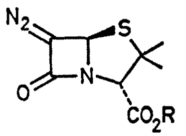
Metal-catalysed Reactions of Benzhydryl 6-Diazopenicillanate with Alcohols

By STEPHEN A. MATLIN* and LAM CHAN
(*Chemistry Department, The City University, Northampton Square, London* EC1V 0HB)

Summary Thiazepines are major products of the copper- and rhodium-catalysed reactions of benzhydryl 6-diazopenicillanate with alcohols; they are formed *via* rearrangement of oxonium ylide intermediates and a competing process gives the 6α-alkoxypenicillanates.

THE copper-catalysed[1] and $BF_3 \cdot Et_2O$-catalysed[2] reactions of α-diazocarbonyl compounds with alcohols afford α-alkoxyketones. The mechanisms of these reactions have been discussed in terms of 'direct' carbene or carbenoid insertion into the O–H bonds, proton transfer processes, and oxonium ylide intermediates.[1,2] Recently, the $BF_3 \cdot Et_2O$-catalysed reaction of a 6-diazopenicillanate ester (**1**; R = CH_2CCl_3) with alcohols has been shown to give the 6α-alkoxypenicillanates (**2**; R^1 = CH_2CCl_3, R^2 = Me, Bu^t, or $PhCH_2$) in high yields.[3] We now report the unexpectedly different behaviour of a 6-diazopenicillanate with metal catalysts which provides a valuable mechanistic insight into the processes involved.

When the diazo ester (**1**; R = $CHPh_2$) was decomposed in ethanol containing a catalytic amount of bisacetylacetonatocopper [$Cu(acac)_2$], the 6α-ethoxypenicillanate (**2**; R^1 = $CHPh_2$, R^2 = Et) was formed in only 20% yield, the major product (29%) being the ethoxythiazepine (**3**; R = Et). Rhodium acetate has been reported to be superior to copper catalysts for insertion into hydroxy-groups.[4] However, in the present case, decompositions of the diazopenicillanate (**1**; R = $CHPh_2$) in ethanol, t-butyl alcohol, and benzyl alcohol containing $Rh_2(OAc)_4 \cdot 2H_2O$ gave mainly the thiazepines (**3**; R = Et, Bu^t, or $PhCH_2$, respectively), and only low yields of 6α-alkoxypenicillanates (Table).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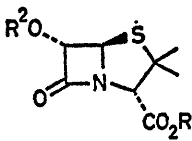
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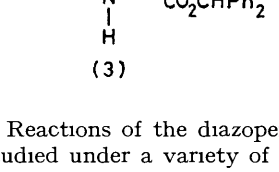
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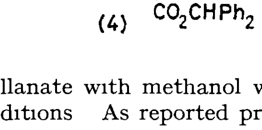
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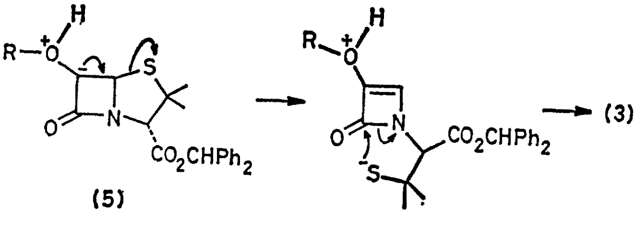
Reactions of the diazopenicillanate with methanol were studied under a variety of conditions. As reported previously,[3] use of $BF_3 \cdot Et_2O$ gave a high yield (72%) of 6α-methoxypenicillanate (**2**; R^1 = $CHPh_2$, R^2 = Me) and no thiazepine was detected. Use of TsOH as catalyst gave an identical result. On the other hand, catalysis by both $Rh_2(OAc)_4$ and $Cu(acac)_2$ led to the formation of methoxythiazepine as well as methoxypenicillanate (Table).

TABLE. Reactions of benzhydryl 6-diazopenicillanate with alcohols.[a]

	$Rh_2(OAc)_4$[c]		$Cu(acac)_2$[d]	
Alcohol[b]	% (**2**)	% (**3**)	% (**2**)	% (**3**)
MeOH	55	19	56	23
EtOH	12	75	20	29
Bu^tOH	6	72	—	—
$PhCH_2OH$	<5	67	—	—
EtOH–DBN	55	20	—	—
CH_2=$CHCH_2OH$	<5	70	9	56

[a] Reactions with $Cu(acac)_2$ were typically complete in 1–2 h, whereas those with $Rh_2(OAc)_4 \cdot 2H_2O$ were appreciably faster. All new compounds gave satisfactory microanalysis and spectroscopic data. [b] The alcohol was the solvent in all the reactions except for those with benzyl and allyl alcohols, where CH_2Cl_2 was used as co-solvent. [c] 0·01 wt % catalyst was used. [d] 0·02 wt % catalyst was used.

Thiazepine products have previously been observed during the base-catalysed epimerisation of 6β-aminopenicillanate derivatives to the 6α-isomers, involving deprotonation at the 6-position.[5,6] Thus, the formation of the ethoxythiazepine is consistent with the intermediacy of the oxonium ylide (**5**) (Scheme). The 6α-ethoxypenicillanate could arise either *via* proton transfer in the ylide (**5**) or by an independent pathway. The trend in product ratios for methanol, ethanol, and t-butyl alcohol with $Rh_2(OAc)_4$ as catalyst parallels the trend in acidity (MeOH > EtOH > Bu^tOH) and is in the same order as the relative rates of rhodium-catalysed O–H insertion reactions of diazoacetic esters with these alcohols.[4] An explanation consistent with these observations is that the product ratio is kinetically controlled by the relative rate of rearrangement of the oxonium ylide (**5**) and a competing proton transfer pathway, which may involve (**5**) as a common intermediate. In agreement with this mechanism, when the diazopenicillanate (**1**; R = $CHPh_2$) was added to 0·1 equiv. of 1,5-diazabicyclo[4.3.0]non-5-ene[5] (DBN) in ethanol containing $Rh_2(OAc)_4$, there was a substantial change in product yields, with the ethoxypenicillanate now being favoured (Table).



SCHEME

In ethanol alone or ethanol–DNB, in the absence of rhodium catalyst, the diazoester showed little decomposition after 48 h and neither ethoxypenicillanate nor ethoxythiazepine could be detected. The effect on product ratios of changing the metal catalyst is also noteworthy and implies a role for the metal either in assisting proton transfer or in co-ordinating to the ylide (**5**).

In an attempt to provide an alternative pathway for the intermediate oxonium ylide to rearrange, the reaction with allyl alcohol was studied. Allyl-substituted ylides of sulphur,[7] selenium,[7] and nitrogen[8] are known to undergo 2,3-sigmatropic shifts affording 6-allyl penicillanates. However, both the rhodium- and copper-catalysed reactions of the diazo compound (**1**: R = $CHPh_2$) with allyl alcohol gave mainly allyloxythiazepine (**3**: R = $CH_2CH{=}CH_2$) and the 6-allyl-6-hydroxypenicillanate (**4**) was not observed. In contrast with these results (Table), the $BF_3.Et_2O$-catalysed reaction with allyl alcohol gave 6α-allyloxypenicillanate (**2**: R^1 = $CHPh_2$; R^2 = $CH_2CH{=}CH_2$) in 70% yield and no thiazepine could be detected.

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