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Purification-Free, Small-Scale Synthesis of Isothiocyanates by Reagentless Fragmentation of Polymer-Supported 1,4,2-Oxathiazoles

Brendan A. Burkett,*[a] Pincheng Fu,[b] Russell J. Hewitt,[a] Su Ling Ng,[b] and Joel D. W. Toh[a]

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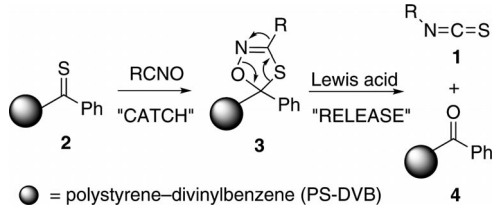
The synthesis of isothiocyanates (ITCs) by employing polymer-supported 1,4,2-oxathiazoles is described. The ITCs are obtained in moderate yields and high purity through a reagentless, thermal fragmentation of polymer-supported 1,4,2-oxathiazoles that are obtained by trapping nitrile oxides with polymer-supported thiocarbonates.

Introduction

Isothiocyanates (ITCs, i.e., **1**) are a class of compounds with a wide range of biological activities from anticancer and chemoprotective[1–3] properties to antimicrobial,[4] pesticidal,[5] fungicidal,[6] and herbicidal[7] activities. Our interest in building libraries of simple ITCs for general screening purposes highlighted the several challenges associated with the small-scale preparation and storage of these compounds. In particular, we wished to avoid the frequent use of hazardous reagents such as thiophosgene and carbon disulfide that are typically employed to generate ITCs.[8,9] We, therefore, revisited our previously reported approach to the synthesis of ITCs that employed a polymer-supported catch-and-release method (see Scheme 1).[10] On the basis of known 1,3-dipolar cycloaddition reactions between a nitrile oxides and thiocarbonyl-containing compounds,[11–15] polymer-supported thiobenzophenone **2** was utilized to "catch" the nitrile oxide through a 1,3-dipolar cycloaddition reaction, which afforded the corresponding polymer-supported 1,4,2-oxathiazole **3**. The subsequent "release" of the ITC from **3** was carried out through a fragmentation reaction under thermal conditions in the presence of a Lewis acid.

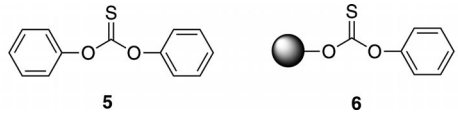
However, there are several limitations that render our previously reported approach impractical for general use to produce small quantities of pure ITCs. The use of Lawesson's reagent and the employment of a Lewis acid in the synthetic sequence are among these limitations, as these substances contribute to the contamination of the final products. To have a truly practical catch-and-release system for the purification-free, small-scale synthesis of ITCs, we



Scheme 1. Previously reported catch-and-release approach to the synthesis of ITCs.

deemed that any such reagents should be avoided. In particular, the all-important fragmentation step should ideally be reagentless, and, therefore, the intrinsic reactivity of the 1,4,2-oxathiazole towards fragmentation needs to be attenuated to occur at a lower temperature. The presence of donor heteroatoms at the 5-position of 1,4,2-oxathiazoles is known to promote fragmentation, particularly for oxathiazoles that are derived from thiourea,[13,16–18] which undergo facile fragmentation to give ITCs. Baxendale and coworkers recently exploited this fact by utilizing a polymer-supported thiourea derivative as an immobilized sulfur-transfer reagent for the synthesis of ITCs under flow conditions.[19]

In contrast, 1,4,2-oxathiazoles that are derived from the cycloaddition of nitriles oxides and diphenyl thiocarbonate (**5**) are isolable materials that fragment efficiently between 60 and 120 °C.[11–13] We, therefore, envisaged a polymer-supported thiocarbonate such as **6** to be an ideal dipolarophile for our purposes, which would allow purification by simply washing the immobilized 1,4,2-oxathiazole.



[a] Institute of Chemical and Engineering Sciences,
8 Biomedical Grove, #07-01, Neuros, Singapore 138665
E-mail: Brendan_Burkett@ices.a-star.edu.sg
www.ices.a-star.edu.sg
[b] School of Chemical and Life Sciences, Singapore Polytechnic,
500 Dover Road, Singapore 139651
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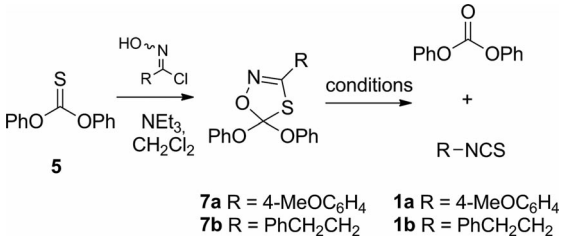
Results and Discussion

Prior to evaluating the polymer-supported systems, we first performed solution-phase optimization studies to ensure that the desired conditions could be satisfied for the reagentless cleavage from a polymer-supported system. Ideally, the cleavage step should be conducted in a solvent with a low boiling point to facilitate isolation of the ITC, and the solvent that is employed should efficiently swell the PS-DVB copolymer to ensure maximum recovery of the product following release. Dichloromethane was chosen as the solvent, however, through the course of our studies, we found that tetrahydrofuran (THF) and chloroform were also suitable alternatives.

To assess the efficiency of the fragmentation, the two model oxathiazoles **7a** and **7b** were prepared by a reaction between commercially available diphenyl thiocarbonate and a nitrile oxide that was generated in situ from the corresponding *N*-hydroximidoyl chloride in the presence of triethylamine (see Scheme 2). The choice of these model systems was made on the basis of the convenient spectroscopic handles that are provided by the 4-methoxy and phenylethyl moieties, which allow for the ratios of compounds containing these groups to be easily determined by ^{1}H NMR spectroscopy. Compound **7b**, with an approximate half-life of 18 h, underwent fragmentation in deuterated chloroform at room temperature to give the corresponding carbonate and ITC. Compound **7a**, with an approximate half-life of five days, was much more stable in deuterated chloroform at room temperature. A range of conditions were then assessed to determine the optimal ones for cleavage in a deuterated solvent to facilitate screening by ^{1}H NMR spectroscopy (see Table 1).



Scheme 2. Synthesis of 1,4,2-oxathiazoles **7b** and **7b** and subsequent fragmentation to isothiocyanates.

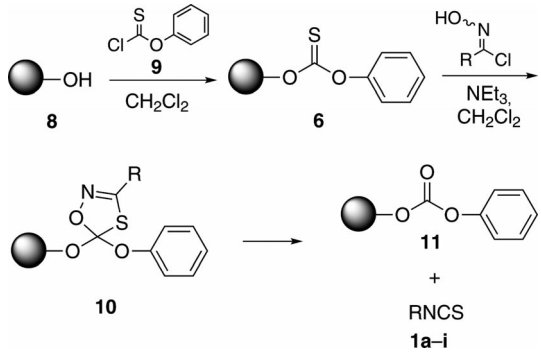
Table 1. Optimization of solution-phase fragmentation conditions.

Entry	R	Conditions	Fragmentation[a]
1	4-$CH_3OC_6H_4$	CD_2Cl_2, 40 °C, 30 min	≈2%
2	4-$CH_3OC_6H_4$	CD_2Cl_2, 100 °C,[b] 15 min	>99%
3	4-$CH_3OC_6H_4$	$CDCl_3$, reflux, 30 min	≈80%
4	4-$CH_3OC_6H_4$	$CDCl_3$, 100 °C,[b] 15 min	>99%
5	$PhCH_2CH_2$	CD_2Cl_2, 40 °C, 30 min	≈12%
6	$PhCH_2CH_2$	CD_2Cl_2, 100 °C,[b] 15 min	>99%
7	$PhCH_2CH_2$	$CDCl_3$, reflux, 30 min	>99%
8	$PhCH_2CH_2$	$CDCl_3$, 100 °C,[b] 15 min	>99%

[a] Fragmentation was determined by integration of known signals for oxathiazoles and the corresponding ITCs. The ITCs were not isolated. [b] Microwave-assisted heating.

As shown in Table 1, the extent of the fragmentation of **7a** and **7b** that was observed in refluxing dichloromethane is not sufficient to be of practical value. Gratifyingly, heating the system to 100 °C for 15 min using microwave irradiation resulted in complete conversion into the desired ITC. For convenience, the same conversions could be achieved by conducting the fragmentation in refluxing deuterated chloroform for 30–60 min.

Having established an efficient system for the complete fragmentation of the oxathiazoles into the corresponding carbonates and ITCs, we then directed our attention to the polymer-supported systems. PS-DVB-supported phenol **8** was treated with phenyl chlorothioformate (**9**) to afford the desired polymer-supported thiocarbonate **6** (see Scheme 3). There were no clearly detectable vibrations in the infrared spectrum of the resulting polymer to determine the success of this reaction, as the C=S stretching vibration,[20–23] which was expected between 1190 and 1250 cm^{-1}, was obscured by the polystyrene backbone vibrations. However, the bands attributed to the phenolic C–O stretching vibration of the starting PS-DVB-supported phenol at approximately 1240–1220 cm^{-1} were clearly shifted to a lower wavenumber and lower intensity, which indicates that the reaction had proceeded. Elemental analysis was performed on the polymer, which confirmed the presence of sulfur and indicated an approximate loading of 1.52% w/w, or 0.47 mmol g^{-1}. On the basis of the loading of the supplied phenol resin (0.74 mmol g^{-1}), the maximum theoretical loading of the thiocarbonate was calculated to be 0.67 mmol g^{-1}, which indicated an experimental yield of 70%.



Scheme 3. Catch-and-release synthesis of ITCs using PS-DVB-supported diphenyl thiocarbonate.

To fully confirm the successful formation of **6**, it was necessary to proceed with the synthetic sequence. Thus, **6** was treated with an excess amount of *N*-hydroxybenzimidoyl chloride in the presence of triethylamine at room temperature for 30 min, and the resulting polymer was washed by using an optimized washing regime. Analysis of the polymer by infrared spectroscopy revealed the appearance of multiple bands in the 1000–1100 cm^{-1} region, which is attributed to multiple C–O stretching vibrations from the newly formed 1,4,2-oxathiazole **10c** (R = Ph). Gratifyingly, when **10c** was suspended in deuterated chloroform at 80 °C for 1 h, a moderate yield of phenyl isothiocyanate (**1c**) was

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obtained (40% based on the loading of **6** as determined by elemental analysis). Importantly, the ^{1}H NMR spectroscopic data indicated that the compound was of high purity, as only signals attributed to phenyl isothiocyanate were observed. The identity of the ITC was confirmed by infrared spectroscopic analysis of the isolated material, which showed the strong characteristic NCS absorbance at approximately 2064 cm^{-1}. Analysis of the recovered polymer by IR spectroscopy showed the appearance of a strong band at 1777 cm^{-1}, which is consistent with the formation of the polymer-supported diphenylcarbonate **11**[24] and further confirmed the successful rearrangement. Repeating the reaction in dichloromethane at 100 °C for 15 min resulted in a similar yield of the ITC (53%). Importantly, the purity of the obtained material was also high, and analysis of the recovered polymer-support system by IR spectroscopy revealed the appearance of the absorbances that are attributed to **11**.

Satisfied that we had established optimal conditions for the generation of pure isothiocyanates through our catch-and-release strategy, we turned our attention to investigate the substrate scope of the reaction. A range of *N*-hydroximidoyl chlorides were then treated with triethylamine in the presence of **6**, and the release of the ITCs was conducted in dichloromethane with microwave-assisted heating. From Table 2, it is evident that the catch-and-release approach to the synthesis of the ITCs is tolerant of a range of functional groups. The variations in the isolated yields are likely to arise from the cycloaddition reactions and washing procedures, which were applied to all cases as general protocols and were not optimized for each individual substrate.

Table 2. Isolated yields of ITCs following thermal treatment of polymer-supported 1,4,2-oxathiazoles **10a–10i**.

Product	R	Conditions	% Yield[a]
1c	Ph	80 °C, $CDCl_3$, 1 h	40
1c	Ph	100 °C, CH_2Cl_2, 15 min	53
1c	Ph	100 °C, CH_2Cl_2, 30 min	46
1c	Ph	100 °C, $CHCl_3$, 15 min	56
1a	4-$CH_3OC_6H_4$	100 °C, CH_2Cl_2, 15 min	71
1b	$PhCH_2CH_2$	100 °C, CH_2Cl_2, 15 min	86
1d	4-$CH_3C_6H_4$	100 °C, CH_2Cl_2, 15 min	61
1e	4-$NO_2C_6H_4$	100 °C, CH_2Cl_2, 15 min	76[b]
1f	4-FC_6H_4	100 °C, CH_2Cl_2, 15 min	30
1g	*tert*-butyl	100 °C, CH_2Cl_2, 15 min	33
1h	*n*-hexyl	100 °C, CH_2Cl_2, 15 min	27
1i	cyclohexyl	100 °C, CH_2Cl_2, 15 min	22

[a] The isolated yields are unoptimized, as general procedures for the cycloaddition, washing, and fragmentation were applied to all cases. [b] ITC isolated from different batch of **6**, and yield reported as percentage of maximum theoretical yield.

In addition, it was generally observed that shorter washing times following the cycloaddition reactions translated into higher yields from the fragmentation, as leakage of the ITC was detected during the washing of the polymer-supported 1,4,2-oxathiazoles, particularly in more polar solvents. This could be minimized, however, by precooling the solvents that were used for washing as well as minimizing the washing time. Pleasingly, the release of 4-nitrophenyl isothiocyanate (**1e**) from the corresponding polymer-supported 1,4,2-oxathiazole proceeded to give **1e** in good yield and high purity. This was not achievable by using our previously reported thiobenzophenone-based system, in which cycloreversion and subsequent dimerization of 4-nitrobenzonitrile oxide was the dominant reaction pathway. Considering all the systems, **1h** was isolated in the lowest purity. We attribute this to the higher reactivity of linear aliphatic ITCs, which result in the formation of side products that are trapped in the resin during the washing procedure.[25]

Through the course of our studies, we considered that libraries of polymer-supported 1,4,2-oxathiazoles could also be used as a convenient way to produce ITCs on demand in pure form, as opposed to storing the polymer-supported compounds in solution or as residues. To assess this potential application, we were fortunate to have small quantities of **10b**–**10d** and **10i** that were refrigerated for over three years. We then used **10c** as our model compound. Infrared spectroscopic analysis of the stored polymer revealed the presence of the characteristic ITC vibrations in the 2100 cm^{-1} region in addition to the carbonate carbonyl stretching vibration at 1777 cm^{-1}, which indicated that the rearrangement had already occurred. A known weight of the polymer was then thoroughly washed with dichloromethane to afford **1c** in approximately 35% yield based on the experimentally determined loading. Significantly, the purity of the material that was washed from the resin was very high. The remaining polymer was then subjected to thermal fragmentation conditions, and approximately an additional 11% of high purity ITC was isolated, which indicated that about 75% of the available ITC had been released upon storage. The combined yield of about 46% ITC that was released from the polymer was in good agreement with previously recorded yields from the same batch over three years earlier. On account of the small quantities that remained, compounds **10b**, **10d**, and **10i** were simply heated under the standard fragmentation conditions to afford the ITCs in 78, 57, and 26% yield, respectively, again in high purity. The fact that pure ITCs can be isolated by washing the resin after three years of refrigerated storage without any special precautions to exclude moisture suggests that the resin essentially encapsulates the product in a hydrophobic environment to protect the material. It is encouraging that after the prolonged refrigerated storage (ca. 4 °C) of **10c**, approximately 25% of the available ITC remained bound to the polymer as the corresponding 1,4,2-oxathiazole. We are confident that the half-life of polymer-supported 1,4,2-oxathiazoles will be extended when the polymer is stored at lower temperatures, and, thereby after prolonged storage, allow for the on-demand, chromatography-free production of small amounts of sensitive ITC samples.

Conclusions

In summary, we have demonstrated a system that enables the synthesis of a range of ITCs from polymer scaffold **6** and readily accessible nitrile oxides. Through our current

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work and that of others,[11–15,19] it is evident that a wide variety of structural types are tolerated by this methodology, which is limited only by the ready accessibility of the requisite *N*-hydroximidoyl chlorides. Nevertheless, with regard to the synthesis of ITCs, a significant advantage of this method over our previously described and other methods is that the use of reagents such as carbon disulfide, thiophosgene, and sulfur-transfer reagents (e.g., Lawesson's reagent) for each individual preparation is avoided. This greatly improves the ease of handling on a small scale and reduces exposure to these highly toxic and sometimes malodorous compounds. It is noteworthy that no purification steps were carried out for the oximes or *N*-hydroximidoyl chlorides prior to generating the nitrile oxides and no chromatography or specialized equipment was required to afford the isolated products. Finally, there is potential for this method to be employed as a "delayed catch-and-release" synthesis of ITCs to prolong the storage lifetime of these compounds.

Experimental Section

General Methods: The ^{1}H and ^{13}C NMR spectroscopic data were recorded with a spectrometer that operated at 400 (for ^{1}H NMR) and 100 MHz (for ^{13}C NMR) and with deuterated chloroform ($CDCl_3$) or dichloromethane (CD_2Cl_2) as the solvents. Chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane (0.00 ppm). The NMR spectroscopic data that were recorded in $CDCl_3$ were referenced to the residual chloroform singlet (δ =7.26 ppm) for ^{1}H NMR and the central peak of the $CDCl_3$ triplet (δ =77.00 ppm) for ^{13}C NMR. The ^{1}H NMR spectroscopic data that were recorded in CD_2Cl_2 were referenced to the residual $CHDCl_2$ triplet at δ = 5.32 ppm. The data are reported as chemical shift (δ), multiplicity [s (singlet), d (doublet), t (triplet), q (quartet), qt (quintet), m (multiplet), dd (doublet of doublets), br. (broad)], coupling constant (*J*), and relative integral. Infrared spectra were recorded with an FTIR spectrometer as thin liquid films and solid samples using an attenuated total reflectance (ATR) accessory or as KBr pellets for all polymeric materials. IR spectroscopic data are reported as frequency ($\tilde{\nu}_{max}$ = cm^{-1}) and strength [br. (broad), s (strong), m (medium), w (weak)]. Oximes and *N*-hydroximoyl chlorides were synthesized according to known literature preparations[26–29] and were used without purification in all cases. Microwave reactions were performed with a Biotage® Initiator microwave reactor using an external IR sensor to monitor temperature. High resolution mass spectra were obtained using electrospray ionization. All commercial materials were used as purchased.

3-(4-Methoxyphenyl)-5,5-diphenoxy-1,4,2-oxathiazole (7a): Diphenyl thiocarbonate **6** (101 mg, 0.44 mmol) and *N*-hydroxy(4-methoxyphenyl)oximidoyl chloride (91 mg, 0.49 mmol) were dissolved in dichloromethane (5 mL), and the resulting solution was then cooled to 0 °C. The reaction mixture was treated dropwise with triethylamine (70 μL, 0.50 mmol) and then stirred at room temperature for 2 h. The mixture was filtered through silica [dichloromethane (20 mL)], and the filtrate was then concentrated. The crude product was purified by column chromatography (hexanes/ethyl acetate, 8:1) to provide **7a** (166 mg, 84%) as a white solid; m.p. 80–81 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 (app d, $^3J_{H,H}$ = 9.0 Hz, 2 H), 7.38–7.27 (m, 8 H), 7.21–7.15 (m, 2 H), 6.86 (app d, $^3J_{H,H}$ = 9.0 Hz, 2 H), 3.81 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 162.0, 156.9, 152.6, 139.6, 129.4, 128.9, 125.6, 121.6, 120.5, 114.2, 55.4 ppm. IR: $\tilde{\nu}_{max}$ = 1607 (m), 1508 (m), 1488 (s), 1258 (s), 1192 (s), 1070 (br. s) cm^{-1}. HRMS-TOF: calcd. for $C_{21}H_{18}NO_4S^+$ [M + H]$^+$ 380.0951; found 380.0956.

3-β-Phenethyl-5,5-diphenoxy-1,4,2-oxathiazole (7b): Diphenyl thiocarbonate (**5**, 121 mg, 0.53 mmol) and *N*-hydroxy(2-phenylethyl)-oximidoyl chloride (106 mg, 0.58 mmol) were dissolved in dichloromethane (5 mL), and the resulting solution was then cooled to 0 °C. The reaction mixture was treated dropwise with triethylamine (70 μL, 0.50 mmol) and then stirred at room temperature for 2 h. The mixture was filtered through silica [dichloromethane (20 mL)], and the filtrate was then concentrated. The crude product was purified by column chromatography (hexanes/ethyl acetate, 8:1) to provide **7b** (142 mg, 84%) as a clear liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48–7.42 (m, 1 H), 7.36–7.29 (m, 4 H), 7.25–7.17 (m, 8 H), 7.07–7.04 (m, 2 H), 2.76–2.67 (m, 4 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.2, 153.6, 152.5, 140.0, 139.3, 129.3, 128.6, 128.3, 126.6, 125.3, 121.7, 33.4, 31.0 ppm. IR: $\tilde{\nu}_{max}$ = 1590 (w), 1489 (s), 1275 (m), 1194 (s), 1178 (s), 1070 (m) cm^{-1}. HRMS-TOF: calcd. for $C_{22}H_{20}NO_3S^+$ [M + H]$^+$ 378.1158; found 378.1160.

Preparation of PS-DVB Diphenyl Thiocarbonate 6: PS-DVB phenol resin (1 g, 0.74 mmol) was swelled in THF for 5 min, and then triethylamine (144 μL, 0.82 mmol) followed by phenyl thiochloroformate (140 mg, 0.82 mmol) was added. The resulting mixture was shaken at room temperature for 1 h along with the occasional venting of the reaction vessel. After this time, the resulting polymer beads were filtered and washed sequentially with THF (15 mL for 2 min), water (15 mL for 2 min), THF (2 × 15 mL for 2 min), THF/CH_2Cl_2 (1:1, 15 mL for 2 min), CH_2Cl_2 (15 mL for 2 min), and finally Et_2O (15 mL for 2 min). The polymer beads were then dried in vacuo for 16 h and stored at room temperature. Theoretical loading of the PS-DVB diphenyl thiocarbonate = 0.67 mmol g^{-1}. Analytical data: calcd. S 2.12; found S 1.52. Experimental loading of PS-DVB diphenyl thiocarbonate = 0.47 mmol g^{-1}.

General Procedure for 1,3-Dipolar Cycloaddition Reactions of Nitrile Oxides with 6: To a suspension of the polymer-supported diphenyl thiocarbonate in THF (15 mL g^{-1} of resin) was added the appropriate *N*-hydroximidoyl chloride (3 equiv. based on theoretical loading) followed by triethylamine (3 equiv. based on theoretical loading). The reaction mixture proceeded at room temperature for 30 min with continuous gentle agitation. The polymer support was then filtered and then washed quickly (30–60 s) and sequentially with cooled CH_2Cl_2 (2 × 15 mL g^{-1}), THF (2 × 15 mL g^{-1}), acetonitrile (2 × 15 mL g^{-1}), acetonitrile/water (1:1, 2 × 15 mL g^{-1}), acetonitrile (2 × 15 mL g^{-1}), and CH_2Cl_2 (2 × 30 mL g^{-1}). The resulting polymer beads were then dried in vacuo (16 h). ***Important note:*** The leakage of the ITC from the polymer supports was observed by analysis of the acetonitrile and acetonitrile/water washings when the procedure was conducted at room temperature. It is imperative to wash with acetonitrile/water for complete removal of the triethylammonium salts that are formed upon nitrile oxide generation. It was found that using precooled (ca. 4 °C) solvents for this purpose minimized the premature release of the ITC.

General Procedure for Thermal Release of Isothiocyanates 1a–1g from the Polymer-Supported 1,4,2-Oxathiazoles 10: The appropriate polymer-supported 1,4,2-oxathiazole (200 mg) was swelled in dichloromethane (5 mL) for 5 min, and the resulting suspension was maintained at 100 °C for 15 min in a microwave reactor. The polymer was filtered and washed with dichloromethane (2 × 10 mL g^{-1}). The washings were collected, and the solvent was removed under reduced pressure. In all cases, the resulting isothiocyanates were obtained in high to very high purity after isolation and gave identical NMR spectroscopic data to previously characterized compounds. ***Caution:*** Heating dichloromethane at 100 °C gives rise

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to approximately 5 bar of pressure. All heating must be conducted in custom-built glassware or reaction vessels that are provided by the manufacturer and rated to at least 10 bar.

4-Methoxyphenyl Isothiocyanate (1a):[8,9] The title compound (5.2 mg, 71% based on loading of 0.44 mmol g^{-1}) was isolated from polymer-supported 5,5-diphenoxy-3-[4-methoxyphenyl]-1,4,2-oxathiazole (100 mg) after heating under microwave conditions. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.17 (d, $^3J_{H,H}$ = 9.0 Hz, 2 H), 6.85 (d, $^3J_{H,H}$ = 9.0 Hz, 2 H), 3.81 (s, 3 H) ppm. IR: $\tilde{\nu}_{max}$ = 2109 (s) cm^{-1}.

β-Phenethyl Isothiocyanate (1b):[30] The title compound (3.1 mg, 86% based on loading of 0.44 mmol g^{-1}) was isolated from polymer-supported 3-β-phenethyl-5,5-diphenoxy-1,4,2-oxathiazole (50 mg) after heating under microwave conditions. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.12 (Ar, 5 H), 3.73 (t, $^3J_{H,H}$ = 7.0 Hz, 2 H), 3.00 (t, $^3J_{H,H}$ = 7.0 Hz, 2 H) ppm. IR: $\tilde{\nu}_{max}$ = 2185 (m), 2110 (s) cm^{-1}.

Phenyl Isothiocyanate (1c):[8,9] The title compound (2.7 mg, 53% based on loading of 0.45 mmol g^{-1}) was isolated from polymer-supported 5,5-diphenoxy-3-phenyl-1,4,2-oxathiazole (80 mg) after heating under microwave conditions. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.33 (m, 2 H), 7.30–7.27 (m, 1 H), 7.25–7.21 (m, 2 H) ppm. IR: $\tilde{\nu}_{max}$ = 2064 (s) cm^{-1}.

4-Methylphenyl Isothiocyanate (1d):[8,9] The title compound (3.2 mg, 61% based on loading of 0.44 mmol g^{-1}) was isolated from polymer-supported 3-[4-methylphenyl]-5,5-diphenoxy-1,4,2-oxathiazole (80 mg) after heating under microwave conditions. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.13 (m, 4 H), 2.35 (s, 3 H) ppm. IR: $\tilde{\nu}_{max}$ = 2174 (s), 2106 (s), 2057 (s) cm^{-1}.

4-Nitrophenyl Isothiocyanate (1e):[8,9] The title compound (7.4 mg, 76% based on theoretical loading of 0.60 mmol g^{-1}) was isolated from polymer-supported 3-[4-nitrophenyl]-5,5-diphenoxy-1,4,2-oxathiazole (90 mg) after heating under microwave conditions. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.24 (d, $^3J_{H,H}$ = 9.0 Hz, 2 H), 7.35 (d, $^3J_{H,H}$ = 9.0 Hz, 2 H) ppm. IR: $\tilde{\nu}_{max}$ = 2099 (s), 1585 (s), 1336 (s) cm^{-1}.

4-Fluorophenyl Isothiocyanate (1f):[8,9] The title compound (2.0 mg, 30% based on loading of 0.44 mmol g^{-1}) was isolated from polymer-supported 3-[4-fluorophenyl]-5,5-diphenoxy-1,4,2-oxathiazole (100 mg) after heating under microwave conditions. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.13 (m, 2 H), 7.04 (m, 2 H) ppm. IR: $\tilde{\nu}_{max}$ = 2101 (m), 2053 (s) cm^{-1}.

***tert*-Butyl Isothiocyanate (1g):**[9] The title compound (1.7 mg, 33% based on loading of 0.45 mmol g^{-1}) was isolated from polymer-supported 3-*tert*-butyl-5,5-diphenoxy-1,4,2-oxathiazole (100 mg) after heating under microwave conditions. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.43 (s, 9 H) ppm. IR: $\tilde{\nu}_{max}$ = 2080 (s), 1976 (m) cm^{-1}.

***n*-Hexyl Isothiocyanate (1h):**[8,31] The title compound (1.7 mg, 27% based on loading of 0.44 mmol g^{-1}) was isolated from polymer-supported 3-hexyl-5,5-diphenoxy-1,4,2-oxathiazole (100 mg) after heating under microwave conditions. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.51 (t, $^3J_{H,H}$ = 6.7 Hz, 2 H), 1.69 (dq, $^3J_{H,H}$ = 8.4, 6.7 Hz, 2 H), 1.48–1.23 (m, 6 H), 0.89 (t, J = 6.7 Hz, 3 H) ppm. IR: $\tilde{\nu}_{max}$ = 2130 (br. s) cm^{-1}.

Cyclohexyl Isothiocyanate (1i):[8,9] The title compound (1.1 mg, 22% based on loading of 0.44 mmol g^{-1}) was isolated from polymer-supported 3-cyclohexyl-5,5-diphenoxy-1,4,2-oxathiazole (80 mg) after heating under microwave conditions. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.69 (tt, $^3J_{H,H}$ = 7.8, 3.7 Hz, 1 H), 1.89 (ddd, $^2J_{H,H}$ = 13.4 Hz, $^3J_{H,H}$ = 7.1, 3.6 Hz, 2 H), 1.80–1.60 (m, 4 H), 1.55–1.30 (m, 4 H) ppm. IR: $\tilde{\nu}_{max}$ = 2103 (br. s) cm^{-1}.

Supporting Information (see footnote on the first page of this article): Characterization data for **7a** and **7b** as well as ^{1}H NMR and IR spectroscopic analysis of the optimized solution-phase fragmentation studies; microwave heating, pressure, and energy profile for optimized fragmentation conditions; IR spectra to accompany each transformation shown in Scheme 3 (for compound **1c**); ^{1}H NMR spectra of crude cleavage mixtures for **10a–10i**; and ^{1}H NMR spectra for products obtained from 3-year-old samples of **10b–10d** and **10i**.

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