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A Solid-Phase Synthesis of N,N′-Disubstituted Ureas and Perhydroimidazo[1,5-*a*]pyrazines via the Curtius Rearrangement

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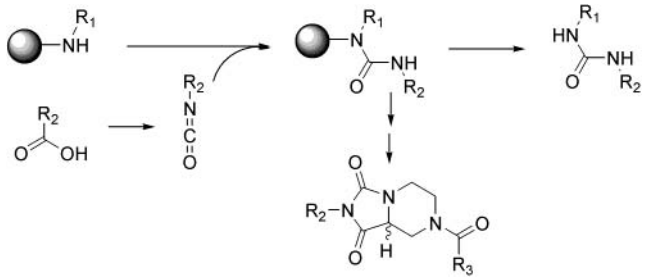
ABSTRACT



An efficient method for trapping isocyanates, generated from the Curtius rearrangement, with resin-bound amines is reported. A commercially available carboxylic acid is treated with diphenylphosphoryl azide, followed by thermal rearrangement, cooling, and trapping in one pot. Cleavage from the resin gives an N,N′-disubstituted urea in excellent purity, as demonstrated with several heterocyclic and aliphatic carboxylic acids. Further utility is shown by preparing several novel perhydroimidazo[1,5-*a*]pyrazines.

The Curtius Rearrangement has proven itself to be a versatile and important chemical tranformation. An important utilitarian feature of this reaction is that a diverse assortment of carboxylic acids can be converted into their corresponding acyl azides which can undergo thermal rearrangement to isocyanates in one pot. Useful carboxylic acids include aliphatic,[1] aromatic,[2] heterocyclic,[3] unsaturated,[4] and chiral acids.[5] Since the number of commercially available carboxylic acids greatly exceed the corresponding pool of isocyantes, the Curtius rearrangement has been used with great success to access noncommercially available isocyantes as they are required in a particular synthesis. However, obtaining many individual isocyantes for use in the synthesis of combinatorial libraries is often not a feasible option due to isocyanate instability and the time needed to prepare and purify such a large number of reagents.

A more reasonable approach would be to generate and trap isocyanates in situ in a parallel fashion. If this task could be accomplished using solid-phase methods and produce reasonable yields of pure products, then such a procedure could find general use in increasing combinatorial diversity when isocyanates are required in the synthesis of a particular library.

Recently, the generation of isocyantes by the Curtius rearrangement and their subsequent trapping with resin-bound alcohols has been demonstrated (Scheme 1).[6]

This procedure involves refluxing a mixture of Wang resin,

(1) Guan, H.-P.; Ksebati, M. B.; Cheng, Y.-C.; Drach, J. C.; Kern, E. R.; Zemlicka, J. *J. Org. Chem.* **2000**, *65*, 1280−1290.
(2) Hitotsuyanagi, Y.; Kobayashi, M.; Morita, H.; Itokawa, H.; Takeya, K. *Tetrahedron Lett.* **1999**, *40*, 9107−9110.
(3) Arranz, M. E.; Diaz, J. A.; Ingate, S. T.; Witvrouw, M.; Pannecouque, C.; Balzarini, J.; De Clercq, E.; Vega, S. *Bioorg. Med. Chem.* **1999**, *7*, 2811−2822.
(4) Pais, G. C. G.; Maier, M. E. *J. Org. Chem.* **1999**, *64*, 4551−4554.
(5) Wiberg, K. B.; Oesterle, C. *J. Org. Chem.* **1999**, *64*, 7763−7767.
(6) Sunami, S.; Sagara, T.; Ohkubo, M.; Morishima, H. *Tetrahedron Lett.* **1999**, *40*, 1721−1724.

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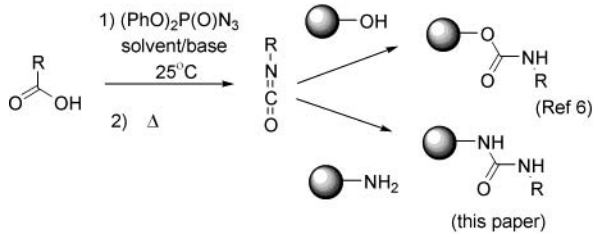
Scheme 1

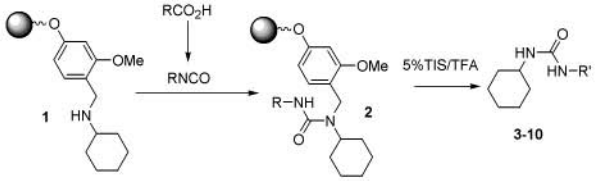


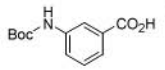
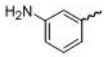
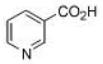
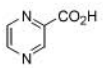
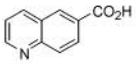
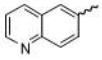
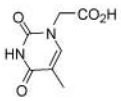
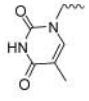
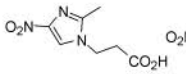
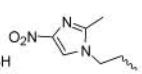
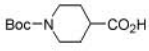
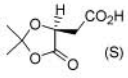
carboxylic acid, triethylamine, and diphenyl phosphoryl azide in toluene to give the resultant resin-bound carbamate, which can be cleaved from the solid support to give an amine in excellent purity. This general concept is appealing in that it allows one to access a large assortment of otherwise unavailable amines via the Curtius rearrangment beginning with commercially available carboxylic acids. However, we sought a more general procedure where the isocyanates could be generated and subsequently trapped using nucleophiles other than oxygen. In particular, using amine-bound resins as the trapping agent would be of substantial interest since the resulting resin-bound urea is an important intermediate in the synthesis of a variety of heterocyclic scaffolds such as hydantions,[7] quinazoline-2,4-diones,[8] and perhydroimidazo[1,5-a]pyrazines (vida infra). Therefore, we sought a method for the generation and reaction of isocyates with a resin-bound amine to give the corresponding urea in high purity. However, several important differences between a resin-bound hydroxy group and a resin-bound amino group render this a much more challenging task. Potential difficulties include the following: the diphenylphosphoryl azide (used to generate the acyl azide) could react with the resin-bound amine,[9] the intermediate acyl azide could react with the resin-bound amine,[10] and the intermediate isocyanate could be thermally unstable. Therefore, initial attempts using the reported conditions[6] were unsucessful, and large amounts of diphenoxyphosphinic acid were obtained after trapping and cleavage.[11] To prevent protecting our resin-bound amine as a diphenyl phosphoramide, we have found it necessary to pre-prepare the acyl azide using a slight excess of the carboxylic acid. It was also found that carrying the Curtius rearrangement to completion, followed by rapidly cooling the mixture to room temperature, was required prior to quenching the intermediate isocyanate with the resin-bound amine.

Several conditions were further explored to fine-tune our procedure, including varying the solvent, base, time and temperatures, and we have found that two distinct sets of conditions were successful for a variety of diverse carboxylic acids; condition A involves treating 1.0 equiv of the acid with 1.1 equiv of Et_3N in toluene at room temperature, followed by the addition of 0.9 equiv $(PhO)_2P(N_3)O$. After stirring for 30 min, the intermediate acyl azide was heated at 90 °C until either nitrogen extrusion ceased or the acyl azide disappeared as determined by TLC (EtOAc/hexanes). Condition B was identical to A, except *N*-methylpyrrolidinone and 2.2 equiv of collidine were substituted for the solvent and base, respectively. At 90 °C, typical reaction times are 20 min for condition A, and 50 min for condition B.

The procedure was carried out in parallel fashion on a variety of commercially available carboxylic acids (Table 1) to prepare the corresponding N,N′-disubstituted ureas. Cyclohexylamine derivatized ArgoGel MB-CHO resin was

Table 1. Ureas from Carboxylic Acids



Entry	RCO_2H	R'	Compound (Yield %, Purity %)[a]	Base/Solvent Conditions[b]
a			**3** (81, >95) **15** (75, >95)	A
b			**4** (50, >90)) **16** (70, >95)	A
c			**5** (52, >95) **17** (59, >95)	A
d			**6** (70, >95) **18** (76, >95)	B
e			**7** (61, >95) **19** (98, >95)	B
f			**8** (71, >95) **20** (79, >95)	B
g			**9** (50, >95) **21** (50, >95)	B
h			**10** (66, >95) **22** (90, >95)	A

a) Yields determined by mass of dry compound, purity determined by HPLC using ELSD detection of unpurified compounds. The main impurity present was diphenoxyphosphinic acid, with the largest amount (<9%) being present in compound 4.
b) A) Toluene, 1.1 equiv. Et_3N; B) NMP,2.2 equiv. collidine

(7) Park, K.-H.; Kurth, M. J. *Tetrahedron Lett.* **1999**, *40*, 5841−5844.
(8) Shao, H.; Colucci, M.; Tong, S.; Zhang, H.; Castelhano, A. L. *Tetrahedron Lett.* **1998**, *39*, 7235−7238.
(9) For references to this protecting group see: Greene T. W.; Wutz, P. G. M. Protective Groups in Organic Synthesis 3rd. Ed., John Wiley & Sons: New York, 1999; p 599.
(10) Rosowsky, A.; Forsch, R. A.; Galivan, J.; Susten, S. S.; Freisheim, J. H. *Mol. Pharmacol.* **1985**, *27*, 141−147.
(11) HPLC/MS and ^1H NMR matched known values.

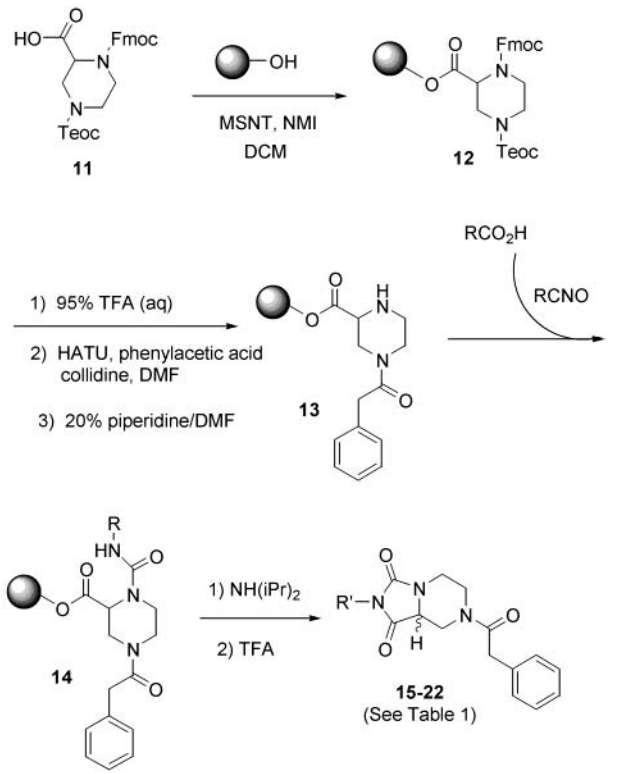
chosen as the model system.[12] We have found that aromatic heterocycles, such as pyridines (entry b), pyrazines (entry c), and quinoline (entry d) as well as aliphatic (primary and secondary) can be successfully trapped.

Certain protecting groups are also applicable in our sequence, such as the Boc group, used in both aromatic (entry a) and aliphatic systems (entry g), as well as the acetonide group (entry h). Thymine-1-acetic acid (entry e) also worked well, despite the presence of the acidic N-3 proton. All ureas were identified by proton NMR and HPLC/MS using ELSD[13] detection to determine purity.

To further demonstrate the utility of this method, we sought to apply our isocyanate trapping method to prepare some novel perhydro imidazo[1,5-*a*]pyrazines (Scheme 2). Our strategy began by coupling an orthogonally protected pyridazine (**11**)[14] to ArgoGel-OH resin, using MSNT, NMI in DCM.[15] The Teoc protecting group could then be removed with 95% TFA (aq) over 4 h.[16] After installation of the phenylacetyl group (HATU, DMF, collidine),[17] the Fmoc could be cleaved with 20% piperidine/DMF over 1 h to give the free amine **13** (Fmoc analysis at 310 nm indicated >85%). The resultant resin-bound amine **13** was then used to trap the isocyanates generated using the aforementioned Curtius rearrangement methodology to give the resin-bound urea **14**. Treatment of **14** with neat diisopropylamine affected a "cyclocleavage" reaction,[18] and, after removal of the Boc groups and acetonide (5%TIS/TFA 1 h), liberated the bicyclic heterocycles **15**−**22**.[19] The structure and purity of compounds **15**−**22** were ascertained by HPLC/MS (ELSD detection), and the structure of compound **18** was confirmed by proton NMR.[20] Further demonstrating the utility of our method, we have prepared larger libraries of >300 members with diverse functionality.

In conclusion, conditions for trapping isocyanates, generated via the Curtius rearrangement, with resin-bound amines in one-pot and in a parallel fashion have been developed and demonstrated to be a practical means for obtaining combinatorial diversity. A wide variety of commercially available carboxylic acids have been used to prepare ureas and novel perhydroimidazo[1,5-*a*]pyrazines.

Scheme 2



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Supporting Information Available: LC/MS data for all compounds are included, along with proton NMR spectra for compounds **3**−**10**, and a proton spectrum of **18** at both 25 °C and 95 °C (DMSO-d_6, 400 MHz).

OL006383N

(12) Swayze, E. E. *Tetrahedron Lett.* **1997**, *38*, 8465−8468.
(13) Fang, L.; Wan, M.; Pennacchio, M.; Pan, J. *J. Comb. Chem.* **2000**, *2 (3)*, 254−257.
(14) Purchased from R. I. Chemicals, Orange, CA
(15) Nielsen, J.; Lyngsoe, L. O. *Tetrahedron Lett.* **1996**, *37*, 8439−8442.
(16) Shute, R. E.; Rich, D. H. *Synthesis* **1987**, *4*, 346−349.
(17) Jefferson, E. A.; Swayze, E. E. *Tetrahedron Lett.* **1999**, *40*, 7757−7760.
(18) Kim, S. W.; Koh, J. S.; Lee, E. J.; Ro, S. *Mol. Diversity* **1999**, *3*, 129−132.
(19) Reversing this sequence and installing the isocyanate first was unsuccessful, since cyclocleavage occurs during the Teoc deprotection.
(20) ^{1}H NMR analysis at 25 °C, 50 °C, and 95 °C indicated a mixture (∼1:1) of rotomers.