An Efficient Synthesis of 6-Oxopenicillanic and 7-Oxocephalosporanic Acid Derivatives

Daijiro Hagiwara, Kozo Sawada, Tetsuo Ohnami, Matsuhiko Aratani, and Masashi Hashimoto*

Central Research Laboratories, Fujisawa Pharmaceutical Co., Ltd., 2-1-6, Kashima, Yodogawa-ku, Osaka 532, Japan

Trifluoromethanesulphonation of benzyl 6-aminopenicillanate (**3**) and the 7-aminocephalosporanates (**7a—c**) with $(CF_3SO_2)_2O$ gave the bis(trifluoromethylsulphonate) derivatives (**5**) and (**8a—c**), which were then converted into the imines (**6**) and (**9a—c**) by treatment with 1,5-diazabicyclo[5.4.0.]undec-5-ene or triethylamine, and subsequently hydrolysed with dilute HCl to give the 6-oxopenicillanic acids (**1**) and 7-oxocephalosporanic acids (**2**), respectively.

Derivatives of 6-oxopenicillanic acid (**1**) and 7-oxocephalosporanic acid (**2**) are versatile intermediates for the preparation of new penam and cephem antibiotics.[1-6] Although several methods are available for the preparation of these intermediates,[1,6-8] they are not always satisfactory owing to the rather tedious manipulations involved. We now report a new, convenient procedure for preparing these key compounds.

Our approach was based on the known β-elimination of trifluoromethanesulphinic acid from some secondary trifluoromethanesulphonamides bearing activated α-protons.[9,10] We envisaged that bistrifluoromethanesulphonation of the corresponding primary amines would make the α-protons more acidic and facilitate the base-catalysed β-elimination of trifluoromethanesulphinic acid to yield the imine intermediates. Mild acid hydrolysis of these reactive species in the penicillin and cephalosporin series would then effect the desired oxidative transformation to provide the 6-oxo (**1**) and 7-oxo (**2**) derivatives.

Trifluoromethanesulphonation of benzyl 6-aminopenicillanate (**3**) using 1.1 equiv. of $(CF_3SO_2)_2O$ in the presence of Et_3N (1.2 equiv.) in CH_2Cl_2 at -78 °C (30 min) gave the monotrifluoromethanesulphonate (**4**) [oil, ν_{max} (CH_2Cl_2) 3310, 1795, 1740, 1390, and 1140 cm^{-1}; $\delta(CD_3COCD_3)$ 5.57 (ABq, *J* 4 Hz, 2H, 5-H and 6-H)] in quantitative yield. On the other hand, when (**3**) was treated with 3 equiv. of $(CF_3SO_2)_2O$ [Et_3N (3 equiv.)–CH_2Cl_2, $-78 \rightarrow 0$ °C, 2 h], the bis(trifluoromethylsulphonate) derivative (**5**) [ν_{max}(Nujol) 1800, 1735, 1725, 1445, and 1120 cm^{-1}; $\delta(CD_3COCD_3)$ 5.65 (d, *J* 4 Hz, 1H, 5-H), 6.26 (d, *J* 4 Hz, 1H, 6-H)]† was obtained, after work up with ice-cooled H_2O and evaporation, also in quantitative yield. This compound was somewhat unstable and decomposed to some extent upon purification by silica gel chromatography. However, the crude product was sufficiently pure to be used for the next step. Exposure of (**5**) to 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) (1.5 equiv.) in CH_2Cl_2 at -78 °C for 1 h gave (**6**), acidification of which with dilute HCl gave (**1**) in good yield after silica gel chromatography‡ (see Table 1).

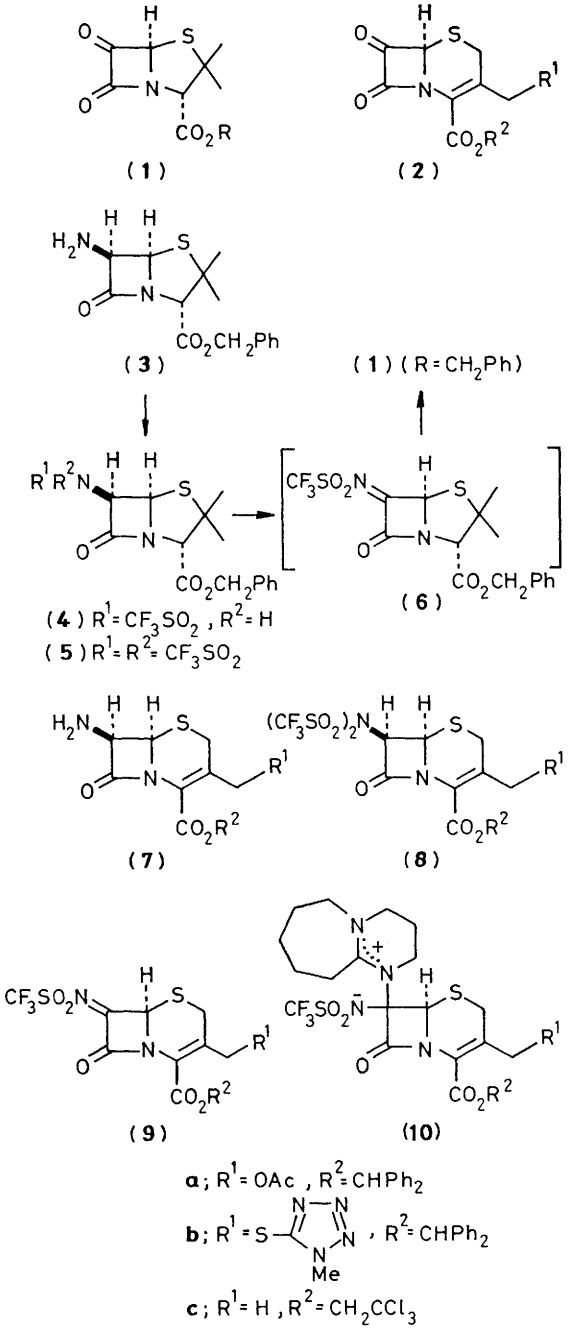
† The physical data were obtained after purification by washing with di-isopropyl ether (76%).

‡ The crude product was contaminated with the co-produced $CF_3SO_2NH_2$, which could be removed by chromatography (benzene–acetone).

Table 1. Preparation of 6-oxopenicillanic and 7-oxocephalosporanic acid derivatives

Starting material	Trifluoromethanesulphonation[a] time/h	Preparation of imine[b] (6) or (9) Base	Time/h	Product[c]	Overall yield/%
(3)	2	DBU	1	(1; R = CH_2Ph)[d]	66
(7a)	2.5	,,	,,	(2a)[e]	26
,,	,,	Et_3N	,,	,,	83
(7b)	1.5	,,	1.5	(2b)[f]	71
(7c)	2.5	DBU	1	(2c)[g]	48
,,	,,	Et_3N	1.5	,,	69

[a] *Reaction conditions:* CH_2Cl_2, $(CF_3SO_2)_2O$ (3 equiv.), Et_3N (3 equiv.), $-78 \rightarrow 0$ °C. All products were obtained in quantitative yields: (**5**), m.p. 104—106 °C; (**8a**), oil; (**8b**), m.p. 100—105 °C; (**8c**), oil. [b] *Reaction conditions:* CH_2Cl_2, base (1.5—1.7 equiv.), −78 °C. Hydrolysis of the imine was completed by treatment with dilute HCl. [c] 7-Oxocephems (**2a**—**c**) were purified by silica gel chromatography. Satisfactory analytical data (±0.4%) for C, H, and N were obtained for all products. [d] Oil (lit.[1,7] oil; m.p. 52 °C[4]); ν_{max} (CH_2Cl_2) 1830, 1780, 1740 cm^{-1}; δ ($CDCl_3$) 5.79(s, 1H). No effort was made to crystallize the product. [e] Oil (lit.[8] oil); ν_{max} (CH_2Cl_2) 1830, 1790 cm^{-1}; δ($CDCl_3$) 5.27 (s, 1H). [f] Oil; ν_{max} (CH_2Cl_2) 1820, 1780 cm^{-1}; δ($CDCl_3$) 5.28 (s, 1H). [g] Oil; ν_{max} (CH_2Cl_2) 1830, 1790 cm^{-1}; δ($CDCl_3$) 5.37 (s, 1H).



These processes were equally successful in converting 7-aminocephalosporanates (**7a**—**c**) *via* (**8a**—**c**) and (**9a**—**c**) into the corresponding 7-oxo derivatives (**2a**—**c**) as shown in Table 1. However, the yields of 7-oxocephems (**2a**, **c**) were less satisfactory when DBU was used as the base. Thus, treatment of (**8a**, **c**) with DBU, as just described, resulted in the formation of polar substances on t.l.c., which were assumed to be DBU adducts (**10**)§ of the imine intermediates (**9a**, **c**). On treatment with HCl, the intermediates (**10**) were for the most part hydrolysed to compounds (**2a**, **c**), which were isolated only in low yields. However, Et_3N was found to be more effective in these cases and provided, after treatment with HCl, 7-oxocephems (**2**) in good yield (see Table 1).

The above three-step sequence could also be more conveniently conducted as a one-pot operation, demonstrated by the conversion of (**7a**) into (**2a**) as follows. After completion of the trifluoromethanesulphonation of (**7a**) to (**8a**), Et_3N (1.5 equiv.) was added to the reaction mixture, which, after stirring for 1 h at −78 to −10 °C, was treated with dilute HCl to produce a 75% overall yield of (**2a**) after purification in a similar way to that for (**1**). Similarly, (**2c**) was obtained in 79% yield from (**7c**).

The reactions described above are highly efficient and offer a convenient method for preparing 6-oxopenicillanic and 7-oxocephalosporanic acid derivatives.

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§ No effort was made to isolate this adduct.