(10) Å, $\alpha = 82.521(3)^{\circ}$, $\beta = 74.574(4)^{\circ}$, $V = 855.27(14) \text{ Å}^3$, R = 0.0396, $wR_2 = 0.109$, T = 173 $\gamma = 78.439(4)^{\circ}$ Crystallographic data for **2b** were deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 964995. The data are obtainable free of charge from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, UK. Fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk.
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- 21. Typical procedure for the reaction of 1 with *l*₂: 2b: To a solution of 1b (0.251 g, 0.947 mmol) in CHCl₃ (51 mL) was added *l*₂ (0.242 g, 0.955 mmol) at room temperature. After being stirred for 2 d at that temperature, the precipitate was obtained. After collection and drying in vacuo, 2b (0.381 g, 0.733 mmol) was obtained in 77% yield as a brown solid: mp 227.4–228.0 °C; ¹H NMR (CDCl₃, 300 MHz) δ 3.75 (s, 3H), 4.25 (s, 3H), 7.46–7.54 (m, 5H), 7.90 (t, *J* = 7.3 Hz, 1H), 8.01 (t, *J* = 7.0 Hz, 1H), 8.46 (d, *J* = 8.4 Hz, 1H), 9.45 (d, *J* = 8.2 Hz, 1H); IR (KBr disk) 3106, 1586, 1458, 1440, 1404, 1304, 1262, 766, 732, 695 cm⁻¹. Anal. Calcd for C₁₇H₁₅l₂NS-2/3CHCl₃: C, 35.44; H, 2.64; N, 2.34%. Found: C, 35.12; H

2.44; N, 2.46%. **2e**: To a solution of **1e** (0.255 g, 0.747 mmol) in CHCl₃ (40 mL) was added I₂ (0.191 g, 0.751 mmol) at room temperature. After being stirred for 2 d at that temperature, the reaction mixture was washed with saturated aq. Na₂S₂O₃ (20 mL). The precipitate was obtained adding EtOAc (20 mL) into the organic layer. After collection and drying in vacuo, **2e** (0.283 g, 0.0.476 mmol) as a mixture of geometric isomers (66:34) was obtained in 63% yield as brown solid: mp 161.6–162.7 °C; ¹H NMR (CDCl₃, 300 MHz) δ 3.68

(s, 1.02H), 4.11 (s, 1.98H), 5.22 (s, 1.32H), 5.88 (s, 0.68H), 7.30–7.49 (m, 10H), 7.69 (t, J = 8.1 Hz, 0.34H), 7.89 (t, J = 7.7 Hz, 0.66H), 7.94 (t, J = 7.0 Hz, 0.34H), 8.00 (t, J = 7.7 Hz, 0.66H), 8.07 (d, J = 8.0 Hz, 0.34H), 8.57 (d, J = 8.1 Hz, 0.66H), 9.45 (d, J = 8.2 Hz, 0.34H), 9.47 (d, J = 8.3 Hz, 0.66H); IR (KBr disk) 3029, 1574, 1453, 1407, 1325, 1306, 1079, 972, 883, 766, 733, 700 cm⁻¹. Anal. Calcd for $C_{23}H_{19}l_2NS^2/5H_2O$: C, 45.85; H, 3.31; N, 2.32%. Found: C, 45.62; H, 3.02; N, 2.31%.