

A polymer-supported thionating reagent

Steven V. Ley,* Andrew G. Leach and R. Ian Storer

University Chemical Laboratory, Lensfield Road, Cambridge, UK CB2 1EW

Received (in Cambridge, UK) 1st November 2000, Accepted 8th January 2001

First published as an Advance Article on the web 22nd January 2001

A new polymer-supported reagent for the conversion of carbonyls to thiocarbonyls has been developed and its use demonstrated on a range of amides. Secondary or tertiary amides are converted cleanly and efficiently through to the corresponding thioamides and primary amides are converted to the corresponding nitriles. The reactions can be facilitated by conventional heating. However, if microwave heating is used, in the presence of an ionic liquid, enhanced reaction rates are achieved.

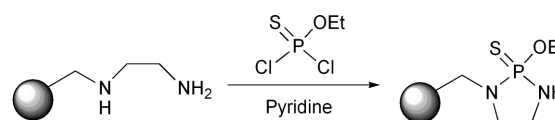
Polymers have been used as supports in organic chemistry for many years.^{1–3} A molecule that is anchored to a solid support may easily be removed from any solution by simple filtration. It is this facile purification method which makes supported technologies ideal, not only for single reaction synthesis, but also for robotic manipulation in high throughput multi-step syntheses.^{4,5} Systems utilising supported substrates with excess solution phase reagent have now been thoroughly investigated.³ However, despite the advantages, these systems frequently suffer due to difficulties in the analysis of reaction products. As a result, optimisation of each reaction is particularly challenging, making multi-step syntheses difficult. These limitations have promoted the development of alternative technologies, with solid-supported reagents and scavengers emerging as one of the most promising.^{1,6}

The greatest advantage of reactions mediated by solid-supported reagents is that they can be optimised and scaled-up extremely readily because solution phase analytical methods (TLC, LC-MS, GC-MS, NMR *etc.*) may be used. Their flexibility in allowing both linear *and* convergent strategies to be selected is of considerable advantage to synthetic chemists building complex molecules.^{7–13} Furthermore, handling support-bound analogues of toxic, explosive, or malodorous reagents is often found to be safer and more convenient than handling the solution phase equivalents.

Until now, a key gap in the expanding toolkit of supported reagents has been one that is capable of converting carbonyls to thiocarbonyls. Among compounds which contain this functionality are thioamides which have important applications in heterocycle synthesis¹⁴ and in the preparation of peptidomimetic molecules.¹⁵

A solution phase reagent which is commonly employed for the transformation of carbonyls to thiocarbonyls is Lawesson's reagent [2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide] which brings about the conversion of amides to thioamides in good yields.^{16–20} However, harsh conditions and long reaction times are often required to facilitate reactions and additionally, isolation of products from reaction mixtures can be extremely difficult. Furthermore, both Lawesson's reagent and reaction side-products have a strong malodour and high toxicity which makes their handling during purification particularly unpleasant. A polymer-supported thionating reagent was therefore a particularly desirable target.

Due to its dimeric structure, Lawesson's reagent itself is a poor candidate for tethering to a support. As an alternative, supported analogues of a range of monomeric thiophosphates, also proven to act as thionating reagents, were investigated.¹⁷ The most useful of these has proven to be an aminothiophosphate resin, synthesised in just one step from a commercially available diamine resin and ethyl dichlorothiophosphate (Scheme 1).²¹



Scheme 1 Synthesis of the polymer-supported thionating reagent.

This reagent is an easily handled, low odour solid that has a loading of 1.8 mmol g⁻¹.²² It can be stored for several months

Table 1 Preparation of secondary and tertiary thioamides *via* conventional heating

Entry	Amide	Product ^a	GC Conversion (%)	GC Purity (%)
1			>99	93
2			>99	88
3			>99	92
4			>99	93
5			>99	66

^a Reaction conditions: toluene, 7.0 equivalents of reagents, 90 °C, 30 hours.

Table 2 Preparation of nitriles *via* conventional heating

Entry	Amide	Product ^a	GC Conversion (%)	GC Purity (%)
1			68	80
2			>99	89
3			>99	94

^a Reaction conditions: toluene, 7.0 equivalents of reagents, 90 °C, 30 hours.

Table 3 Preparation of secondary and tertiary thioamides *via* microwave heating

Entry	Amide	Product ^a	Equivalents of reagent	GC Conversion (%)	GC Purity (%)
1			3.0	>99	95
2			3.5	96	95
3			3.5	>99	98
4			3.5	>99	98
5			3.5	>99	95
6			8.0	>99	98
7			4.4	96	95
8			10.0 20.0	60 98	95 92
9			5.0	>99	97

^a Reaction conditions: toluene, 1-ethyl-3-methyl-1*H*-imidazolium hexafluorophosphate, 200 °C, 15 minutes.

below 0 °C under an inert atmosphere without any detectable loss in activity.

It has now been demonstrated that this new reagent readily converts secondary and tertiary amides to thioamides in high yield and purity (Table 1). As is the case with many supported reagent mediated reactions, extended reaction times (30 hours) were required to facilitate complete conversion to product.²³ Reaction work-up involved only filtration through a short plug of silica and because all phosphorous oxide by-products remained bound to the polymer, there was no need for any further purification.²⁴

In contrast to secondary and tertiary amides, primary amides were generally converted to the corresponding nitriles in good yields and purity (Table 2).²⁵ This type of dehydration has also been observed in some of Lawesson's work on thionating reagents.¹⁸ Unexpectedly, however, the reaction of benzamide gave the thioamide as the major product but in reduced yield and purity due to some formation of the nitrile.

A number of publications have demonstrated that the use of microwave irradiation can decrease reaction times relative to

conventionally heated reactions.^{26,27} Therefore, following the publication of a report²⁸ which describes how microwave irradiation has been used to improve the yields of thionation reactions, the use of microwaves with this polymer-supported variant was investigated (Table 3).²⁹ The thionation reactions showed a marked acceleration, with total conversion being achieved after irradiation for only 10–15 minutes in toluene at 200 °C in a sealed tube.³⁰ It is interesting to note that, even after heating at these elevated temperatures, no damage was caused to the polymeric support.³¹ As toluene is not an optimum solvent for the absorption and dissipation of microwave energy, a small amount of ionic liquid (1-ethyl-3-methyl-1*H*-imidazolium hexafluorophosphate) was added to the reaction mixture to ensure an even and efficient distribution of heat. Acetonitrile was also investigated as an alternative microwave absorbent and proved effective, but less efficient than the ionic liquid. In all cases examined, secondary and tertiary amides were cleanly converted to their corresponding thioamides. As expected, the nucleophilicity of the amides was dependent on the nitrogen functionality. Tertiary amides generally required less reagent to

Table 4 Preparation of nitriles *via* microwave heating

Entry	Amide	Product ^a	Equivalents of reagent	GC Conversion (%)	GC Purity (%)
1		Ph-CN	3.5	>99	95
2			3.5	>99	>99
3			3.5	>99	98

^a Reaction conditions: toluene, 1-ethyl-3-methyl-1*H*-imidazolium hexafluorophosphate, 200 °C, 15 minutes.

facilitate complete conversion than secondary amides. In the case of *N*-phenylamides, the reaction was markedly slower than for amides bearing simple *N*-alkyl substituents. However, if a larger excess of reagent was used, even these reactions could be driven to completion (Table 3, entry 8).

In all cases investigated, primary amides gave clean conversion to the corresponding nitriles under microwave heating (Table 4).³² The improved results were thought to be due to the higher temperature driving even the reaction with benzamide to the nitrile.

In conclusion, a new polymer-supported thionating reagent has been developed as an easily handled, low odour alternative to Lawesson's reagent. Its use has been demonstrated in the conversion of secondary or tertiary amides to thioamides and primary amides to nitriles. The benefits of microwave technology have been illustrated and the use of a small amount of ionic liquid to promote efficient heating in such systems has been proven to be effective.

Acknowledgements

We would like to thank BBSRC and Novartis for a Research Fellowship (S. V. L.) and a CASE award (A. G. L.). Also, we thank AstraZeneca for generous additional funding (R. I. S.).

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- Typical experimental procedure: Ethyl dichlorothiophosphate (12 ml, 90 mmol) was added dropwise to a suspension of *N*-(2-aminoethyl)aminomethyl polystyrene (NovaBiochem, 9.35 g, 2.8 mmol g⁻¹, 21 mmol) in pyridine (150 ml) at 0 °C. The resulting suspension was allowed to warm to room temperature and then shaken at room temperature for 4 hours. Following filtration and washing with dichloromethane (5 × 200 ml) and diethyl ether (5 × 200 ml) residual solvent was removed *in vacuo* to yield the polymeric reagent as an orange solid; Found: S, 5.8%, P, 5.9%; Loading: 1.8 mmol g⁻¹; ν_{\max} (single bead)/cm⁻¹ 3090, 2850, 1676, 1623, 1603, 1494, 1454, 1115, 1029, 761.
- Loading of the resin was calculated from sulfur and phosphorous elemental analysis.
- Example thioamide formation (conventional heating): Thiophosphorylated amine resin (466 mg, 0.84 mmol) was added in one portion to a solution of *N,N*-dimethylbenzamide (28 mg, 0.19 mmol) in toluene (3.0 ml). The resulting suspension was heated without agitation to 90 °C for 14 hours. Further reagent (256 mg, 0.46 mmol) was then added and the suspension was heated at 90 °C for a further 16 hours. The reaction mixture was then cooled to room temperature and filtered through a short pad of silica gel (eluent: diethyl ether). The solvent was then evaporated under reduced pressure, giving the corresponding thioamide (99%) as a yellow solid; (GC) 98%; ν_{\max} (film)/cm⁻¹ 1518 (C=S); δ_{H} (400 MHz; CDCl₃, Me₄Si) 7.40–7.26 (5 H, m, Ph), 3.59 (3 H, m, NCH₃), 3.15 (3 H, s, NCH₃); δ_{C} (100 MHz; CDCl₃, Me₄Si) 201.4 (C=S), 143.4 (Ph), 128.5 (Ph), 128.3 (Ph), 125.7 (Ph), 44.1 (CH₃), 43.2 (CH₃); *m/z* (EI) 165.0618 (M⁺ – C₉H₁₁NS requires 165.0612).
- Although the new polymer-supported reagent itself has only a low odour, one should be aware that the low molecular weight thioamides did themselves have a strong odour.
- Example nitrile formation (conventional heating): Thiophosphorylated amine resin (490 mg, 0.88 mmol) was added in one portion to a solution of 4-methoxybenzamide (30 mg, 0.20 mmol) in toluene (3.0 ml). The resulting suspension was heated without agitation to 90 °C for 14 hours. Further reagent (278 mg, 0.50 mmol) was then added and the suspension was heated at 90 °C for a further 16 hours. The reaction mixture was then cooled to room temperature and filtered through a short pad of silica gel (eluent: diethyl ether). The solvent was then evaporated under reduced pressure, giving the corresponding nitrile (99%) as a colourless solid; (GC) 98%; ν_{\max} (film)/cm⁻¹ 1518 (C=S); δ_{H} (400 MHz; CDCl₃, Me₄Si) 7.58 (2 H, d, *J* 9.0, Ph), 6.95 (2 H, d, *J* 9.0, Ph), 3.88 (3 H, s, OCH₃); δ_{C} (100 MHz; CDCl₃, Me₄Si) 162.9 (Ph), 134.0 (Ph), 119.2 (CN), 114.7 (Ph), 104.0 (Ph), 55.5 (CH₃).
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- 29 The experiments were performed using Coherent Synthesis™ technology on a Smith Workstation (Personal Chemistry AB, Sweden).
- 30 Example thioamide formation (microwave heating): Thiophosphorylated amine resin (335 mg, 0.60 mmol) was added in one portion to a solution of ϵ -caprolactam (20 mg, 0.12 mmol) in a mixture of toluene (2.5 ml) and 1-ethyl-3-methyl-1*H*-imidazolium hexafluorophosphate (120 mg) (or toluene (2.5 ml) and acetonitrile (0.5 ml)). The resulting suspension was heated with stirring to 200 °C for 15 min using microwave irradiation. The reaction mixture was then cooled to room temperature and filtered through a short pad of silica gel (eluent: diethyl ether). The solvent was then evaporated under reduced pressure, giving the corresponding thioamide (>99%) as a colourless solid; (GC) 97%; $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 1520 (C=S); $\delta_{\text{H}}(400 \text{ MHz}; \text{CDCl}_3, \text{Me}_4\text{Si})$ 9.20–8.77 (1 H, br s, NH), 3.36 (2 H, dd, J 10.1, 5.9, CH_2N), 2.97 (2 H, m, CH_2), 1.80–1.61 (6 H, m, CH_2); $\delta_{\text{C}}(100 \text{ MHz}; \text{CDCl}_3, \text{Me}_4\text{Si})$ 210.3 (C=S), 47.0 (CH_2), 44.8 (CH_2), 30.2 (CH_2), 28.0 (CH_2), 24.4 (CH_2); m/z (EI) 129.0613 ($\text{M}^+ - \text{C}_6\text{H}_{11}\text{NS}$ requires 129.0612).
- 31 The polymer beads were examined at 40 times magnification.
- 32 Example nitrile formation (microwave heating): Thiophosphorylated amine resin (158 mg, 0.29 mmol) was added in one portion to a solution of adamantane-1-carboxamide (17.1 mg, 0.095 mmol) in a mixture of toluene (2.5 ml) and 1-ethyl-3-methyl-1*H*-imidazolium hexafluorophosphate (120 mg) (or toluene (2.5 ml) and acetonitrile (0.5 ml)). The resulting suspension was heated with stirring to 200 °C for 15 min using microwave irradiation. The reaction mixture was then cooled to room temperature and filtered through a short pad of silica gel (eluent: diethyl ether). The solvent was then evaporated under reduced pressure, giving the corresponding nitrile (>99%) as a colourless solid; (GC) >99%; $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 2253 (CN); $\delta_{\text{H}}(400 \text{ MHz}; \text{CDCl}_3, \text{Me}_4\text{Si})$ 2.04 (9 H, br s, CH, CH_2), 1.74 (3 H, d, J 14.0, CHH), 1.73 (3 H, d, J 14.0, CHH); $\delta_{\text{C}}(150 \text{ MHz}; \text{CDCl}_3, \text{Me}_4\text{Si})$ 125.2 (CN), 39.9 (CH_2), 35.7 (CH_2), 30.2 (C), 27.1 (CH); m/z (EI) 161.1195 ($\text{M}^+ - \text{C}_{11}\text{H}_{15}\text{N}$ requires 161.1205).