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Radical cyclisations of methylenecyclopropyl azetidinones—synthesis of novel tricyclic β-lactams

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Abstract

Addition of lithium bis(methylenecyclopropyl)cuprates to acetoxy azetidinones gives methylenecyclopropyl azetidinones, which can be converted to various radical cyclisation precursors. Attempted 4-*exo* cyclisation of **3** led only to reduced product, while cyclisation of **5**, using CuCl/bipy, gave a carbacephem, via a 5-*exo* cyclisation, but in low yield. Cyclisation of **6** and **7**, however, gave novel tricyclic β-lactams, as the result of 7-*endo* cyclisation, in good yield, and a cyclisation of bromide **23** led to the tricyclic β-lactam **24**, via a radical cascade sequence.

Keywords: methylenecyclopropane; cuprate; radical cyclisation; β-lactam.

β-Lactam compounds remain among the most effective antibiotics available and despite a long history of development, the search for novel, active β-lactam derivatives remains a very active area.[1] Several groups have investigated the use of radical cyclisations as a method for preparing β-lactam derivatives, focussing largely on cyclisations of suitable radicals onto appended alkenes and alkynes.[2] In earlier work we have developed cascade processes for the construction of polycyclic systems, based around a radical cyclisation onto a methylenecyclopropane, ring opening of the resulting cyclopropylmethyl radical and trapping of the resulting methylenecyclohexyl radical with additional radical acceptor functionality.[3] We reasoned that introduction of a methylenecyclopropane unit to a β-lactam might provide an opportunity to use such cascade processes for the synthesis of novel β-lactams. In this paper we describe our efforts to prepare such methylenecyclopropyl azetidinones and investigation of possible modes of radical cyclisation.

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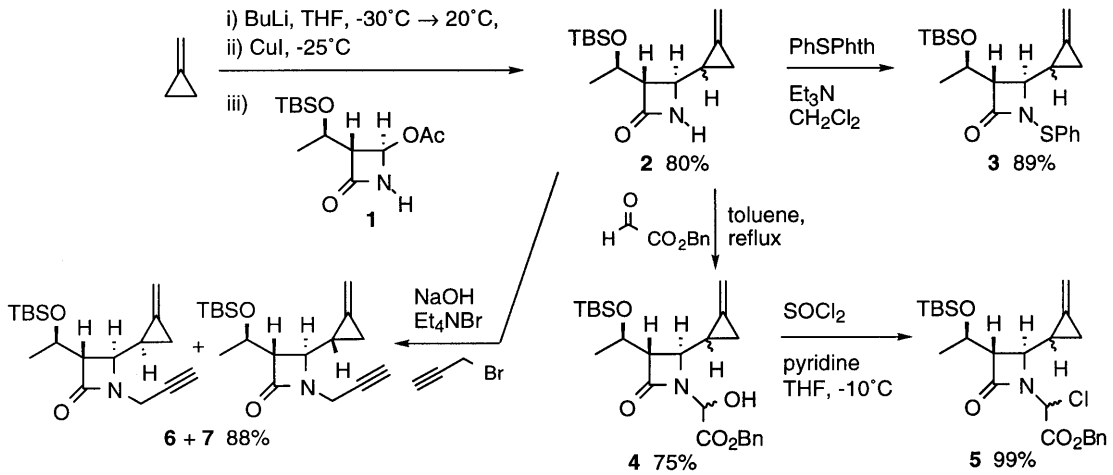
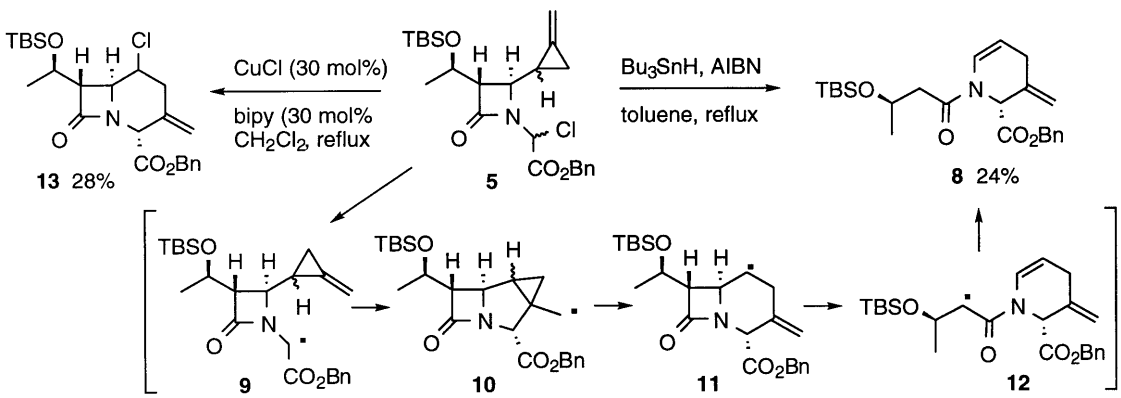
In order to introduce a methylenecyclopropane to a β-lactam, we chose to use the well-documented coupling of an organocuprate with an acetoxy azetidinone.[4] Thus lithium bis(methylenecyclopropyl)cuprate[5] was added to azetidinone **1** to give the desired adduct **2** in good yield and as 1:1 mixture of diastereosiomers (Scheme 1).



Scheme 1.

Although 4-*exo* radical cyclisations are rarely successful, we none-the-less converted azetidinone **2** to the corresponding phenylthioamide **3**. Attempted radical cyclisation of **3**, however, using Bu_3SnH/AIBN, predictably yielded only reduced product **2**.

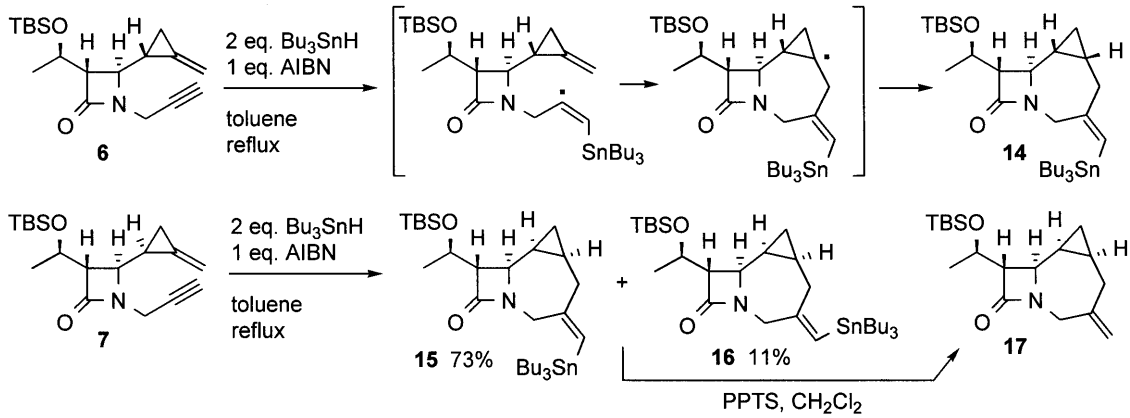
Condensation of azetidinone **2** with benzyl glyoxalate followed by treatment with $SOCl_2$/pyridine[6] gave chloride **5**, a suitable precursor for a 5-*exo*/6-*endo* cyclisation (Scheme 1). Treatment of chloride **5** with Bu_3SnH, under standard conditions, gave the cyclic enamide **8** in 24% yield, as a single diastereosiomer whose relative stereochemistry at the chlorine atom was not determined (Scheme 2).[7]



Scheme 2.

The formation of **8** presumably arises from 5-*exo* cyclisation onto the methylenecyclopropane and ring opening of the cyclopropylmethyl radical **10**, to give radical **11**, which then opens the β-lactam ring to give the relatively stable radical **12**. However, generating the starting radical **9** under atom transfer conditions, using CuCl/bipyridine,[8] gave the carbacephem **13** as a single diastereoisomer, but only in a modest yield of 28% (Scheme 2). Now, presumably, the radical intermediate **11** is trapped to give the chloride in preference to the ring opened enamide.[9]

In order to investigate a possible 6-*exo*/7-*endo* radical cyclisation, azetidinone **2** was alkylated with propargyl bromide, under phase transfer conditions, to give azetidinones **6** and **7**, which could be separated by careful chromatography (Scheme 1). Slow addition of Bu_3SnH/AIBN to a refluxing solution of **6** gave tricyclic vinylstannane **14** as a single stereoisomer in 42% yield, whereas cyclisation of **7** under identical conditions gave tricycles **15** and **16** in 73 and 11% yield, respectively, in all three cases via a 7-*endo* cyclisation (Scheme 3).[10]



Scheme 3.

Treatment of vinyl stannanes **15** and **16** with PPTS in CH_2Cl_2 yielded a common tricyclic product **17** whose structure was proved by X-ray crystallographic analysis (Fig. 1).[11]

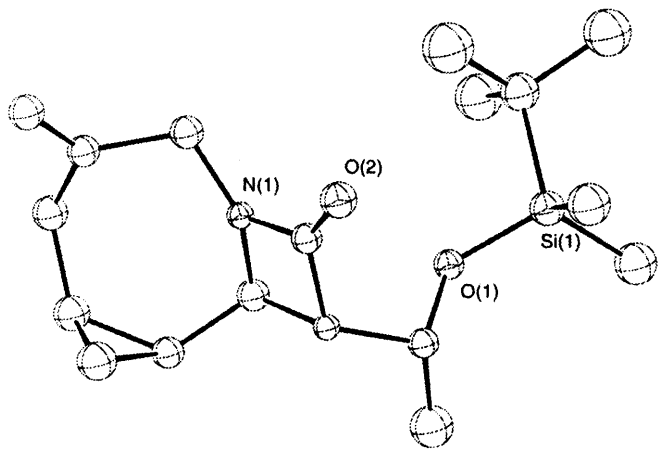
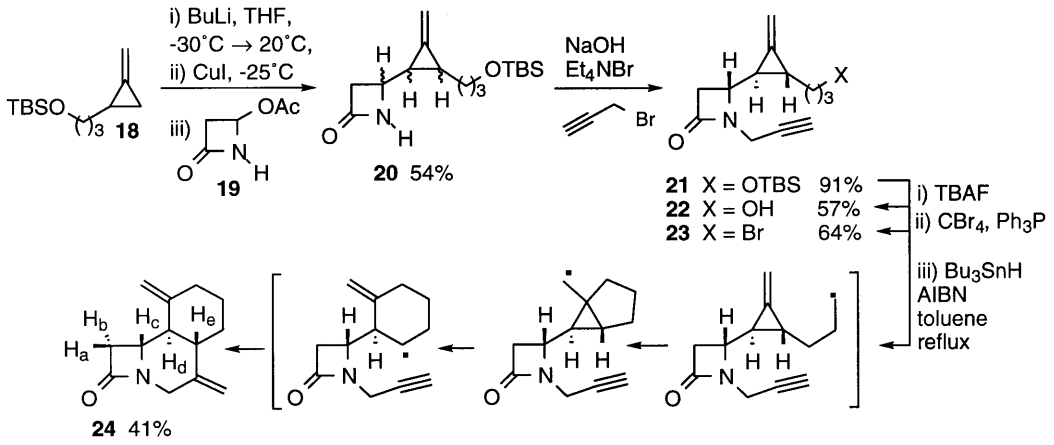


Fig. 1. X-Ray structure of **17**

Although the results described above did not bode well for the development of a cascade cyclisation based around the radical cyclisation onto a methylenecyclopropane, we were able to set up such a cascade using bromide **23**. Addition of the organocuprate derived from methylenecyclopropane **18** to acetoxy azetidinone **19**, gave adduct **20** as a mixture of diastereoisomers (Scheme 4). Alkylation with propargyl bromide and removal of the silyl-protecting group allowed isolation of alcohol **22** now as a single isomer. Conversion to the bromide **23** and radical cyclisation, led to the tricyclic β-lactam **24** via the anticipated cascade process. β-Lactam **24** was isolated as a single diastereoisomer, with a *trans* fusion of the two six-membered rings.[12]



Scheme 4.

Thus, the methylenecyclopropane unit can be readily introduced to β-lactams and the resulting adducts can be used in a range of radical cyclisations, providing access to novel β-lactam derivatives.

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10. Although simple alkenyl radicals are generally expected to prefer the *exo*-cyclisation pathway (Beckwith, A. L. J. *Tetrahedron*, **1981**, *37*, 3073), radical annelation to give fused-bicyclic β-lactams frequently prefers the *endo*-cyclisation pathway (see Ref. 2a and references cited therein), so formation of **14**–**16** is not surprising. In addition we have observed preferential 7-*endo* cyclisations with other methylenecyclopropane derivatives (Ref. 3d).
11. The intensity data were collected on a Rigaku AFC7S four-circle diffractometer (Mo Kα radiation, $\lambda = 0.71073$ Å). The structures were solved by Patterson heavy atom methods and refined on F by full-matrix least-squares refinements. Full details have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 148204. $T = 150$ K, formula $C_{18}H_{31}NO_2Si$, $M = 321.53$, orthorhombic, space group $P2_12_12_1$, $Z = 4$, $a = 11.123(4)$ Å, $b = 21.242(9)$ Å, $c = 8.376(2)$ Å, $V = 1979(1)$ Å^3, $D_c = 1.079$ g cm^{-3}, μ(Mo Kα) = 0.1254 mm^{-1}. Colourless prism, crystal size 0.25×0.24×0.10 mm, θ range: 2.0–25.0°, 697 unique data and 89 parameters, $R_1[F>2\sigma(F)] = 0.058$, wR_2(all data) = 0.111. The Flack parameter did not establish the absolute configuration and it is assigned from the synthetic method.
12. Stereochemistry of **24** was assigned based on coupling constants ($J_{cd} = J_{de} = 10$ Hz) and NOE's from $H_b \rightarrow H_d$ (2.5%) and from $H_c \rightarrow H_e$ (2.5%).