Carbon–Carbon Bond Formation at the C-4 Position of an Azetidin-2-one Ring by Intermolecular Radical Coupling Reactions: a Route to Tribactams

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The β-lactam **4** was linked to the enones **8–10** using a radical reaction mediated by tri-*n*-butyltin hydride to give the 2,6-disubstituted cyclohexanones **11–16**, respectively: **13** was converted into the protected tribactam **18** in two steps.

Recently, a new family of totally synthetic β-lactam antibiotics, the tribactams **1**, with the novel feature of a tricyclic skeleton, has been discovered by Glaxo S.p.A.[1] We report herein the construction of tribactams of type **2** by intermolecular radical C–C bond formation at C-4 of the azetidin-2-one ring.

The use of radical chemistry in the synthesis of β-lactam antibiotics has attracted considerable attention previously, not least because the β-lactam ring is inert under most of the relevant reaction conditions. For example, Bachi has employed intramolecular radical cyclization techniques to form carbapenam, oxacepham and oxacephem systems.[2] Similarly, Kametani's syntheses of carbacephams and carbacephems also involved intramolecular radical annulation.[3] In contrast intermolecular radical addition reactions have received little attention.

The seleno compound **4** was obtained from the 4-acetoxy-β-lactam **3** by a known procedure,[4] and from **4** the radical intermediate **5** was generated using tri-*n*-butyltin hydride (Scheme 1).

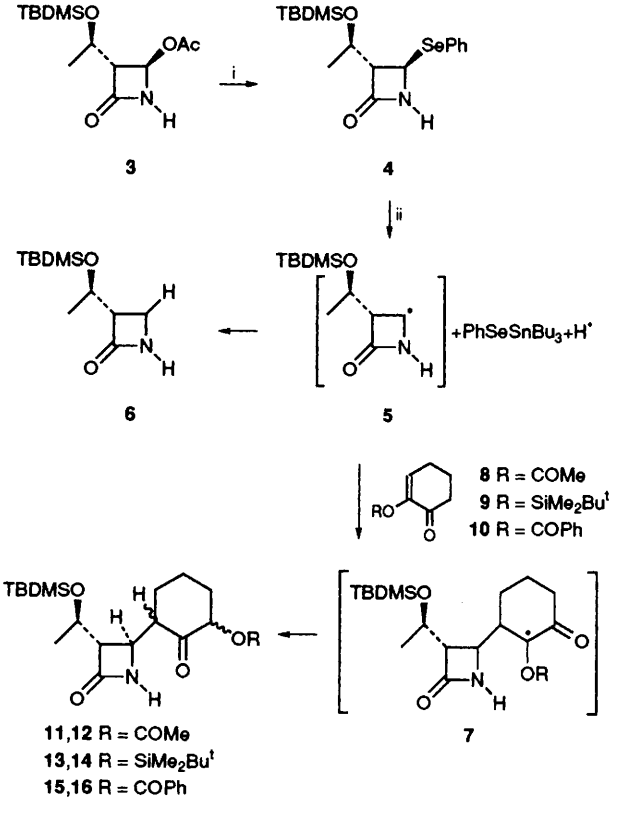
To maximise the amount of coupled product formed, the tri-*n*-butyltin hydride and AIBN were added simultaneously (*via* a syringe pump) to a refluxing solution of the enol ether and the β-lactam in THF. The results are shown in Table 1. Coupling of the 3-substituted azetidinone **4** with the enol ether **8** afforded an inseparable mixture of the two diastereoisomers **11** and **12** in the ratio 1 : 1. Compound **6** was present in the crude reaction mixture, but it could not be isolated. The structures of the products **11** and **12** were deduced by NMR studies after acquisition of NOE data. In both isomers the protons at C-2 and C-6 in the cyclohexanone ring were *cis* oriented.

The postulated mechanism involves the rearrangement of the initially formed capto-dative radical **7** to give a less sterically compressed system which abstracts an hydrogen atom from tributyltin hydride to give the products.[5] Coupling of compound **4** with the *tert*-butyldimethylsilyl (TBDMS) enol ether **9** of cyclohexanedione gave a very satisfactory result, yielding equal quantitites of the adducts **13** and **14** (combined yield 60%) and a relatively small amount of the β-lactam **6** (21%) (Table 1). It is noteworthy that the *tert*-butyldimethylsilyl group again migrates to afford a 2,6-disubstituted cyclohexanone system.

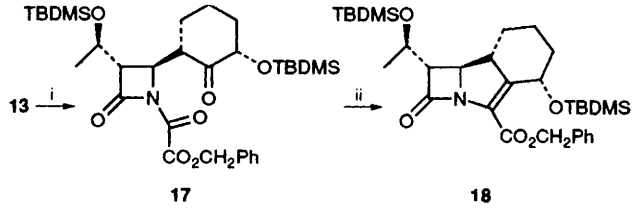
Similarly, coupling of the azetidinone with the benzoyl enol ether **10** gave the ketones **15** and **16** (Table 1) through benzoyl group migration.

The intermediate **13** was converted into the requisite target by the modified Woodward's phosphorane cyclization reaction, *i.e.* the oxalimide cyclization route.[6] Thus, compound **13** was *N*-alkylated by treatment with benzyl oxalyl chloride to give the oxalimide **17**, which was heated under reflux in xylene in the presence of triethyl phosphite to yield the tribactam **18** (Scheme 2).

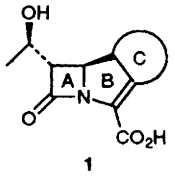
These studies showed that coupling of the radical **5** to α-acyloxy- or α-silyloxy-α-, β-cyclohexenones can take place efficiently, to give, as the initially formed species, a capto-dative radical. Migration of an acyl or silyl group then takes place to give 2,6-*cis*-substituted cyclohexanones exclusively. This methodology was used as the key step in the synthesis of tribactams. At present we are investigating extensions of this method to provide other types of 2, *n*-disubstituted cycloalkanones.



Scheme 1 *Reagents and conditions*: i, Bu_3P, $(PhSe)_2$, NaOH, THF, 85%; ii, Bu_3SnH, AIBN(cat), THF, 48 h



Scheme 2 *Reagents and conditions*: i, $ClCOCO_2CH_2Ph$, Et_3N, CH_2Cl_2, 81%; ii, $P(OEt)_3$, xylene, reflux, 58%



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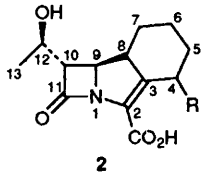

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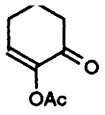
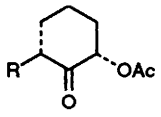
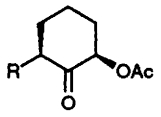
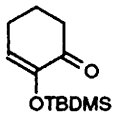
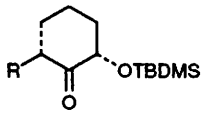
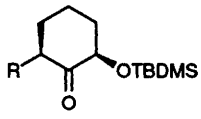
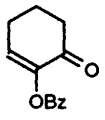
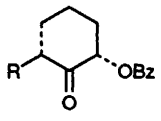
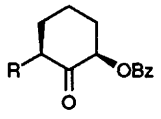
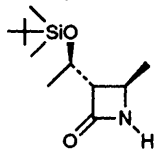
Table 1 Products formed by reaction of compound **4** with tri-*n*-butyltin hydride in the presence of the selected alkene

Entry	Alkene	Molar excess of alkene	Coupling products/(%)[a]		Compound **6**/(%)[a]
1	 **8**	4	 **11** 25	 **12** 25	
2[b]	 **9**	4.5	 **13** 30	 **14** 30	21
3	 **10**	10	 **15** 27	 **16** 28	

[a] Yields relate to purified compounds and are not optimised. [b] Tris(trimethylsilyl)silane has also been used instead of tri-*n*-butyltin-hydride. TBDMS = $SiMe_2Bu^t$; Bz = COPh, R = 

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