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SYNTHETIC STUDIES ON β-LACTAM ANTIBIOTICS. VII.[1]
MILD REMOVAL OF THE BENZYL ESTER PROTECTING GROUP WITH ALUMINUM TRICHLORIDE

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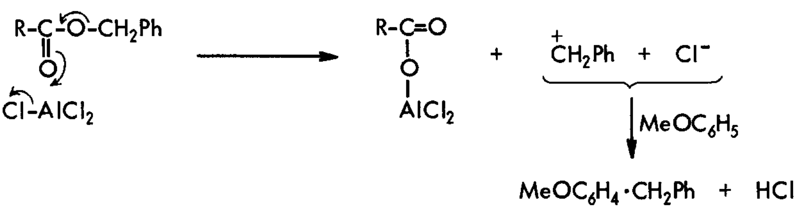
Summary The benzyl ester protecting group in β-lactam derivatives can be cleanly removed by treatment with aluminum trichloride under mild conditions, preferably in the presence of anisole, to give the corresponding free acids in high yields.

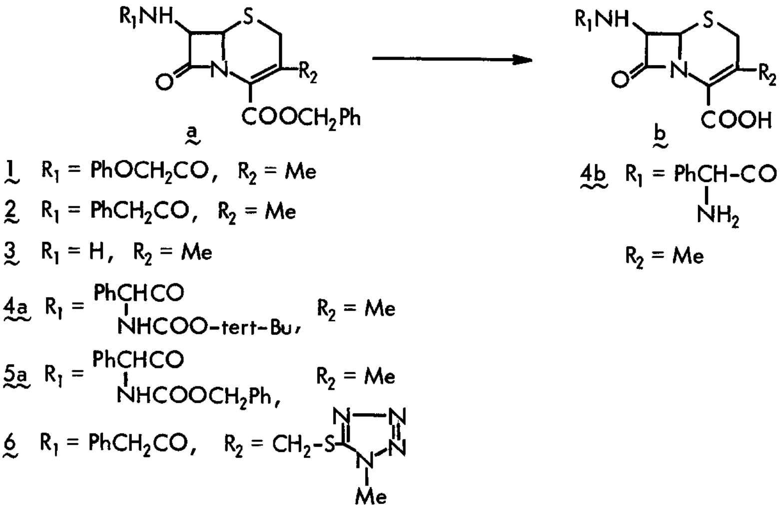
The benzyl ester has been widely used as a carboxyl protecting group in organic syntheses. In the field of β-lactam chemistry, however, the use of this ester has been limited on laboratory scale and sometimes is disadvantageous, because deprotection by hydrogenolysis usually needs a large amount of a metal catalyst or a prolonged reaction time owing to poisoning by the sulfur atom at position 1 of penicillins and cephalosporins.[2] An alternative method using a strong acid results in cleavage of the β-lactam ring. We wish to report that aluminum trichloride is effective for facile removal of the benzyl ester in β-lactam derivatives. While our process was submitted to the patent literature three years ago,[3] Fujita et al. very recently reported dealkylation of alkyl and benzyl esters by SN2 reaction using an aluminum halide-thiol combination.[4]

Our process is based on the expectation that aluminum trichloride, a strong Lewis acid having a high affinity for oxygen, would coordinate with the carbonyl oxygen to assist generation of the benzyl cation which is, in turn, trapped by anisole, as shown in the following equation:



The Table summarizes the results on deblocking of cephalosporin esters. In a typical procedure (run 3), a solution of $AlCl_3$ (950 mg) in nitromethane (20 ml) was added to a solution of benzyl 7β-phenoxyacetamido-3-methyl-3-cephem-4-carboxylate (**1a**) (1.0 g) and anisole (1.5 g)

Table



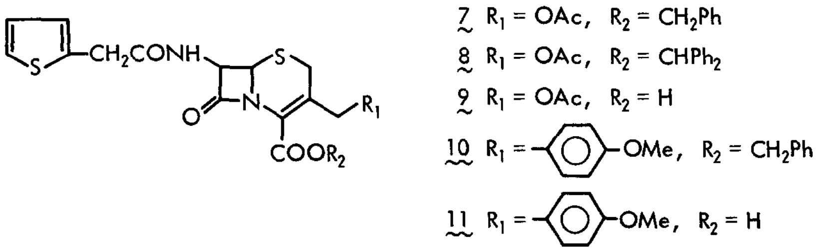
Run	Substrate	$AlCl_3$[a]	Anisole[a]	Solvent (ratio)	Time[b] (hr)	Product	Yield (%)	M.p. (°C)
1	**1a**	3.00	0	CS_2-$MeNO_2$ (1:1)	6	**1b**	95.1	168-173[c]
2	**1a**	3.08	6	CS_2-$MeNO_2$ (1:1)	5	**1b**	93.4	184-186[c]
3	**1a**	3.12	6	CH_2Cl_2-$MeNO_2$ (1:1)	5	**1b**	93.9	180-183[c]
4	**1a**	3.00 ($TiCl_4$)	6	CH_2Cl_2	4.4	**1b**	86.0	179-183[c]
5	**2a**	3.00	6	CH_2Cl_2-$MeNO_2$ (1:1)	4.5	**2b**	86.1	193-196[d]
6	**3a**	5.92	12	CH_2Cl_2-$MeNO_2$ (5:2)	4.5	**3b**	81.7[e]	Purity 96.8%
7	**4a**	6.00	6	CH_2Cl_2-$MeNO_2$ (2:1)	3	**4b**	88.0[f]	(Powder)
8	**5a**	6.00		Anisole	5	**4b**	73.4[f]	(Powder)
9	**6a**	3.00	3	CH_2Cl_2-$MeNO_2$ (1:1)	1/6	**6b**	80.0	(Powder)

[a] Molar equiv. [b] The reaction was carried out at room temperature, unless otherwise stated. [c] Lit,[5] m.p. 186-188°. [d] Lit,[5] m.p. 198-200°. [e] The product was isolated from the reaction mixture by treatment with diluted hydrochloric acid followed by adjustment of pH to 2.4 with aqueous sodium hydroxide. Purity was determined by HPLC. [f] The reaction mixture was diluted with water and adjusted to pH 1.5 with hydrochloric acid. The aqueous layer was concentrated and the concentrate was passed through a column filled with Diaion HP-20 which was eluted with aqueous ethanol. Concentration of the eluates gave crude **4b**.

in methylene chloride (20 ml) under ice cooling, and the mixture was stirred for 5 hours at room temperature. The reaction solution was diluted with ethyl acetate, washed with diluted hydrochloric acid and extracted with 5% aqueous $NaHCO_3$. The aqueous extract was acidified witl hydrochloric acid and extracted with ethyl acetate. The extract was washed with water, dried, and evaporated to give a crystalline residue, which was recrystallized from acetone-pentane to yield acid 1b (745 mg).

In the absence of anisole (run 1), purity of the product is inferior as evident from its lower melting point. Titanium tetrachloride is another Lewis acid which effected deblocking of ester 1a (run 4). Under similar conditions, the action of boron trifluoride etherate or stannic chloride on 1a accompanied fission of the β-lactam ring. Concurrent deprotection of the carboxyl and amino protecting groups in compounds 4a and 5a was successful (run 7 and 8), giving cephalexin, an important oral antibiotic,[6] in good yields. Run 7 also demonstrates that the tert-butyl ester protecting group was smoothly deblocked by this procedure. Interestingly, the reaction with 6a having a tetrazolylthiomethyl group at position 3 occurred quite rapidly even at ice-cooling temperature.

Treatment of cephalothin benzyl ester 7 with 3 molar equiv of aluminum trichloride caused substitution of the acetoxy group with the p-methoxyphenyl group giving 10 and 11 in addition to the desired cephalothin 9.[7] However, the corresponding benzhydryl ester 8 underwent smooth deprotection even under ice-cooling giving 9 exclusively. This result clearly indicates that the benzhydryl ester group, another important protecting group in the field of β-lactam chemistry, can be more easily deblocked by the present method.[8]



With the mild reaction conditions necessary for the deprotection and with the good compatibility with labile functionalities, this aluminum trichloride process would be well applicable in other fields of organic chemistry, especially to deprotection of benzyl, benzhydryl, or tert-butyl esters in derivatives having acid- and/or alkali-sensitive functional groups.

References and Notes

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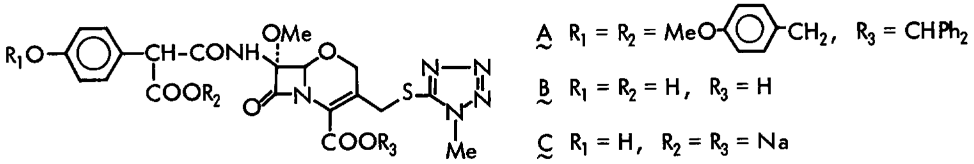

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