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The Deblocking of Cephalosporin Benzhydryl Esters with Formic Acid

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The synthesis of benzhydryl esters of cephalosporin derivatives (**4**—**6**) and removal of the benzhydryl protecting group with formic acid are described.

Keywords——cephalexin; cephapirin; 7-aminocephalosporanic acid; benzhydryl ester; formic acid

Benzhydryl ester is one of the most important protecting groups[1] for carboxylic acids and alcohols, because of its facile removal over palladium or platinum catalysts under neutral reduction conditions. In the synthesis of β-lactam antibiotics, most of which are labile to both acidic and alkaline conditions, this ester group has often been used as a carboxylic acid protecting group with the advantage of simple formation under neutral conditions by reacting appropriate acids with diphenyldiazomethane. A convenient procedure for deblocking of this group is catalytic hydrogenolysis, which, however, cannot be applied to the compounds bearing reduction-labile groups, such as a nitro group or carbon-carbon multiple bond. Another satisfactory deblocking method is hydrolysis[2-4] with acid, such as hydrochloric acid, hydrobromic acid, acetic acid or trifluoroacetic acid in an appropriate solvent. Application of the latter method is sometimes unsuitable for β-lactam antibiotics, since these acids would decompose the antibiotics. Among the above acids, trifluoroacetic acid is preferred, but this reagent is very expensive from an industrial point of view. Therefore, the development of effective deblocking methods for benzhydryl esters to generate free acids without decomposition of the original molecule is desirable. We wish to report a mild and convenient deblocking method for benzhydryl ester with inexpensive formic acid[5] and the application of this procedure for the synthesis of cephalosporin derivatives.

It is noteworthy that in the synthesis of cephalosporin derivatives from 7-aminocephalosporanic acid by modification of the amino group at the C_7-position, the carboxylic acid at the C_4-position should generally be masked to obtain the desired product in a satisfactory yield.

Cephalexin benzhydryl ester (**4**), prepared from cephalexin (**1**)[6] by treatment with diphenyldiazomethane[7] in 67% yield, was warmed in 98—100% formic acid at 40—45°C for 0.5 h. After evaporation of the solvent at the same temperature, the residue was solidified with ether to give cephalexin (**1**), in 70% yield; this product was identical with the authentic

Table I. The Deblocking of Benzhydryl Esters with Formic Acid[a]

$$R\text{–}CO_2CHPh_2 + HCO_2H \longrightarrow R\text{–}CO_2H$$

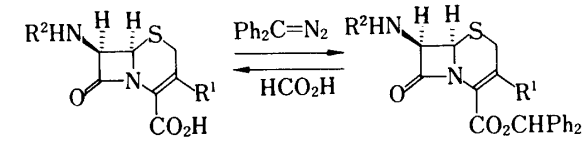
Ester	Acid	Yield (%)
4	**1**	70
5	**2**	90
6	**3**	84
8	**7**	89
10	**9**	97

a) All the reactions were carried out at 40—45°C for 0.5 h with 20- to 100-fold molar excess of formic acid.

specimen. Similarly, 7-aminocephalosporanic acid (**3**) was treated with diphenyldiazomethane to afford its benzhydryl ester[8] (**6**) in quantitative yield, and the deblocking reaction of **6** with formic acid was carried out as above to give rise to 7-aminocephalosporanic acid (**3**) in 84% yield. 7-Aminocephalosporanic acid benzhydryl ester (**6**) was converted to cephapirin benzhydryl ester (**5**) according to the known method by treatment of **6** with 4-thiopyridylacetyl chloride in 67% yield. Removal of the benzhydryl group with formic acid afforded cephapirin[10] (**2**) in 90% yield. These products (**1**—**3**) obtained above were identical with authentic samples and did not require any further purification.

Finally, this procedure was applied to 2-nitro-4,5-dimethoxyphenylacetic acid[11] (**9**) and 3,4-methylenedioxycinnamic acid (**7**),[12] both of which have a reduction-labile functional group in the molecule.

Treatment of **7** and **9** with diphenyldiazomethane in ethyl acetate–methylene chloride (2: 1 v/v) solution gave the corresponding ester (**8** and **10**), in 89% and 86% yields, respectively, and treatment with formic acid furnished the acids (**7** and **9**) in 89% and 97% yields, respectively.



1: R^1=Me, R^2=COCH(NH_2)Ph
2: R^1=CH_2OAc, R^2=$COCH_2S$-(4-pyridyl)
3: R^1=CH_2OAc, R^2=H
4: R^1=Me, R^2=COCH(NH_2)Ph
5: R^1=CH_2OAc, R^2=$COCH_2S$-(4-pyridyl)
6: R^1=CH_2OAc, R^2=H

7: R=H
8: R=$CHPh_2$
9: R=H
10: R=$CHPh_2$

Chart 1

Thus, a facile deblocking procedure for benzhydryl esters by treatment with formic acid, with advantage of simple work-up, has been established, and should be applicable to various types of multi-functionalized compounds.

Experimental

Melting points were measured on a Yazawa melting point apparatus and are uncorrected. Infrared (IR) spectra were measured with a Hitachi 260-10 infrared spectrophotometer, and nuclear magnetic resonance (NMR) spectra with a JEOL JNM-FX100 spectrometer, using tetramethylsilane as an internal reference.

General Procedure for the Deblocking of Benzhydryl Esters with Formic Acid——A solution of the benzhydryl esters (**4**, **5**, **6**, **8**, and **10**) (each 200 mg) in 98—100% formic acid (1 ml) was warmed at 40—45°C for 0.5 h with stirring. After evaporation of excess formic acid at the same temperature, the residue was crystallized from an appropriate solvent in the yield shown in the table.

Cephalexin Benzhydryl Ester (**4**)——Cephalexin (**3**) (1 g) was added to a stirred solution of diphenyldiazomethane, prepared from benzophenone hydrazone (1.25 g), in methylene chloride–methanol (1: 1 v/v) (8 ml) at ambient temperature, and the resulting mixture was further stirred for 20 h. After evaporation of the solvent, the residue was crystallized from ether to give cephalexin benzhydryl ester (**4**) (1.0 g, 67%) as a colorless powder, mp 90—93.5°C (dec.) (ether–*n*-hexane). *Anal.* Calcd for $C_{29}H_{27}N_3O_4S \cdot 0.25H_2O$: C, 67.23; H, 5.35; N, 8.11. Found: C, 67.18; H, 5.34; N, 7.95%. IR ν_{max}^{KBr} cm^{-1}: 3300 (NH_2), 1780, 1725, 1690 (C=O); NMR ($CDCl_3$) δ: 1.74 (2H, br s, NH_2), 2.11 (3H, s, Me), 3.18 (1H, d, J=18 Hz, C_2–H), 3.51 (1H, J=18 Hz, C_2–H), 4.59 (1H, s, >C<u>H</u>–NH_2), 4.98 (1H, d, J=5 Hz, C_6–H), 5.78 (1H, dd, J=5 and 10 Hz, C_7–H), 6.91 (1H, s, >C<u>H</u>Ph_2), 7.25—7.43 (15H, m, Ar<u>H</u>), 7.92 (1H, d, J=10 Hz, NH).

Cephapirin Benzhydryl Ester (**5**)——Propylene oxide (5.8 g) was added to a stirred solution of 7-amino-

cephalosporanic acid benzhydryl ester (**6**) (4.38 g) in methylene chloride (48 ml). The mixture was stirred for 0.2 h at ambient temperature, then the hydrochloride of 4-pyridylthioacetyl chloride (2.7 g) was added to the above solution in one portion and the resulting mixture was further stirred for 1 h. The mixture was diluted with water and acidified with 10% hydrochloric acid to pH 0.6—0.7. The acidic aqueous layer was extracted with methylene chloride and the extract was washed with water, dried (Na_2SO_4) and concentrated to give the benzhydryl ester (**5**) (5.76 g, 93%) as a colorless powder, mp 108—114°C (ether–*n*-hexane). *Anal.* Calcd for $C_{30}H_{27}N_3O_6S_2$: C, 61.10; H, 4.62; N, 7.13. Found: C, 60.95; H, 4.95; N, 7.04%. IR ν_{max}^{KBr} cm^{-1}: 3270 (NH), 1780, 1740, 1720 (sh), 1660 (C=O); NMR ($CDCl_3$) δ: 2.00 (3H, s, OAc), 3.24 (1H, d, J=17 Hz, C_2–H), 3.48 (1H, d, J=17 Hz, C_2–H), 3.75 (2H, s, SCH_2CO), 4.72 (1H, d, J=13 Hz, $-\underset{\underset{H}{|}}{C}-OAc$), 5.02 (1H, d, J=13 Hz, $\underset{\underset{H}{|}}{C}-OAc$), 5.80 (1H, dd, J=5 and 10 Hz, C_7–H), 6.95 (1H, s, $CHPh_2$), 7.10—7.18 (2H, m, pyridine protons), 7.20—7.52 (11H, m, ArH and NH), 8.40—8.52 (2H, m, pyridine protons).

3,4-Methylenedioxycinnamic Acid Benzhydryl Ester (**8**)——3,4-Methylenedioxycinnamic acid (800 mg) was added to a stirred solution of diphenyldiazomethane [prepared from benzophenone hydrazone (2.5 g), in ethyl acetate–methylene chloride (2: 1 v/v) (30 ml)] at room temperature, and the resulting mixture was stirred at the same temperature for 20 h. After evaporation of the solvent, the residue was crystallized from ether–*n*-hexane (1: 1 v/v) to give the ester (**8**) (1.3 g, 89%) as colorless needles, mp 119.5—121°C (from ether–*n*-hexane). *Anal.* Calcd for $C_{23}H_{18}O_4 \cdot 0.25H_2O$: C, 73.39; H, 5.36. Found: C, 73.71; H, 4.92%. IR ν_{max}^{KBr} cm^{-1}: 1710 (C=O); NMR ($CDCl_3$) δ: 5.97 (2H, s, OCH_2O), 6.37 (1H, d, J=16 Hz, ArCH=CH, 6.70—7.40 (13H, m, ArH), 7.23 (1H, s, $CHPh_2$), 7.67 (1H, d, J=16 Hz, ArCH=CH–).

4,5-Dimethoxy-2-nitrophenylacetic Acid Benzhydryl Ester (**10**)——The esterification of the acid (**9**) (0.96 g) with diphenyldiazomethane was carried out as above to afford the ester (**10**) (1.4 g, 86%) as a pale yellowish powder, mp 120—121.5°C (from ether–*n*-hexane). *Anal.* Calcd for $C_{23}H_{21}NO_6$: 67.80; H, 5.20; N, 3.44. Found: C, 67.78; H, 5.09; N, 3.30%. IR ν_{max}^{KBr} cm^{-1}: 1740 (C=O), 1520, 1335 (NO_2); NMR ($CDCl_3$) δ: 3.90 (3H, s, OMe), 3.94 (3H, s, OMe), 4.09 (2H, s, $ArCH_2$), 6.70 (1H, s, C_6–H), 6.90 (1H, s, $CHPh_2$), 7.30 (10H, s, ArH), 7.72 (1H, s, C_3–H).

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