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# Synthesis of allylic thiocyanates and novel 1,3-thiazin-4-ones from 2-(bromomethyl)alkenoates and S-nucleophiles in aqueous medium

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**Abstract**

Allylic thiocyanates and novel heterocycles containing the 1,3-thiazin-4-one core are easily obtained in high yields and mild conditions by nucleophilic displacement of 2-(bromomethyl)alkenoates (derived from Morita–Baylis–Hillman adducts) with sulphur-centred nucleophiles in aqueous acetone at 25 °C. Treatment of allylic bromides with NaSCN gave the corresponding (*Z*)-2-(thiocyanomethyl)alkenoates, while the reaction with thiourea followed by a basic work-up selectively produced (5*Z*)-2-amino-5-arylidene-1,3-thiazin-4-ones. The structural assignments were confirmed by X-ray diffraction analysis.


*Keywords:* Allylic thiocyanate; 1,3-Thiazinone; 2-(Bromomethyl)alkenoate; S-Nucleophiles; Aqueous solvent

α-Methylene-β-hydroxy esters **1** are readily available by the Morita–Baylis–Hillman reaction[1] and have been widely employed as versatile building blocks in organic synthesis (Fig. 1).[2] The multifunctional allylic backbone found in **1** can be further manipulated by converting the hydroxyl group into a suitable leaving group, thus generating acetates **2** and bromides **3**, which participate as nucleophile acceptors in many useful synthetic transformations en route to heterocycles and biologically-active compounds.[3]

While the reactions of acetates **2** with various C-, N- and O-centred nucleophiles have been intensely investigated, few reports describe the preparation of sulphur-containing products from S-nucleophiles, which include arenesulphinates,[4] thiolates,[5] and, more recently, thiocyanate ion.[6]

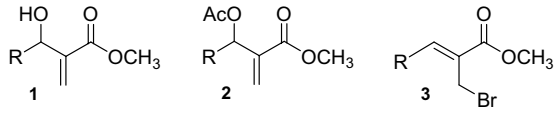


Fig. 1.

The latter transformation involves a high-yield synthesis of allylic thiocyanates by nucleophilic displacement of Morita–Baylis–Hillman acetates with a combination of $NH_4SCN$ and $KHCO_3$ in DMF. Although the synthesis of allylic nitriles by a nucleophilic displacement of acetates **2** with cyanide anion in a biphasic water–diethyl ether environment under phase-transfer catalysis has been successfully developed, the attempted reaction of KSCN with **2** under these conditions did not produce the corresponding thiocyanates.[7] Given that allylic bromides **3** are more prone to nucleophilic displacement than the corresponding acetates **2**, it is quite surprising that the former is still underutilized in such transformations involving S-nucleophiles.[5d]

In the course of our recent work on Morita–Baylis–Hillman chemistry,[8] we have demonstrated the superior reactivity of allylic bromides **3** towards azide anion ($N_3^-$) in aqueous medium and the development of an efficient method to obtain (*E*)-2-(azidomethyl)acrylates in a short period and excellent yield.[9] In this Letter, we wish to describe the straightforward preparation of allylic thiocyanates and novel sulphur-containing heterocycles by exploiting the unique ability of allylic bromides **3** to react with S-nucleophiles under aqueous medium.

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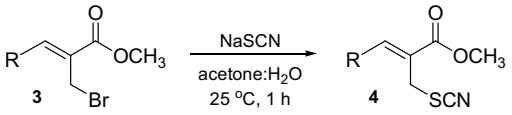
Table 1
Synthesis of allylic thiocyanates **4** from bromides **3** in aqueous acetone

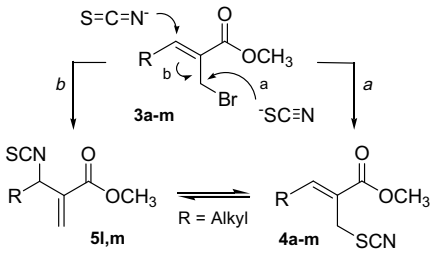



| Product | R | Yield[a] (%) |
|---|---|---|
| **4a** | $C_6H_5$ | 90 |
| **4b** | 2-$C_{10}H_7$ | 80 |
| **4c** | 4-$ClC_6H_4$ | 85 |
| **4d** | 2-$ClC_6H_4$ | 84 |
| **4e** | 2,4-$(Cl)_2C_6H_3$ | 87 |
| **4f** | 4-$NO_2C_6H_4$ | 91 |
| **4g** | 2-$NO_2C_6H_4$ | 85 |
| **4h** | 4-$CH_3OC_6H_4$ | 85 |
| **4i** | 3,4-$(CH_3O)_2C_6H_3$ | 87 |
| **4j** | 3,4-$(OCH_2O)C_6H_3$ | 81 |
| **4k** | (*E*)-$C_6H_5CH{=}CH$ | 80 |
| **4l** | $CH_3$ | 84[b] |
| **4m** | $CH_3CH_2$ | 89[b] |

[a] Isolated yields (not optimized).
[b] Inseparable mixture of thiocyanate **4** and isothiocyanate **5** (see text).

We found that aromatic-substituted allylic thiocyanates **4** can be prepared simply by mixing the corresponding bromides **3** with NaSCN in aqueous acetone at 25 °C for 30–60 min without the use of an external base. The expected products were isolated in high yields after purification in a short plug of silica gel (Table 1).[10] The assignment of the structure of thiocyanates **4a**–**m** was made based upon the characteristic signals[11] for the SCN group in the IR (sharp band in 2140–2155 $cm^{-1}$) and $^{13}C$ NMR (111–113 ppm) spectra of all purified products. These results were further confirmed by X-ray crystallographic analysis[12a] after the isolation of thiocyanate **4j** as a single crystal from hexane–ethyl acetate (Fig. 2).

However, when aliphatic-substituted allylic bromides **3l**,**m** were subjected to the present protocol, the formation of the expected allylic thiocyanates **4l**,**m** was accompanied by an inseparable minor product, which was assigned as the rearranged isothiocyanates **5l**,**m** (IR: 2080–2110 $cm^{-1}$; $^{13}C$ NMR: 133–134 ppm). Because of the ambident character of $[SCN]^-$, a nucleophilic attack of sulphur (path a) or nitrogen (path b) on allylic bromides **3** would lead to the production of thiocyanates **4** (R–SC≡N) or isothiocyanates **5** (R–N=C=S), respectively (Scheme 1). Furthermore, a rearrangement between thiocyanates and isothiocyanates[13] may also be involved in this case. Experimental support for this hypothesis comes from the observation that an initial 7:1 mixture of isomers **4m**:**5m** underwent slow equilibration to a 1:6 ratio after standing for several months on the bench.

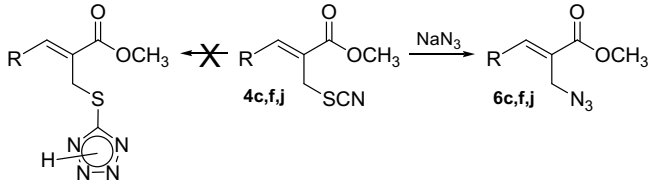



Scheme 1.

It is worth noting that aromatic-substituted acetates **2** (R = Aryl) were not reactive towards NaSCN in aqueous acetone and were recovered unchanged from the crude reaction mixture. Therefore, the mild conditions and the absence of base were only suitable for the more electrophilic bromides **3**.

The unusual behaviour of organic thiocyanates and their application as key intermediates in various transformations for the preparation of sulphur-containing compounds[14] provided the motivation for further studies dealing with the reactivity of allylic thiocyanates **4**. However, attempted synthesis of sulphur-substituted tetrazoles by a $ZnBr_2$-mediated 1,3-dipolar cycloaddition of **4** and azide anion in aqueous medium as described by Sharpless and others[15] led only to a high-yield formation of allylic azides **6** (Scheme 2).[9] Interestingly, the nucleophilic displacement of SCN by $N_3$ could be achieved under mild conditions without the presence of $ZnBr_2$.[16] These results are in agreement with the leaving-group ability of thiocyanate towards nitrogen-centred nucleophiles as reported by Oae et al.[17]

The remarkable combination of allylic bromides **3** and thiocyanate anion in aqueous medium under mild conditions stimulated further studies employing sulphur-containing nucleophiles with ambident character that could be managed to participate in subsequent transformations.




Scheme 2.

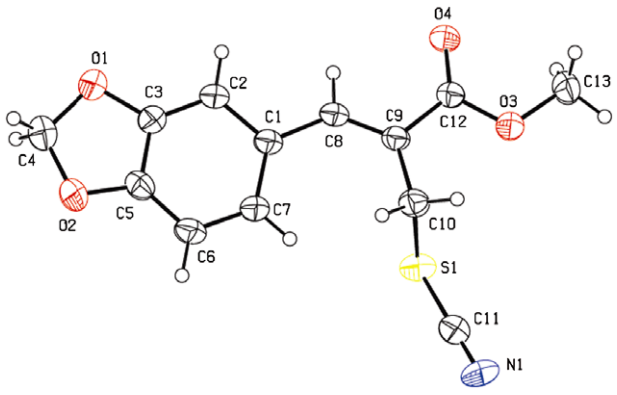
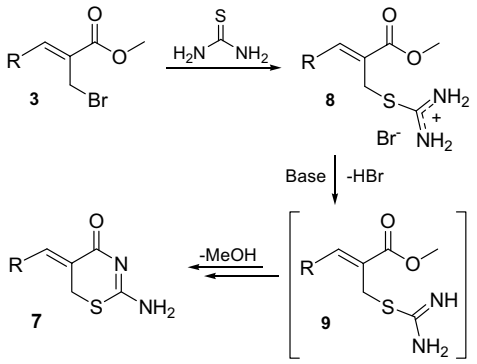



Fig. 2. The ORTEP plot of compound **4j** (ellipsoids are drawn at the 40% probability level).




Scheme 3.

Accordingly, the reaction of **3a** with thiourea in the presence of $NaHCO_3$ (as an acid scavenger) furnished an insoluble solid, which was assigned as 2-amino-1,3-thiazin-4-one **7a** on the basis of the collected spectral data (Scheme 3). Therefore, the $^1H$ NMR spectrum confirmed the disappearance of the methoxyl ester group at 3.87 ppm, while the IR displayed a carbonyl shift from 1717 to 1641 $cm^{-1}$ that was indicative of a replacement of the ester group in the starting material by an amide-like functionality in the product. Fortuitously, a careful crystallization of **7a** from aqueous DMSO provided crystals suitable for X-ray crystallographic analysis,[12b] allowing its complete structural elucidation (Fig. 3). Consequently, the localization and the absolute configuration of each double bond in the solid-state structure of compound **7a** were unambiguously assigned (see Supplementary data), confirming that the (*Z*)-stereochemistry found in the starting bromides **3** is preserved in thiazinones **7**.

A reasonable mechanism to account for this transformation involves the intermediacy of isothiouronium bromide **8** (which is primarily formed[18] by a nucleophilic displacement of bromide **3** by thiourea) followed by deprotonation under basic conditions to generate a reactive intermediate **9** that ultimately leads to **7** via cyclization to a six-membered ring and elimination of methanol (Scheme 3). In fact, the isolation of hydrobromide salt **8** can be easily effected if the reaction of **3** and thiourea is carried out in the absence of base. Subsequent treatment of water-soluble salt **8** with satd $NaHCO_3$ furnished thiazinone **7a** in a 90% yield, thus supporting the proposed mechanism.

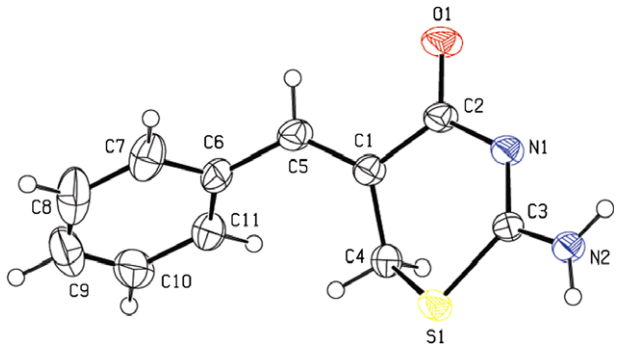
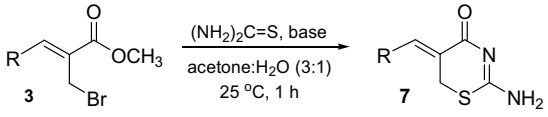


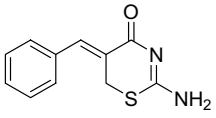
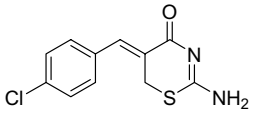
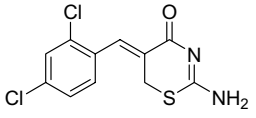
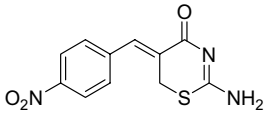
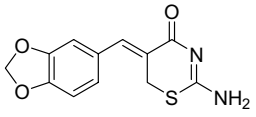
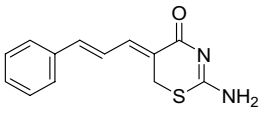

Fig. 3. The ORTEP plot of compound **7a** (ellipsoids are drawn at the 40% probability level).

After optimizing the conditions, we found that better yields and easier purification of thiazinones **7** are achieved if the transformation is performed in a two-step approach, by first generating isothiouronium **8** in solution (from the reaction of bromide **3** and thiourea in acetone/$H_2O$) and then adding an aqueous solution of $NaHCO_3$ to the reaction medium followed by extraction of thiazinone with $CH_2Cl_2$.[19] Therefore, a series of representative thiazinones **7** was prepared by this protocol, generally in high yield and purity (Table 2). Finally, it is important to mention that, contrary to the results obtained with allylic bromides **3**, the less electrophilic acetates **2** failed to react with thiourea in aqueous acetone (with or without an added base) and were recuperated intact after 1 h under the present conditions.

In conclusion, we developed a simple and efficient methodology to access novel sulphur-containing compounds from nucleophilic displacement of allylic bromides with

Table 2
Synthesis of 1,3-thiazin-4-ones **7** from bromides **3** in aqueous acetone




| Product | | Yield[a] (%) |
|---|---|---|
| **7a** |  | 90 |
| **7c** |  | 91 |
| **7e** |  | 75 |
| **7f** |  | 85 |
| **7j** |  | 87 |
| **7k** |  | 76 |

[a] Isolated yields (not optimized).

easily available S-nucleophiles in aqueous medium. Besides being obtained in good yield, high purity and excellent selectivity, the allylic thiocyanates and 1,3-thiazin-4-ones are multifunctional products that can be explored in further synthetic manipulations. The reactivity of allylic bromides towards other functionalized nucleophiles, as well as their synthetic application and mechanistic considerations, is under current investigation.

## Supplementary data

Full crystallographic tables (excluding structure factors) for compounds **4j** and **7a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 666027 (**4j**) and CCDC 666028 (**7a**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 lEZ, UK [fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

## Acknowledgements

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10. *Typical procedure for the synthesis of allylic thiocyanates* (**4**): To a stirred solution of allylic bromide **3** (1.0 mmol) in 4.0 mL of acetone/$H_2O$ (3:1 v/v) at 25 °C was added 2.0 mmol of NaSCN. After stirring for 1 h, the final mixture was diluted with $CH_2Cl_2$ and washed with $H_2O$ and brine. The organic extract was dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by chromatography (hexane/ethyl acetate 9:1) to give the corresponding (*Z*)-2-(thiocyanomethyl)alkenoates **4**. Spectral and analytical data of selected compounds are as follows:
*Methyl (Z)-3-(2-chlorophenyl)-2-(thiocyanomethyl)propenoate* (**4d**): 84%; white solid, mp 77.6–78.0 °C; IR (KBr): $\nu$ 3089, 3009, 2951, 2145, 1713, 1635 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 3.89 (s, 3H), 3.94 (s, 2H), 7.36–7.46 (m, 4H), 8.01 (s, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 31.4, 53.0, 112.1, 127.4, 128.4, 130.1, 130.2, 131.1, 132.6, 134.3, 141.8, 166.0. Anal. Calcd for $C_{12}H_{10}ClNO_2S$: C, 53.83; H, 3.76; N, 5.23; S, 11.98. Found: C, 54.06; H, 3.60; N, 5.36; S, 11.68.
*Methyl (Z)-3-(4-nitrophenyl)-2-(thiocyanomethyl)propenoate* (**4f**): 91%; white solid, mp 101.1–101.7 °C; IR (KBr): $\nu$ 3106, 2955, 2148, 1718, 1606, 1593, 1344, 1273 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 3.90 (s, 3H), 4.01 (s, 2H), 7.57 (d, $J = 8.8$ Hz, 2H), 8.01 (s, 1H), 8.29 (d, $J = 8.8$ Hz, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 30.4, 52.8, 111.3, 124.0 (2 × CH), 129.0, 129.8 (2 × CH), 139.9, 141.6, 147.9, 165.3. Anal. Calcd for $C_{12}H_{10}N_2O_4S$: C, 51.79; H, 3.62; N, 10.07; S, 11.52. Found: C, 52.02; H, 3.57; N, 10.08; S, 11.19.
*Methyl (Z)-3-(3,4-methylenedioxyphenyl)-2-(thiocyanomethyl)propenoate* (**4j**): 81%; white solid, mp 74.2–74.9 °C; IR (KBr): $\nu$ 2903, 2144, 1712, 1594, 1482, 1344, 1241 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 3.86 (s, 3H), 4.16 (s, 2H), 6.02 (s, 2H), 6.86–6.97 (m, 3H), 7.86 (s, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 31.7, 52.9, 102.0, 109.1, 109.4, 112.1, 123.9, 125.1, 127.7, 144.9, 148.6, 149.5, 166.8. Anal. Calcd for $C_{13}H_{11}NO_4S$: C, 56.31; H, 4.00; N, 5.05; S, 11.56. Found: C, 56.64; H, 3.96; N, 4.96; S, 11.29.
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12. (a) *Selected crystallographic data*: Compound **4j**: formula $C_{13}H_{11}NO_4S$, space group $P\bar{1}$, FW 277.29, $a = 6.635(2)$ Å, $b = 8.968(1)$ Å, $c = 10.838(2)$ Å, $\alpha = 83.52(1)°$, $\beta = 88.64(2)°$, $\gamma = 80.60(1)°$, $V = 632.2(2)$ $Å^3$, $Z = 2$, $D_{calcd} = 1.457$ $Mg/m^3$, $\mu = 0.265$ $mm^{-1}$, unique = 2237 ($R_{int} = 0.0177$), GOF ($F^2$) = 1.069, $R_1 = 0.0472$ [$I > 2\sigma(I)$], $wR_2 = 0.1394$ (all data); (b) Compound **7a**: formula $C_{11}H_{10}N_2OS$, space group $P\bar{1}$, FW 218.27, $a = 7.273(1)$ Å, $b = 10.921(1)$ Å, $c = 13.671(1)$ Å, $\alpha = 83.511(6)°$, $\beta = 78.094(8)°$, $\gamma = 86.296(9)°$, $V = 1054.75(19)$ $Å^3$, $Z = 4$, $D_{calcd} = 1.375$ $Mg/m^3$, $\mu = 0.279$ $mm^{-1}$, unique = 3736 ($R_{int} = 0.0187$), GOF ($F^2$) = 1.061, $R_1 = 0.0333$ [$I > 2\sigma(I)$], $wR_2 = 0.0917$ (all data).
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16. *Typical procedure for the synthesis of allylic azides* (**6**) *from thiocyanates* (**4**): To a stirred solution of allylic thiocyanate **4** (1.0 mmol) in 4.0 mL of acetone/$H_2O$ (3:1 v/v) was added 2.0 mmol of $NaN_3$, and the mixture was heated at 80 °C (oil bath) for 30 min. After cooling down to 25 °C, the reaction was diluted with $CH_2Cl_2$ and washed with $H_2O$ and brine. The organic extract was dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by chromatography (hexane/ethyl acetate 9:1) to give the corresponding (*E*)-2-(azidomethyl)alkenoates **6** in 85–95% yield. All products were characterized spectroscopically and showed physical and spectral data in accordance with their expected structure and by comparison with authentic samples.[9]
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19. *Typical procedure for the synthesis of 2-amino-1,3-thiazin-4-ones* (**7**): To a stirred solution of allylic bromide **3** (1.0 mmol) in 4.0 mL of acetone/$H_2O$ (3:1 v/v) at 25 °C was added 2.0 mmol of thiourea. After stirring for 1 h, the final mixture was extracted with $CH_2Cl_2$ and the organic extract was discarded. The aqueous phase was then treated with 5.0 mL of satd $NaHCO_3$ and the remaining basic solution was immediately extracted with $CH_2Cl_2$. The organic extract was concentrated under reduced pressure and the resulting solid was washed with $H_2O$, EtOH and acetone to give 1,3-thiazin-4-ones **7**. Spectral and analytical data of some selected compounds are as follows:

*(5Z)-2-Amino-5-benzylidene-5,6-dihydro-1,3-thiazin-4-one* (**7a**): 90%; white solid, mp 170.5–173.0 °C; IR (KBr): *v* 3288, 2987, 1641, 1602, 1488, 1313 $cm^{-1}$; $^1H$ NMR (400 MHz, TFA-$d_1$, $C_6D_6$ as internal standard): $\delta$ 4.23 (s, 2H), 7.18–7.28 (m, 5H), 7.98 (s, 1H); $^{13}C$ NMR (100 MHz, TFA-$d_1$, $C_6D_6$ as internal standard): $\delta$ 25.9, 118.6, 129.4 (2 × CH), 129.8 (2 × CH), 131.8, 132.5, 149.3, 166.1, 174.3. Anal. Calcd for $C_{11}H_{10}N_2OS$: C, 60.53; H, 4.62; N, 12.83; S, 14.69. Found: C, 60.40; H, 5.01; N, 12.67; S, 14.32.

*(5Z)-5-(4-Chlorobenzylidene)-2-amino-5,6-dihydro-1,3-thiazin-4-one* (**7c**): 91%; white solid, mp 211.0–213.5 °C; IR (KBr): *v* 3326, 3036, 1637, 1600, 1482, 1310 $cm^{-1}$; $^1H$ NMR (400 MHz, TFA-$d_1$, $C_6D_6$ as internal standard): $\delta$ 4.73 (s, 2H), 7.67 (d, $J = 8.5$ Hz, 2H), 7.79 (d, $J = 8.5$ Hz, 2H), 8.45 (s, 1H); $^{13}C$ NMR (100 MHz, TFA-$d_1$, $C_6D_6$ as internal standard): $\delta$ 25.8, 119.3, 129.7 (2 × CH), 130.9, 131.1 (2 × CH), 138.6, 147.5, 165.7, 174.1. Anal. Calcd for $C_{11}H_9ClN_2OS$: C, 52.28; H, 3.59; N, 11.08; S, 12.69. Found: C, 51.92; H, 3.45; N, 11.44; S, 12.77.

*(5Z)-2-Amino-5,6-dihydro-5-[(E)-3-phenyl-2-propenylidene]-1,3-thiazin-4-one* (**7k**): 76%; yellow solid, mp 203.5–205.5 °C; IR (KBr): *v* 3288, 2984, 1632, 1587, 1485, 1308 $cm^{-1}$; $^1H$ NMR (400 MHz, TFA-$d_1$, $C_6D_6$ as internal standard): $\delta$ 4.65 (s, 2H), 7.52 (dd, $J = 11.5$ and 15.5 Hz, 1H), 7.70 (d, $J = 15.5$ Hz, 1H), 7.73–7.75 (m, 3H), 7.89–7.91 (m, 2H), 8.19 (d, $J = 11.5$ Hz, 1H); $^{13}C$ NMR (100 MHz, TFA-$d_1$, $C_6D_6$ as internal standard): $\delta$ 25.1, 114.7, 120.2, 128.4 (2 × CH), 129.2 (2 × CH), 131.5, 135.0, 148.4, 150.9, 166.1, 174.6. Anal. Calcd for $C_{13}H_{12}N_2OS$: C, 63.91; H, 4.95; N, 11.47; S, 13.12. Found: C, 63.57; H, 4.68; N, 11.11; S, 12.83.