Pergamon

Tetrahedron Letters 42 (2001) 3081–3083

TETRAHEDRON LETTERS

Functionalized eight-membered lactams via [3,3] sigmatropic rearrangement of 2-azetidinone-tethered 1,5-dienes

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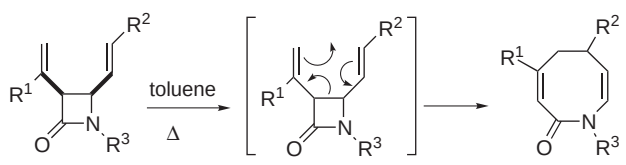
Received 3 March 2001; revised 6 March 2001; accepted 7 March 2001

Abstract—The thermally induced [3,3] sigmatropic (Cope) rearrangement of *cis*-β-lactams **1** having alkenyl groups at both the C3 and C4 positions to yield new functionalized eight-membered lactams (tetrahydroazocinones) **2**, in racemic as well as optically pure forms, is reported. This process involves a novel, concerted C3–C4 bond breakage of the β-lactam nucleus helped by ring strain. © 2001 Elsevier Science Ltd. All rights reserved.

Since its first report by Vogel in 1958,[1] the thermal $\sigma^2s+\pi^2s+\pi^2s$ (Cope) rearrangement of *cis*-1,2-divinylcyclobutane has emerged as one of the most attractive and powerful methods for the synthesis of cyclooctane derivatives.[2] Driven by the release of cyclobutane ring strain, this Cope rearrangement often proceeds at significantly lower temperatures (60–140°C) than analogous reactions involving acyclic 1,5-dienes. On the other hand, the strain of the 2-azetidinone ring has been claimed as being responsible for the biological activity of β-lactam antibiotics.[3] In spite of its synthetic potential, the behavior of the 2-azetidinone nucleus[4] under thermal conditions remains still almost unknown.[5] In particular, thermally induced Cope reactions involving β-lactams as part of the diene moiety have not been studied yet.

In connection with our studies on the synthesis and synthetic applications of functionalized 2-azetidinones,[6] we reasoned that the presence of alkenyl groups attached to adjacent ring positions (C3 and C4) of the β-lactam ring might provide an opportunity to use such thermal [3,3] sigmatropic rearrangement for the synthesis of eight-membered lactams, through the C3–C4 bond breakage.[7] Monocyclic medium size ring nitrogens occur in a range of natural and unnatural products and possess wide and diverse medicinal and biological properties.[8] Medium sized rings, in particular the eight- and nine-membered rings, are difficult to prepare using conventional cyclization methods due to unfavorable enthalpic and entropic factors.[9] Current synthetic methodology for the preparation of these types of compounds still remains very specific, with limited attention having been paid to stereocontrol.[10] We report here the first example of a Cope rearrangement in which the C3–C4 bond of the β-lactam nucleus is the central bond of the 1,5-hexadiene system, thus providing an easy and efficient entry to novel, and in some cases optically pure, functionalized azocinones (Scheme 1).

Starting substrates, *cis*-2-azetidinone-tethered dienes **1**, were prepared both in the racemic and optically pure forms using standard methodology. Racemic compounds **1a–c** were obtained as single *E*-isomers by Wittig olefination of racemic *cis*-4-formyl β-lactams **3**. Aldehydes **3** were prepared according to our previously reported one-pot synthesis for related compounds, using glyoxal diimine derived from *p*-anisidine.[11] Racemic compound **1d** and enantiomerically pure divinyl-β-lactams **1e** were prepared as single *cis*-diastereoisomers from the appropriate cinnamylideneimine, derived from benzylamine or *R*-(+)-α-methylbenzylamine, respectively, through a Staudinger reaction with the corresponding system acid chloride/triethylamine, in refluxing dichloromethane



Scheme 1.

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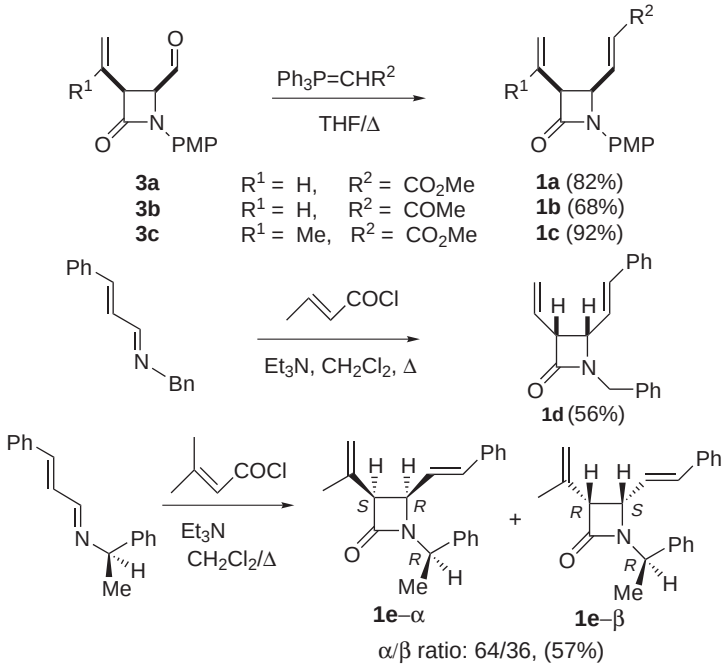
PII: S0040-4039(01)00391-4



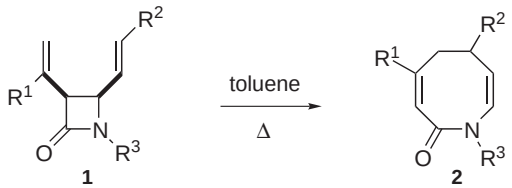
Scheme 2.

(Scheme 2).[12] Compound **1e** was obtained as a mixture of diastereoisomers which are enantiomers at the C3 and C4 stereocenters of the β-lactam ring. These isomers were easily separated by flash chromatography. On the basis of the reported data for related β-lactam systems concerning the ^{1}H NMR chemical shift of the signal corresponding to the exocyclic methine proton H1′ attached to N1, configuration (1′*R*,3*S*,4*R*) and (1′*R*,3*R*,4*S*) was assigned for major (α) and minor (β) isomers, respectively.[13]

In an initial reaction, a solution of compound **1a** in toluene was heated at 120°C in a sealed tube for 2 hours. Analysis by ^{1}H NMR spectroscopy revealed a quantitative conversion (>97%) to the desired tetrahydroazocinone **2**. Next, we tried the same reaction in refluxing toluene, with similar results after 4 hours.[14] Table 1 summarizes our results for the different 2-azetidinones tested. Pure compounds **2a**–**e** were isolated in good to excellent yields (75–90%) by flash chromatography.[15]

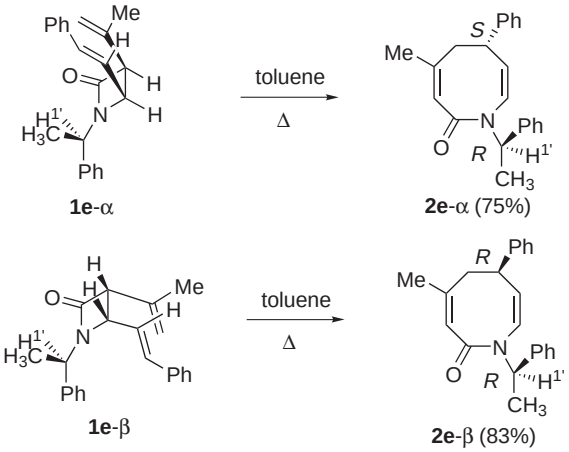
Of particular interest were the reactions of enantiomerically pure substrates **1e**-α and **1e**-β, which cleanly rearranged to the corresponding optically pure products **2e**-α and **2e**-β, respectively (Table 1). Also, when a mixture of isomers **1e**-α and **1e**-β was used, a mixture of the corresponding azocinones **2e**-α and **2e**-β was obtained in the same relative proportions. Moreover, an isomeric mixture (α/β) of compound **2e** was more

Table 1. Preparation of azocinones **2** by Cope rearrangement of divinyl-β-lactams **1**



Product[a]	R^1	R^2	R^3	*t* (h)	Yield %[b,c]
2a	H	CO_2Me	PMP[d]	5	86
2b	H	COMe	PMP	4	85
2c	Me	CO_2Me	PMP	5	90
2d	H	Ph	Bn	2.5	79
2e-α	Me	Ph	*R*-CH(Me)Ph	3	75
2e-β	Me	Ph	*R*-CH(Me)Ph	3	83

[a] Only pure *E*-isomers were used in all cases.
[b] Complete conversion in all cases by ^{1}H NMR spectroscopy.
[c] Yields are for pure products purified by column chromatography with correct analytical and spectroscopic data.
[d] PMP = 4-methoxyphenyl.



Scheme 3.

amenable to chromatographic purification than the corresponding isomers of compound **1e**. Above results show, not unexpectedly, the stereospecificity of these Cope rearrangements, and may be interpreted via a boat-like transition state as shown in Scheme 3.[16]

In conclusion, a rapid stereoselective synthesis of functionalized tetrahydroazocinones **2** both in racemic and in optically pure forms, starting from 2-azetidinone-tethered 1,5-dienes **1** has been developed. Furthermore, as far as we know this is the first example of a Cope rearrangement in which the C3–C4 bond of the β-lactam nucleus is the central bond of the 1,5-hexadiene system, allowing structure variability and facile incorporation of functional groups. Studies concerning the scope and generality of this methodology, are underway in our laboratory, and further details will be reported in due course.

Acknowledgements

We are grateful to the DGI (MCYT-Spain) for financial support of this research (Project BQU2000-0645). C. Rodríguez and A. Rodríguez thank the DGI (CEC-Comunidad de Madrid-Spain) for a predoctoral and postdoctoral fellowship, respectively.

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14. A solution of the corresponding *cis*-2-azetidinone **1** (0.40 mmol) in dry toluene (5 mL) was heated at reflux until complete disappearance of the starting material (tlc). The reaction mixture was allowed to cool to room temperature, the solvent was removed under reduced pressure and after flash chromatography eluting with hexanes/ethyl acetate, the appropriate azocinone **2** was obtained.
15. All new compounds were fully characterized by ^{1}H NMR, ^{13}C NMR, MS and IR and gave correct elemental analysis. Representative data are given for compound **2c**. ^{1}H NMR ($CDCl_3$) δ 1.81 (s, 3H), 2.41 (br s, 1H), 2.67 (br d, 1H, $J=15.6$), 3.63 (m, 1H), 3.69 (s, 3H), 3.76 (s, 3H), 5.60 (t, 1H, $J=8.1$ Hz), 5.84 (br s, 1H), 6.19 (d, 1H, $J=6.8$ Hz), 6.95 (d, 2H, $J=8.7$ Hz), 7.16 (d, 2H, $J=8.7$ Hz). ^{13}C NMR ($CDCl_3$) δ 176.1, 167.4, 158.2, 138.9, 132.1, 130.6, 127.2, 123.3, 120.2, 114.1, 55.3, 52.2, 39.5, 37.2, 25.7. IR ($CHCl_3$, cm^{-1}) ν 1736, 1664, 1624, 1508, 1248. MS (EI), m/z: 301 (M^+, 40), 286 (2), 242 (65). Anal. calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.57; H, 6.44; N, 4.49.
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