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Reverse-Cope elimination versus 1,3-dipolar cycloaddition in the reaction of enantiopure 2-azetidinone-tethered alkynylaldehydes with *N*-methylhydroxylamine

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Abstract

Enantiopure 2-azetidinone-tethered alkynylaldehydes **1** react stereoselectively under mild conditions with *N*-methylhydroxylamine to yield products derived from either intramolecular reverse-Cope elimination or 1,3-dipolar cycloaddition, depending on both the length of the tether and the experimental conditions.

Keywords: reverse-Cope elimination; cycloadditions; azetidinones; alkynylaldehydes.

Cycloaddition reactions are among the most powerful methods for the construction of rings.[1] In particular, intramolecular cycloadditions with high regio- and stereocontrol are important tools for the efficient assembly of complex molecular structures. We have recently initiated a study of various types of intramolecular cycloadditions of appropriately substituted 2-azetidinones.[2] Our aim is to develop efficient routes for the stereocontrolled construction of fused polycyclic β-lactams with different ring connectivities.[3] The development of new approaches to the stereocontrolled synthesis of β-lactam systems is a subject of interest in the context of their possible use as biologically active compounds or as versatile chiral building blocks.[4,5]

The intramolecular nitrone–alkene cycloaddition (INAC) reaction has experienced impressive growth and found broad application in organic synthesis.[6] In contrast to the extensive studies involving intramolecular reactions of alkenylnitrones, very little attention has been paid to related reactions with alkynylnitrones. This fact may be due to the known instability of the produced isoxazolines and the variety of their decomposition pathways which depend mainly on the substitution pattern of the alkyne.[7] The only previous report was by LeBel which described the reaction of 6-octyn-2-one with *N*-methylhydroxylamine in ethanol.[8] Presumably, the initial strained bridgehead C–C double bond of the resulting 2,3-dihydroisoxazole reacted with ethanol under the reaction conditions to give two isomeric

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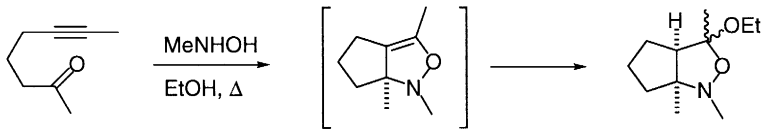
bicyclic isoxazolidines as the final products (Scheme 1). We wish to disclose that the reaction of several 2-azetidinone-tethered alkynylaldehydes **1** with *N*-methylhydroxylamine result in the regio- and stereoselective formation of different novel polycyclic β-lactams (types **3**–**5**) derived from two competitive processes, namely reverse-Cope elimination and 1,3-dipolar cycloaddition.



Scheme 1.

The starting substrates, enantiopure alkynylaldehydes **1a**–**c**, were conveniently synthesised from readily available *cis*-2-azetidinones **2a**–**c** following simple transformations[3a,b] (Fig. 1). Compounds **2** were easily prepared as single *cis*-enantiomers from imines of (*R*)-2,3-*O*-isopropylidenepropanal, through Staudinger reactions with the corresponding acid chlorides in the presence of Et_3N.[9]

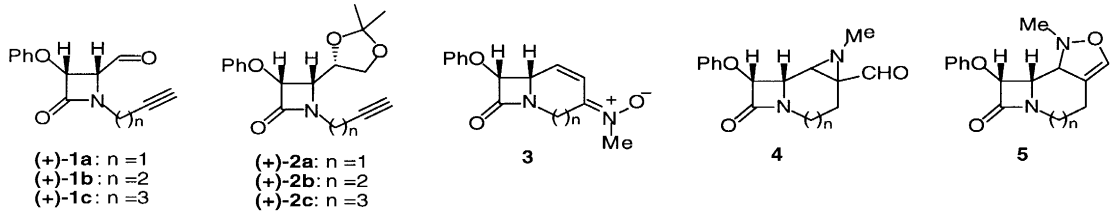
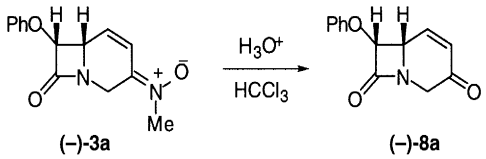


Fig. 1.

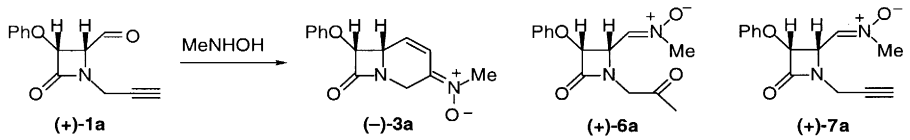
The outcome of the reactions of compounds **1** with *N*-methylhydroxylamine is determined by the length of the linking chain to the β-lactam nucleus and the experimental conditions. First, we studied reactions of enantiopure (3*R*,4*R*)-1-propargyl-4-formyl-2-azetidinone **1a** with *N*-methylhydroxylamine (1.5 equiv.) under different reaction conditions (Table 1). We were pleased to find that depending on the solvent and the temperature, different nitrones **3a**, **6a** and **7a** were obtained selectively. Thus, bicyclic nitrone **3a** was isolated in 53% yield after column chromatography, when the reaction was performed in refluxing benzene for 30 min. Keto-nitrone **6a** was the major product from the reaction both in toluene at room temperature and upon heating in chloroform (45% isolated yield), while nitrone **7a** was the only product (65% isolated yield) when the reaction was carried out in methanol at room temperature. The structure of the bicyclic nitrone **3a** was deduced on the basis of spectral data as well as by its facile transformation to 3-oxocarbacephem **8a**, previously prepared by us through a different route (Scheme 2).[2b] This synthesis of **8a** represents a more direct and convenient access to this interesting β-lactam system.



Scheme 2.

The formation of compounds **3a** and **6a** is the result of a formal reverse-Cope elimination reaction of the intermediate α-hydroxy-hydroxylamine as shown in Scheme 3.[10,11] Thus, retro-Cope cyclization of the initially formed carbinolamine **9** gives bicyclic *N*-oxide **10** which ring opens to *N*-hydroxyenamine aldehyde **11**, the key intermediate in the process.[12] Reacting as a *C*-nucleophile, compound **11** pro-

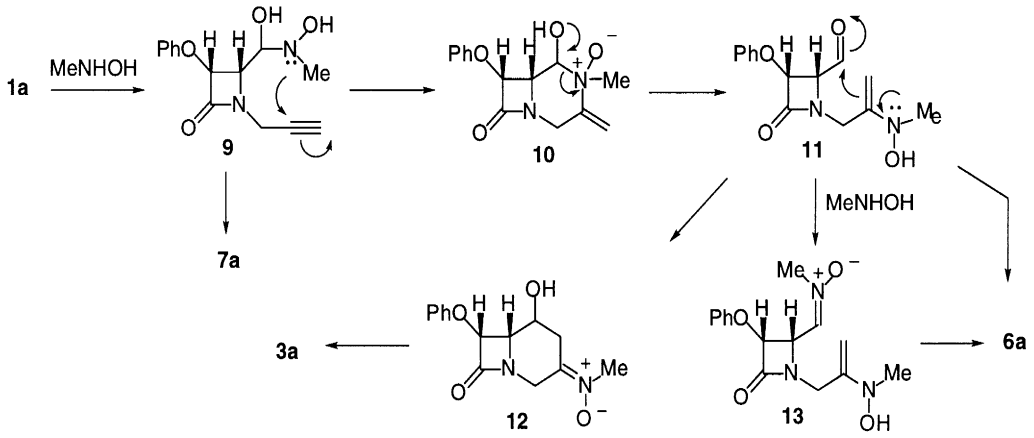
Table 1
Reaction between alkynylaldehyde **1a** and *N*-methylhydroxylamine[a]



				product ratio[b]			yield(%)[c, d]		
entry	solvent	T(°C)	t(h)	**3a**	**6a**	**7a**	**3a**	**6a**	**7a**
1	Benzene	r.t.	18	-	60	40		40	32
2	Benzene	Δ	0.5	60	15	25	53	-	10
3	Toluene	r.t.	18	-	66	34	-	45	26
4	Toluene	Δ	1.5	39	11	50	28	-	30
5	$CHCl_3$	r.t.	2	-	10	90	-	-	58
6	$CHCl_3$	Δ	2	-	64	36	-	45	28
7	CH_3OH	r.t.	2	-	-	100	-	-	65

[a] Molar ratio at room temperature: **1a**:MeNHOH·HCl:Et_3N = 1:1.5:1.5. Molar ratio at reflux temperature: **1a**:MeNHOH·HCl:Et_3N = 1:1.5:3. [b] The ratio was determined by integration of well-resolved signals in the ^1H NMR spectra of the crude reaction mixtures before purification. [c] Yield of pure, isolated product with correct analytical and spectral data. [d] Specific rotations given in deg per dm at 20 °C in $CHCl_3$: **3a**: $[\alpha]_D$ = –347.3 (*c* 1.5). **6a**: $[\alpha]_D$ = +2.3 (*c* 1.5). **7a**: $[\alpha]_D$ = +128.5 (*c* 2).

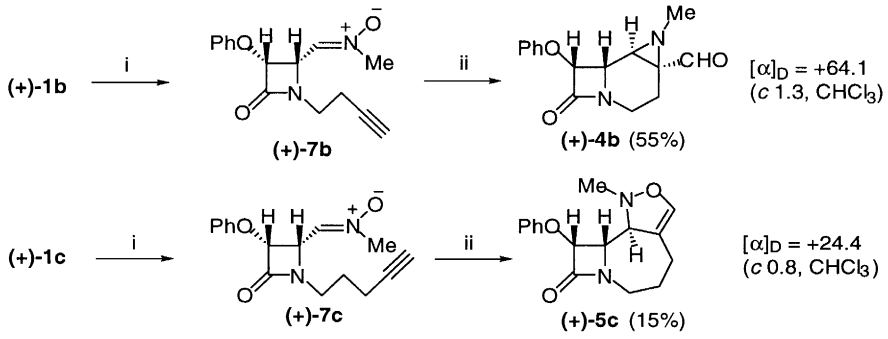
vides bicyclic hydroxynitrone **12** and, finally, the α,β-unsaturated nitrone **3a** by dehydration. On the other hand, compound **11** may produce enamine-nitrone **13**[12] by reaction with a new molecule of *N*-methylhydroxylamine. Further hydrolysis of the enamine moiety in **13** yields keto-nitrone **6a**. Compound **6a** could be alternatively formed by transamination of compound **11**.



Scheme 3.

Next, we studied reactions of the homologous 1,4-tethered alkenylaldehydes **1b** and **1c**, respectively, which behaved differently when heated in toluene under reflux. Thus, while compound **1b** afforded the corresponding aziridine carbaldehyde **4b** as the sole product (55% pure, isolated yield), compound **1c** gave a (1:3) mixture of cycloadduct **5c** and nitrone **7c**, the former being obtained in 15% yield as pure product (Scheme 4). Clearly, the 4-isoxazoline (type **5**) is the intermediate, and aziridine carbaldehyde

4b may arise by thermal sigmatropic rearrangement according to Baldwin et al.[13] In contrast, nitrone **7a** on heating in toluene under similar conditions gave a complex mixture of unidentified products. The ring size and the stereochemistry (by vicinal proton couplings and NOE experiments) of compounds **3**–**5** were established by NMR including two-dimensional techniques.[14]



Scheme 4.

The above results demonstrate the utility of the reported methodology for the elaboration of highly functionalised enantiopure bicyclic and tricyclic β-lactam systems relevant to the synthesis of antibiotics. Furthermore, as far as we know, these are the first examples of intramolecular reverse-Cope eliminations in the reactions of alkynylaldehydes with monosubstituted hydroxylamines. Other aspects of this chemistry will be reported in due course.

Acknowledgements

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