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Diisocyanates as Scaffolds for Combinatorial Libraries. The Solid-Phase Synthesis of Bis-ureas from Polymer-Supported Diisocyanates§

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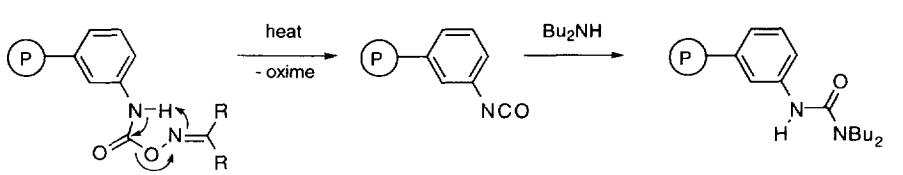
Abstract. A general method for preparation of bis-ureas has been developed from oxime resin-derived carbamates of diisocyanates. Directional urea synthesis is achieved by sequential amine addition which demonstrates the utility of thermolabile oxime-derived carbamate linkages to a polymer support. The products, obtained in good yield in three steps, are of high chemical purity.

Methods in combinatorial chemistry have demonstrated the parallel syntheses of large numbers of compounds or combinatorial libraries.[1,2] The *molecular diversity* of these libraries is enhanced by incorporating a variety of chemistries and diverse building blocks, which accentuates the differences in presentation of functionality on a particular set of molecular scaffolds. Moreover, the facile manipulation of reactive functionality leading to efficient chemical transformations is essential in the development of methods for combinatorial syntheses. Recently much effort has been directed towards the development of synthetic approaches to non-oligomeric, small molecule libraries as a tool for new drug discovery and development.[3] Mostly, the solid-phase syntheses of these libraries either rely on acid hydrolysis[4] or photo-labile functionality[5] for the release of the compound from the polymer support. We now wish to report the use of a thermolytically cleavable oxime-derived carbamate[6] polymer linkage and its application to the preparation of bis-urea libraries[7] from diisocyanates.

The isocyanate functional group is sufficiently reactive to be considered an ideal reacting functionality for combinatorial synthesis. Because isocyanates and diisocyanates easily are derived from the phosgenation of primary amines and diamines respectively, many structurally diverse inputs are commercially available, or can easily be prepared. Diisocyanates have been utilized as monomers in high performance polyurethanes and impart desirable hard-segment properties in mixed elastomers such as Lycra®. Initially we thought that if differential termini functionalization can be achieved, these would be ideal scaffolds to incorporate two sites of diversity given their clean addition reactions with protic nucleophiles such as alcohols and amines to afford ureas and carbamates respectively. Oxime-derived carbamates of isocyanates serve as heat-cleavable blocking groups.[8,9] On heating, an electrocyclic reaction ensues to regenerate oxime in its tautomeric form and the isocyanate functionality (**Figure 1**).[10,11]

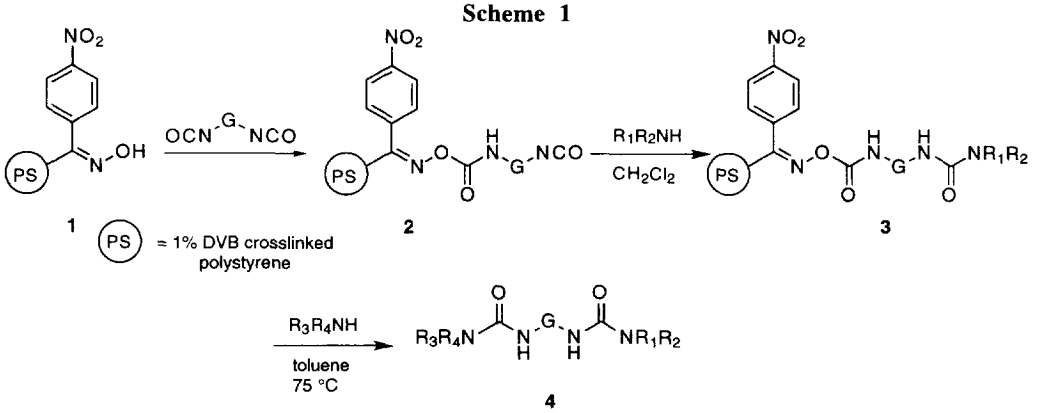
Figure 1



The free isocyanate is then available to react with nucleophiles such as amines to afford ureas. Ureas and in particular, oligoureas have been the focus of several research groups as a key hydrogen bonding functionality in molecular receptors,[12-17] templates for artificial β-sheets[18-22] and have recently been employed as an alternative to amide-linkages in peptidomimetics.[23-25]

With the notion that a polymer-bound oxime can be used to link isocyanates to a solid support, we turned our attention to p-Nitrophenyl(polystyrene)ketoxime resin **1** originally developed by DeGrado and Kaiser for solid-phase peptide synthesis.[26,27] By supporting diisocyanates on this resin, selective directional urea synthesis may be achieved. Crosslinking between oxime sites on the polymer could be minimized by using a large excess of diisocyanate and the presence of the terminal isocyanate is easily determined by IR spectroscopy where isocyanates have a strong absorbance near 2260 cm^{-1}. This is a good window in the IR spectrum for the observation of supported chemistry on polystyrene and can further be utilized in looking at the disappearance of the isocyanate peak after amine addition results in urea formation. In the presence of excess diisocyanate (*ca.* 10 eqs.), oxime resin **1** underwent clean mono-addition as verified by the isocyanate peak near 2260 cm^{-1} in the IR spectrum of functionalized resins **2** (**Scheme 1**).

Scheme 1



These diisocyanate-functionalized oxime resins appear to be stable when stored under nitrogen at ambient temperature. Nitrogen analysis of these functionalized resins indicated nearly quantitative incorporation of the diisocyanates at each oxime site on the polymer (**Table 1**).[28,29] Treatment with excess amines (primary or secondary) at room temperature in dichloromethane gave complete addition to the free terminal isocyanate without decomposition of the oxime-carbamate linkage, as verified by disappearance of the isocyanate peak and appearance of the urea-carbonyl peak in the IR spectrum of the polymer-bound ureas **3**. Heating these resins in toluene to 75°C in the presence of a second trapping amine cleanly gave bis-urea products **4** in good isolated yield and purity (**Table 2**).[30] For the sake of product purity, one equivalent of trapping amine (based on loading) or an excess of a volatile amine was used in the final addition. In some cases, precipitated bis-urea products within the resin were observed and resulted in lower isolated yields. Symmetrical bis-ureas derived from the trapping amine and diisocyanate were not observed which verifies that the diisocyanate addition did not result in crosslinking between oxime sites on the polymer. Inspection of the IR spectrum of the recovered oxime resin also verified complete cleavage of the diisocyanate scaffold from the polymer support.[31]

In summary we have demonstrated the use of the DeGrado-Kaiser oxime resin as a solid-phase support for diisocyanate scaffolds. These polymer-linked diisocyanates can be differentially functionalized to provide combinatorial libraries of bis-ureas. We are currently investigating the breadth of this chemistry.

Table 1

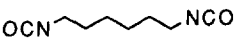
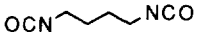
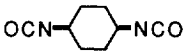
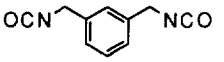
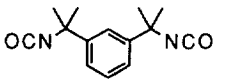
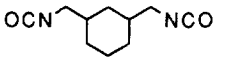
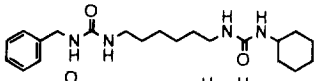
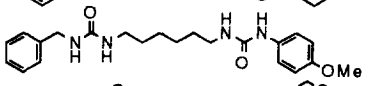
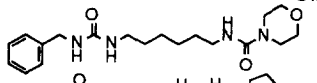
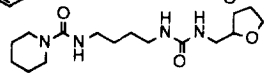
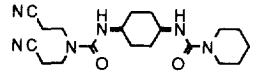
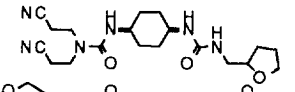
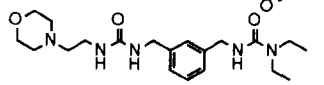
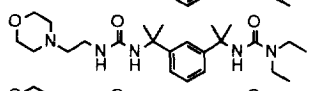
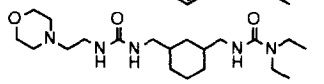
Diisocyanate	IR(cm^{-1}) -NCO	C=O	%N Calcd.	%N Obs.	% Conversion	Loading (mmol/g resin)
	2265	1749	3.68	3.63	97%	0.625
	2262	1751	3.82	3.60	86%	0.593
	2255	1750	3.75	3.64	92%	0.609
	2256	1747	3.63	3.52	92%	0.590
	2251	1758	3.51	3.36	88%	0.550
	2258	1750	3.62	3.43	86%	0.556

Table 2

Bis-urea Structure	Yield	HPLC purity	M+H Calcd.	APCI MS. Obs.	HRMS Obs.
	70	nd	375.2760	375.4	375.2766
	94	89%	399.2396	399.27	399.2114
	90	77%	363.2396	363.3	363.2377
	78	-	327.2396	327.24	327.2554
	80	-	375.2508	375.25	375.2537
	50	-	391.2451	391.26	391.2566
	70	92%	392.2622	392.2	392.2676
	67	94%	448.3288	448.3	448.3449
	56	-	398.3131	398.2	398.3300

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28. Nitrogen analysis, when correcting for the added carbon, hydrogen and oxygen weight of the diisocyanate scaffold, is an accurate measure of substrate loading on the polymer and indeed correlates quite well with the observed yields of products.
29. **Typical Procedure**: Oxime resin (prepared by method described in ref. 27) was swelled with dichloromethane and treated with excess diisocyanate in dichloromethane and shaken at room temperature overnight. The resin was then filtered and washed with copious amounts of dichloromethane and dried under high vacuum overnight. IR (KBr) of the resin showed peaks near 2260 cm^{-1} and 1750 cm^{-1} (**Table 1**) corresponding to the terminal isocyanate and the oxime-derived carbamate respectively. Nitrogen analysis (see footnote 28) verified high efficiency of loading. This resin was swelled again with dichloromethane and treated with excess amine in dichloromethane and shaken at room temperature overnight. The resulting resin was filtered, washed and dried as before and IR (KBr) showed complete loss of the isocyanate peak. This resin was swelled again with dichloromethane and treated with trapping amine (excess if volatile under high vacuum or 1 eq. if non-volatile) in toluene and the vial was sealed and heated to 75°C overnight. After allowing to cool, sampling of the resin and taking an IR can be done to see if the thermolytic release of the isocyanate is complete. In the examples illustrated in **Table 2**, reaction times between 24 and 48 hours were sufficient for complete reaction. Filtration followed by washing with copious amounts of dichloromethane then methanol at least three times and evaporation of the solvents under vacuum gave the bis-urea products which were analyzed directly without purification.
30. All new compounds displayed spectroscopic data consistent with their structural assignments. Low resolution mass spectra were obtained with a VG Trio-2000 quadrapole mass spectrometer using the electrospray atmospheric pressure chemical ionization (APCI) technique. High resolution mass spectra were obtained using a ZAB 2F magnetic sector high resolution mass spectrometer. HPLC analyses were performed on a Hewlett-Packard 1090 liquid chromatography system using a photodiode array detector and a Zorbax SB-C18 column, 2.1 x 150 mm, starting at 5% acetonitrile/water/0.1% HOAc -> 99.9% acetonitrile/0.1% HOAc.
31. Mechanistic studies of the thermolytic cleavage of polymer-supported oxime-derived carbamates are currently in progress and results will be reported in due course.

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