The Preparation and Use of Metallo-6-vinylidene Penams

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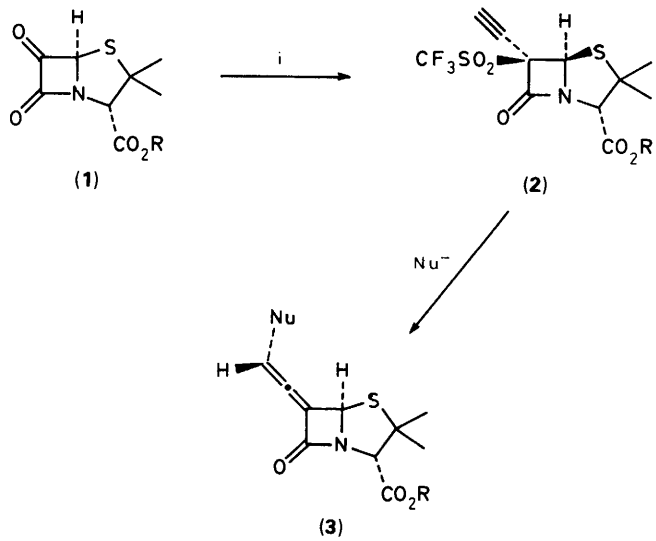
The parent unsubstituted 6-vinylidenepenam and various 6-acetylenic penams are shown to be available from corresponding allenyl iodides.

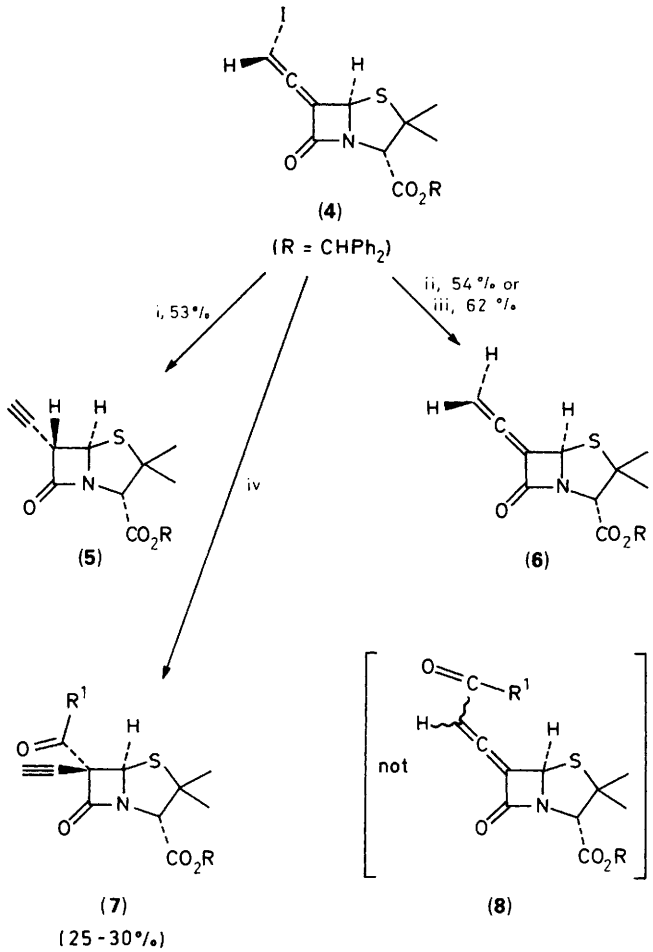
Selected 6-unsaturated penams have been shown to be excellent inhibitors of some types of β-lactamase.[1] Further interest in the use of penicillin-related species as enzyme inhibitors is fuelled by the recent discovery by workers at Merck that certain cepham esters are excellent elastase inhibitors.[2] As an expansion of our earlier work on the synthetic utility of allenes in the preparation of established β-lactamase inhibitors[3] and our recognition of the many excellent allene-derived enzyme inhibitors,[4] we earlier reported that α-vinylidene penams [*e.g.*, (**3**)] could be prepared as shown in Scheme 1. The readily available 6-oxopenicillanic acid[5] is sequentially treated with either lithium or cerium acetylide and then trifluoromethanesulphonic anhydride to yield the propynylic trifluoromethanesulphonates (**2**). These materials can then be treated with copper(I) halides in dimethylformamide (DMF) at room temperature to yield the corresponding allenyl halides [(**3**) Nu = X] or with certain higher order cuprates in tetrahydrofuran (THF) at −78 °C to prepare the alkylated allenes [(**3**) Nu = alkyl]. We now report that the terminal iodovinylidenepenam is a versatile intermediate in the preparation of various 6-vinylidene derivatives of penicillin including the parent unsubstituted compound (**5**).†

† Structure of key compounds confirmed by ^{1}H NMR, ^{13}C NMR, IR, and HRMS.

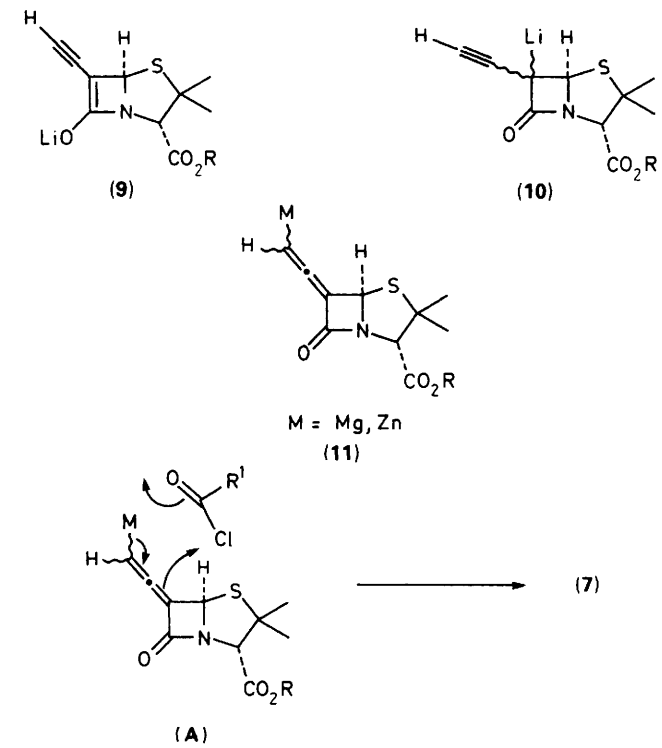
The iodoallene (**4**) is stereospecifically generated by attack of CuI (in DMF) on the trifluoromethanesulphonate [(**2**); R = allyl or $CHPh_2$]. This material readily undergoes halogen–metal exchange generating a series of useful organometallics.[6]

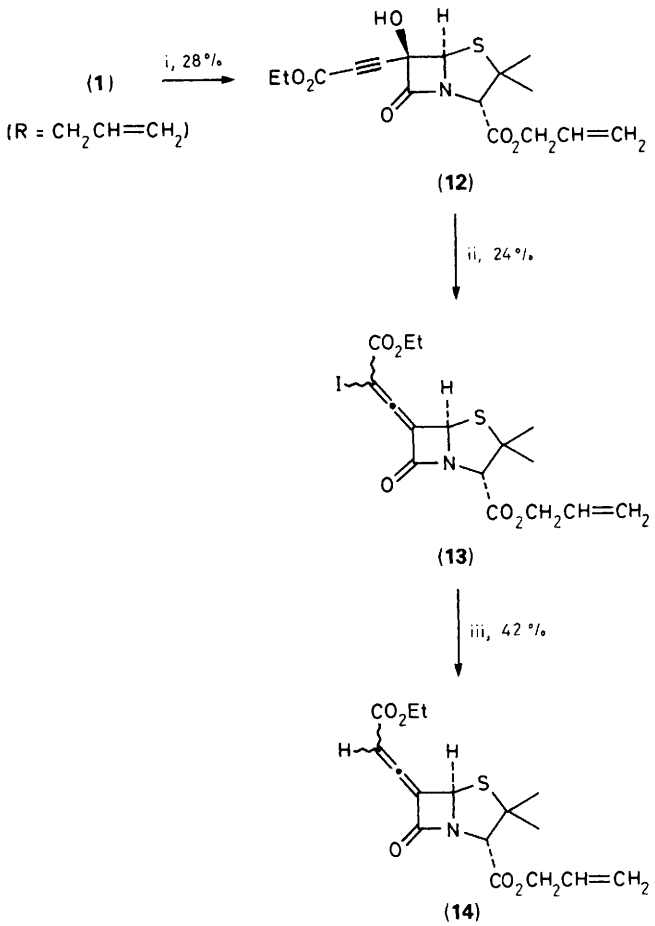


Scheme 1. *Reagents*: i, H–C≡CM, then $(CF_3SO_2)_2O$, pyridine.



Scheme 2. *Reagents and conditions:* i, Bu^{s}Li, then HOAc; ii, Zn/Cu, NH_4Cl; iii, MeMgBr, then HOAc; iv, Bu^{s}Li, then R^1COCl.





Scheme 3. *Reagents and conditions:* i, $EtO_2CC{\equiv}CLi$, then NH_4Cl; ii, $(CF_3SO_2)_2O$, then CuI, DMF; iii, EtMgBr, −78 °C, then NH_4Cl.

As shown in Scheme 2, lithiation by treatment with s-butyllithium and quenching with acid produced the isomeric acetylene (**5**). Conversely, treatment of iodoallene (**4**) with Zn/Cu couple in methanolic ammonium chloride led to the parent unsubstituted vinylidene penam (**6**). This material can also be prepared by reaction of iodoallene with methylmagnesium bromide followed by quenching the intermediate allenylmagnesium with acid. Acylation of the intermediate organolithium produced the 6-acyl-6-acetylenic penam [(**7**) R^1 = Me, *p*-MeC_6H_4, or *p*-$MeOC_6H_4$] in poor yield. Acylation of the allenylmagnesium intermediate was much slower but also produced the acetylenic compound (**7**) in low yield and not the terminally acylated derivative (**8**).

The dichotomy of behaviour towards protonation suggests that the organolithium intermediate might be best described as the enolate (**9**) or the 6-lithiopenam (**10**), while the magnesium and zinc derivatives appear to maintain their original allenic character as illustrated by structure (**11**). The acylation of the allenylmagnesium most likely occurs *via* the well precedented[7] cyclic pathway illustrated in structure (A).

Since we also desired to prepare the terminally acylated allenes as potential enzyme inhibitors, we considered incorporating such functionality as a portion of the acetylene. In this regard, our previously described methodology for the formation and reduction of the halo allenes proved useful. As shown in Scheme 3, the ethyl propiolate anion can be added to 6-oxopenicillanic ester to produce the propynylic alcohol(**12**), which was converted to allenyl iodide (**13**). Treatment of the allenyl iodide with Bu^{s}Li and quenching with a proton source

yielded a 1:1 mixture of diastereoisomers of the desired allenic ester (**14**).

These and related compounds are being explored as inhibitors of several classes of enzymes. The results will be reported shortly.

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