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A Polymer-Supported [1,3,2]Oxazaphospholidine for the Conversion of Isothiocyanates to Isocyanides and Their Subsequent Use in an Ugi Reaction

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Abstract—The design and synthesis of a new polymer supported reagent for the clean conversion of isothiocyanates to isocyanides under microwave conditions was accomplished. The structurally diverse isocyanides generated were used in an Ugi 3CC, allowing the rapid generation of 2-isoindolinone-7-carboxamide analogues.

The generation of compound collections for evaluation as enzyme or receptor ligands is an important component of the modern drug industry. This revolution in high-throughput synthesis enables the delivery of functionally diverse compounds in a rapid and efficient fashion. The methods, however, rely on the availability of large monomer sets as primary building blocks. Also, multicomponent reactions (MCRs), that enable the simultaneous combination of certain of these reactive monomers, are proving to be particularly useful in the generation of combinatorial arrays.[1] Nevertheless, these routes are often constrained by the commercial availability of the starting materials and consequently this creates a demand for new structures and alternative synthesis methods. For this reason solid-supported reagents (SSRs) offer an attractive alternative to conventional solution-phase procedures for molecular assembly.[2] The successful application of SSRs to the synthesis of complex libraries,[3] natural products,[4–6] and drug molecules[7] has established some of the advantages of these methods for parallel synthesis.

Since isocyanides represent an important class of monomers, due to their unique reactivity in MCRs these have become ideal targets for synthesis.[8] However, despite this, general solution-phase methods for their preparation are not always satisfactory and often result in the use of toxic reagents and can often generate malodorous products.[9–11] Not surprisingly these valuable compounds are under represented in the directories of available chemicals. We have therefore chosen to develop a supported reagent to generate isocyanides 'on-demand' from readily available isothiocyanates. The results of this study, along with some applications of the use of the products in an Ugi 3CC reaction are reported below.

Mukaiyama demonstrated that 3-methyl-2-phenyl-[1,3,2] oxazaphospholidine **1** mediates the efficient conversion of isothiocyanates to their corresponding isocyanides (Scheme 1).[12]

Despite the mild reaction conditions employed in this conversion, the approach was not generally accepted due to the toxicity and instability of the phosphorus derived reagent. Moreover, the necessity to isolate the products from a complex crude mixture, using vacuum distillation, was frequently complicated by the volatility and extreme malodor of many isocyanides. We decided therefore to covalently attach the active [1,3,2]oxazaphospholidine to a polymer support matrix and thereby circumvent some of the drawbacks of the solution phase method.

Reaction of commercial Merrifield resin **2**, suspended in *N*,*N*-dimethylformamide at 80 °C, with 2-aminoethanol **3** in the presence of excess potassium carbonate yielded 2-(polystyrylmethylamino) ethanol **4** (Scheme 2). While this compound has been described previously in the literature,[13] the new route, using an excess of potassium carbonate, gives a significant reaction rate enhancement.

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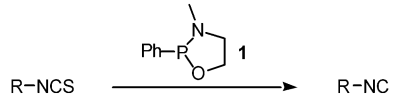
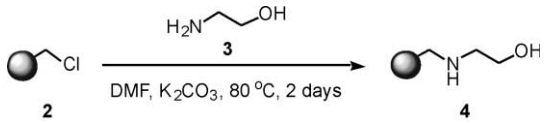


Scheme 1.



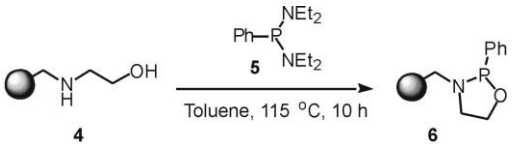
Scheme 2.

Although polymers containing 1.1, 4.4, and 5.9 mmol g^{-1} (chlorine) were subjected to this amination procedure, the results indicated that an optimal product loading was achieved with a 1.1 mmol g^{-1} (chlorine) starting material. In addition, the lower loading Merrifield resin reduced the potential for polymer-backbone crosslinking, providing an opportunity for enhanced functional activity in the target polymer.

The condensation of **4** with bis(diethylamino)phenyl phosphine[14] **5** was achieved by the controlled addition of the phosphine to an anhydrous suspension of **4** in toluene at 115 °C, producing 3-polystyrylmethyl-2-phenyl[1,3,2] oxazaphospholidine **6** (Scheme 3).

The polymer product was isolated, washed under anhydrous and anaerobic conditions and then dried in vacuo, prior to a new solid phase purification strategy. The crude resin product, suspended in toluene, was stirred with excess macroporous tosic acid resin (MP-TsOH, Argonaut Technologies), isolated within IRORI Kans. This efficiently scavenged residual diethylamine trapped within the polymer matrix of **6**, whilst the utilization of IRORI Kans enabled the facile separation of product and scavenger polymer beads. Subsequent Soxhlet extraction yielded **6** in high purity. Elemental analysis indicated **6** to contain 0.78 mmol g^{-1} (phosphorus). Gel-phase ^{31}P NMR confirmed the presence of a phosphorus (III) atom (δ 144 ppm), whilst magic angle spinning ^{1}H, ^{13}C, and COSY NMR were used to confirm the presence of the [1,3,2]oxazaphospholidine methylene protons. In contrast to the solution phase reagent **1**, the supported variant **6** was found to be stable for over 1 month, when stored under an inert atmosphere at −60 °C. Moreover, the solid reagent was not malodorous and was easily handled in air under ambient conditions.

The new solid supported reagent **6** was initially applied to the conversion of isothiocyanates to isocyanides under conventional thermal conditions. Whilst isocyanides were successfully produced, the products were susceptible to a competing rearrangement process, generating the corresponding nitriles after prolonged heating.[15]

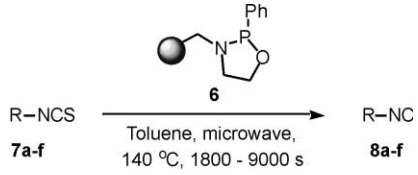


Scheme 3.

Microwave irradiation of chemical reactions is known to greatly enhance the rate of many thermal reaction processes.[16] It was proposed that this rate enhancement may increase the production of the desired isocyanide at the expense of the competing thermal rearrangement pathway.

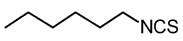
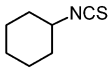
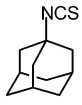
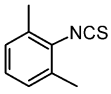
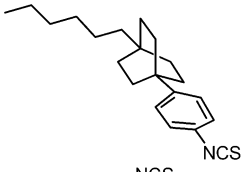
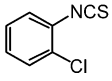
Optimization of the microwave protocol indicated that the most effective conditions for isocyanide formation were produced by the irradiation of a mixture containing the isothiocyanate substrate **7a–f** and **6** (1.5–3.0 equiv) suspended in toluene (Scheme 4).

The successful reduction of the parent isothiocyanates **7a–f** (Table 1) enabled the preparation of primary, secondary and tertiary alkyl isocyanides, and three less stable aromatic analogues, **8a–f**, exhibiting diverse stereo and electronic environments. The isocyanides were produced in excellent yields and high purity, although



Scheme 4.

Table 1. Isothiocyanate substrates **7a–f**

Ref	Substrate isothiocyanate	Microwave[a]	Equiv[b]	Yield (purity)[c]
a		140, 1800	2.0	85 (100)
b		140, 2700	2.0	87 (100)
c		140, 9000	3.0	96 (100)
d		140, 1800	1.5	84 (94)
e		140, 1800	2.0	96 (98)
f		140, 1800	2.0	54 (78)[d]

[a]Microwave conditions described as temperature/(°C), time/(s).
[b]Resin equivalents, based on an active loading of 0.4 mmol g^{-1}.
[c]Yield based on isolated mass. Purity determined by GC and ^{1}H NMR.
[d]2-Chlorophenyl isocyanide **7f** was found to be extremely unstable.

2-chlorophenyl isocyanide **8f** decomposed rapidly, due to its intrinsic instability.

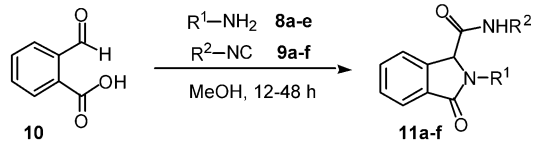
This procedure offers several key advantages. The reactions are simple to perform and are therefore suitable for high-throughput and parallel synthesis programs. If necessary, product purification can be achieved by simple filtration through a frit of silica, yielding the isocyanide monomers for direct utilization. Moreover, user exposure is minimized as the volatile and malodorous isocyanides are produced in sealed microwave vessels, simplifying the handling of these noxious materials. Subsequent in situ manipulation of the isocyanide products was also investigated.

To demonstrate the application of **6** in the production of monomers for library synthesis, the isocyanides **8a–e**, derived from the supported reagent protocol, were combined with a collection of amines **9a–f** (Table 2) in an Ugi 3CC procedure based on a 2-carboxybenzaldehyde **10** scaffold (Scheme 5).[17]

These reactions were performed in a parallel fashion using generic conditions (see experimental section), leading to the one-pot formation of the decorated 2-isoindolinone-7-carboxamide core structures **11a–r** (Table 3). The reactions were high yielding, and the target molecules were isolated in excellent purity following reverse-phase autopreparative chromatography.

The compound collection produced serves to highlight the power of supported reagent and MCR technologies in the rapid generation of small-molecule libraries. The incorporation of non-commercial isocyanides in the combinatorial array synthesis produced several compounds possessing novel structures, illustrating the concept of monomer set expansion and its application to the enrichment of established library syntheses. In a further development of this methodology, it was shown that the crude product from the polymer assisted isocyanide syntheses could be directly incorporated into the Ugi process. Therefore, isocyanides **8a** and **8b**, used to synthesize products **11a** and **11e**, were isolated by filtration alone. Despite the omission of both the silica frit and the solvent evaporation steps from the protocol, products **11a** and **11e** were produced in yields and purity comparable to those previously obtained.

The novel polymer supported reagent **6** was successfully synthesized and shown to effect the conversion of six diverse isothiocyanates to their corresponding isocyanides. The reaction proceeded in excellent yields, generating products of high purity. The procedure was simple to perform, efficient and the products required minimal purification. Operator exposure to the volatile and malodorous isocyanides was minimized and the toxic phosphorus components remained isolated on the reagent support matrix further limiting toxicity and malodor. The isocyanides generated using **6** were introduced into an MCR process, constructing a library of drug-like molecules based upon the 2-isoindolinone-7-carboxamide core template **11**. This highlighted the potential value of SSR technology in the enrichment of monomer sets for combinatorial compound synthesis. Given the scope and versatility of isocyanide MCR reactions, the parallel synthesis of isocyanides using SSR **6** provides an effective approach to these valuable monomers.



Scheme 5.

Experimental

Reagents and solvents were purified and rigorously dried by standard techniques. Microwave irradiation was performed using a Personal Chemistry 'Smith

Table 2. Isocyanide and amine monomers employed in the Ugi 3CC

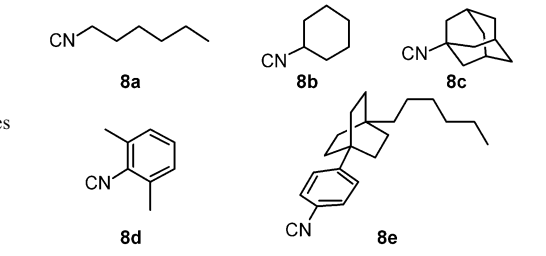
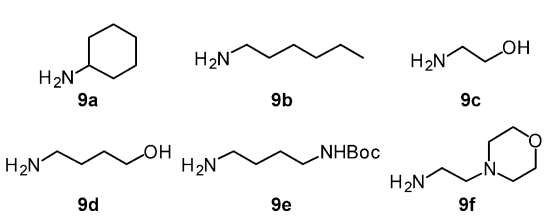
Monomer structures	
Isocyanides (R^2-NC)	
Amines (R^1-NH_2)	

Table 3. Array of 2-isoindolinone-7-carboxamides

Entry	Isocyanide[a]	Amine[a]	Product reference	Yield
1	**8a**	**9a**	**11a**	84
2	**8a**	**9b**	**11b**	92
3	**8a**	**9c**	**11c**	89
4	**8a**	**9d**	**11d**	95
5	**8b**	**9a**	**11e**	93
6	**8b**	**9b**	**11f**	88
7	**8b**	**9c**	**11g**	97
8	**8b**	**9d**	**11h**	98
9	**8b**	**9e**	**11i**	91
10	**8c**	**9a**	**11j**	86
11	**8c**	**9b**	**11k**	83
12	**8c**	**9c**	**11l**	91
13	**8c**	**9f**	**11m**	82
14	**8d**	**9b**	**11n**	74
15	**8e**	**9a**	**11o**	78
16	**8e**	**9b**	**11p**	86
17	**8e**	**9c**	**11q**	78
18	**8e**	**9f**	**11r**	72

[a]Refer to Table 2 for monomer structures.

Synthesizer' multimode machine [the heating protocol is defined as: temperature/(°C), time/(s)]. Microwave reactions were performed in sealed tubes supplied by Personal Chemistry, Uppsala, Sweden.

3-Polystyrylmethyl-2-phenyl[1,3,2]oxazaphos-pholidine 6. Compound **5** (3.0 g, 12.0 mmol) was added via syringe pump (6.2 h, 0.5 cm^3 h^{-1}) to a rigorously dried suspension of **4** (4.0 g, ca. 4.0 mmol) in toluene (25 cm^3) at 115 °C. After stirring for a further 4 h, the mixture was cooled to room temperature and the supernatant solvent was drawn off through a dry fritted glass tube under a positive pressure of argon gas. Using the same equipment, the residual solid was consecutively washed with toluene, dichloromethane, diethyl ether, dichloromethane, diethyl ether and dichloromethane (4×25 cm^3 each) then dried in vacuo. The resulting polymer was suspended in toluene (50 cm^3) and stirred with IRORI Kans containing a macroporous tosic acid resin (2.0 g, 1.40 mmol g^{-1}, MP-TsOH Argonaut Technologies) for 7.5 h. The resin was collected by filtration, under an inert atmosphere, and then further purified by Soxhlet extraction using dichloromethane [continuously distilled from molecular sieves (10.0 g) and MP-TsOH (2.0 g, 1.40 mmol g^{-1}, Argonaut Technologies)] for 2 days. The isolated polymer was dried under a stream of argon and then in vacuo (1×10^{-3} mm Hg) to give **6** as a pale yellow resin (3.4 g). δ_H (400 MHz, MAS-NMR, $CDCl_3$) 7.91 (ArH), 7.73 (ArH), 7.65 (ArH), [3.12, 3.04, 3.00, 2.65 (4H, NCH_2CH_2)]; δ_C (100 MHz, MAS-NMR, $CDCl_3$) 145 (ArC), 65 (OCH_2), 16 (NCH_2); δ_P (243 MHz, gel-phase NMR, $CDCl_3$) 144; elemental analysis: P (0.78 mmol g^{-1}).

Isocyanide synthesis, 8a–f. The appropriate isothiocyanate **7a–f** (30–90 μmol) was added to a suspension of **6** (300–600 mg) in toluene (2–3 cm^3) and the reaction mixture exposed to microwave radiation for 1800–9000 s at 140 °C. The mixture was then filtered and the residue washed with toluene (3×10 cm^3). The combined organic phases were concentrated in vacuo. The resulting residue was dissolved in 5% diethyl ether in light petroleum and purified by filtration through a silica frit. Solvents were removed under reduced pressure to yield the target isocyanides **8a–f** as colorless solids or oils (84–96%).

2-Isoindolinone-7-carboxamide synthesis, 11a–r. A solution of **10** (50 mg, 0.31 mmol) and the amine component (Table 2, 0.31 mmol) in methanol (1.0 cm^3), was added to a solution of the isocyanide component (Table 2, 0.31 mmol) in a minimum volume of methanol (ca. 0.5 cm^3) and the resulting mixture was stirred until complete consumption of the isocyanide was observed by TLC (usually 12–48 h). If a white precipitate formed, a minimum volume of dimethylsulfoxide (<0.5 cm^3) was added until the solid redissolved. The reaction mixture was subsequently diluted with acetonitrile (1.0 cm^3) and directly purified by reverse-phase autopreparative HPLC, yielding the target molecules **11a–r** as white solids or colorless oils.

Acknowledgements

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