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DEPROTECTION OF CARBOXYLIC ESTERS ASSISTED BY HYDROGEN BONDING NETWORK IN PHENOLIC MEDIA. ITS APPLICATION TO β-LACTAM ANTIBIOTIC SYNTHESES[1]

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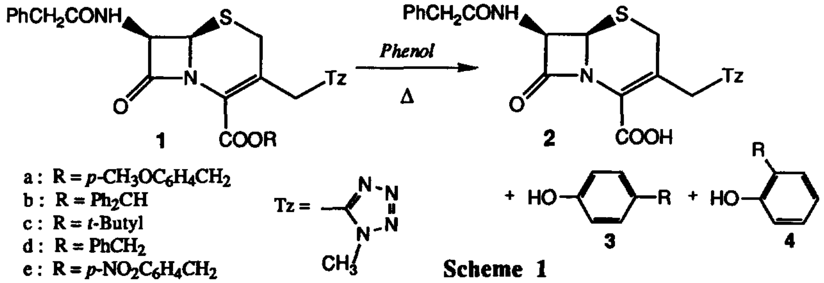
Summary: Deprotection of *p*-methoxybenzyl, diphenylmethyl, and *tert*-butyl ester groups, which is an essential step of β-lactam antibiotic synthesis, can be performed successfully by gentle heating in phenolic media.

Protection and deprotection of carboxyl groups are essential steps in the multi-step syntheses of complex carboxylic acids. *p*-Methoxybenzyl (PMB), diphenylmethyl (BH), and *tert*-butyl (Bu^t) groups have been widely used for this purpose. Removal of the protecting groups has be performed by treatment with acids[2], *e.g.*, trifluoroacetic acid (TFA),[3] formic acid,[4] and combination of Lewis acids with anisole[5] or thiol.[6] In most cases, however, stoichiometric or excessive amounts of acids are required to complete the reaction and these facts cause the restriction of the use of the protecting groups for acid labile carboxylic acids. We report herein a new method of deprotection of PMB, BH, and Bu^t moieties of the esters **1** assisted by a hydrogen bonding network in phenolic media,[7] which may reduce the amount of acids significantly, in a particular case, to zero so as to be successfully applied to the synthesis of acid labile β-lactam antibiotics.



a : R = p-$CH_3OC_6H_4CH_2$
b : R = Ph_2CH
c : R = *t*-Butyl
d : R = $PhCH_2$
e : R = p-$NO_2C_6H_4CH_2$

Scheme 1

A typical reaction procedure is as follows (entry 1 in Table 1): A mixture of *p*-methoxybenzyl cephem-4-carboxylate **1a** (R = PMB; 3.5 mmol) and TFA (3.5 mmol) in phenol (7 g) was heated to 45 °C for 1 h. The mixture was diluted with ethyl acetate (60 ml) and extracted twice with aq. $NaHCO_3$. The aqueous extracts were combined and acidified (ca. pH 1) with aqueous 10% HCl under ice-cooling, affording the corresponding acid **2** (91%) as colorless crystals. From the organic layer, *p*- and *m*-(*p*-methoxybenzyl)phenol (**3a** and **4a**) were isolated in 57% and 15% yields, respectively. The amount of TFA can be reduced to 0.5-0.1 equiv., if necessary, by a slight modification of the reaction conditions (entries 1-3).[8] In place of TFA, various acids, such as HCl, H_2SO_4, $KHSO_4$, and *p*-toluene sulfonic acid (PTS), can be used effectively (entries 4-7). More astonishingly, the reaction proceeded even without adding any acid catalysts; thus, heating of a mixture of **1a** and phenol at 60 °C for 3 h afforded **2a** in satisfactory yields (entries 8 and 9). The unusual character of phenol *(vide supra)* can be explained by assuming a hydrogen bonding network surrounding the ester as illustrated in Figure 1, wherein the proton would be relayed smoothly to the ester moiety.[7,9]

Table 1. Effects of Acid Catalysts on Deprotection of PMB Ester **1a** in Phenol[a].

entry	acid (equiv.)	temp/°C	time/h	yield/%	entry	acid (equiv.)	ttemp/°C	time/h	yield/%
1	TFA (1)	45	1	91	6	$KHSO_4$ (1.2)[b]	45	1	86
2	TFA (0.5)	45	1	95	7	PTS (0.05)	45	1	92
3	TFA (0.1)	60	1.2	96	8	none	45	1	30 (69)[c]
4	HCl (0.03)	45	1	91	9	none	60	3	96
5	H_2SO_4 (0.05)	45	1	89					

a) Carried out in the manner as described in the text. b) Scarcely soluble in phenol.
c) Number in parenthesis: recovered **1a**.

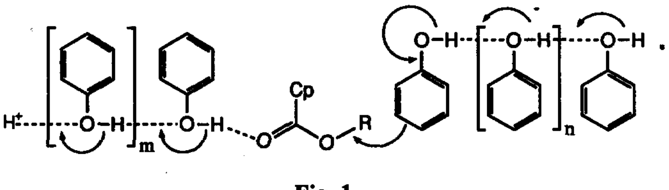
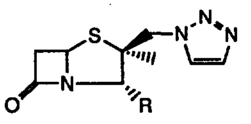


Fig 1



5 R = Ph_2CH
6 R = H

The present method was successfully applied to BH and Bu^t esters **1b** and **1c**, affording **2** in 92 and 64% yields, respectively (Scheme 1), whereas benzyl and *p*-nitrobenzyl esters **1d** and **1e** were recovered intact after heating at 45°C for 1 h in phenol containing TFA (1 equiv.) The advantage of the method was well demonstrated by the deprotection of BH ester **5** in *m*-cresol (4 L) at 50°C for 2 h, liberating "Tazobactam" **6**, a new β-lactamase inhibitor (90%). The conventional methods with either TFA/anisole, formic acid, or $AlCl_3$/anisole resulted in the formation of a complex mixture due to the acid lability of **6**.

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7) A similar hydrogen bond network system in phenolic media has been proposed in the alkylation of phenols with *tert*-alkyl chlorides: H. Hart and J. H. Simons, *J. Am. Chem. Soc.*, **71**, 345 (1949).
8) Deprotection of the PMB ester **1a** in anisole with 3 equiv. of TFA for 2 h afforded only 55% yield of acid 2 together with recovered **1a** (39%).
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