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Optimization of Urea Formation with Phoxime™ Resin using the Nautilus™ 2400

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Abstract: Phosgenated *p*-nitrophenyl(polystyrene)ketoxime (Phoxime™) resin (**1**) has been previously utilized as a latent isocyanate equivalent. The Nautilus™ 2400 automated organic synthesizer was used to determine the optimal temperature for thermolysis of the polymer-bound oxime-carbamate derived from Phoxime resin and subsequent amine addition to give a urea in solution.

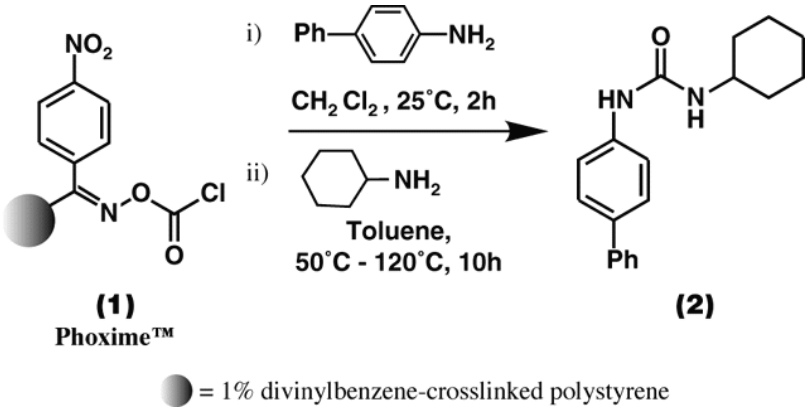
Introduction

Isocyanates are useful building blocks for combinatorial synthesis and have been utilized for the preparation of ureas,[1-3] carbamates,[4-6] sulfonylureas[7-9] and heterocycles such as hydantoins[10,11] and quinazoline-2,4-diones.[12-14] Polymer-bound oxime carbamates derived from the addition of isocyanates to *p*-nitrophenyl(polystyrene) ketoxime or Phoxime resin[15,16] have been shown to serve as latent isocyanates upon thermolysis.[17] Phosgenation of the oxime resin to afford its chloroformate and subsequent addition of a primary amine, results in the formation of an oxime-carbamate.[18] Urea formation then occurs in solution upon thermolysis[19] of the polymer-bound oxime-carbamate in the presence of an amine.

The suitability of the Nautilus 2400 automated synthesizer for development and optimization of organic synthesis has been well established. Typical optimization studies include: reaction temperature, reaction time, reagents, solvents and stoichiometry. To examine the dependence of isolated urea yield and purity on the thermolysis temperature for the polymer-bound oxime-carbamate derived from Phoxime resin, the Nautilus 2400 was employed to independently control reactor temperature from vessel-to-vessel. As a case study, we chose to look at the synthesis of cyclohexyl-4-biphenyl urea (**2**).

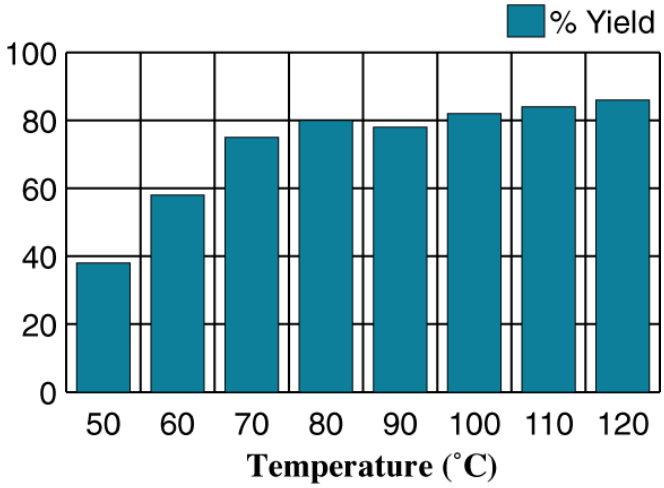
Experimental

Scheme 1 - Solid Phase Synthesis of Cyclohezyl-4-biphenyl urea



Phoxime resin **1** (200 mg, 0.15 mmol) was added to eight, 8 mL reaction vessels (RV's) on the Nautilus 2400. Three molar equivalents of 4-biphenylamine in dichloromethane (DCM) was added to each reaction vessel and agitated (25 °C, 2 h) to afford a resin-bound oxime carbamate intermediate, which was washed with DCM followed by methanol **(Scheme 1)**. Heating of the oxime-derived carbamate resin in toluene at eight independent temperatures from 50 sC to 120 sC at 10 sC increments for 10h in the presence of four equivalents of cyclohexylamine formed cyclohexyl-4-biphenyl urea **2** in solution.

Table 1 - Yield of Cyclohexyl-4-biphenylurea as a Function of Temperature



Urea products **2** were evaporated to dryness and analyzed by ^{1}H NMR,mass spectroscopy and HPLC.18 High purity (HPLC area %) and chemical yields were observed. For this particular case, optimum thermolytic cleavage conditions appear to be above 80 °C as shown in **Table 1**. Additionally, inspection of the IR spectra of the recovered oxime resin from the higher temperatures indicated complete cleavage of the polymer-supported oxime carbamate (CO stretch: 1750 cm^{-1}).

Summary

- The Nautilus 2400 automated synthesizer was employed to examine the dependence of isolated urea yield on cleavage temperature.
- Temperature dependence studies were facilitated by the individual temperature control capabilities of the Nautilus 2400.

The thermolytic cleavage of biphenylamine-derived oxime carbamate was found to be optimal at temperatures greater than 80 °C.
Phoxime resin can be derivatized with primary amines to generate oxime carbamates which can be trapped with amines to afford ureas on the Nautilus 2400.

References and Notes

Phoxime is a trademark of the DuPont Company.

Nautilus 2400 is a trademark of Argonaut Technologies Inc.

1. Nowick, J. S.; Holmes, D. L.; Noronha, G.; Smith, E. M.; Nguyen, T. M.; Huang, S.-L. J. Org. Chem. 1996, 61, 3929 - 3934.
2. Burgess, K.; Linthicum, D. S.; Shin, H. Angew. Chem. Int. Ed. Engl. 1995, 34, 907 - 909.
3. Meyers, H. V.; Dilley, G. J.; Durgin, T. L.; Powers, T. S.; Winssinger, N. A.; Zhu, H.; Pavia, M. R. Molecular Diversity 1995, 1, 13 -20.
4. Knolker, H.-J.; Braxmeier, T. Tetrahderon Lett. 1996, 37, 5861 - 5864.
5. Pirrung, M. C.; Chen, J. J. Am. Chem. Soc. 1995, 117, 1240 - 1245.
6. Duggan, M. E.; Imagire, J. S. Synthesis 1989, 131 - 132.
7. Cervello, J.; Sastre, T. Synthesis 1990, 221 - 222.
8. Irie, H.; Nishimura, M.; Yoshida, M.; Ibuka, T. J. Chem. Soc. Perkin Trans. 1989, 1, 1209 - 1210. Bell, S.; Bonadio, A.; Watson, K. G. Aust. J. Chem. 1995, 48, 227.
9. Hobbs DeWitt, S.; Kiely, J. S.; Stankovic, C. J.; Schroeder, M.C.; Reynolds Cody, D.M.; Pavia, M. R. Proc. Nat. Acad. Sci. USA 1993, 90, 6909 -6913.
10. Hanessian, S.; Yang, R.-Y. Tetrahedron Lett. 1996, 37,, 5835 - 5838.
11. Buckmann, B.; Mohan, R. Tetrahedron Lett. 1996, 37, 4439 - 4442.
12. Gouilleux, L.; Fehrentz, J.-A.; Winternitz, F.; Martinez, J. Tetrahedron Lett. 1996, 37, 7031.
13. Smith, A. L.; Thompson, C. G.; Leeson, P. D. Bioorganic & Medicinal Chemistry Letters 1996, 6, 1483 - 1486.
14. DeGrado, W. F.; Kaiser, E. T. J. Org. Chem. 1980, 45, 1295 - 1300.
15. DeGrado, W. F.; Kaiser, E. T. J. Org. Chem. 1982, 47, 3258 - 3261.
16. Scialdone, M. A. Tetrahedron Lett. 1996, 37, 8141 - 8144.
17. Scialdone, M. A.; Shuey, S. W. J. Org. Chem. 1997, 62, in press.
18. For recent reports of thermolytic cleavage from a polymer support, see refs. 14, 17 and a) Kolodziej, A. A.; Hamper, B. C. Tetrahedron Lett. 1996, 37, 5277 - 5280; b) Tietze, L. F.; Steinmetz, A. Synlett 1996, 667 -668 and c) Dressman, B. A.; Spangle, L. A.; Kaldor, S. W. Tetrahedron Lett. 1996, 37, 937 - 940.

Comments

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