Pergamon

Tetrahedron Letters, Vol. 38, No. 36, pp. 6335-6338, 1997
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0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01457-3

β-Lactams on Solid Support: Mild and Efficient Removal of Penicillin Derivatives from Merrifield Resin using Aluminum Chloride

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Abstract: Penicillin derivatives linked to Merrifield resin are efficiently released from this support under mild conditions using aluminum chloride in dichloromethane/nitromethane. Extension to Wang resin-linked analogues and studies on the solid-phase oxidation of penicillin is also reported.

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The preparation of small organic molecules on solid phase is emerging as an expedient method and is being utilized for generating compounds combinatorialy in order to prepare libraries for screening against biological systems and enhance the drug discovery effort.[1] The development of new chemistry and the extension of known solution chemistry to resin-supported substrates will increase the scope of combinatorial chemistry, thus a substantial effort has been put into the optimization of solid-phase organic reactions.[2] We are particularly interested in the application of solid-phase synthesis to the clinically valuable penicillins. So far, the solid-phase synthesis of β-lactam compounds has been scarcely explored.[3] Recently, considerable attention has been devoted to the development of novel agents to treat bacterial infections that have become increasingly unresponsive to standard antibacterial therapy.[4]

During our solid-phase research directed to the synthesis of libraries of 2β-methyl substituted penicillins, we reasoned that Merrifield resin would be one of the most versatile solid support, allowing a broader range of reaction conditions due to its acid stability. However, the preferred method for cleaving this linkage is anhydrous hydrofluoric acid[5] which would be a drawback for sensitive functional groups such as the β-lactam ring. We have now devised a high yielding methodology for cleaving penicillin derivatives from Merrifield and Wang resin under very mild conditions.

The preparation of different resin-linked penicillins was chosen for an initial investigation of their chemistry on solid support (see Scheme 1). Merrifield resin (**1**) was coupled with penicillanic acids such as **2a-c**, *via* KF/DMF to provide Merrifield resin-bound derivatives **3a-c**.[6] We corroborated that the solid phase oxidation of **3a-c** by *m*-chloroperbenzoic acid (MCPBA) (1.4 equiv., 20 h, 0ºC) gave the corresponding sulfoxides **4a-c**[8] in a selective manner, while no reaction was detected when other oxidizing systems, such as Oxone®/acetone,[9] were used. Literature on solid-phase oxidation of sulfides is scarce and the conversion to sulfones has proved to be difficult.[10] However, we found that sulfones **5a-c** can be exclusively obtained using excess of MCBPA (5 equiv., 96 h, r.t.).[11,12] In order to extent this study to other commercially available resins, penicillins linked to Wang resin (**7a-c**)[14] and their sulfoxides (**8a-c**)[15] were also obtained (Scheme 1).

Scheme 1

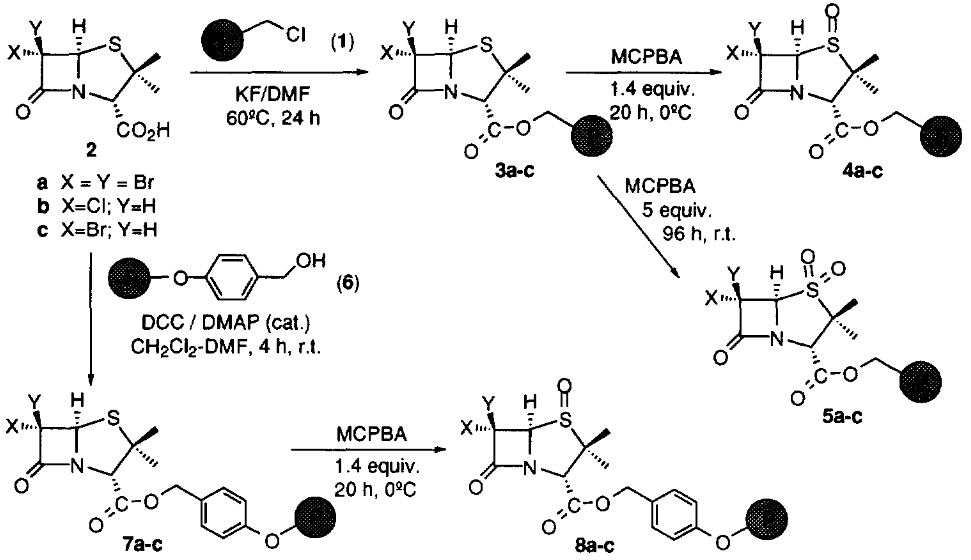
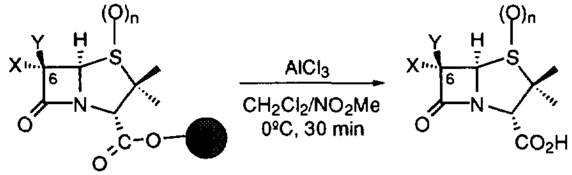


Table 1 shows that the cleavage of Merrifield and Wang resin-bound penicillin derivatives using aluminum chloride in dichloromethane/nitromethane,[16] affords good to excellent yields of the corresponding penicillanic acids. In a typical experiment, Merrifield resin-bound 6,6-dibromopenicillanic acid (**3a**) (88.5 mg, 0.62 mmol/g, theoretical load) was swelled in CH_2Cl_2 (1 mL) for 30 min at room temperature. After cooling to 0°C, aluminum chloride (30 mg, 0.225 mmol, 4 equiv.) in nitromethane (0.75 mL) was added and the mixture stirred for 30 min at the same temperature. The resin was filtered and washed with EtOAc (3 x 2 mL). The filtrate was transferred to a separatory funnel, washed with 0.5N HCl (2 x 2.5 mL) and aqueous layers extracted with EtOAc (1 x 3 mL). The combined extracts were dried and evaporated to give the 6,6-dibromopenicillanic acid (**2a**) (19.5 mg, 98% yield).

Entries 4-6 and 13-15 show the stereochemical result of the solid-phase oxidation of penam sulfides to sulfoxides. In terms of diastereoselectivity, this oxidation proceeds similarly to that in solution phase[17] regardless of the resin used, and it is influenced by the nature of the C-6 halogen substituents, giving the α sulfoxide as the major isomer for 6,6-dibromopenicillanate derivatives **4a** and **8a**, and the β sulfoxide as the major product for 6α-halopenicillanates derivatives **4b-c** and **8b-c**. In the case of Wang resin-bound penicillins (entries 10-15), we have found that the cleavage can be also performed by 10% trifluoroacetic acid (TFA) in CH_2Cl_2 (25°C, 1 h) with very good to excellent yields.

In summary, the protocol reported herein is the method of choice for cleaving penicillins linked to Merrifield resin and it is potentially useful for the removal of other sensitive "drug like" molecules from this resin. This is also an alternative method to 10% TFA/CH_2Cl_2 for cleaving Wang resin-linked small molecules. To the best of our knowledge, this communication constitutes the first report on solid-phase chemistry of penicillins and the application of this chemistry during the synthesis of solid-supported 2β-methyl substituted penicillins is currently in progress and will be reported in due course.

Table 1. Cleavage of resin-bound penicillins by aluminum chloride.[18]



Entry		Starting material	Yield, %[a]	Diastereoisomeric ratio (α:β sulfoxides)[c]
1	**3a**	X = Y = Br; n = 0; P = Merrifield resin	98	
2	**3b**	X = Cl, Y = H; n = 0; P = Merrifield resin	88	
3	**3c**	X = Br, Y = H; n = 0; P = Merrifield resin	76[b]	
4	**4a**	X = Y = Br; n = 1; P = Merrifield resin	96	93 : 7
5	**4b**	X = Cl, Y = H; n = 1; P = Merrifield resin	78	6 : 94
6	**4c**	X = Br, Y = H; n = 1; P = Merrifield resin	81	6 : 94
7	**5a**	X = Y = Br; n = 2; P = Merrifield resin	80	
8	**5b**	X = Cl, Y = H; n = 2; P = Merrifield resin	70	
9	**5c**	X = Br, Y = H; n = 2; P = Merrifield resin	82	
10	**7a**	X = Y = Br; n = 0; P = Wang resin	91 (95)[d]	
11	**7b**	X = Cl, Y = H; n = 0; P = Wang resin	100 (100)[d]	
12	**7c**	X = Br, Y = H; n = 0; P = Wang resin	96[b] (98)[d]	
13	**8a**	X = Y = Br; n = 1; P = Wang resin	83 (95)[d]	93 : 7
14	**8b**	X = Cl, Y = H; n = 1; P = Wang resin	66 (90)[d]	5 : 95
15	**8c**	X = Br, Y = H; n = 1; P = Wang resin	97 (95)[d]	9 : 91

[a]Based on mass difference[7] as theoretical resin load. [b]A further purification is required: organic phase was extracted with 5% aqueous $NaHCO_3$ (2x), aqueous phase acidified with 0.5N HCl and extracted with EtOAc (3x). [c]Calculated on the basis of the ^1H NMR signals of the methyl ester derivatives. [d]Yields of 10% TFA/CH_2Cl_2 cleavage are given in parenthesis.

Acknowledgments: Financial support from Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Argentina and The Royal Society of Chemistry, (U.K.) is gratefully acknowledged. I am also grateful to Prof. O.A. Mascaretti for his interest in this work and S. Pellegrinet for careful reading the manuscript.

References and Notes

1. For recent reviews on combinatorial libraries and molecular diversity, see: a) Terrett, N.K.; Gardner, M.; Gordon, D.W.; Kobylecki, R.J.; Steele, J. *Tetrahedron* **1995**, *51*, 8135-8173. b) Lowe, G. *Chemical Society Reviews* **1995**, *24*, 309-317. c) Thompson, L.A.; Ellman, J.A. *Chem. Rev.* **1996**, *96*, 555-600. d) Patel, D.V.; Gordon, E.M. *Drug Discovery Today* **1996**, *1*, 134-144. For recent highlights, see *Acc. Chem. Res.* **1996**, *29*, No. 3.

2. For reviews on recent advances in solid-phase organic reactions, see: a) Hermkens, P.H.H.; Ottenheijm, H.C.J.; Rees, D. *Tetrahedron* **1996** *52*, 4527-4554. b) Früchtel, J.S.; Jung, G. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 17-42.

3. A work concerning to monolactam linked to resin has been recently published: Ruhland, B.; Bhandari, A.; Gordon, E.M.; Gallop, M.A. *J. Am. Chem. Soc.* **1996**, *118*, 253-254.

4. a) Chu, D.T.W.; Plattner, J.J.; Katz, L. *J. Med. Chem.* **1996**, *39*, 3853-3873. b) Stinson, S.C. *Chem. Eng. News* **1996**, *74* (39), 75-100.

5. Stewart, J.M.; Young, J.D. *Solid Phase Peptide Synthesis*, Pierce Chemical Company: Rockford, 1984; pp 38-40.

6. *General method for the preparation of 6,6-dihalo- and 6α-halopenicillanates linked to Merrifield resin (**3a-c**).* Merrifield resin (**1**) (1g, ≈0.8 mmol/g) was first swelled in DMF (7 mL) for approximately 30 min. In sequential order, 6,6-dibromopenicillanic acid (**2a**) (0.431 g, 1.2 mmol) in DMF (1 mL) and potassium fluoride (0.14 g, 1.4 mmol) were added to the reaction vessel at room temperature and under argon atmosphere. The reaction was stirred at 60ºC for 24 h and then filtered, washed with EtOH (3x), water (3x), MeOH (3x) and CH_2Cl_2 (3x), and finally dried *in vacuo*. The FT-IR of the resin at this point exhibits a strong β-lactam stretch at *ca.*1780 cm^{-1} and an ester stretch at *ca.* 1740 cm^{-1} that corroborate the linkage. Mass difference[7] was used to determine resin loading. Typically, coupling was achieved with 90-100% efficiency (the above sequence was repeated for optimal coupling).

7. Miziguchi, T.; Shigezane, K.; Takamura, N. *Chem. Pharm. Bull.* **1970**, *18*, 1465-1474.

8. *General method for solid-phase synthesis of sulfoxides (**4a-c**).* Merrifield resin-bound 6,6-dibromopenicillanic acid (**3a**) (0.624 g, 0.62 mmol/g, theoretical load) was swelled in CH_2Cl_2 (10 mL) for 30 min. To this slurry, MCPBA (0.095 g, 0.546 mmol, 1.4 equiv.) in CH_2Cl_2 (2 mL) was added at 0ºC. The mixture was stirred for 20 h at the same temperature. The resin was then filtered, washed successively with MeOH (3x), EtOAc (3x) and CH_2Cl_2 (3x), and finally dried *in vacuo*.

9. For a review on recent advances in the synthesis of sulfoxides from sulfides, see: Mata, E.G. *Phosphorus, Sulfur and Silicon* **1996**, *117*, 231-286.

10. Pátek, M.; Drake, B.; Lebl, M. *Tetrahedron Lett.* **1995**, *36*, 2227-2230.

11. *General method for solid-phase synthesis of sulfones (**5a-c**).* Merrifield resin-bound 6,6-dibromopenicillanic acid (**3a**) (0.168 g, 0.62 mmol/g, theoretical load) was swelled in CH_2Cl_2 (1.5 mL) for 30 min. To this slurry, MCPBA (0.085 g, 0.49 mmol, 5 equiv.) in CH_2Cl_2 (1 mL) was added at 0ºC. The mixture was stirred for 96 h at room temperature. The resin was then filtered, washed with MeOH and CH_2Cl_2 (this sequence of washing is repeated three times), and dried *in vacuo*.

12. Reaction was not observed when classical penicillin oxidation ($KMnO_4$/AcOH)[13] was used.

13. Chow, A.W.; Hall, N.M.; Hoover, J.R.E. *J. Org. Chem.* **1962**, *27*, 1381-1383.

14. *General method for attachment penicillin derivatives to Wang resin.* Wang resin (**6**) (1.643 g, 0.96 mmol/g) was suspended in a 1:1 mixture of CH_2Cl_2-DMF (24 mL) and stirred with 6,6-dibromopenicillanic acid (**2a**) (1.5 g, 4.178 mmol), dicyclohexylcarbodiimide (DCC) (1.55g, 7.5 mmol) and catalytic 4-dimethylaminopyridine (DMAP) for 4 h. The reaction mixture was then filtered, washed with CH_2Cl_2 (3x), DMF (3x) and MeOH (3x), and dried *in vacuo*. Typically, coupling was achieved with 70-100% efficiency (determined by mass difference[7] and rechecked by quantitative measurement of the material after cleaving with 10% TFA/CH_2Cl_2).

15. Sulfoxides **8a-c** were obtained in a similar way to that used for the synthesis of **4a-c**, see Ref. 8.

16. For solution-phase deprotection of benzyl penicillanates with aluminum chloride, see: Danelon, G.O.; Mata, E.G.; Mascaretti, O.A.; Girardini, J.; Marro, M.; Roveri, O.A. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2037-2040.

17. Harrison, C.R.; Hodge, P. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1772-1775.

18. All products gave satisfactory ^1H NMR spectra after converting into the corresponding methyl esters (CH_2N_2, Et_2O-CH_2Cl_2). Identification was achieved by comparison of these spectra with literature data (see: Belinzoni, D.U.; Setti, E.L.; Mascaretti, O.A. *J. Chem. Res. (S)* **1988**, 176; *(M)* **1988**, 1501 and references cited therein).

(*Received in USA* 22 *February* 1997; *accepted* 3 *July* 1997)