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Polymer-supported thiobenzophenone: a self-indicating traceless 'catch and release' linker for the synthesis of isothiocyanates

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Abstract—The use of a thiobenzophenone as a self-indicating linker in the polymer-supported synthesis of isothiocyanates via a traceless 'catch and release' strategy is reported. Isothiocyanates were furnished via 1,3-dipolar cycloaddition of nitrile oxides with the polymer-supported thiobenzophenone linker, followed by Lewis acid-assisted fragmentation of the resulting polymer-supported oxathiazole.

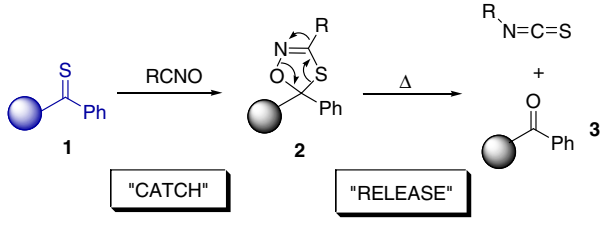
The ability to monitor reactions performed on polymer-supported substrates easily is arguably the most important consideration when conducting a polymer-supported synthesis. Whilst a number of well-established colorimetric tests are available to detect the appearance or absence of certain functional groups,[1–6] these tests are limited in their application and usually result in destruction of precious polymer-supported substrates. IR spectroscopy is also widely applied for monitoring polymer-supported reactions,[1,7] but this technique is not without limitations. The absence of strongly IR active functional groups in a polymer-supported molecule renders IR spectroscopy virtually useless due to the fact that key vibrations of lesser intensity are often obscured by the polystyrene backbone vibrations. Finally, whilst NMR spectroscopy has also been used to monitor polymer-supported reactions,[1,8] the technique is highly dependent on scale as well as access to suitable probes for successful and routine implementation.

Given these limitations, we recently became interested in the development of highly coloured linkers designed to play a pivotal role in the reactions being conducted on the polymer support. We envisaged that any colour change associated with reactions of such linkers would enable us to monitor polymer-supported reactions with the unaided eye and in real time. Herein, we present our preliminary results describing the use of a self-indicating linker for the polymer-supported synthesis of isothiocyanates (ITCs).

Our approach towards the synthesis of ITCs is based on a traceless 'catch and release' methodology. Specifically, we aim to 'catch' reactive nitrile oxides using polymer-supported thiobenzophenone **1** via a 1,3-dipolar cycloaddition to afford the corresponding polymer-supported 1,4,2-oxathiazoles **2** (Scheme 1). 'Release' of ITCs would then be conducted under thermal conditions via fragmentation of the 1,4,2-oxathiazole.

The self-indicating nature of this strategy is the result of thiobenzophenone being intense blue in colour[9] whereas 1,4,2-oxathiazoles are typically colourless. Monitoring reactions involving the polymer-supported variant of this species should therefore be easily achievable by simple visualisation of the polymer support.

Whilst the cycloaddition reactions of thioketones are well documented,[10] the fragmentation of 1,4,2-oxathiazoles



Scheme 1. Proposed traceless 'catch and release' synthesis of ITCs.

Keywords: Self-indicating; Polymer-supported synthesis; Isothiocyanates; Catch and release.
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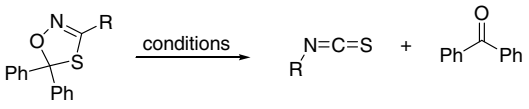
has not been widely studied with only a few examples appearing in the literature.[11–14] High temperatures (>200 °C) are typically required in order to effect the fragmentation in all but a few systems, which has implications in the development of a polymer-supported adaptation of this reaction. Too high a temperature would result in degradation of the polymer support, whilst too low a temperature would render the system unsuitable for a successful catch and release approach. Therefore, prior to investigation of the polymer-supported systems, preliminary solution phase studies were conducted to ascertain the optimal conditions for the fragmentation of benzophenone-derived 1,4,2-oxathiazoles.

Starting from readily accessible and inexpensive aldehydes and benzophenone, 1,4,2-oxathiazoles **4**–**6** were synthesised from the in situ generation of nitrile oxides from their corresponding hydroximoyl chlorides in the presence of thiobenzophenone (Scheme 2). Interestingly, *p*-nitrophenyl-derived 1,4,2-oxathiazole **7** could not be isolated as it underwent easy cycloreversion at room temperature as evidenced by the immediate return of blue colouration upon standing. This cycloreversion was further confirmed upon analysis of the reaction by TLC.

With 1,4,2-oxathiazoles **4**–**6** in hand, fragmentation studies were then pursued (Scheme 3). Oxathiazoles **4** and **5** were found to undergo fragmentation when heated neat at 240 °C for 2 h; however, **6** did not fragment under these conditions.

It is likely that with higher temperatures **6** could be forced to undergo fragmentation; however we did not pursue this possibility and instead moved to an investigation of solvent mediated systems.

Our initial studies involved an investigation of the behaviour of **4** under a range of conditions (Table 1, entries 1–9). It is evident from these results that the solvent has a bearing on the efficiency of the fragmentation with low conversion to ITCs observed in the case of refluxing xylenes and toluene. Upon moving to acetonitrile (entry 3) the conversion to products improved dramatically. This solvent effect prompted us to consider that an ionic or asynchronous concerted mechanism may be in operation and we therefore turned our attention towards the



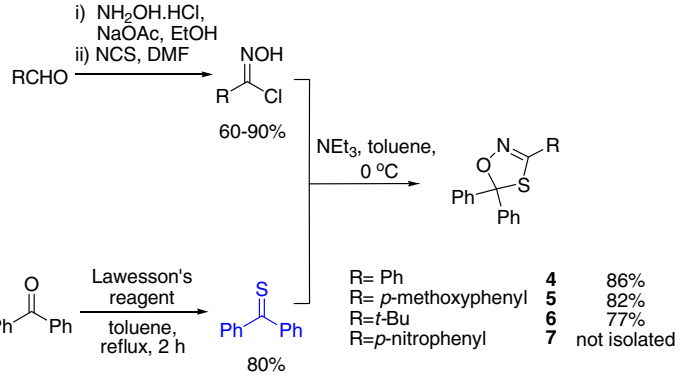
Scheme 3. Fragmentation of 1,4,2-oxathiazoles **4** and **5**.

investigation of various Lewis acids on the fragmentation reactions (Table 1, entries 4–9).

The effect of Lewis acid on the fragmentation was immediately obvious with reactions performed in refluxing xylenes or toluene showing a significant increase in the conversion to products. In some cases, fragmentation was shown to proceed with competing cycloreversion as evidenced by the appearance of thiobenzophenone in the reaction mixture (entries 4–6). Gratifyingly, zinc chloride provided us with a consistently high conversion to the corresponding ITCs, which were isolated in good yields—far superior to those obtained from performing the reaction neat under thermal conditions. Importantly, there was no evidence of cycloreversion taking place under these conditions. We propose that the zinc ion coordinates to the sulfur of the oxathiazole thereby reducing the bond order of the C5–S bond. This would then provide the impetus for formation of the ketone fragment and concomitant migration of the C3-substituent. It is interesting to note that 'harder' Lewis acid types led to some cycloreversion, which would be a result of co-ordination to harder Lewis base sites. Application of the fragmentation conditions to oxathiazoles **5**–**6** showed similar trends with the best conversion and yields being observed using zinc chloride in acetonitrile.

Having determined the optimal conditions for fragmentation of 1,4,2-oxathiazoles, we turned our attention to the polymer-supported system (Scheme 4). Thus 2% PS-DVB co-polymer was acylated with benzoyl chloride in the presence of $FeCl_3$ to afford polymer-supported benzophenone. Successful reaction was evident from the appearance of a strong absorbance for the carbonyl stretching vibration at 1657 cm^{-1}.

Estimation of the loading of the acylated polymer was achieved using IR spectroscopy, which indicated a loading of ~2 mmol g^{-1}. Subsequent treatment of this poly-

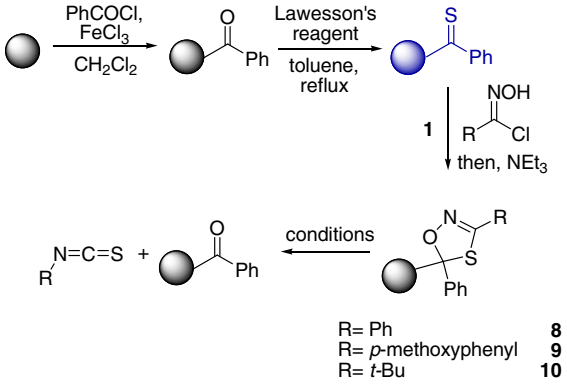


Scheme 2. Solution phase synthesis of 1,4,2-oxathiazoles.

Table 1. Isolated yield of ITCs as a function of fragmentation conditions

Entry	R	Conditions	Yield[a] (%)
1	Ph	Xylenes, reflux, 24 h	8
2	Ph	Toluene, reflux, 24 h	NR
3	Ph	Acetonitrile, reflux, 24 h	30
4	Ph	$AlCl_3$ (0.2 equiv) xylenes, reflux, 24 h	60[b]
5	Ph	$FeCl_3$ (0.2 equiv) xylenes, reflux, 24 h	55[b]
6	Ph	LiCl (0.2 equiv) acetonitrile, reflux, 24 h	30[b]
7	Ph	$ZnCl_2$ (0.2 equiv), xylenes, reflux, 24 h	90
8	Ph	$ZnCl_2$ (0.2 equiv), toluene, reflux, 24 h	79
9	Ph	$ZnCl_2$ (0.2 equiv), acetonitrile, reflux, 12 h	80
10	*p*-$MeOC_6H_4$	Toluene, reflux, 24 h	NR[c]
11	*p*-$MeOC_6H_4$	Acetonitrile, reflux, 12 h	30
12	*p*-$MeOC_6H_4$	$ZnCl_2$ (0.2 equiv), toluene, reflux, 24 h	79[d]
13	*p*-$MeOC_6H_4$	$ZnCl_2$ (0.2 equiv), acetonitrile, reflux, 12 h	78
14	*t*-Bu	Toluene, reflux, 24 h	NR[c]
15	*t*-Bu	Acetonitrile, reflux, 12 h	25
16	*t*-Bu	$ZnCl_2$ (0.2 equiv), toluene, reflux, 24 h	75[d]
17	*t*-Bu	$ZnCl_2$ (0.2 equiv), acetonitrile, reflux, 12 h	78

[a] Isolated yields. Spectroscopic analysis of the isolated compounds (^1H and ^{13}C NMR) was in concordance with those reported in the literature (see Refs. 15–17).
[b] Cycloreversion noted.
[c] <5% conversion in refluxing xylenes.
[d] Similar results were obtained for the reaction conducted in refluxing xylene.



Scheme 4. Polymer-supported synthesis of ITCs.

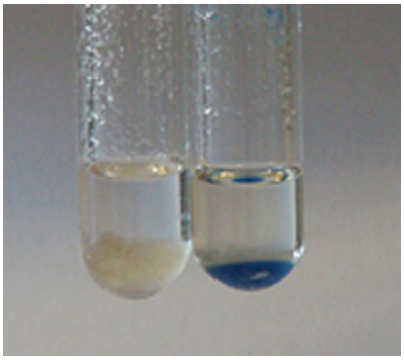


Figure 1. Polymer-supported benzophenone (left) and polymer-supported thiobenzophenone (right) prepared as illustrated in Scheme 4.

mer with Lawesson's reagent afforded the thiobenzophenone polymer **1**.[18] The success of this reaction was immediately evident from the change in colour of the resin, which became intense blue (Fig. 1). Conversion to the thione was also monitored by IR spectroscopy, which revealed complete disappearance of the benzophenone carbonyl stretch at 1657 cm^{-1} after 5 h. In addition, the appearance of a less intense band associated with the presence of a thiocarbonyl was observed at 1094 cm^{-1}.

The blue polymer beads were then swollen in a solution of the desired hydroximoyl chloride in dichloromethane at 0 °C, prior to the addition of triethylamine.[19] The resulting 1,3-dipolar cycloaddition was easily monitored by the gradual disappearance of the blue colour from the beads without resorting to spectroscopic techniques. It is noteworthy that observation of the key IR absorptions for the polymer-supported oxathiazoles is problematic owing to the characteristic bands being obscured by the polystyrene backbone vibrations. In particular, the thione absorbance at 1094 cm^{-1} is not a reliable diagnostic peak for the success of the cycloaddition reaction. This further illustrates the value of the self-indicating properties of the current system.

Subsequent fragmentation of the polymer-supported oxathiazoles **8–10** was then conducted under optimal solution-phase conditions (Table 2).[20]

Our initial optimisation studies with oxathiazole **8** (Table 2, entries 1–3) indicated that toluene was the solvent

Table 2. Polymer-supported 'catch and release' synthesis of ITCs

Entry	R	Conditions	Yield[a] (%)
1	Ph	$ZnCl_2$ (0.2 equiv), xylenes, 24 h	77
2	Ph	$ZnCl_2$ (0.2 equiv), toluene, 24 h	84
3	Ph	$ZnCl_2$ (0.2 equiv), acetonitrile, 12 h	55
4	*p*-$MeOC_6H_4$	$ZnCl_2$ (0.2 equiv), toluene, 24 h	82
5	*t*-Bu	$ZnCl_2$ (0.2 equiv), toluene, 24 h	60

[a] Isolated yield based on a loading of 2 mmol g^{-1} of benzophenone.

of choice when performing this strategy on a polymer-supported system. We attribute this superior performance to the greater swelling of the resin in toluene or xylenes as compared to acetonitrile. Extending the optimised conditions to **9** and **10** also gave rise to synthetically useful yields of the desired ITCs.

Significantly, the cleaved products had a high degree of purity with only small amounts of, as yet, uncharacterised impurities evident in the ^{1}H NMR spectra of the crude cleavage mixtures. It is likely that these trace impurities arise from the presence of byproducts from Lawesson's reagent that remain trapped in the polymer support as in all cases, resonances attributed to *p*-OMe protons were evident.

In conclusion, we have demonstrated the viability of a self-indicating linker for polymer-supported synthesis via the first traceless 'catch and release' synthesis of ITCs. This method is readily applicable to the synthesis of small libraries of ITCs for preliminary biological screening. This methodology is unique in that the synthesis of the polymer-supported thione and the 'catching' of nitrile oxides can be conveniently and non-destructively monitored by unaided visualisation of the polymer support. Studies further investigating the scope and limitations of this methodology are in progress and will be reported in due course.

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18. Polymer-supported benzophenone (2 mmol g^{-1}) was swelled in dry, degassed toluene (16 mL/g of resin) under an inert atmosphere for 10 min and the resulting suspension was heated at reflux. Lawesson's reagent (1.5 equiv) was added in one portion and the polymer beads turned blue within 5 min. Heating was continued for a further 5 h after which time 10 mL of acetone was added to the mixture. The resulting mixture was allowed to react for a further hour before filtering the hot reaction mixture. The resulting polymer-supported thione was filtered and washed with dichloromethane (5×40 mL/g of polymer). The blue thiobenzophenone polymer-support **1** was then dried in vacuo and used immediately in the next step.
19. *General procedure for 1,3-dipolar cycloaddition reactions with* **1**. To a degassed suspension of polymer-supported thione **1** (assuming a loading of 2 mmol g^{-1}) in dichloromethane (20 mL/g) was added the appropriate hydroximoyl chloride (1.1 equiv). The resulting mixture was shaken gently under an inert atmosphere for 5 min followed by the addition of triethylamine (1.1 equiv) dropwise over a period of a few minutes. The reaction was allowed to proceed for 2 h. Complete cycloaddition was evident from the complete disappearance of the blue colour from the polymer beads. The polymer support was then filtered and washed with boiling toluene (2×40 mL/g), acetone (2×40 mL/g), diethyl ether (2×40 mL/g) and dichloromethane (2×100 mL/g). The resulting beads were then dried in vacuo and stored under nitrogen.
20. *General procedure for release of isothiocyanates from the polymer-supported 1,4,2-oxathiazoles.* A sample of polymer-supported 1,4,2-oxathiazole **8**–**10** was swollen in dry toluene under an inert atmosphere for 10 min after which time 0.2 equiv (based on a loading of 2 mmol g^{-1}) of zinc chloride (anhydrous) was added. The reaction was allowed to proceed under reflux for 24 h and the polymer was filtered and washed with dichloromethane (2×10 mL/g). The washings were collected and the solvent was removed under reduced pressure. In all cases the resulting isothiocyanates were isolated in good yield and were of high purity.