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VINYL PROTECTING GROUP FOR BENZIMIDAZOLE NITROGEN: SYNTHESIS OF BENZIMIDAZOLE-PENAM ALCOHOL

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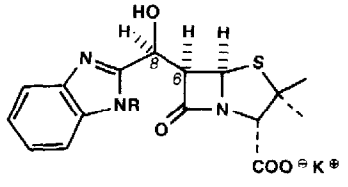
Summary: Use of the vinyl moiety as a protecting group for benzimidazole nitrogen in the synthesis of benzimidazole 2-carboxaldehyde is described. The protected carboxaldehyde is an intermediate in the synthesis of 6-(2-benzimidazole)hydroxymethyl penicillanic acid (1). Deprotection is achieved by ozonolysis.

As part of a research program on β-lactam antibacterials, we were interested in the preparation of (6β)-benzimidazole-penam alcohol 1. Direct condensation of the carbanion derived from dibromopenicillanate with 2-formylbenzimidazole[1] at -78°C failed to give any adducts; as a result, introduction of an appropriate protecting group for the benzimidazole nitrogen was deemed necessary. Many groups, including dialkoxymethyl,[2] benzyl,[3] methoxymethyl,[4] trityl,[5] acetyl,[6] 2-(trimethylsilyl)ethoxy methyl,[7]; 1-(1-ethoxyethyl),[8] and arylsulfonyl,[9] have been utilized for protecting imidazoles and benzimidazoles. Reaction of several N-protected (e.g., dimethoxymethyl, trityl, acetyl, etc.) benzimidazoles with organolithium agents followed by formylation failed to give an N-protected-2-formylbenzimidazole. The trimethylsilylethoxy methyl group was not attempted, because our previous work[10] showed that removal of the silyl group with tetrabutylammonium fluoride led to epimerization at the C-6 center of the penam alcohol. Herein, we describe the synthesis of 1 using the vinyl protecting group for the benzimidazole nitrogen, in which the vinyl group was deblocked under mild conditions (1 eq. ozone at -78°C).

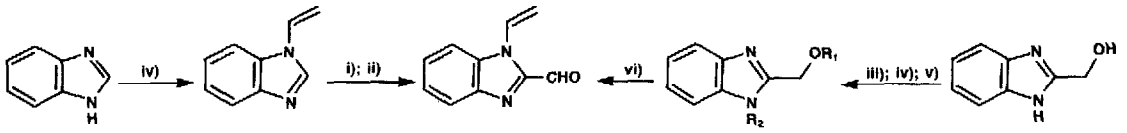


1, R=H
7, R=vinyl

Two routes for the preparation of 1-vinyl-2-formylbenzimidazole (2) are illustrated in Scheme I. Both routes involve direct vinylation[11] of the benzimidazole nitrogen with vinyl acetate in the presence of catalytic amounts of mercuric acetate and acid to yield the corresponding N-vinyl benzimidazoles, 3 or 5. Metalation of N-vinylbenzimidazole (3) followed by formylation gave 2 in 87% yield. The alternative method which involved removal of the acetyl group of 5, followed by oxidation of 6 with MnO_2, afforded an 80% yield of 2. In this sequence, protection of 2-hydroxymethylbenzimidazole with an acetyl group was necessary in order to obtain a good yield in the vinylation step. The aldehyde 2 was coupled with the anion derived from allyl 6,6-dibromopenicillanate to give a mixture of 4 isomers which

was used in the subsequent tributyltin hydride reduction and deallylation.[12] The desired (6β,8S)-penam alcohol 7 was isolated in 21% overall yield. Removal of the N-vinyl group of 7 was achieved with 1 eq. of ozone[13] in MeOH at -78°C while following the reaction by HPLC (1:1 MeOH/0.02 M NH_4OAc). A quantitative yield of 1[14] was obtained. Compounds 7 and 1 possess antibacterial and β-lactamase inhibitory activity (Table I).

SCHEME I



3 **2**

4 R_1: Ac; R_2: H (mp 162-163°C)
5 R_1: Ac; R_2: vinyl (oil)
6 R_1: H; R_2: vinyl (mp 112-113°C)

LDA/THF/-78°C, 0.5 h; ii) EtOCHO or DMF/-78°C (1 h), 0°C (0.5 h); iii) Ac_2O/AcOH, reflux, 1 h, iv) 10 eq. vinyl acetate/5% eq. mercuric acetate/H_2SO_4 (cat.), reflux, 24 h; v) KOH/MeOH, rt, 0.5 h; vi) MnO_2/CH_2Cl_2.

Table I. Antibacterial and synergy data

	MIC (μg/ml)				
Organism	*Ampicillin*	*7*	*1*	*Ampicillin + 7 (1:1)*	*Ampicillin + 1 (1:1)*
S. aureus 01A400	**50**	**0.78**	**12.5**	**<0.2**	**0.78**
H. influenzae 51A042	**>200**	**0.78**	**6.25**	**0.78**	**0.78**

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14. ^{1}HNMR (D_2O, 300 MHz) δ 1.42 (s, 3H), 1.63 (s, 3H), 4.26 (s, 1H), 4.30 (dd, J = 4 & 10 Hz, 1H), 5.43 (d, J = 4 Hz, 1H); 5.43 (d, J = 10 Hz, 1H); 7.3-7.4 (m, 2H), 7.6-7.7 (m, 2H) ppm; ^{13}CMNR (D_2O) δ 27.0, 30.9, 56.2, 63.8, 64.8, 65.9, 73.0, 116.0, 116.1, 124.1, 153.9, 175.6, 176.1 ppm; IR (KBr) 1599, 1744, 3404 cm^{-1}.

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