Pergamon

Tetrahedron Letters 42 (2001) 4737–4739

TETRAHEDRON LETTERS

Nucleophilic and radical chemistry of benzylselenides: preparation of novel selenocephems and selenopenams

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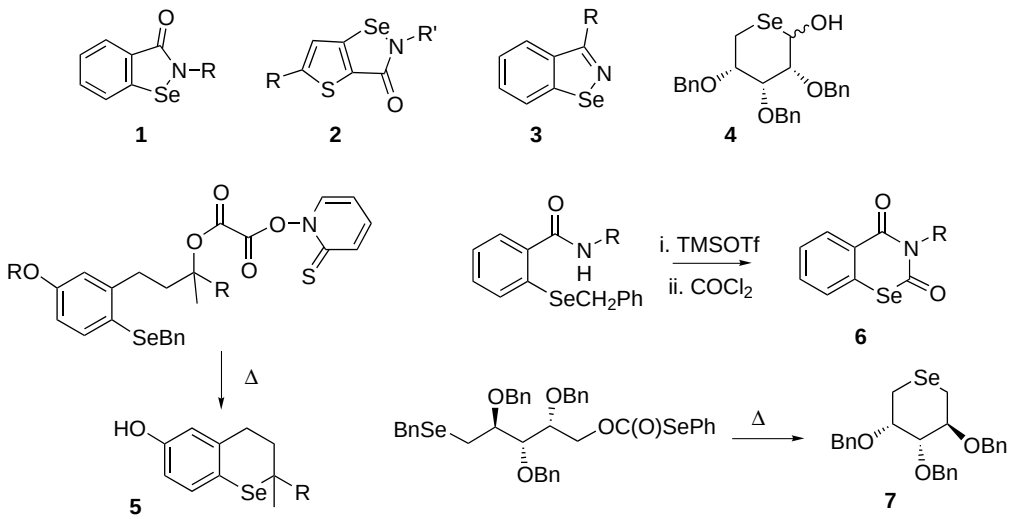
Received 11 April 2001; accepted 15 May 2001

Abstract—Selenocephems (**14** and **15**) and selenopenams (**18**, **20**, **24** and **25**) can be prepared in 18–85% yields through the intramolecular homolytic substitution of aryl or alkyl radicals at the selenium atom in suitably-substituted 4-benzylseleno-β-lactams, or through intramolecular nucleophilic substitution by the benzylseleno moiety in 4-halo-β-lactam precursors.

Free-radical homolytic substitution chemistry is rapidly gaining acceptance as a versatile synthetic method.[1] Over the past few years, we have demonstrated the effectiveness of this chemistry for the preparation of selenium and tellurium-containing higher heterocycles. Indeed, so versatile is the free-radical approach that many classes of compound including some of hitherto unknown structure have been successfully prepared. Among these are included tetrahydroselenophenes, selenanes, selenopanes,[2] 1,2-benzisoselenazol-3(2*H*)-ones (**1**)[3] and analogues (**2**)[4] (including the glutathione peroxidase mimic, Ebselen), benzisoselenazoles (**3**),[5] 5-deoxy-5-seleno pyranose sugars (**4**),[6] and novel selenium and tellurium analogues (**5**)[7] of the important antioxidant, α-tocopherol. A representative example is provided in Scheme 1.

More recently we showed that in appropriately constructed systems, the benzylseleno moiety can become involved in nucleophilic ring-closure chemistry.[8,9] Indeed, the previously unknown benzoselenazine-2,4-dione system (e.g. **6**)[8] and some selenium-containing carbohydrates (**7**)[6] are effectively prepared in this manner (Scheme 1).

It is generally appreciated that β-lactam based antibiotics have a limited future given increased resistance demonstrated by many strains of bacteria.[10] There is an



Scheme 1.

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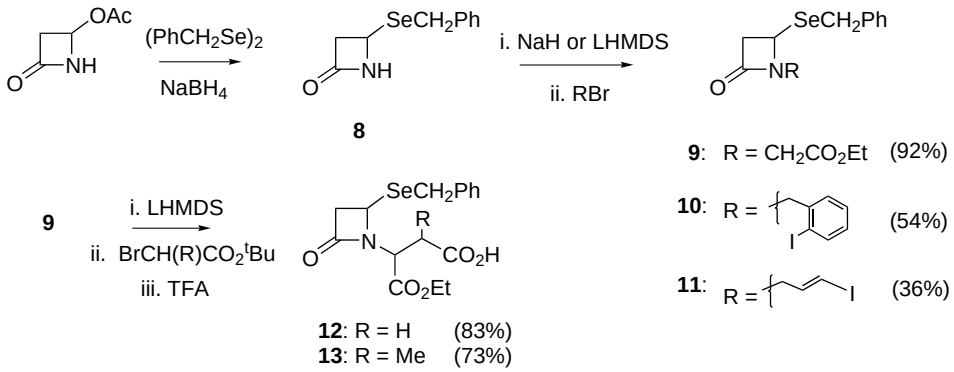
0040-4039/01/$ - see front matter
PII: S0040-4039(01)00826-7

urgent need for the development of new classes of antibiotic and many laboratories have made significant progress in this area, especially with the introduction of peptide-based agents.[11] As part of ongoing work, we have explored methods of incorporating selenium into penem and cephalosporin nuclei with the aim of providing some novel compounds of potential biological significance. To the best of our knowledge, selenium analogues of β-lactam antibiotics have been reported on one previous occasion together with limited biological testing data.[12] New methods for the preparation of these interesting systems are therefore important objectives. We now report that selenium analogues of β-lactam antibiotic nuclei are conveniently prepared by extension of our previously established radical and nucleophilic methodologies.

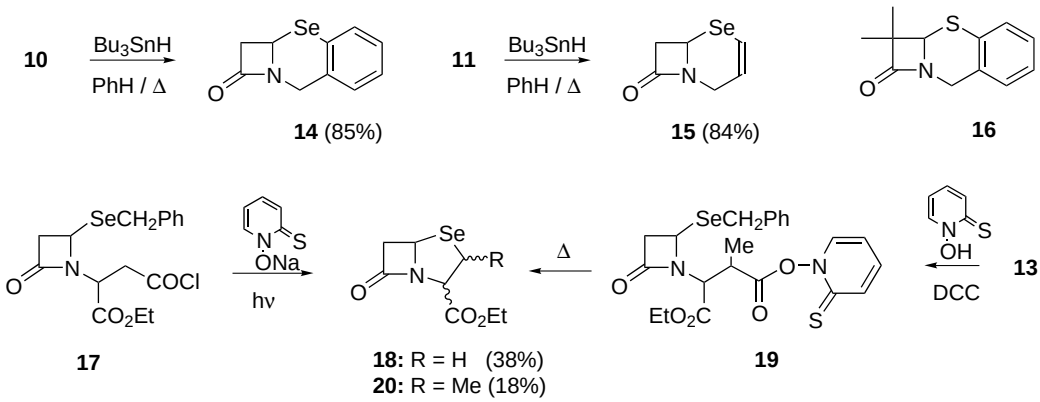
Initial preparative endeavours began with commercially-available 4-acetoxyazetidinone which was converted readily into 4-benzylselenoazetidinone (**8**) by the action of sodium benzylselenoate under standard conditions.[2–9] Subsequent treatment with either lithium hexamethyldisilazide (LHMDS) in THF at −78°C or sodium hydride in DMF at 0°C followed by an activated electrophile afforded the *N*-alkylated products (**9**–**11**) in 36–92% yield.[13] The ester (**9**) was further treated with LHMDS and *tert*-butyl bromoacetate or *tert*-butyl bromopropionoate followed by standard deprotection to afford the carboxylic acids (**12** and **13**) in good yield (Scheme 2). Compounds **12** and **13** were obtained as 1:1 and 5:2:2:1 mixtures of diastereoisomers respectively as evidenced by ^{1}H NMR spectroscopy.

To our delight, treatment of iodides (**10** and **11**) with tributyltin hydride in benzene (0.03 M) under reflux afforded the selenocephems (**14** and **15**) in 85 and 84% yields, respectively (Scheme 3). Presumably **14** and **15** are formed by homolytic attack of the first-formed aryl and vinyl radicals respectively at the selenium moiety, with expulsion of the benzyl leaving group; these compounds exhibited ^{77}Se NMR signals at δ 323 and 295 respectively, in the appropriate range for cyclic selenides.[14] In addition, **14** displayed signals at δ 4.15 ($J=18$ Hz) and δ 4.79 ($J=18$ Hz) in its ^{1}H NMR spectrum assigned to the non-equivalent benzylic protons, and at δ 5.10 for the C-4 proton. These values are in good agreement with those reported by Beckwith for the closely-related sulfur analogue (**16**).[15]

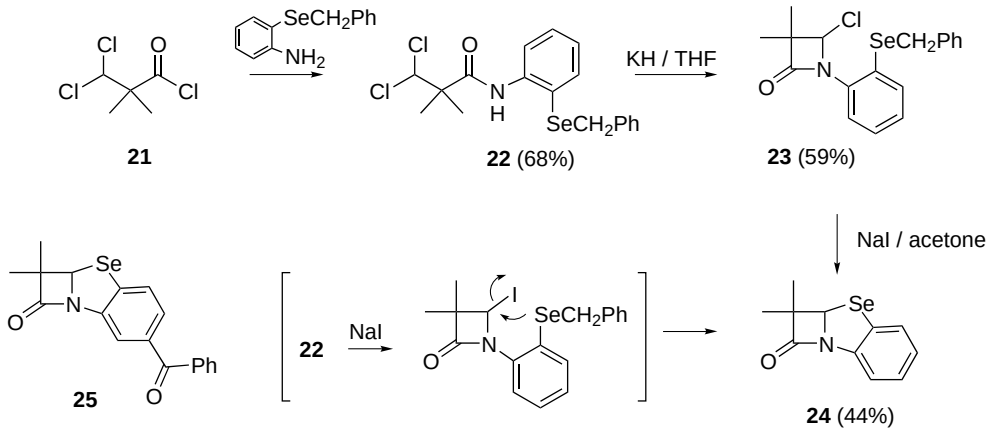
When a solution of the acid chloride (**17**), in benzene, was slowly added to a water-cooled, irradiated (250 W tungsten lamp) suspension of the sodium salt of *N*-hydroxypyridinethione in benzene, the selenopenam analogue (**18**) was isolated in 38% yield as a 7:3 mixture of diastereoisomers; **18** exhibited a single signal at δ 301 in the ^{77}Se NMR spectrum. Once again, **18** is most likely formed by homolytic substitution at selenium by the radical generated through decarboxylative cleavage of the in situ prepared Barton ester. In similar fashion, when the Barton ester (**19**) of **13** was heated in benzene



Scheme 2.



Scheme 3.



Scheme 4.

under reflux, the selenocycle (**20**) was isolated in 18% yield (Scheme 3).

Our alternative approach to these classes of compound began with the previously reported 3,3-dichloro-2,2-dimethylpropionyl chloride[15] (**21**) which was converted firstly into the corresponding benzylseleno amide (**22**) by reaction with 2-benzylselenoaniline and then into the chloroazetidinone (**23**) following the general procedure reported by Beckwith and Boate.[15] To our surprise, treatment of chloride (**23**) with one equivalent of sodium iodide in acetone did not provide the expected iodide, rather, the ring-closed selenopenem nucleus (**24**) was obtained in 44% isolated yield (Scheme 4).[16] Presumably the corresponding iodide is formed in situ, but undergoes rapid intramolecular attack by the nucleophilic benzylseleno moiety to provide **24**. Indeed, this transformation represents a further example of the synthetic utility of the intramolecular nucleophilic chemistry associated with benzyl selenides.[8,9]

In order to demonstrate the generality of this methodology, the acyl-substituted selenopenem (**25**) was prepared in an analogous manner starting with **21** and the readily available 2-benzylseleno-4-benzoylaniline in 39% yield.

In summary, we report that the selenocephem and selenopenam nuclei are conveniently prepared by either intramolecular homolytic or nucleophilic substitution chemistry involving the benzylseleno moiety. These compounds and further derivatives which are currently under investigation are expected to exhibit interesting biological properties.

Acknowledgements

Generous support from the Australian Research Council is gratefully acknowledged. The award of a Melbourne University Research Scholarship to M.W.C. is also acknowledged.

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13. These transformations were always accompanied by the formation of quantities of dibenzyl diselenide, presumably formed through elimination processes competitive with alkylation. When poorer electrophiles were employed (e.g. MeI), dibenzyl diselenide became the only identifiable product.
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16. This transformation is catalytic in sodium iodide. While 5–10% mol NaI will effect cyclisation, the reaction proceeds at a more convenient rate with the addition of one equivalent of NaI. In our hands, addition of more than one equivalent proved detrimental with lower yields of product.