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REACTIONS OF 6-DIAZOPENICILLANATES WITH ALLYLIC SULPHIDES, SELENIDES, AND BROMIDES

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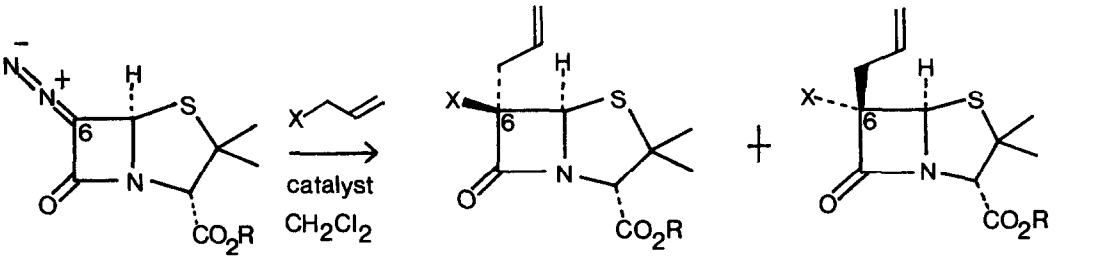
Abstract. 6-Diazopenicillanates react with allylic sulphides, selenides and bromides, to give 6,6-disubstituted penicillanates *via* [2,3]-sigmatropic rearrangements.

Since the discovery of derivatives of olivanic acid,[2] and thienamycin,[3] the synthesis of penicillin analogues with a carbon side-chain at C-6 has been of considerable interest. Esters of 6-diazopenicillanic acid have already proved to be useful starting materials for the preparation of a range of modified penicillins.[4] We now report the reactions of these 6-diazopenicillanates with allylic sulphides, selenides, and bromides, which result in the addition of a carbon side-chain to C-6 *via* [2,3]-sigmatropic rearrangements. This work complements the recently reported reactions of 6-diazopenicillanates with vinyl ethers,[5] and is related to the [2,3]-sigmatropic rearrangements of 6-alkylaminopenicillanates reported by Baldwin.[6]

Addition of $BF_3.Et_2O$ to a mixture of phenyl allyl sulphide and 2,2,2-trichloroethyl 6-diazopenicillanate (1) in anhydrous dichloromethane, resulted in the rapid evolution of nitrogen, and led to the formation of three products, which were separated by column chromatography on silica, and identified as the two C-6 epimers of 2,2,2-trichloroethyl 6-allyl-6-phenylthiopenicillanate (3) and (4), together with 2,2,2-trichloroethyl 6α-phenylthiopenicillanate (11). The 6,6-disubstituted penicillanates (3) and (4) were purified further by recrystallization from ethyl acetate-light petroleum, and were found to have m.p.'s of 87-88°C, and 58-59°C, respectively.[7] In the presence of $BF_3.Et_2O$, 2,2,2-trichloroethyl 6-diazopenicillanate (1) also reacts with methyl allyl sulphide to give the 6-allyl-6-methylthiopenicillanates (5) and (6), together with 6α-methylthiopenicillanate (12), and 2,2,2-trichloroethyl and benzyl 6-diazopenicillanates (1) and (2) react with phenyl allyl selenide to give the corresponding 6-allyl-6-phenylselenylpenicillanates (7)-(10), together with a 6α-phenylselenylpenicillanate (13) or (14). Subsequently it was found that the formation of the 6α-monosubstituted products could be avoided by using $Cu(acac)_2$ as catalyst. Thus in the presence of $Cu(acac)_2$, 2,2,2-trichloroethyl 6-diazopenicillanate (1) reacts with phenyl allyl sulphide, methyl allyl sulphide, and phenyl allyl selenide, to give the corresponding 6,6-disubstituted penicillanates (3)-(8) with none of the 6α-monosubstituted products being obtained. These results are summarized in the Scheme and Table below.[7]

All the products were obtained pure by column chromatography, and, for the 6,6-disubstituted penicillanates, by subsequent recrystallization from ethyl acetate-light petroleum. The only product that was not fully characterized in this way, was the minor 6,6-disubstituted

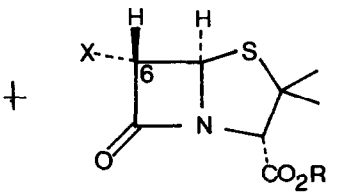
Scheme



(1) $R = CH_2CCl_3$
(2) $R = CH_2Ph$

(3) $X = PhS$, $R = CH_2CCl_3$
(5) $X = MeS$, $R = CH_2CCl_3$
(7) $X = PhSe$, $R = CH_2CCl_3$
(9) $X = PhSe$, $R = CH_2Ph$

(4) $X = PhS$, $R = CH_2CCl_3$
(6) $X = MeS$, $R = CH_2CCl_3$
(8) $X = PhSe$, $R = CH_2CCl_3$
(10) $X = PhSe$, $R = CH_2Ph$



(11) $X = PhS$, $R = CH_2CCl_3$
(12) $X = MeS$, $R = CH_2CCl_3$
(13) $X = PhSe$, $R = CH_2CCl_3$
(14) $X = PhSe$, $R = CH_2Ph$

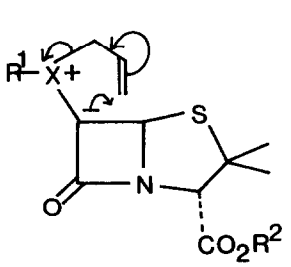
Table

Starting 6-Diazo-penicillanate	X	Catalyst	Yields of 6,6-Di-substituted Products (%)	Ratios of 6,6-Di-substituted Products	Yields of 6α-Mono-substituted Products (%)
(1)	X = PhS	$BF_3.Et_2O$	47	(3) : (4) = 56:44	5
(1)	X = MeS	"	49	(5) : (6) = 80:20	16
(1)	X = PhSe	"	48	(7) : (8) = 66:34	15
(2)	X = PhSe	"	33	(9) : (10) = 63:37	8
(1)	X = PhS	$Cu(acac)_2$	65	(3) : (4) = 87:13	0
(1)	X = MeS	"	60	(5) : (6) = 80:20	0
(1)	X = PhSe	"	64	(7) : (8) = 50:50	0

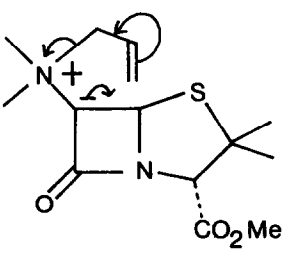
penicillanate (6) from the methyl allyl sulphide reactions. This was never obtained free of the major isomer (5), but was identified on the basis of spectroscopic data (^1H n.m.r., m.s.) of a mixture enriched (75%) in the minor isomer (6).

The configurations of the 6,6-disubstituted penicillanates (3)-(10) at C-6 have not been unambiguously assigned. However, the major isomer in each case has provisionally been assigned the configuration shown, i.e. with the heteroatom substituent in the 6β-position. This is in agreement with the earlier work of Baldwin,[6] and has been supported by the observation of a NOE effect of 13% between the allylic CH_2 of the side chain and H-5 for the major phenyl allyl sulphide product, which is consistent with the allyl side-chain being in the 6α-position.

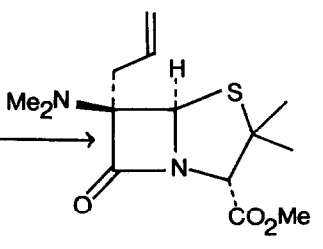
The formation of these insertion products contrasts with the copper catalysed reactions of 6-diazopenicillanates and vinyl ethers which give cyclopropane derivatives,[5] and can be rationalized in terms of a [2,3]-sigmatropic rearrangement of an intermediate ylid (15).[8] These rearrangements are analogous to that of the nitrogen ylid (16), which is known[6] to rearrange to the 6α-allyl-6β-dimethylaminopenicillanate (17).



(15)

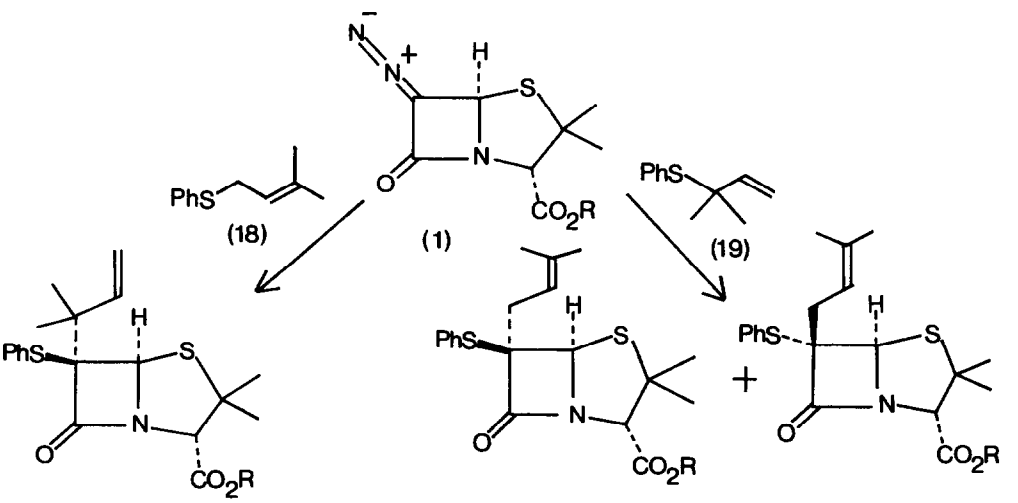


(16)



(17)

This mechanism is supported by reactions between 6-diazopenicillanate (1) and the unsymmetrical allylic sulphides (18) and (19). Treatment of 6-diazopenicillanate (1) with 3-methylbut-2-en-1-yl phenyl sulphide (18) in the presence of $Cu(acac)_2$ catalyst, led to the formation of one major product identified as the rearranged 6,6-disubstituted penicillanate (20) (70%). In contrast the analogous reaction with 3-methylbut-1-en-3-yl phenyl sulphide (19) was less efficient, and gave two products identified as the penicillanates (21) and (22) No crossover of products was detected by ^1H n.m.r. of the crude product mixtures, suggesting that the [2,3]-sigmatropic rearrangement pathway, is the exclusive mode of product formation.

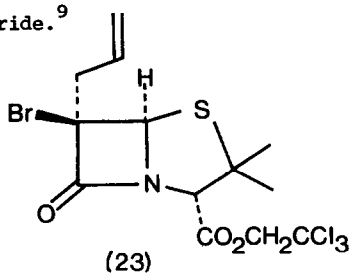


(18) (1) (19)

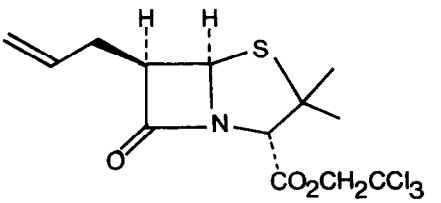
(20) (21) (22)

R = CH_2CCl_3

As an extension of this work, 6-diazopenicillanate (1) was treated with neat allyl bromide in the presence of a catalytic amount of $Cu(acac)_2$. Rapid column chromatography on alumina of the product gave a material identified as 6α-allyl-6β-bromopenicillanate (23). This product appeared to be homogeneous, but was rather unstable, and difficult to purify. The configuration at C-6 was assigned by analogy, as discussed above. In order to confirm the structure of this product, it was reduced to 6β-allylpenicillanate (24) using tri-n-butyltin hydride.[9]

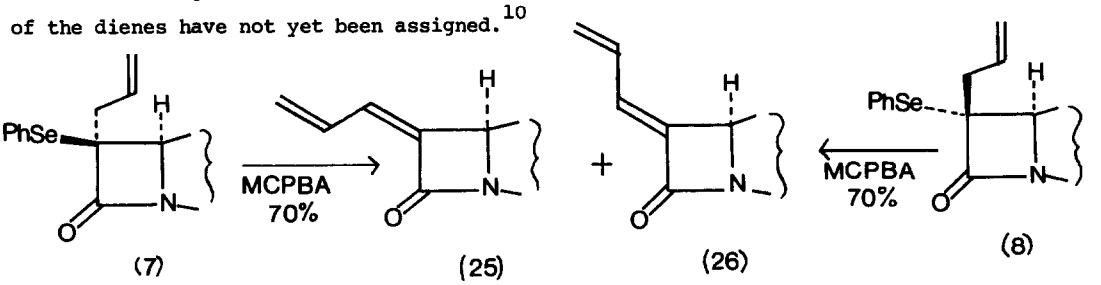


(23)



(24)

Finally the oxidation-elimination of 6-allyl-6-phenylselenylpenicillanates (7) and (8) was briefly explored. It was found that treatment of either of these selenides with one equivalent of m-chloroperoxybenzoic acid resulted in the rapid formation of two new products which were separated by column chromatography, and identified as the dienes (25) and (26). Both selenides gave the same dienes in approximately the same ratio, 2:1, but the geometries of the dienes have not yet been assigned.[10]



(7) (25) (26) (8)

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Notes and References

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