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A new entry to *N*-unsubstituted β-lactams through a solid-phase approach

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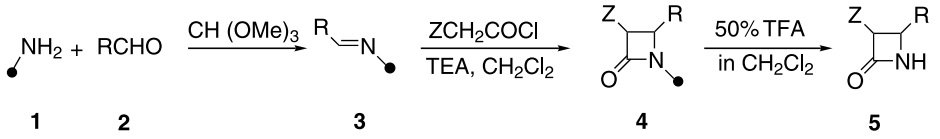
Abstract—A remarkable new entry to *N*-unsubstituted β-lactams using rink resin as the solid-support has been developed.

A continuous and intense effort has been directed to developing methods for synthesizing β-lactams because of their enormous impact on different diseases.[1] *N*-Unsubstituted β-lactams plays a central role as key intermediates in the synthesis of several biologically active antibiotics.[2] The importance of these types of compounds for the semi-synthesis of the novel anticancer agents Taxol and Taxotere is also well documented.[3] Oxidative cleavage by cerric ammonium nitrate of an activated aromatic moiety attached to the nitrogen of the β-lactam ring offers the most direct synthesis of *N*-unsubstituted β-lactams.[4] This method has some shortcomings, however, since it is very sensitive to acid-labile compounds and in many cases the yields are poor. To overcome these problems, a synthetic method that employs neutral conditions using cobalt carbonyl has been reported.[5] Many other less frequently methods known in the literature are not popular.[6] Although these methods tolerate labile functionalities, their practical application is limited. One alternative we are exploring is the use of solid phase support.

We want to take advantage of a current focus in organic chemistry, the extension of principles of organic reactions that take place in homogeneous conditions to analogous reactions that take place on solid-support.[7] Solid-phase synthesis of 1,2,3-trisubstituted β-lactams using Sasrin resin has been reported in a pioneering work.[8] *N*-Unsubstituted β-lactams using TentaGel S resin under a photochemical method has been investigated.[9] Encouraged by these two reports and in continuation of our own efforts to synthesize β-lactams[10] of biological significance, we report here a new method of synthesizing *N*-unsubstituted 3,4-disubstituted β-lactams using rink resin as the solid support. Although the use of rink resin in various chemical transformations has been reported frequently,[11] it has never been used in β-lactam synthesis.

Although a number of methods for synthesizing β-lactam rings have been developed, the Staudinger reaction is still the best for this purpose.[12] To test the feasibility of the rink resin approach, we prepared a number of imines first using rink resin and a variety of aldehydes using trimethyl orthoformate. Then cycloaddition was performed on these using triethyl amine as the base and dichloromethane as the solvent at temperatures ranging from 0°C to room temperature. FT-IR was used to monitor the progress of the reaction. The disappear-



Scheme 1.

Keywords: solid-phase; *N*-unsubstituted β-lactams.

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ance of the imines peaks indicated the completion of the reaction. Finally, rink resin was cleaved by using 50% trifluoroacetic acid in dichloromethane, and the product, *N*-unsubstituted β-lactam, was isolated in excellent yield (Scheme 1).[13]

Notably, a number of groups (acetoxy, phthalimido, ether, ester and the ring itself) remained intact during the acid treatment. The stereochemistry of the products followed earlier observation (Table 1).

Considering the solid-supported reaction, excess reagent was used in each step to assure complete conversion, and so, the yield of the final product was high. Excess reagents were removed by simply washing the resin with polar solvents (dichloromethane or methanol).

In conclusion, we have demonstrated for the first time that rink resin-derived imines can be used in a cycloaddition reaction with acid chlorides (or equivalent) and the resin bound β-lactam can be easily cleaved to the *N*-unsubstituted β-lactam. Owing to the smooth and excellent yield, this method has broad applicability. In addition, resin-bound β-lactams can serve as intermediates for the synthesis of various other natural and non-natural compounds. That is, the resin attached to the nitrogen of the β-lactam ring can actually act as a novel protective group during these transformations. Application of the rink resin and other solid-support mediated approaches toward the synthesis of β-lactam and other compounds will be reported in due course.

Acknowledgements

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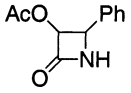
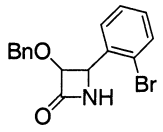
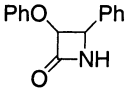
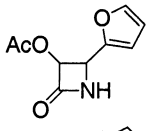
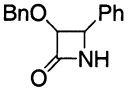
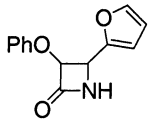
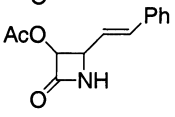
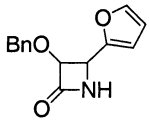
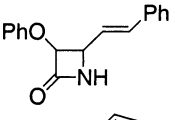
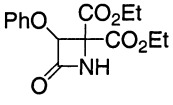
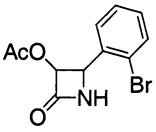
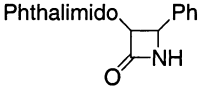
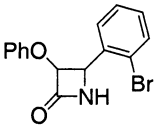
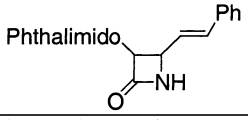
Table 1. Preparation of *N*-unsubstituted β-lactams

Entries	Compounds	Yields (%)[a]	Entries	Compounds	Yields (%)[a]
1		60	8		68
2		64	9		63
3		62	10		68
4		62	11		62
5		68	12		68
6		64	13		61[b, c]
7		67	14		62[b]

a: Overall yields based on the original loading of the rink amide resin b: Phthalimido acetic acid in the presence of Mukaiyama reagent was used c: A mixture of *cis* and *trans* isomers (30: 70) was obtained.

References

1. For a recent example, see: Bose, A. K.; Manhas, M. S.; Banik, B. K.; Srirajan, V. In *The Amide Linkage: Selected Structural Aspects in Chemistry, Biochemistry, and Material Science*; Greenberg, A.; Breneman, C. M.; Liebman, J. F., Eds.; Wiley-Interscience: New York, 2000; Chapter 7, p. 157 (β-Lactams: cyclic amides of distinction).
2. (a) Kant, J.; Walker, D. G. In *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; 1993; p. 121; (b) Durckheimer, W.; Blumbach, J.; Lattrell, R.; Scheunemann, K. H. *Angew Chem., Int. Ed. Engl.* **1985**, *24*, 180; (c) O'Sullivan, J.; Abraham, E. P. In *Antibiotics*; Corocoran, J. W., Ed.; Springer: Berlin, 1981; Vol. 4; (d) Cooper, R. D. G. In *Topics in Antibiotics Chemistry*; Sammes, P. G.; Horwood, E., Eds.; Chichester, 1980; Vol. 3.
3. Suffness, M. *Taxol Science and Applications*; CRC Press: Boca Raton, FL, USA, 1995.
4. Kronenthal, D. K.; Han, C. Y.; Taylor, M. K. *J. Org. Chem.* **1982**, *47*, 2765.
5. Alcaide, B.; Perez-Castells, J. P.; Sanchez-Vigo, B.; Sierra, M. A. *J. Chem. Soc., Chem. Commun.* **1994**, 587.
6. (a) DiPietro, D.; Borzilleri, R. M.; Weinreb, S. M. *J. Org. Chem.* **1994**, *59*, 5856; (b) Boger, D. L.; Myers, J. B., Jr. *J. Org. Chem.* **1991**, *56*, 5385; (c) Georg, G. I.; He, P.; Kant, J.; Mudd, J. *Tetrahedron Lett.* **1990**, *31*, 451; (d) Lasarte, J.; Palomo, C.; Picard, J. P.; Dunogues, J.; Aizupurua, J. M. *J. Chem. Soc., Chem. Commun.* **1989**, 72; (e) Arrieta, A.; Lecea, B.; Palomo, C. *J. Chem. Soc., Perkin Trans 1* **1987**, 845; (f) Colvin, E. W.; McGarry, D. G. *J. Chem. Soc., Chem. Commun.* **1985**, 539; (g) Fukuyama, T.; Laird, A. A.; Schmidt, C. A. *Tetrahedron Lett.* **1984**, *25*, 4709; (h) Bose, A. K.; Manhas, M. S.; Vincent, J. E.; Gala, K.; Fernandez, I. F. *J. Org. Chem.* **1982**, *47*, 4075.
7. (a) Mata, E. G. *Cur. Pharm. Design* **1999**, *5*, 955; (b) Furman, B.; Thurmer, R.; Kaluza, Z.; Lysek, R.; Voelter, W.; Chmielewski, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 1121.
8. Ruhland, B.; Bhandari, A.; Gordon, E. M.; Gallop, M. A. *J. Am. Chem. Soc.* **1996**, *118*, 253.
9. Fitch, W. L.; Detre, G.; Holmes, C. P.; Shoolery, J. N.; Keifer, P. A. *J. Org. Chem.* **1994**, *59*, 7955.
10. (a) Ghatak, A.; Becker, F. F.; Banik, B. K. *Heterocycles* **2000**, *53*, 2769; (b) Banik, B. K.; Ghatak, A.; Becker, F. F. *J. Chem. Soc., Perkin Trans 1* **2000**, *14*, 2179; (c) Banik, B. K.; Becker, F. F. *Tetrahedron Lett.* **2000**, *41*, 6551; (d) Ng, S.; Banik, I.; Okawa, A.; Becker, F. F.; Banik, B. K. *J. Chem. Res.* **2001**, 118.
11. Du, X.; Armstrong, R. W. *J. Org. Chem.* **1997**, *62*, 5678 and references cited therein.
12. Staudinger, H. *Liebigs Ann. Chem.* **1907**, *356*, 51.
13. A general experimental condition is given below: The rink amide resin (loading 0.71 mmol/g) was deblocked by using 20% piperidine/DMF. The polymer bound imines **3** were prepared by condensing the carbonyl compounds **2** with rink amine **1** and trimethyl orthoformate. To the polymer-bound imine **3** (100 mg) was added dry dichloromethane (4 mL) and triethyl amine (6 equiv.). The suspension was cooled to 0°C and to it was added dropwise a solution of the acid chloride (3 equiv.) in dichloromethane (1 mL). The mixture was stirred overnight at room temperature. The resin was then filtered and washed with dichloromethane (20 mL) and dried. The β-lactam bound resin **4** was stirred in 50% TFA/CH_2Cl_2 for 1 h, and the mixture was neutralized by adding saturated sodium bicarbonate solution and filtered. The resin was washed several times with dichloromethane. The organic layer was separated and washed with brine and dried over anhydrous sodium sulfate. The β-lactam **5** (90% pure) was obtained by evaporating the solvent. The crude β-lactam **5** was purified by passing through a small florisil column (1 gm) using ethyl acetate–hexanes (1:1) as the solvent. Compounds (Table 1, entries 1–8 and 13–14) were characterized by a direct comparison with authentic samples prepared by following a literature method[4] (mp, IR and NMR spectra). The other compounds (Table 1, entries 9–12) gave a comparable analytical data.