Preparation of *tert*-Butyl 6-Aminopenicillanate and its 6-Oxo and 6-Diazo Derivatives†

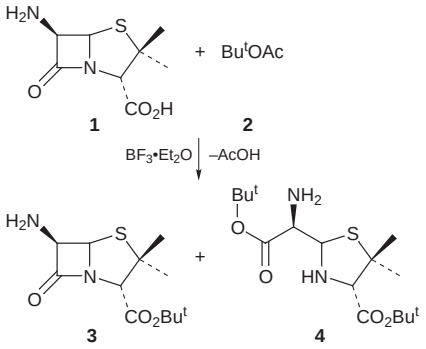
J. Chem. Research (S), 1999, 270–271†

Grigory Veinberg,* Maxim Vorona, Dan Musel, Nora Grigan and Edmunds Lukevics

Latvian Institute of Organic Synthesis, 21 Aizkraukles Street, Riga, LV 1006, Latvia

A 1:1 1,4-dioxane–*tert*-butyl acetate mixture and BF_3 etherate were used for an effective 6-aminopenicillanic acid conversion into the *tert*-butyl ester (64 ± 3% yield) which could be easily transformed into *tert*-butyl 6-oxo- and 6-diazo-penicillanates.

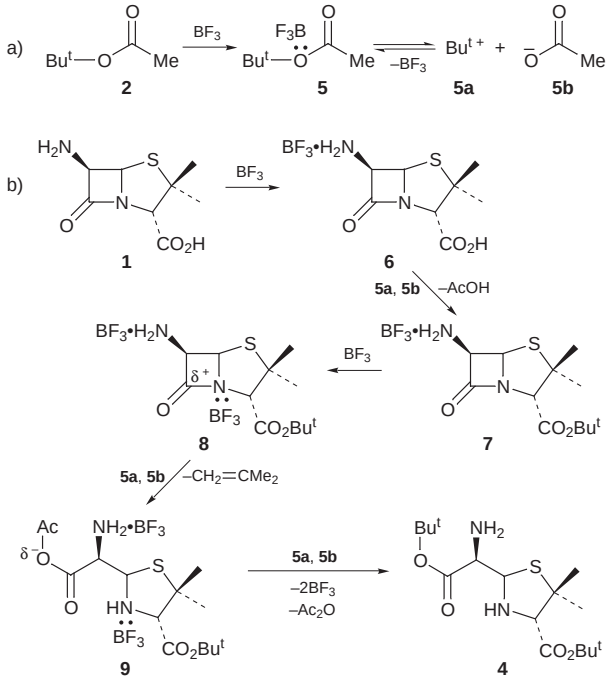
6-Aminopenicillanic acid (6-APA) esters are widely used as starting materials for the preparation of various clinically useful substances. The chemical lability of the β-lactam ring dramatically reduces the choice of the carboxyl protective groups to those which can be introduced and eliminated under mild conditions. The *tert*-butyl group is one such, but in contrast to 7-aminocephalosporanic acid (7-ACA) and 7-aminodeacetoxycephalosporanic acid (7-ADCA), there are only few examples of its utilization in the case of 6-APA (**1**) obviously due to the low reactivity of *O*-*tert*-butyl-*N,N'*-dicyclohexyl isourea (10.8%).[1] In a previous report we have described a simple and highly effective method for *tert*-butyl esterification of 7-aminocephalosporanic acid using a mixture of *tert*-butyl acetate (**2**) and boron trifluoride etherate and an attempt to apply these reagents for the preparation of *tert*-butyl APA (**3**).[2]



It was found that treatment of 6-APA in pure **2**, gave target ester **3** in 21% yield and a side product identified as the di-*tert*-butyl ester of penicic acid (**4**). Formation of the latter could be explained by the specific ability of BF_3, as a strong Lewis acid, to convert **2** into the intermediate ions **5a**, **5b** (Scheme 1, *reaction a*), and to facilitate their addition to the intermediates **8** and **9** (Scheme 1, *sequence b*).

Therefore, according to Scheme 1, the yield of **3** could be increased by inhibition of the reaction sequence at the stage of monoester **7** by preventing its conversion into the undesirable intermediate **8**. This problem could be solved by addition to the reaction mixture of solvents capable of behaving as electron donors and competing with penam nitrogen for BF_3.

The investigation of their effect on the yield and quality of **3** *vs.* the control (Table 1, entry 1) led to the following results. Diethyl ether, ethyl acetate and acetone did not affect the esterification process. Addition of DMF and methanol to **2** caused a detrimental effect and only acetonitrile and 1,4-dioxane increased the yield **3** (Table 1).



Scheme 1

The optimal 64 ± 3% yield of pure *tert*-butyl 6-aminopenicillanate was reached using a 1:1 dioxane–*tert*-butyl acetate mixture. Attempts to improve the yield by varying the ratio failed (Table 1, entries 4 and 5).

Attempts to recover 6-APA by treatment of **3** with trifluoroacetic or Lewis acids in dichloromethane according to procedures published in ref. 4 led to destruction of the β-lactam ring. However **3** proved to be stable under other types of chemical transformations.

It was found that, contrary to the benzhydryl protecting group, *tert*-butyl favored the transformation of **3** into 6-oxopenicillanate **10** in the manner described by Hagiwara *et al.*[5] Treatment of **3** in dichloromethane with isopropyl nitrite in the presence of catalytic amounts of trifluoroacetic

Table 1 Effect of solvents on the yield of *tert*-butyl 6-APA

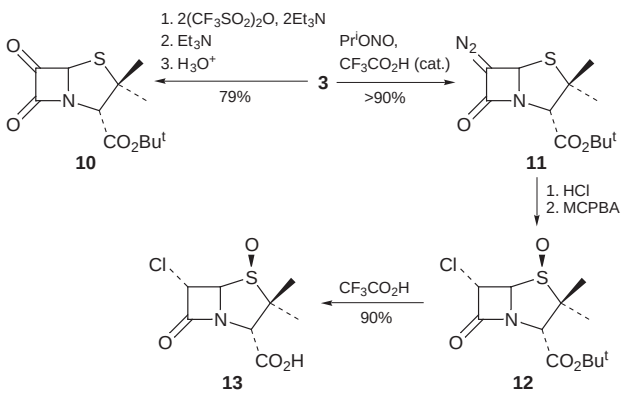
Entry	Solvent	*tert*-butylacetate–solvent ratio	*t*/h	Yield (%)
1	*tert*-Butyl acetate	–	6	21[a]
2	Acetonitrile	1:1	6	35[b]
3	1,4-Dioxane	1:1	3	64 ± 3
4	1,4-Dioxane	5:3	3	44
5	1,4-Dioxane	3:5	4	48

[a] Crude product contaminated with **9** (TLC: $R_f = 0.53$). [b] Crude product contaminated with unidentified substance (TLC: $R_f = 0.06$).

* To receive any correspondence.

† This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1999, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

acid resulted in its almost quantitative conversion into 6-diazopenicillanate **11**. Its subsequent transformation into 6α-chloropenicillanate 1-oxide **13** serves as an example of efficient carboxyl deprotection (Scheme 2).



Scheme 2

The presented data demonstrate the successful application of a simple and effective transacylation protocol for the synthesis of previously scarcely available *tert*-butyl 6-APA, simple and efficient removal of the protective group, and its beneficial effect on the transformation of this amino ester into 6-oxo and 6-diazo derivatives.

Experimental

The ^{1}H NMR spectra were recorded on a Bruker WH-90 spectrometer (90 MHz) using $CDCl_3$ as solvent. Chemical shifts were registered in ppm relative to TMS. IR spectra were recorded on a Perkin-Elmer 580B spectrophotometer. HPLC analyses were performed on a Dupont Model 8800 chromatograph with a UV detector ($\lambda = 254$ nm). Microanalytical data were obtained on a Carlo Erba 1108 apparatus. All reactions were monitored by TLC carried out on Merck Kieselgel plates (ethyl acetate–hexane, 1:1) using ninhydrin as a visualizing agent. Merck Kieselgel (0.063–0.230 mm) was used for preparative column chromatography.

General Procedure for the tert-*Butyl Esterification of* 6-*APA*.—A suspension of 6-APA (1.0 g, 4.6 mmol) in a mixture of *tert*-butyl acetate (10 ml, 74 mmol), boron trifluoride diethyl etherate (2.0 ml, 15.8 mmol) and an equal volume of the tested solvent was stirred at 14–16 °C for 3–6 h. On completion of the process, the reaction mixture was quenched with water (50 ml). The aqueous solution was separated, neutralized with K_2CO_3, and extracted with ethyl acetate (50 ml). The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give the crude product, which if necessary was purified by column chromatography (ethyl acetate-hexane, 1:1) to afford *tert*-butyl 6-aminopenicillanate (**3**) with 98–99% purity by HPLC assay.

Penicic acid di-tert-butyl ester (**4**) isolated from reaction mixtures (Table 1, entry 1) by column chromatography (ethyl acetate–hexane, 1:1) had mp 84–86 °C, δ_H ($CDCl_3$)1.42–1.55 (m, 21 H, CH_3, 2 Bu^t), 1.61 (s, 3 H, CH_3) 2.51 (br s, 2 H, NH_2), 3.55 (s, 1 H, 4-H thiazolidine), 3.71 (d, 1 H, $J = 4$ Hz, 2-H thiazolidine), 5.06 (d, 1 H, $J = 4$ Hz, 2-$CHCO_2$); IR (film): 3300, 2980, 2920, 1730, 1680 cm^{-1}. (Found: C, 55.84; H, 8.73; N, 7.64. $C_{16}H_{30}N_2O_4S \cdot 0.1C_6H_{12}$ requires C, 56.15; H, 8.90; N, 7.88%).

tert-Butyl 6-Oxopenicillanate (**10**) was prepared according to procedure of Buynak *et al.*[6] δ_H ($CDCl_3$) 1.49 (3 H, s, Me), 1.51 (9 H, s, Bu^t), 1.57 (3 H, s, Me), 4.66 (1 H, s, 3-H), 5.77 (1 H, s, 5-H). IR (Nujol): 1830, 1790, 1740 cm^{-1}.

tert-Butyl 6-Diazopenicillanate (**11**) was prepared according to ref. 7. IR (film): 2980, 2940, 2080, 1770, 1740 cm^{-1}.

6α-*Chloropenicillanate* 1-*Oxide* (**13**).—*tert*-Butyl 6α chloropenicillanate 1-oxide (**12**) (800 mg, 2.60 mM) prepared from **11** according to ref. 8 was dissolved in trifluoroacetic acid (3 ml) and stirred at room temperature for 1 h. The reaction mixture was concentrated *in vacuo* and the residue purified by column chromatography (ethyl acetate) to afford 600 mg (91%) of **13** with ^{1}H NMR and IR data identical to published in the literature.[9]

We are grateful to Taiho Pharmaceutical Co. for generous gift of 6-APA.

Received, 4th November 1998; Accepted, 20th January 1999
Paper E/9/08587K

References

1 B. M. Bain and E. P. Tiley, *Br. Pat.*, 1327102, 1970.
2 N. Grigan, D. Musel, G. A. Veinberg and E. Lukevics, *Synth. Commun.*, 1996, **26**, 1183.
3 P. Proctor, N. P. Gensmantel and M. I. Page, *J. Chem. Soc., Perkin Trans. 2*, 1982, 1185.
4 M. Valencic, T. van der Does and E. de Vroom, *Tetrahedron Lett.*, 1998, **39**, 1625.
5 D. Hagiwara, K. Sawada, T. Ohnami, M. Aratani and M. Hashimoto, *J. Chem. Soc., Chem. Commun.*, 1982, 578.
6 J. D. Buynak, K. Wu, B. Bachmann, D. Khasnis, L. Hua, H. K. Nguyen and C. L. Carver, *J. Med Chem.*, 1995, **38** 1022.
7 T. J. Blacklock, J. W. Butcher, P. Sohar, T. R. Lamanec and E. J. J. Grabowski, *J. Org. Chem.*, 1989, **54**, 3907.
8 G. Veinberg, R. Bokaldere, K. Dikovskaya, M. Vorona, D. Musel, H. Kazhoka, I. Turovsky, I. Shestakova, I. Kanepe, I. Domracheva and E. Lukevics, *Khim. Geterotsikl. Soed.*, 1998, 1494.
9 L. S. Changov, B. K. Vasileva-Lukanova, N. N. Agapova, M. M. Tsenkova, D. M. Mondeshka and Z. T. Ivanova, *Antibiot. Khimioterap.*, 1990, **35**, No. 8, 12.