

New Synthesis of 6-Alkylpenicillanic Acid Derivatives

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Summary Benzhydryl 6-diazopenicillanate condenses with furan to give 6-(4-oxobut-2-enylidene)penicillanates in high yield.

FOLLOWING the discovery of thienamycin,¹ there has been considerable interest in the preparation of penicillin

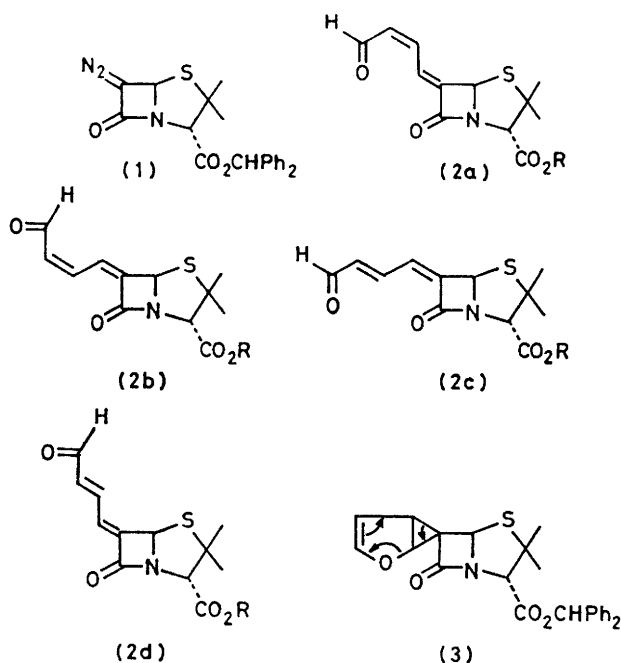
analogues in which the C-6 position carries a carbon rather than nitrogen substituent.² We now report a new, simple, and highly efficient synthesis of penicillanate esters carrying a dienal side-chain at C-6.

Addition of benzhydryl 6-diazopenicillanate (1) to furan containing 0.05 equiv. of $\text{Rh}_2(\text{OAc})_4 \cdot 2\text{H}_2\text{O}$ led to the rapid

TABLE. Spectroscopic properties of the dienals (**2a**—**d**) (side chain labelled H^aCOCH^b=CH^c-CH^d=C<)

Compound	H ^a	¹ H N.m.r. (CDCl ₃) τ (multiplicity)				J _{bc} /Hz	Main u.v. band (MeCN) λ _{max} /nm (log ε)
		H ^b	H ^c	H ^d			
(2a)	-0.16 (d)	3.86 (dd)	2.38 (dd)	2.72 (d)	11.2	277 (4.28)	
(2b)	-0.24 (d)	3.74 (dd)	3.16 (dd)	2.42 (d)	10.7	277 (4.33)	
(2c)	0.30 (d)	3.56 (dd)	2.86 (dd)	3.15 (d)	14.3	279 (4.30)	
(2d)	0.32 (d)	3.62 (dd)	2.20 (dd)	3.49 (d)	15.9	279 (4.47)	

and quantitative formation (as judged by n.m.r. and t.l.c.) of a 2:1 mixture of the isomeric dienals (**2a**: R = CHPh₂) and (**2b**: R = CHPh₂). The condensation could also be effected by copper catalysts [*e.g.* Cu(acetylacetonato)₂], but less cleanly (*ca.* 70% isolated yield) and, interestingly, resulting in a different (1:1) ratio of the dienals (**2a**) and (**2b**). The formation of dienals in the condensation of carbenoids with furan has been observed previously³ and probably involves the intermediate cyclopropadihydrofuran (**3**).

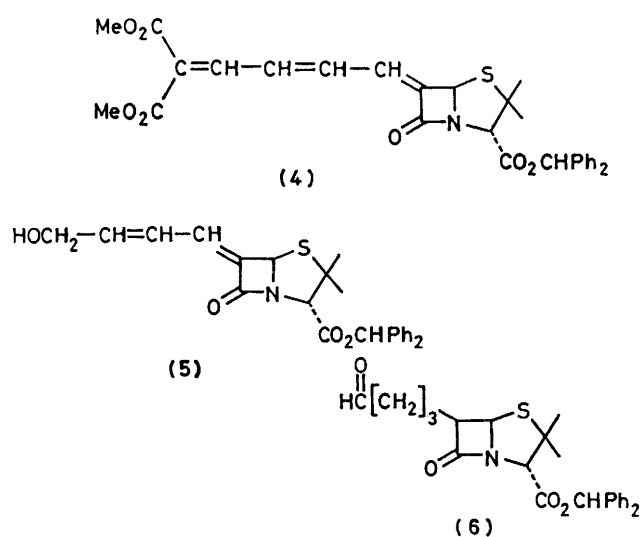


The mixture of dienals (**2a**: R = CHPh₂) and (**2b**: R = CHPh₂) was separated by chromatography on silica, but during this process some isomerisation to the dienals (**2c**: R = CHPh₂) and (**2d**: R = CHPh₂) occurred. The isomerisation also occurred slowly on stirring a solution of (**2a**) and (**2b**) in CH₂Cl₂ with silica, or more rapidly on heating the isomers (**2a**) and (**2b**). The four isomers could be isolated individually by rapid chromatography and were readily distinguishable by their ¹H n.m.r. spectra (Table).

Since the diazopenicillanate (**1**) is available in high yield (> 90%) by diazotisation of the corresponding 6-aminopenicillanate, the subsequent reaction with furan provides, overall, a two-step method affording the dienals (**2**) very

efficiently. The high degree of functionality incorporated in the side chain of the dienals makes them attractive intermediates for the synthesis of a variety of new penicillanates.

Deprotection of the ester function in the dienals (**2a**—**d**: R = CHPh) was readily accomplished by brief dissolution in trifluoroacetic acid-anisole, the acids (**2a**—**d**: R = H) being formed with concomitant geometric isomerisations about the side-chain double bonds. Derivatives of the aldehyde function were prepared, including the 2,4-dinitrophenylhydrazone and the Knoevenagel condensation product with dimethyl malonate as a mixture of stereoisomers (**4**). Reduction of a mixture of the dienals (**2a**—**d**:



R = CHPh₂) with sodium borohydride in wet acetonitrile afforded a mixture of the corresponding dienyl carbinols (**5**). Oxidation of the dienals (**2**: R = CHPh₂) with chromic acid did not proceed cleanly, but the crude reaction product showed spectroscopic evidence in accordance with the presence of the expected dienoic acids, which appear to be unstable. The dienals (**2**: R = CHPh₂) were hydrogenated with Pd/C at atmospheric pressure to give the saturated aldehydes (**6**) as a mixture of α- and β-epimers.

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