

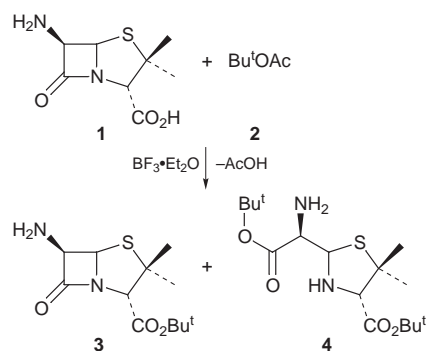
Preparation of *tert*-Butyl 6-Aminopenicillanate and its 6-Oxo and 6-Diazo Derivatives†

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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 ($64 \pm 3\%$ 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



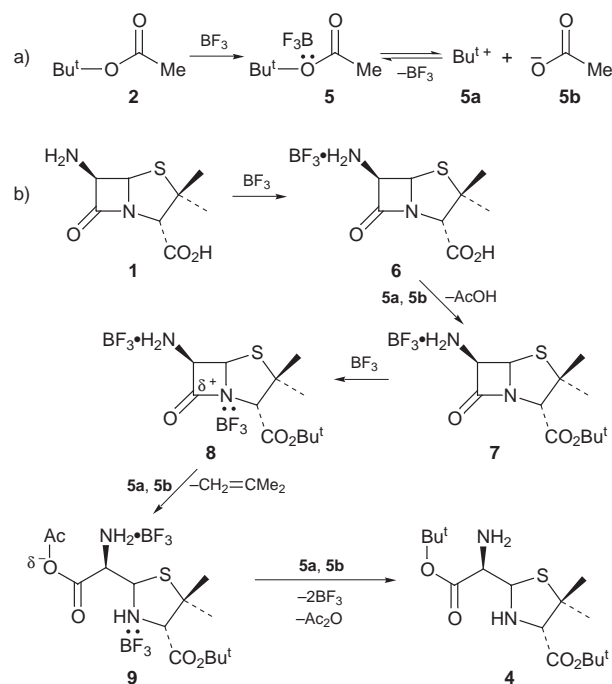
It was found that treatment of 6-APA in pure **2**, gave target ester **3** in 21% yield and a side product identified as the di-*tert*-butyl ester of penicillanic acid (**4**). Formation of the latter could be explained by the specific ability of BF_3 , as a strong Lewis acid, to convert **2** into 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).

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† 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)*.



Scheme 1

The optimal $64 \pm 3\%$ 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.

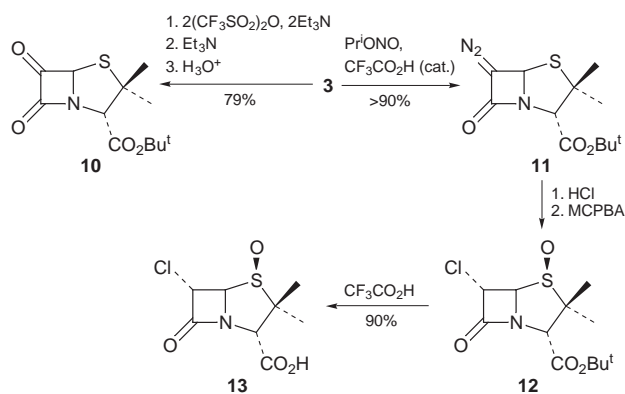
It was found that, contrary to the benzhydryl protecting group, *tert*-butyl favored the transformation of **3** into 6-oxopenicillanate **10** in the manner described by Hagiwara *et al.*⁵ Treatment of **3** in dichloromethane with isopropyl nitrite in the presence of catalytic amounts of trifluoroacetic

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

Entry	Solvent	<i>tert</i> -butylacetate– solvent ratio	t/h	Yield (%)
1	<i>tert</i> -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: $R_f = 0.06$).

acid resulted in its almost quantitative conversion into 6-diazopenicillanate **11**. Its subsequent transformation into 6 α -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 ^1H 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 ($\lambda = 254\text{ nm}$). 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, $J = 4\text{ Hz}$, 2-H thiazolidine), 5.06 (d, 1 H, $J = 4\text{ Hz}$, 2- CHCO_2); IR (film): 3300, 2980, 2920, 1730, 1680 cm^{-1} . (Found: C, 55.84; H, 8.73; N, 7.64. $\text{C}_{16}\text{H}_{30}\text{N}_2\text{O}_4\text{S} \cdot 0.1\text{C}_6\text{H}_{12}$ 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} .

6 α -Chloropenicillanate 1-Oxide (13).—***tert*-Butyl 6 α chloropenicillanate 1-oxide (12)** (800 mg, 2.60 mmol) 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 ^1H NMR and IR data identical to published in the literature.⁹

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References

- B. M. Bain and E. P. Tiley, *Br. Pat.*, 1327102, 1970.
- N. Grigan, D. Musel, G. A. Veinberg and E. Lukevics, *Synth. Commun.*, 1996, **26**, 1183.
- P. Proctor, N. P. Gensmantel and M. I. Page, *J. Chem. Soc., Perkin Trans. 2*, 1982, 1185.
- M. Valencic, T. van der Does and E. de Vroom, *Tetrahedron Lett.*, 1998, **39**, 1625.
- D. Hagiwara, K. Sawada, T. Ohnami, M. Aratani and M. Hashimoto, *J. Chem. Soc., Chem. Commun.*, 1982, 578.
- J. D. Buynak, K. Wu, B. Bachmann, D. Khasnis, L. Hua, H. K. Nguyen and C. L. Carver, *J. Med. Chem.*, 1995, **38** 1022.
- T. J. Blacklock, J. W. Butcher, P. Sohar, T. R. Lamanec and E. J. J. Grabowski, *J. Org. Chem.*, 1989, **54**, 3907.
- 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.
- 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.