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Solid-phase synthesis of 2β-methyl substituted penam derivatives through penicillin sulfoxide rearrangement

Carina M. L. Delpiccolo and Ernesto G. Mata *

Instituto de Química Orgánica de Síntesis. CONICET - Universidad Nacional de Rosario, Facultad de Ciencias Bioquímicas y Farmacéuticas, Casilla de Correo 991, 2000 Rosario, Argentina

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Abstract

A new, robust protocol for the solid-phase synthesis of 2β-methyl substituted penam derivatives is described. This synthetic sequence works reliably in good to high overall yields using Merrifield resin as support. The key step involves the thermal rearrangement of the corresponding penicillin sulfoxide.

Combinatorial chemistry of small molecules has generated a great deal of interest due to its impact on lead structure identification and optimization.[1] Solid-phase organic synthesis (SPOS) has been widely used for preparation of a large number of structurally diverse compounds for combinatorial libraries. Although much progress has been made in recent years,[2] the application of this technique to penicillins[3] and other β-lactam compounds[4] has been barely documented. The development of novel agents to treat bacterial infections is currently of great importance due to the increasing bacterial resistance against standard therapy.[5]

Our laboratory has recently developed methodologies for tethering different resins to the penam nucleus, together with a new, mild and efficient procedure for the removal of sensitive moieties, such as penicillin derivatives, from Merrifield and Wang resins.[3] In this paper, we wish to report a new resin-based chemistry for the synthesis of 2β-methyl substituted penicillins through the rearrangement of the corresponding sulfoxides.[6] The 2β-methyl substituted penicillins are a group of potentially active enzyme inhibitors.[7]

Our investigation began with the immobilization of 6,6-dibromopenicillanic acid (**1**) onto Merrifield resin and oxidation with *m*-chloroperbenzoic acid (MCPBA) to obtain the resin-bound sulfoxide **3** (Scheme 1).[3] These reactions were monitored by FT-IR, showing characteristic absorptions at 1780 and 1740 (C=O) cm^{-1} and 1045 (S–O) cm^{-1}. The unsymmetrical azetidinone disulfide **4** is a versatile intermediate[8] that could be obtained when the sulfenic acid, formed by a thermal rearrangement of **3**, is trapped by the 2-mercaptobenzothiazole (2-MBT).[9] Thus, sulfoxide **3** was treated with 2-MBT in

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* Corresponding author. Tel: +54 341 4804600; fax: +54 341 4370477; e-mail: iquiosra@citynet.net.ar

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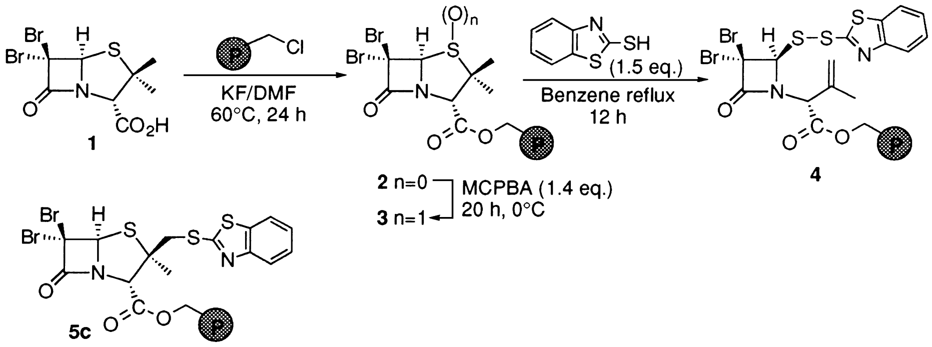
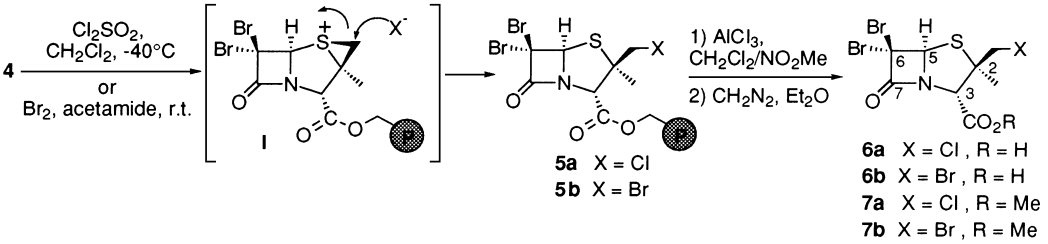
refluxing toluene during 4 h to give disulfide **4** in a mixture with the 2β-(benzothiazol-2-yl)thiomethyl derivative **5c**. This result was quite surprising since the thermolysis which led to the obtention of **5c** has not been reported before in solution phase, working on related structures under similar conditions.[6a] After some experimentation, we found that this thermolysis can be avoided by heating **3** with 2-MBT in benzene at reflux, leading to a clean formation of compound **4**. In solution-phase chemistry, the synthesis of disulfides related to **4** usually requires a series of, at least, two purification steps by column chromatography to eliminate by products. In solid-phase chemistry these impurities are eliminated simply by filtration.



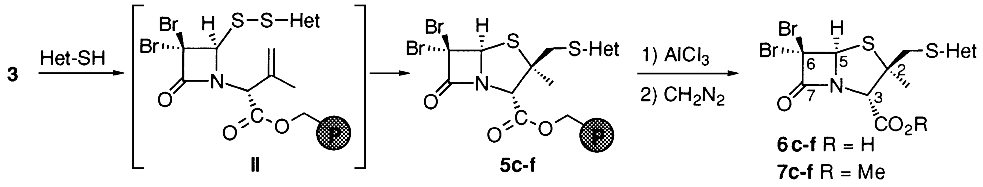
Scheme 1.

Having optimized the synthesis of disulfide **4**, we next carried out the synthesis of the 2β-halomethyl substituted penicillins. This recyclization proceeds via an episulfonium ion **I** which is subsequently opened by a nucleophilic attack of the halide (Scheme 2). Thus, the resin-bound 2β-chloromethyl derivative **5a** was nicely prepared by the addition of sulfuryl chloride to a suspension of disulfide **4** in dichloromethane at −40°C. The penicillin **5a** was found to be efficiently and cleanly liberated from the resin by treatment with $AlCl_3$ to afford the free acid **6a**, which was then esterified to the corresponding methyl ester **7a**. The overall isolated yield for the five step sequence was 70% (based on manufacturer's loading of the Merrifield resin). Similarly, treatment of **4** with bromine gave the 2β-bromomethyl derivative **5b** which, after cleaving and esterification, led to compound **7b** in a 50% overall isolated yield.[10]



Scheme 2.

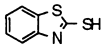
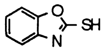
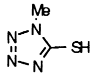
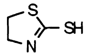
To extend the scope of this methodology, we have also considered the synthesis of 2β-(heterocyclylthio)methyl substituted penicillins. Heterocyclic thio substituents have been identified as pharmacophores in β-lactam chemistry, particularly with activity against methicillin-resistant *Staphylococcus aureus* (MRSA).[11] Thus, thermolysis of **3** in the presence of a heterocyclic thiol (4 equiv.) and catalytic amounts of *p*-toluenesulfonic acid gave exclusively the corresponding 2β-(heterocyclylthio)methyl derivative (**5c**–**f**), without isolation of the disulfide intermediate **II** (Scheme 3).[12]



Scheme 3.

After cleavage and esterification, yields of the products **7c**–**f** ranged from 45 to 52% (based on initial loading of the Merrifield resin) (Table 1).[13,14]

Table 1
Solid-phase synthesis of 2β-(heterocyclylthio)methyl substituted penicillins

Entry	Het-SH	product	yield (%)[a]
1		**7c**	45
2		**7d**	49
3		**7e**	55
4		**7f**	48

[a]Overall isolated yield after column chromatography (based on the initial loading level of Merrifield resin, 4 step sequence).

In summary, we have developed the first solid-phase synthetic sequence of penicillin derivatives and one of the few examples of rearrangements on solid support.[2] This protocol works reliably in good to high overall yields using a commercially available and cost-effective support such as Merrifield resin. Moreover, the mild reaction conditions made the approach applicable to the generation of combinatorial libraries of penicillins for use in the drug discovery process.

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10. Representative procedure for solid-phase synthesis of 2β-halomethyl substituted penicillins. Preparation of compound **7a**: The solid-supported 6,6-dibromopenicillin **2** (478 mg, 0.62 mmol/g) was swollen by gentle stirring in CH_2Cl_2 (5 mL) for 30 min. MCPBA (66 mg, 0.379 mmol) in CH_2Cl_2 (1.5 mL) was added at 0°C. The reaction mixture was stirred overnight at the same temperature. After filtration, the resin was washed three times with each of the following solvents: CH_2Cl_2, EtOAc, MeOH and finally with CH_2Cl_2. The resin **3** was then dried in vacuo overnight. A portion of this resin (241 mg, 0.153 mmol) was swollen in benzene (5.9 mL) for 30 min, treated with 2-mercaptobenzothiazole (38 mg, 0.23 mmol, 1.5 equiv.) and the suspension was gently stirred at reflux for 12 h. Filtration, washing three times each with CH_2Cl_2, EtOAc, DMF, MeOH and drying in vacuo overnight, afforded the resin intermediate **4**. A portion of this resin (99 mg, 0.06 mmol) was then swollen in CH_2Cl_2 (1.3 mL) for 30 min, cooled to −40°C and treated with sulfuryl chloride (9 mg, 0.067 mmol). The reaction mixture was stirred for 1 h at the same temperature and then quenched by adding 5% $NaHCO_3$. The resulting resin **5a** was collected by filtration, washed with water and three times each with MeOH, AcOEt, CH_2Cl_2 and dried in vacuo overnight. Cleavage from the support was effected by treatment with $AlCl_3$ in CH_2Cl_2/NO_2Me for 30 min.[3] Esterification with CH_2N_2 afforded the crude product that was then purified by column chromatography (silica gel, AcOEt:hexane 2:98) to give pure **7a** as white crystals (16 mg, 70% overall yield based on initial loading of the Merrifield resin). Mp 128.5–130.5°C; IR (KBr) 1780 (β-lactam), 1752 (ester) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.54 (s, 3H, Me-α), 3.58 (d, 1H, AB system, J=12 Hz, CH_2Cl), 3.67 (d, 1H, AB system, J=12 Hz, CH_2Cl), 3.82 (s, 3H, Me ester), 5.09 (s, 1H, 3-H), 5.85 (s, 1H, 5-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.08 (C-2′α), 51.9 (C-2′β), 52.61 (CH_3 ester), 58.26 (C-2), 64.12 (C-3), 68.32 (C-6), 80.03 (C-5), 163.56 (C-7), 166.57 (C=O ester).
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13. Purification by column chromatography eliminates by products, usually the methyl 7,7-dibromo-3-cephem-4-carboxylate (**8**)[6b] and the disulfide **II**. For example, crude compound **7f** is obtained in 65% yield, showing by ^1H NMR the presence of **8** (ca. 6%) and **II** (ca. 4%).
14. Representative procedure for solid-phase synthesis of 2β-(heterocyclylthio)methyl substituted penicillins. Preparation of compound **7c**: Merrifield resin-bound sulfoxide **3** (300 mg, 0.191 mmol) (see Ref.10) was swollen in toluene (5 mL) for 30 min. The suspension was treated successively with 2-mercaptobenzothiazole (140 mg, 0.84 mmol, 4.4 equiv.) and catalytic *p*-TsOH, and then heated at reflux for 4 h. The resin was thoroughly washed with CH_2Cl_2, AcOEt, DMF, MeOH and dried

in vacuo overnight. Cleavage with $AlCl_3$ followed by esterification with CH_2N_2 gave the crude product that was purified by column chromatography (silica gel, AcOEt:hexane 2.5:97.5) to give pure **7c** as an oil (38 mg, 45% overall yield based on initial loading of the Merrifield resin). IR (film) 1796 (β-lactam), 1748 (ester) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.54 (s, 3H, Me-α), 3.77 (d, 1H, AB system, J=14 Hz, CH_2S-Het), 3.80 (s, 3H, Me ester), 4.04 (d, 1H, AB system, J=14 Hz, CH_2S-Het), 4.97 (s, 1H, 3-H), 5.85 (s, 1H, 5-H), 7.26–7.43 (m, 2H, Ar), 7.75 (d, 1H, J=9 Hz, Ar), 7.89 (d, 1H, J=9 Hz, Ar); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.49 (C-2′α), 45.45 (C-2′β), 52.6 (*C*H_3 ester), 58.63 (C-2), 66.71 (C-3), 69.44 (C-6), 80.37 (C-5), 120.93, 121.67, 124.51, 126.08, 135.50, 152.51 (Ar), 163.44 (C=O ester), 164.78 (Ar), 166.61 (C-7).