Notes

Phosgenated *p*-Nitrophenyl(polystyrene)ketoxime or Phoxime Resin. A New Resin for the Solid-Phase Synthesis of Ureas via Thermolytic Cleavage of Oxime-Carbamates†

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Methods in combinatorial chemistry have been exploited in the parallel synthesis of a large number of compounds or combinatorial libraries. Recent efforts in this area have been directed toward the development of synthetic reactions leading to nonoligomeric, small molecule libraries as a tool for new drug and agrochemical discovery and development.[1,2] The facile manipulation of reactive functionality is a key factor in the development of efficient, high-yielding reactions for combinatorial syntheses. The enviable reactivity of isocyanates is most suitable for combinatorial synthesis and has been utilized to prepare molecules with biologically relevant functionalities such as ureas,[3−7] carbamates,[8,9] sulfonylureas,[10−12] and heterocycles such as hydantoins[13−16] and quinazoline-2,4-diones.[17−19] Oxime-derived carbamates serve as heat-labile blocking groups and have been employed as blocked isocyanate-terminated prepolymers in powder coatings.[20,21] Inspired by the advantages of solid-phase methods for the synthesis of combinatorial libraries, we have previously reported the use of *p*-nitrophenyl(polystyrene)ketoxime resin **1**[22,23] as a polymer support for the differentiation of diisocyanates in the preparation of nonsymmetrical bis-ureas utilizing this thermolytic cleavage (Scheme 1).[24,25] Key to this strategy is the thermolabile polymer-bound oxime carbamate **3** formed by reacting oxime resin **1** with diisocyanates. Alternatively, the oxime carbamate may be generated by the addition of a primary amine to the chloroformate **2**[26,27] of the oxime resin. Herein, we describe the preparation and utilization of phosgenated *p*-nitrophenyl(polystyrene)ketoxime or Phoxime resin **2**, whose corresponding carbamates serve as latent isocyanates.[28,29]

Phosgenation of *p*-nitrophenyl(polystyrene)ketoxime resin **1** (prepared by method described in ref 23) up to 100 g scale was performed using 3 molar equiv of phosgene or the commercially available phosgene equivalent triphosgene[30] in dichloromethane at room temperature overnight (Scheme 2).

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(1) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555−607.
(2) Lam, K. S.; Lebl, M.; Krchnak, V. *Chem. Rev.* **1997**, *97*, 411−448.
(3) (a) Burgess, K.; Linthicum, D. S.; Shin, H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 907−909. (b) Burgess, K.; Ibarzo, J.; Linthicum, D. S.; Russel, D. H.; Shin, H.; Shitangkoon, A.; Totani, R.; Zhang, A. J. *J. Am. Chem. Soc.* **1997**, *119*, 1556−1564.
(4) Nowick, J. S.; Holmes, D. L.; Noronha, G.; Smith, E. M.; Nguyen, T. M.; Huang, S.-L. *J. Org. Chem.* **1996**, *61*, 3929−3934.
(5) Meyers, H. V.; Dilley, G. J.; Durgin, T. L.; Powers, T. S.; Winssinger, N. A.; Zhu, H.; Pavia, M. R. *Mol. Diversity* **1995**, *1*, 13−20.
(6) Brown, P. J.; Hurley, K. P.; Stuart, L. W.; Willson, T. M. *Synthesis* **1997**, *16*, 778−782.
(7) Other isocyanate equivalents in urea synthesis. Use of *p*-nitrophenyl carbamates, see: (a) Hutchins, S. M.; Chapman, K. T. *Tetrahedron Lett.* **1994**, *35*, 4055−4058. (b) Kim, J.-M.; Wilson, T. E.; Norman, T. C.; Schultz, P. G. *Tetrahedron Lett.* **1996**, *37*, 5309−5312. (c) Choy, N.; Moon, K. Y.; Park, C.; Son, Y. C.; Jung, W. H.; Choi, H.; Lee, C. S.; Kim, C. R.; Kim, S. C.; Yoon, H. *Org. Prep. Proc.* **1996**, *28*, 173−177. (d) Kruijtzer, J. A. W.; Lefeber, D. J.; Liskamp, R. M. J. *Tetrahedron Lett.* **1997**, *38*, 5335−5338. Use of di-*tert*-butyl dicarbonate, see: (e) Knolker, H.-J.; Braxmeier, T.; Schlechtingen, G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2497−2500. (f) Knolker, H.-J.; Braxmeier, T.; Schlechtingen, G. *Synlett* **1996**, 502−504. (g) Lamothe, M.; Perez, M.; Colovray-Gotteland, V.; Halazy, S. *Synlett* **1996**, 507−508. Use of *S*,*S*-dimethyl dithiocarbonate, see: (h) Leung, M.-k.; Lai, J.-L.; Lau, K.-H.; Yu, H.-h.; Hsiao, H.-J. *J. Org. Chem.* **1996**, *61*, 4175−4179.
(8) Pirrung, M. C.; Chen, J. *J. Am. Chem. Soc.* **1995**, *117*, 1240−1245.
(9) Duggan, M. E.; Imagire, J. S. *Synthesis* **1989**, 131−132.
(10) Cervello, J.; Sastre, T. *Synthesis* **1990**, 221−222.
(11) Irie, H.; Nishimura, M.; Yoshida, M.; Ibuka, T. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1209−1210.
(12) Bell, S.; Bonadio, A.; Watson, K. G. *Aust. J. Chem.* **1995**, *48*, 227.
(13) Hobbs DeWitt, S.; Kiely, J. S.; Stankovic, C. J.; Schroeder, M. C.; Reynolds Cody, D. M.; Pavia, M. R. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 6909−6913.
(14) For use of commercially available *p*-nitrophenyl carbonate resin from Novabiochem (Catal. No. 01-64-0131) as the phosgene equivalent in hydantoin library synthesis, see: Dressman, B. A.; Spangle, L. A.; Kaldor, S. W. *Tetrahedron Lett.* **1996**, *37*, 937−940. Two similar active carbonate resins have been recently been reported; see: Alsina, J.; Chiva, C.; Ortiz, M.; Rabanal, F.; Giralt, E.; Albericio, F. *Tetrahedron Lett.* **1997**, *38*, 883−886 and Cuny, G. D.; Cao, J.; Hauske, J. R.*Tetrahedron Lett.* **1997**, *38*, 5237−5240.
(15) Hanessian, S.; Yang, R.-Y. *Tetrahedron Lett.* **1996**, *37*, 5835−5838.
(16) Kim, S. W.; Ahn, S. Y.; Koh, J. S.; Lee, J. H.; Ro, S.; Cho, H. Y. *Tetrahedron Lett.* **1997**, *38*, 4603−4606.
(17) Buckmann, B.; Mohan, R. *Tetrahedron Lett.* **1996**, *37*, 4439−4442.
(18) Gouilleux, L.; Fehrentz, J.-A.; Winternitz, F.; Martinez, J. *Tetrahedron Lett.* **1996**, *37*, 7031.
(19) Smith, A. L.; Thompson, C. G.; Leeson, P. D. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1483−1486.
(20) Wicks, Z. W. *Prog. Org. Coat.* **1975**, *3*, 73−99.
(21) Wicks, Z. W. *Prog. Org. Coat.* **1981**, *9*, 3−28.
(22) DeGrado, W. F.; Kaiser, E. T. *J. Org. Chem.* **1980**, *45*, 1295−1300.
(23) DeGrado, W. F.; Kaiser, E. T. *J. Org. Chem.* **1982**, *47*, 3258−3261.
(24) Scialdone, M. A. *Tetrahedron Lett.* **1996**, *37*, 8141−8144.
(25) For other recent reports of thermolytic cleavage off a polymer support, see refs 14, 18, 19, and: (a) Kolodziej, A. A.; Hamper, B. C. *Tetrahedron Lett.* **1996**, *37*, 5277−5280. (b) Tietze, L. F.; Steinmetz, A. *Synlett* **1996**, 667−668.
(26) Letsinger, R. L.; Kornet, M. J.; Mahadevan, V.; Jerina, D. M. *J. Am. Chem. Soc.* **1964**, *86*, 5163−5165.
(27) A TentaGel-derived chloroformate has been utilized as a carbamate linking group for solid-phase synthesis; see: Hauske, J. R.; Dorff, P. *Tetrahedron Lett.* **1995**, *36*, 1589−1592.
(28) Levine, A. W.; Frech, J. *J. Org. Chem.* **1972**, *37*, 1500−1503.
(29) Levine, A. W.; Frech, J. *J. Org. Chem.* **1972**, *37*, 2455−2460.
(30) Triphosgene is available from Aldrich (cat. no. 33, 075-2). Phosgene solutions in either toluene or dichloromethane are also suitable for this transformation.

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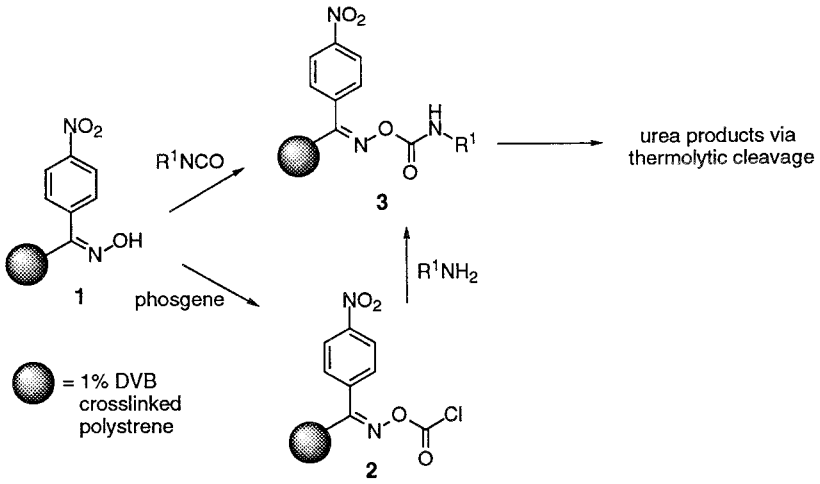
Scheme 1



Filtration and liberal washing with dichloromethane gave the phosgenated oxime resin **2**, which was verified by the presence of the chloroformate carbonyl peak at 1800 cm^{-1} in the IR spectrum. Chlorine analysis[31] of the thoroughly dried resin showed the phosgenation to be nearly quantitative. Unlike typical chloroformate reactivity behavior, little to no decomposition was observed on prolonged exposure to air.[32] Phosgenated resin **2** is essentially a stable phosgene equivalent that is easily handled and stored. Primary amine addition was carried out using 3 molar equiv of amine in dichloromethane, affording the polymer-bound carbamate **3**.[33] A shift of the carbonyl peaks after the first amine addition from 1800 to 1770−1750 cm^{-1} is consistent with carbamate formation.

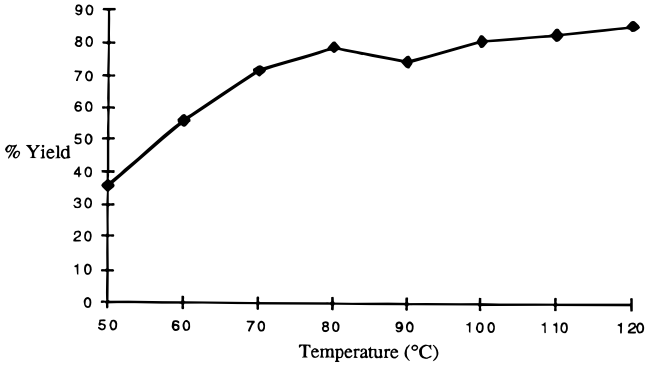


Figure 1. Isolated yield of cyclohexyl-4-biphenylurea (**4h**) as a function of cleavage temperature.

Temperature dependence for the thermolytic cleavage was carried out on a Nautilus 2400 automated synthesizer,[34] which is equipped with 24 reaction vessels and can independently control the individual reactor vessel temperature. The synthesis of cyclohexyl-4-biphenylurea (**4h**) from the thermolysis of the 4-biphenylamine-derived oxime carbamate in the presence of excess cyclohexylamine in toluene was carried out at variable temperatures from 50 to 120 °C for 8 h (Figure 1). Temperatures above 80 °C gave satisfactory yields for this particular case. However, the optimum cleavage temperatures may vary depending on the particular oxime-derived carbamate employed.

(31) Elemental analysis on thoroughly dried resin, when correcting for the added carbon, hydrogen, and oxygen, is an accurate measure of substrate loading on the polymer and indeed correlates quite well with the observed yields of products of this chemistry. Adventitious solvent or precipitates within the resin will introduce error in this analysis, and it may not be applicable to all solid-supported chemistry. The loadings were determined using elemental analysis (see the Experimental Section for derivation) of *p*-nitrophenyl(polystyrene) ketone resin **5**, *p*-nitrophenyl(polystyrene)ketoxime resin **1**, and phosgenated *p*-nitrophenyl(polystyrene)ketoxime resin **2**. For the acylation of the polystyrene to the resin **5**,[23] $N_0 = 0$ (nitrogen is not present before the reaction), $A_N = 14.01$ (the atomic weight of nitrogen), $\Delta n = 1$, $w_N = 1.13\%$ (from nitrogen analysis), the loading of the resin **5** (L) is

$$L = 0.0113/(14.01 \times 1) = 0.807 \times 10^{-3}\ \text{(mol/g resin)}$$

In the formation of the oxime resin **1**,[23] $N_0 = 0.807 \times 10^{-3} \times 1$ (the loading of the ketone resin **5** is 0.807×10^{-3} mol/g and one nitrogen atom per functional group), $A_N = 14.01$ (the atomic weight of nitrogen), $\Delta m = 15.02$ (NH = NOH − O, molecular weight change upon the reaction), and $\Delta n = 1$, $w_N = 2.15\%$ (from nitrogen analysis); therefore, the number of reacted sites from 1 g of the ketone resin **5** (S), the reaction conversion (C), and the loading of the resin **1** (L) are

$$S = \frac{0.0215 - (14.01 \times (0.807 \times 10^{-3}))}{(14.01 \times 1) - (0.0215 \times 15.02)} = 0.745 \times 10^{-3}\ \text{(mol)}$$

$$C = 0.745/0.807 = 92.3\%$$

$$L = \frac{0.0215 - (14.01 \times (0.807 \times 10^{-3}))}{14.01(1 - (0.745 \times 10^{-3})15.02)} = 0.737 \times 10^{-3}$$

(mol/g resin)

This value is in good agreement with the value, 0.766×10^{-3}, obtained by the established picric acid test method.[38] For the third reaction, chlorine analysis of phosgenated resin **2** was used instead of nitrogen analysis. In this case, $N_0 = 0$ (chlorine is not present before the reaction), $A_{Cl} = 35.45$ (the atomic weight of chlorine), $\Delta m = 62.46$ (COCl − H, molecular weight change upon the reaction), and $\Delta n = 1$, $w_{Cl} = 2.52\%$ (from chlorine analysis); therefore, the number of reacted sites from 1 g of the oxime resin **1** (S), the reaction conversion (C), and the loading of the resin **2** (L) are

$$S = \frac{0.0252 - (35.45 \times 0)}{(35.45 \times 1) - (0.0252 \times 62.46)} = 0.744 \times 10^{-3}\ \text{(mmol)}$$

$$C = 0.744/0.737 = 101\%$$

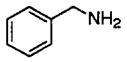
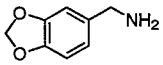
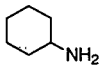
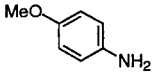
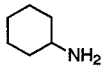
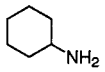
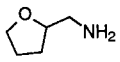
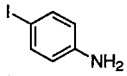
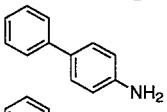
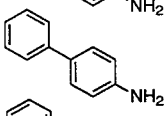
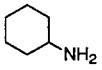
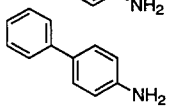
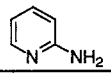
$$L = 0.0252/(35.45 \times 1) = 0.711 \times 10^{-3}\ \text{(mmol/g resin)}$$

(32) Storage of the phosgenated resin **2** and the carbamate resins **3** at room temperature exposed to air for greater than 1 month has little to no effect on their reactivities.

(33) Oxime-derived carbamates of secondary amines do not undergo urea formation upon thermolysis under the standard conditions. This observation is consistent with the accepted mechanism for thermolytic decomposition of the oxime-derived carbamates to give isocyanates (see refs 28 and 29). Mechanistic studies of the cleavage of polymer-supported oxime-derived carbamates indicate isocyanate formation upon thermolysis: Scialdone, M. A.; Hamuro, Y.; DeGrado, W. F. *J. Am. Chem. Soc.*, manuscript in preparation.

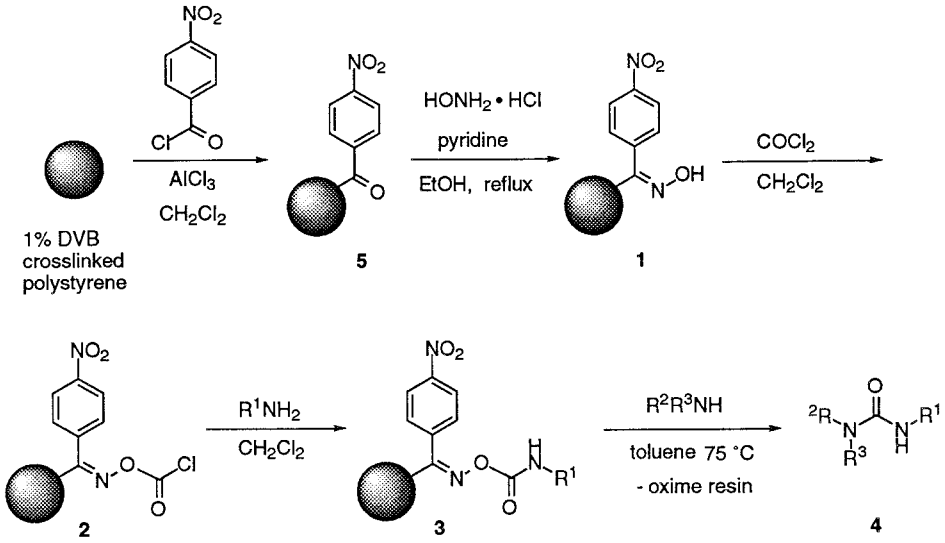
(34) Argonaut Technologies Inc., San Carlos CA.

Table 1. Synthesis of Ureas 4a–j by Phosgenated *p*-Nitrophenyl(polystyrene)ketoxime Resin 2

Compound	R_1NH_2	IR (cm^{-1})[a]	R_2R_3NH	Molecular Weight[b] Calcd.	Found	Yield[c]	Purity[d]
4a		1751	Et_2NH	206.3	207.2	98%	93%
4b		1751	Et_2NH	250.3	251.2	98%	76%
4c		1752		248.3	249.3	88%[e]	87%[e]
4d		1752		212.3	213.2	86%	>90%[f]
4e		1752		226.3	227.2	95%	>90%[f]
4f		1756		334.2	334.9	89%[e]	96%[e]
4g		1761		284.0	285.0	90%[e]	92%[e]
4h		1761		294.4	295.2	91%	98%
4i		1761		193.3	194.1	99%	97%
4j		1764		207.2	208.1	77%	92%

[a]Frequency of carbonyl stretch of carbamate resins **3**. [b]Mass spectra were obtained using the electrospray APCI technique (see Experimental Section). [c]Reported yields are on crude, unpurified products obtained directly from thermolytic cleavage based on 0.711 mmol/g resin loading. [d]Purity assessment by HPLC (see Experimental Section). [e]Yield and purity after solid phase extraction (see text). [f]NMR spectrum shows greater than 90% purity.

Scheme 2



Several oxime-carbamate resins **3** were heated in toluene to 80 °C in the presence a 4 molar equiv excess of varying trapping amines afforded the corresponding ureas **4a–j** (Table 1). The thermolysis reactions were monitored by inspecting the IR spectrum of the recovered resin after filtration, washing, and drying. Complete cleavage of the carbamates was verified by the disappearance of the carbamate carbonyl peak. Importantly, if the carbamate peak were still present, the recovered resin can be resubmitted to the above reaction conditions

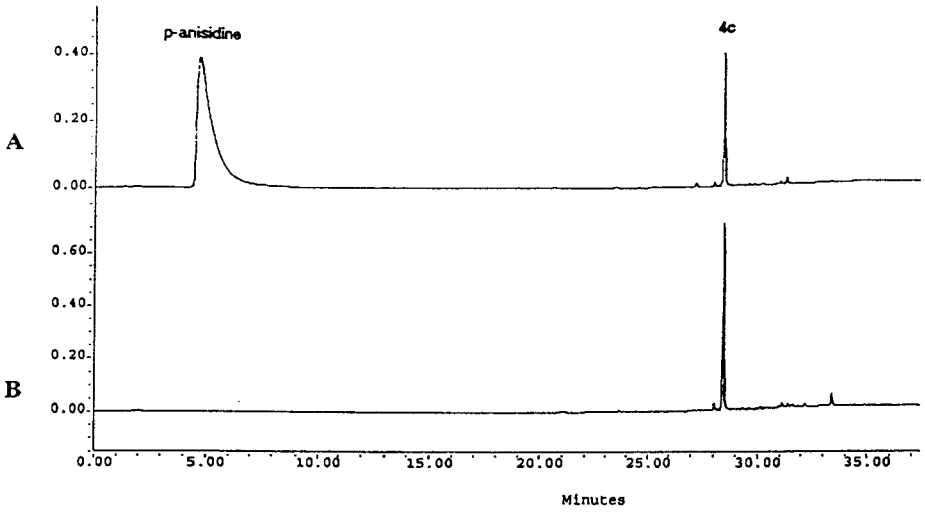


Figure 2. HPLC traces of the reaction of excess *p*-anisidine in thermolysis with cyclohexyl oxime carbamate resin (**4c** in Table 1) before solid-phase extraction with Dowex AG 50W-X8 resin (A) and after (B).

until the cleavage is complete. In most cases, particularly the aniline-derived oxime carbamates, the reaction was complete overnight.

Facile removal of excess trapping amine and solvent was accomplished by evaporation under vacuum in the case of volatile amines or by solid-phase extraction of the thermolysis filtrate with Dowex AG 50W-X8 acid resin followed by evaporation in the case of nonvolatile amines (see Figure 2 and compounds **4c,f,g** in Table 1).[35] Purity assessment by HPLC was good (average 91% ± 6%) owing to the high reactivity of the isocyanate functionality at elevated temperatures. The observed isolated yields (average 91% ± 6%) correlated quite well to the loading of phosgenated oxime resin **2**. Although carbamate resin **3** may be obtained through the addition of isocyanates to oxime resin **1**, many primary amines do not undergo clean phosgenation to afford stable, isolable isocyanates. The utility of Phoxime resin is highlighted by the demonstration to synthesize ureas of 2-isocyanatopyridine[36,37] (**4j**) using the general method depicted in Scheme 2. This general approach gives access to oxime carbamates of isocyanates that are not stable enough to isolate. Furthermore, the fidelity of the protocols for generating ureas should be useful in future syntheses of related combinatorial libraries.

In conclusion, we have demonstrated the use of phosgenated *p*-nitrophenyl(polystyrene) ketoxime **2** or Phoxime resin, as an air-stable polymer-bound phosgene-transfer reagent. Through the heat-labile, oxime-derived carbamate linkage, this new resin can serve as a vehicle for the delivery of isocyanates in solution at elevated temperatures where reaction with amines afford ureas in excellent yields and high chemical purities. Using this methodology, many isocyanates can be readily accessed, which can be useful for the generation of more structurally diverse products. The application of this resin for use in other isocyanate reactions and combinatorial library generation is currently under investigation.

(35) Siegel, M. G.; Hahn, P. J.; Dressman, B. A.; Fritz, J. E.; Grunwell, J. R.; Kaldor, S. W. *Tetrahedron Lett.* **1997**, *38*, 3357−3360.

(36) Access to 2-isocyanatopyridine via Curtius rearrangement of 2-picolinoyl azide, see: Otsuji, Y.; Koda, Y.; Kubo, M.; Fukukawa, M.; Imoto, E. *Nippon Kagaku Zasshi* **1959**, *80*, 1307−1309.

(37) For a review of six-membered heterocyclic isocyanates, see: L'abbe, G. *Synthesis* **1987**, *6*, 525−531.

(38) The picric acid test was carried out after oxime resin was coupled under standard conditions with Boc-Gly-OH followed by TFA deprotection of the Boc group. See: (a) Scarr, R. B.; Findeis, M. A. *Peptide Res.* **1990**, *3*, 238−241. (b) Stewart, J. M.; Young, J. D. *Solid-Phase Peptide Synthesis*, 2nd ed.; Pierce Chemical Co.: Rockford, IL, 1984.

Experimental Section

General Experimental Procedures. Biobeads SX-1 (1% cross-linked polystyrene) and Dowex AG 50W-X8 resin were purchased from Biorad. Scintillation vials (20 mL) were purchased from Kimble Glass Inc., Vineland, NJ. Microanalyses were carried out by Micro Analysis Inc. of Wilmington, DE. IR spectra of the functionalized resins were obtained with a Perkin-Elmer FT1600 infrared spectrometer using a KBr die. Low-resolution mass spectra were obtained with a VG Trio-2000 quadrople mass spectrometer using the electrospray atmospheric pressure chemical ionization (APCI) technique. High-resolution mass spectra were obtained with a Micromass VG-70SE. ^{1}H and ^{13}C NMR were carried out on Bruker DRX-300 and DRX-400 spectrometers.

HPLC analyses were performed on a Hewlett-Packard 1090 liquid chromatography system with a photodiode array detector, a Zorbax SB-C18 column (2.1 × 150 mm), 1.0 mL/min flow rate, a nonlinear gradient elution from 5% to 100% acetonitrile in 0.1% AcOH buffered water or a Waters 2010 liquid chromatography system with a photodiode array detector and a Vydac C18 column (2.1 × 150 mm), 1.0 mL/min flow rate, a nonlinear gradient elution from 0% to 100% acetonitrile in 0.01% TFA buffered water. HPLC purities in the text were determined by the area integration at 220 nm.

Preparation of *p*-Nitrophenyl(polystyrene)ketone (5). Ketone resin **5** was prepared by the procedure in ref 23 from Biobeads SX-1 (1% cross-linked polystyrene). The loading of the resin was calculated as 0.807 mmol/g by the method described in the text: IR 3024, 2917, 1942, 1871, 1803, 1662, 1600, 1525, 1491, 1449, 1347, 1309 cm^{-1}. Anal. Found: N, 1.13.

Preparation of *p*-Nitrophenyl(polystyrene)ketoxime (Oxime Resin, 1). Oxime resin **1** was prepared by the procedure in ref 23 from the resin **5**. The loading of the resin was calculated as 0.737 mmol/g by the method described in the text: IR 3508, 3024, 2919, 1942, 1871, 1802, 1600, 1522, 1491, 1450, 1344 cm^{-1}. Anal. Found: N, 2.15.

Preparation of Phosgenated *p*-Nitrophenyl(polystyrene)ketoxime (Phoxime, 2). A solution of triphosgene (Aldrich, 6.0 g, 20 mmol, 4 equiv) in CH_2Cl_2 (75 mL) was added to oxime resin **1** preswelled in CH_2Cl_2 (75 mL), and the mixture was shaken overnight at room temperature (this process was carried out in a drybox). The resin was collected on a glass filter, and remaining phosgene in the filtrate was quenched by a

solution of EtOH in CH_2Cl_2. The resin was further washed with CH_2Cl_2 (ca. 350 mL) and dried under vacuum overnight to afford the desired resin **2**. The loading of the resin was calculated as 0.711 mmol/g by the method described in the text: IR 3025, 2922, 1944, 1871, 1800, 1601, 1525, 1492, 1451, 1347 cm^{-1}. Anal. Found: Cl, 2.52.

General Procedure for the Preparation of Oxime-Derived Carbamate Resin (3). Phosgenated oxime resin **2** (3.0 mmol) was placed in a 60 mL bottle. A solution of a primary amine (9.24 mmol, 3.1 equiv) in dry CH_2Cl_2 (50 mL) was added to the resin, and the mixture was sealed and vortexed overnight at room temperature. The resin was collected on a glass filter, washed with CH_2Cl_2 and MeOH (500 mL total), and dried under high vacuum overnight to afford the titled resins **3**: IR (for biphenylamine carbamate) 3024, 2920, 1944, 1761, 1599, 1524, 1491, 1449, 1344 cm^{-1}.

General Procedure for Thermolytic Cleavage (4a−j). Oxime-derived carbamate resin **3** (0.5 mmol) was placed in a 20 mL vial and swelled with CH_2Cl_2 until saturated (6 mL). An amine (2.0 mmol, 4.0 equiv) was added, and the total volume was taken to 15 mL with toluene. The vial was then capped, sealed with tape, and heated on a vortex or heating block to 80 °C overnight. The mixture was then allowed to cool to room temperature, and the resin was removed by filtration and washed with CH_2Cl_2 (20 mL) and MeOH (3 × 10 mL). Inspection of the IR spectrum of the recovered resin can verify the completion of the cleavage. If the carbamate peak was still present, the recovered resin was resubmitted to the above reaction conditions until it was verified that the cleavage was complete. In the case of nonvolatile trapping amine, the combined filtrates were shaken with an excess of Dowex AG 50W-X8 resin for 1 h and then filtered.[35] Evaporation of the filtrates to dryness under high vacuum afforded the urea products **4a**−**j** which were characterized by mass spectroscopy directly without any further purification.

***N*,*N*-Diethyl-*N*′-benzylurea (4a):** HPLC purity at 220 nm, 93%; mass recovery, 98%; ^{1}H MNR (500 MHz, methanol-d_4) δ 7.4−7.2 (m, 5H, aromatics), 4.39 (s, 2H, Ph CH_2), 3.4−3.3 (m, 4H, CH_2CH$_3$), 1.16 (t, J = 7.0 Hz, CH$_2$CH_3); ^{13}C MNR (125 MHz, DMSO-d_6) δ 160.5, 142.5, 130.1, 128.8, 128.5, 46.0, 43.1, 14.8; HRMS *m*/*e* calcd for $C_{12}H_{18}N_2O$ (M + H$^+$) 206.1419, found 206.1420.

***N*,*N*-Diethyl-*N*′-piperonylurea (4b):** HPLC purity at 220 nm, 76%; mass recovery, 98%; ^{1}H MNR (500 MHz, methanol-d_4) δ 6.80 (s, 1H), 6.76 (m, 2H), 5.91 (s, 2H, OCH_2O), 4.29 (s, 2H, NHCH_2), 3.33 (q, J = 7.1 Hz, 4H, CH_2CH$_3$), 1.15 (t, J = 7.1 Hz, 6H, CH$_2$CH_3); ^{13}C MNR (125 MHz, methanol-d_4) δ 159.5, 138.5, 135.6, 124.4, 121.3, 108.8, 108.7, 102.1, 45.0, 42.4, 42.3, 14.0, 13.9; HRMS *m*/*e* calcd for $C_{13}H_{18}N_2O_3$ (M$^+$) 250.1317, found 250.1317.

***N*-(*p*-Methoxyphenyl)-*N*′-cyclohexylurea (4c):** HPLC purity at 220 nm, 87%; mass recovery, 88%; ^{1}H MNR (500 MHz, methanol-d_4) δ 7.23 (dd, J = 8.9, 2.0 Hz, 2H, aromatics), 6.85 (dd, J = 8.9, 2.0 Hz, 2H, aromatics), 3.77 (s, 3H, OCH_3), 3.57 (m, NHCH), 1.93 (m, 2H), 1.76 (m, 2H), 1.64 (m, 1H), 1.40 (m, 2H), 1.24 (m, 3H); ^{13}C MNR (125 MHz, methanol-d_4) δ 157.0, 133.8, 129.5, 122.9, 122.6, 115.0, 55.9 34.7, 26.7, 26.0 (1C under methanol-d_4 peak); HRMS *m*/*e* calcd for $C_{14}H_{20}N_2O_2$ (M$^+$) 248.1525, found 248.1526.

***N*-(Cyclohexylaminocarbonyl)morpholine (4d):** mass recovery, 86%; ^{1}H MNR (500 MHz, methanol-d_4) δ 3.65 (m, 4H, OCH_2CH$_2$N), 3.55 (m, 1H, NHCH), 3.37 (m, 4H, OCH$_2$CH_2N), 1.89 (m, 2H), 1.79 (m, 2H), 1.66 (m, 1H), 1.4−1.1 (m, 5H); ^{13}C MNR (125 MHz, methanol-d_4) δ 158.3, 66.2, 50.0, 44.0, 33.1, 25.3, 25.2; HRMS *m*/*e* calcd for $C_{15}H_{22}N_3O_3$ (M + H$^+$) 212.1525, found 212.1520.

***N*-Cyclohexyl-*N*′-tetrahydrofurfurylurea (4e):** mass recovery, 95%; ^{1}H MNR (500 MHz, methanol-d_4) δ 3.99 (m, 1H, OCH), 3.89 (m, 1H, OCHH), 3.77 (m, 1H, OCHH), 3.51 (m, 1H, NHCH), 3.36 (m, 1H, NHCHH), 3.21 (m, 1H, NHCHH), 2.04−1.88 (m, 5H), 1.78−1.74 (m, 2H), 1.66−1.60 (m, 2H), 1.40−1.35 (m, 2H), 1.27−1.23 (m, 3H); ^{13}C MNR (125 MHz, methanol-d_4) δ 159.2, 78.3, 67.9, 49.5, 44.1, 33.0, 28.1, 25.4, 25.3, 24.6 (1C under methanol-d_4 peak); HRMS *m*/*e* calcd for $C_{12}H_{22}N_2O_2$ (M$^+$) 226.1681, found 226.1681.

***N*-(*p*-Iodophenyl)-*N*′-(3-methoxypropyl)urea (4f).** After solid-phase extraction: HPLC purity at 220 nm, 96%; mass recovery, 89%; ^{1}H MNR (500 MHz, methanol-d_4) δ 7.56 (d, J = 8.8 Hz, 2H), 7.20 (d, J = 8.8 Hz, 2H), 3.49 (t, J = 6.0 Hz, 2H, OCH_2), 3.36 (s, 3H, OCH_3), 3.29 (t, J = 6.7 Hz, CH_2NH), 1.79 (quintet, J = 6.4 Hz, 2H, CH_2CH$_2$COCH$_3$); ^{13}C MNR (125 MHz, methanol-d_4) δ 156.1, 139.3, 136.9, 120.1, 83.2, 69.8, 57.0, 36.5, 29.1; HRMS *m*/*e* calcd for $C_{11}H_{15}N_2O_2I$ (M$^+$) 334.0178, found 334.0179.

***N*-(*p*-Phenylphenyl)-*N*′-(3-methoxypropyl)urea (4g).** After solid-phase extraction; HPLC purity at 220 nm, 92%; mass recovery, 90%; ^{1}H MNR (500 MHz, DMSO-d_6) δ 7.6−7.4 (m, 8H, aromatics), 7.29 (t, J = 6.7 Hz, 1H, aromatic), 3.50 (t, J = 6.1 Hz, 2H, CH$_2$CH_2COCH$_3$), 3.37 (s, 3H, OCH_3), 3.34−3.30 (m, 2H, NHCH_2), 1.81 (quintet, J = 6.4 Hz, 2H, CH_2CH$_2$COCH$_3$); ^{13}C MNR (125 MHz, DMSO-d_6) δ 159.1, 142.9, 141.2, 137.3, 130.6, 129.1, 128.6, 128.3, 121.3, 72.5, 59.7, 39.2, 31.6; HRMS *m*/*e* calcd for $C_{17}H_{20}N_2O_2$ (M$^+$) 284.1525, found 284.1524.

***N*-(*p*-Phenylphenyl)-*N*′-cyclohexylurea (4h):** HPLC purity at 220 nm, 98%; mass recovery, 91%; ^{1}H MNR (500 MHz, methanol-d_4) δ 7.58 (d, J = 7.8 Hz, 2H, aromatic), 7.53 (d, J = 8.6 Hz, 2H, aromatic), 7.45−7.40 (m, 4H, aromatic), 7.29 (t, J = 7.3 Hz, 1H, aromatic), 3.61 (m, 1H, NHCH), 1.96 (m, 2H), 1.78 (m, 2H), 1.65 (m, 1H), 1.43 (m, 2H), 1.29 (m, 3H); ^{13}C MNR (125 MHz, methanol-d_4) δ 157.5, 142., 140.5, 136.4, 129.8, 128.3, 127.8, 127.5, 120.3, 34.6, 26.7, 26.0 (1C under methanol-d_4 peak); HRMS *m*/*e* calcd for $C_{19}H_{22}N_2O$ (M$^+$) 294.1732, found 294.1731.

***N*-((*p*-Phenylphenyl)aminocarbonyl)morpholine (4i):** HPLC purity at 220 nm, 97%; mass recovery, 99%; ^{1}H MNR (500 MHz, methanol-d_4) δ 7.60 (d, J = 7.3 Hz, 2H), 7.56 (d, J = 8.7 Hz, 2H), 7.48 (d, J = 8.7 Hz, 2H), 7.42 (t, J = 7.8 Hz, 2H), 7.31 (t, J = 7.5 Hz, 1H), 3.74 (t, J = 4.8 Hz, 4H, O(CH_2CH$_2$)$_2$N), 3.55 (t, J = 4.9 Hz, 4H, O(CH$_2$CH_2)$_2$N); ^{13}C MNR (125 MHz, methanol-d_4) δ 159.2, 143.1, 141.3, 138.4, 130.9, 129.2, 129.0, 128.7, 123.4, 68.8, 46.7; HRMS *m*/*e* calcd for $C_{17}H_{18}N_2O_2$ (M$^+$) 282.1368, found 282.1369.

***N*-((2-Pyridyl)aminocarbonyl)morpholine (4j):** HPLC purity at 220 nm, 83%; mass recovery, 71%; ^{1}H MNR (500 MHz, DMSO-d_6) δ 9.15 (s, 1H, PyNH), 8.24 (ddd, J = 0.8, 1.9, 4.8 Hz, 1H, Py-6H), 7.80 (d, J = 8.4 Hz, 1H, Py-3H), 7.69 (ddd, J = 2.0, 7.2, 8.3 Hz, 1H, Py-4H), 6.99 (ddd, J = 1.0, 4.9, 7.2 Hz, 1H, Py-5H), 3.72 (m, 4H, O(CH_2CH$_2$)$_2$N), 3.47 (m, 4H, O(CH$_2$CH_2)$_2$N); ^{13}C MNR (125 MHz, DMSO-d_6) δ 156.2, 155.4, 149.7, 139.8, 120.1, 115.7, 68.3, 45.8; HRMS *m*/*e* calcd for $C_{10}H_{13}N_3O_2$ (M$^+$) 207.1008, found 207.0998.

Calculation of the Loading Level Using Elemental Analysis. The loading level of the resin can be estimated by the reaction equation, the elemental analysis data, and the loading level of the prereaction resin. As the weight percent of any element reported by elemental analysis of a resin depends on the amount of that element present and on the total mass of the polymer, it is crucial for the analysis that the resin analyzed is completely dry and free of any other contaminants that will affect the analysis. The general equations for the analysis are derived as follows.

The number of moles of the element analyzed and the mass of the resin after the reaction from 1 g of the prereaction resin are:

$$N = N_0 + (\Delta n \times S)\ (\text{mol})$$

$$M = 1 + (\Delta m \times S)\ (\text{g resin})$$

The element weight fraction after the reaction is, therefore:

$$w_X = \frac{A_X \times N}{M} = \frac{A_X \times [N_0 + (\Delta n \times S)]}{1 + (\Delta m \times S)}\ (\text{no unit})$$

This can be rearranged to calculate S, the number of sites actually reacted at the reaction from 1 g of the prereaction resin:

$$S = \frac{w_X - (A_X \times N_0)}{(A_X \times \Delta n) - (w_X \times \Delta m)}\ (\text{mol})$$

The conversion of the reaction is simply given by $C = S/L_0$ (no unit)

However, for the loading of the resin after the reaction (mol/g resin), the change of the resin weight has to be taken into account, therefore:

$$L = \frac{S}{M} = \frac{S}{1 + (\Delta m \times S)} = \frac{w_X - (A_X \times N_0)}{A_X \times (\Delta n - N_0 \times \Delta m)} \text{ (mol/g resin)}$$

In the special case where $N_0 = 0$, the loading (L) is obtained in a simpler and more intuitive form:

$$L = \frac{w_X}{A_X \times \Delta n} \text{ (mol/g resin)}$$

where

Δm = the change in molecular weight (g/mole) per site as a result of the reaction,

Δn = the change in number of the element atoms analyzed per site as a result of the reaction,

M = the mass (g) of the resin after the reaction from 1 g of the prereaction resin,

N_0 = the number (mol) of the element analyzed on 1 g of the prereaction resin,

N = the number (mol) of the element analyzed on the resin after the reaction from 1 g of the prereaction resin,

A_X = the atomic weight of the element (X) analyzed after the reaction,

w_X = the weight fraction of the element (X) from the elemental analysis (g element/g resin),

S = the number (mol) of sites on the resin actually participating in the reaction from 1 g of prereaction resin,

L_0 = the loading onto polystyrene resin before the reaction (mol/g resin),

L = the loading onto polystyrene resin after the reaction (mol/g resin).

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Supporting Information Available: IR spectra of resins **5**, **1**, **2**, **3h** and representative HPLC, ^{1}H and ^{13}C NMR spectra (for **4c** and **4h**) (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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