

Thiol on silica as a ‘catch and release’ support for isocyanates to afford ureas

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Abstract—Silica-bound thiocarbamates were prepared by Curtius rearrangement of carboxylic acids in the presence of thiol on silica gel. The solid supported thiocarbamates were found to be stable isocyanate equivalents, which upon treatment with amines efficiently afforded di- and tri-substituted ureas. The urea products released from the catch and release support were, in the majority of cases, greater than 95% pure and required no further work up.
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The urea functionality is common to many biologically active compounds.¹ The prevalence of this group in medicinal chemistry may be attributed to the metabolic stability of the N–C(O)–N linkage and to the large number of variations possible. Moreover, the urea scaffold is an attractive target for combinatorial and parallel synthesis approaches since up to four different substituents are possible on this low molecular weight core.

Among the reported routes to ureas, those based on solid phase chemistry that include a diversity-building resin cleavage reaction show great promise for the quick and efficient synthesis of diverse sets of ureas.² In these approaches, the polymer-bound carbamoyl or urea synthons are easily handled and can be purified from the excess reagents used to drive reactions to completion by using simple filtration and washing protocols. Whilst, a diversity-building cleavage reaction allows for yet further diversification of the urea synthon concomitant with releasing the product from the resin. However, the structural diversity of ureas that can be prepared by some of these methods is limited by the number of commercially available isocyanates.^{2a–c} Many of the other reported routes are not compatible with the synthesis of basic ureas since strong cationic exchange resins are used in the final workup to scavenge excess starting materials or reagents.^{2d–f} Herein, we wish to

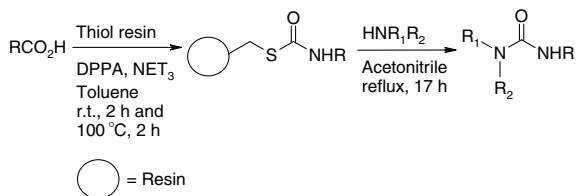
report an efficient route to ureas that is not reliant on commercially available isocyanates and one in which the products released from diversity-building cleavage reaction do not require further purification.

The Curtius rearrangement reaction is a well-known method for the synthesis of ureas that is not dependent on commercially available isocyanates. A carboxylic acid is converted into the corresponding acyl azide that undergoes a thermal rearrangement to the isocyanate in one pot. The isocyanate is then treated with an amine to afford the desired urea product. As there are over 40,000 commercially available carboxylic acids, an impressive list of diverse ureas is possible.³ Practically, however, the Curtius approach involves a purification step, typically chromatography, of either the intermediate isocyanate or the final urea product that detracts from the potential of preparing analogues quickly. Furthermore, the instability of isocyanates, especially alkyl substituted, makes the isolation of the intermediate isocyanates a difficult task. It was clear to us that the Curtius route would be much more practical if the intermediary isocyanates were captured as resin-bound isocyanate equivalents, that upon treatment with amines afforded ureas.^{4,5} We are pleased to report that thiol resin, an odourless solid-support, can be used as catch and release resin to trap isocyanate intermediates as thiocarbamates and then to release the urea products by treating the resin-bound thiocarbamates with amines (Scheme 1).^{6,7}

In our method development, 3-bromobenzoic acid was subjected to a Curtius rearrangement with diphenyl

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Scheme 1.

Table 1. Optimization of reaction conditions

○ = Resin

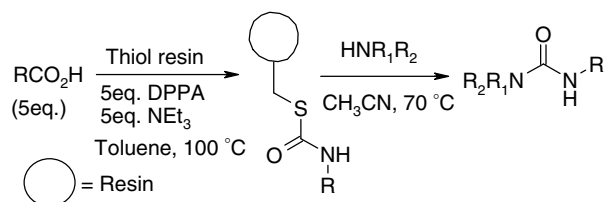
Entry	Additives (step 2)	Equivalent	Yield ^a (%)
1	None	—	44
2	AgOTf	2	11
3	NEt ₃	3	49
4	NEt ₃	3	90 ^b

^a Isolated yield.^b The mixture was stirred at room temperature for 2 h before heating at 100 °C in step 1.

phosphoryl azide (DPPA) in the presence of thiol support (1 equiv) (Table 1).^{8,9} The resulting solid bound thiocarbamate was treated with 3-chlorobenzyl amine (0.9 equiv) to give the corresponding urea in 44% yield. Attempts to boost the yield by using silver triflate as an activator in step 2 were unsuccessful and a considerable amount of the symmetrical urea (dibenzyl) by-product was detected. However, an excellent conversion to the desired urea was obtained by stirring the mixture of step 1 at room temperature prior to heating and by adding triethyl amine in step 2. Therefore, in our optimized conditions, the carboxylic acid (3–5 equiv) was treated with DPPA (3–5 equiv) and triethylamine (3–5 equiv) in toluene at room temperature for 2 h followed by the addition of thiol resin (1 equiv) and heating overnight at 100 °C. After washing and drying, the resin was treated with an amine (0.9 equiv) in the presence of triethylamine (1 equiv) in acetonitrile and stirred overnight. After simple evaporation, the urea products were isolated with >95% purity in most cases.

In order to explore the scope of carboxylic acids tolerated by this route, 5 different carboxylic acids were treated with 2 different amines: 3-chlorobenzyl amine, a representative primary amine and morpholine, a representative secondary amine (Table 2). Reactions worked well for both electron rich and most electron deficient benzoic acids with an average yield of 78% for 3-chlorobenzyl amine (e.g., 1, 3, 5 and 8) and 76% for morpholine (e.g., 2, 4, 6 and 9). Poorer yields were realized

Table 2. Variation of acids



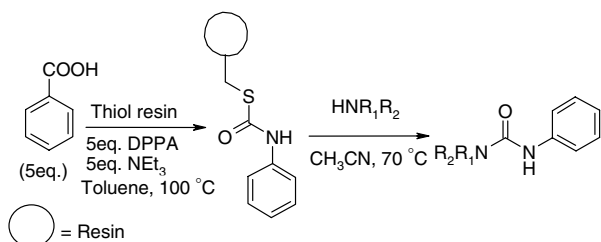
Entry	Amine (HNR ₁ R ₂)	Acid (RCO ₂ H)	Yield ^a (%)
1			77
2			65
3			99
4			79
5			80
6			87
7			45
8			55
9			74

^a Isolated yield after chromatography, purities >95% by ¹H NMR.

using benzoic acids substituted with strong electron withdrawing groups such as cyano (e.g., 7, 45% yield).

Next, we investigated the scope of amines tolerated in the diversity-building resin cleavage reaction (Table 3). Primary amines, including the hindered cyclohexyl amine, gave excellent yields of di-substituted ureas. In addition, secondary amines, both cyclic and acyclic, gave products in high yields and purities. Importantly, no purification was necessary following cleavage from the resins as the products were >95% pure. Anilines, on the other hand, under these conditions gave only low yields, probably because of the poorer nucleophilicity of these amines. The reactions with anilines were not aided by the use of a stronger base such as sodium hydride and in this case, the products were contaminated with the symmetrical ureas (bis anilino).

In summary, we have demonstrated that silica gel thiol resin can be used as a catch and release resin for the synthesis of ureas starting from carboxylic acids via the Curtius rearrangement reaction. Urea products were obtained with good yields and excellent purities from a

Table 3. Reactions with amines

Entry	Amine (HNR ₁ R ₂)	Yield ^a (%)	Purity ^b (%)
1		89	>95
2		92	>95
3		87	>95
4		98	>95
5		88	>95
6		73	>95
7		98	>95
8		85	>95
9		45	>95
10		52	65

^a Isolated yield.^b Determined by LC/MS and ¹H NMR after removal of solvent.

variety of acids and amines making this a general method for the synthesis of di- and tri-substituted ureas that is amenable to combinatorial chemistry. It is worthy to note that our thiocarbamate resin can be stored at room temperature in a closed container without any decomposition and as such is a stable-canned version of isocyanates.¹⁰

Currently we are in the process of evaluating the possibility of expanding the chemistry of our polymer-bound thiocarbamates. In particular we are interested in evaluating the stability of this group to other reaction types as

well as alkylation of the thiocarbamates to allow for the synthesis of tetra-substituted ureas.

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Supplementary data

General procedure and NMR and LC/MS data for all the compounds in the tables are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.05.050.

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- No loss in yield was observed in step 2 after storing the resin at room temperature for over 2 months.