Pergamon

Tetrahedron Letters 42 (2001) 1503–1505

TETRAHEDRON LETTERS

General and efficient synthesis of β-lactams bearing a quinone moiety at N1, C3 or C4 positions

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Received 29 November 2000; accepted 16 December 2000

Abstract—A general and efficient synthesis of *cis*- and *trans*-β-lactams bearing a quinone moiety at N1, C3 or C4 positions has been developed in a racemic form. In some cases this methodology offers the possibility of achieving the 2-azetidinone-quinone in an optically pure form. © 2001 Elsevier Science Ltd. All rights reserved.

The development of new synthetic methods for the efficient construction of biologically active compounds is an important field in organic chemistry. In this context, natural products are of particular interest as leading structures. However, the isolation of new natural products is rather difficult and time consuming. Therefore, the concept of synthesizing natural product hybrids and analogues, containing two different pharmacophoric subunits, has been recently devised.[1]

Similarly, the synthesis of β-lactams and their biological application is an increasingly active area. The development of efficient approaches to the stereocontrolled synthesis of β-lactams continues to be of crucial importance within the context of the most widely employed class of antimicrobial agents to date.[2] Besides, the ever-growing new applications of azetidine-2-ones in the enzyme inhibition field justify a renewed interest in these compounds.[3] On the other hand, quinones are a large group of naturally occurring products that display a broad range of biological properties such as antiviral, antifungal and antitumor effects as well as enzymeinhibitory activity.[4] Although many investigations have been made in these fields into various types of β-lactams and quinones separately, no information is available regarding the synthesis of compounds involving the coupled-2-azetidinone/quinone system. Continuing with our work on the synthesis and synthetic applications of chiral, functionalized 2-azetidinones,[5] we wish to report a general and efficient synthesis of different types of *cis*- and *trans*-β-lactams bearing a quinone moiety at N1, C3 or C4 positions, which can be regarded as hybrids of the pharmacologically relevant subunits of β-lactam and quinone.

The starting substrates, 2,5-dimethoxyphenyl substituted β-lactams **1**, were prepared both in racemic and optically pure forms using standard methodology. Racemic compounds **1a**–**f** were obtained as single *cis*-diastereoisomers from the appropriate imine, through Staudinger reaction with the corresponding acid chloride in the presence of Et_3N (Table 1, entries 1–6).[6] Enantiomerically pure 2-azetidinones (+)-**1g**,**h** were obtained from the acid/$Cl_2P(O)OPh$/Et_3N modification of the Staudinger reaction,[7] using the Evans–Sjögren chiral auxiliary (*S*)-4-phenyl-2-oxooxazolidin-3-yl acetic acid (Table 1, entries 7 and 8).[8] The assignment of a (3*S*,4*R*)-stereochemistry for the 2-azetidinones derived from Evans–Sjögren ketenes is based on the current model for asymmetric induction in the Staudinger reaction.[9] However, compounds **1i**–**k** were obtained as single *trans*-diastereoisomers using the ketene–imine [2+2] cycloaddition (Table 1, entries 9–11).

The aim of the present study is to achieve the polyfunctionalized system of quinone β-lactam. The target molecules **2** were prepared smoothly via oxidative demethylation[10] of the appropriate 2,5-dimethoxyphenyl substituted β-lactams **1** using ceric ammonium nitrate (CAN) in aqueous acetonitrile. This strategy allowed us to employ a large arsenal of commercially available aldehydes, amines and acid chlorides. The reaction was carried out at room temperature in a mixture of CH_3CN/H_2O (3:1) and proceeded almost instantaneously.[11] The process was extremely sensitive to the solvents ratio. In fact, the greater the amount of water, the greater the complexity of the reaction mixtures. This transformation tolerates different substituents at the 2-azetidinone ring, such as alkyl, alkenyl, alkynyl, heteroaryl, alkoxy, 2-oxooxazolidin-3-yl,

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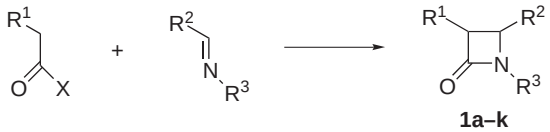
PII: S0040-4039(00)02298-X

and carboxymethyl moieties. Pure compounds **2a–j** were isolated in fair to excellent yields (44–98%) by flash chromatography (Scheme 1).[12]

Importantly, the β-lactam ring stereochemistry was unaffected by this process. The *cis*- or *trans*-stereochemistry of the four-membered ring is set during the cyclization step to form the 2-azetidinone ring, and it is transferred unaltered during the further synthetic steps.[13] This methodology offers the possibility of achieving 2-azetidinone-quinones **2** in racemic and optically pure forms.

Because quinones are among the best dienophiles traditionally used in Diels–Alder reactions,[14] we decided to attempt the use of 2-azetidinone-quinones **2** as dienophiles. The cycloaddition took place pyrolytically with 2,3-dimethyl-1,3-butadiene giving rise to the adduct **3a**, while the reaction with Danishefsky's diene proceeded in the presence of a Lewis acid (zinc iodide) affording cycloadduct **3b** (Scheme 2).[15] The facial selectivity of these cycloaddition reactions may be controlled by the substituted β-lactam ring at the dienophile in which one face of the quinone is blocked; thus, the diene preferentially

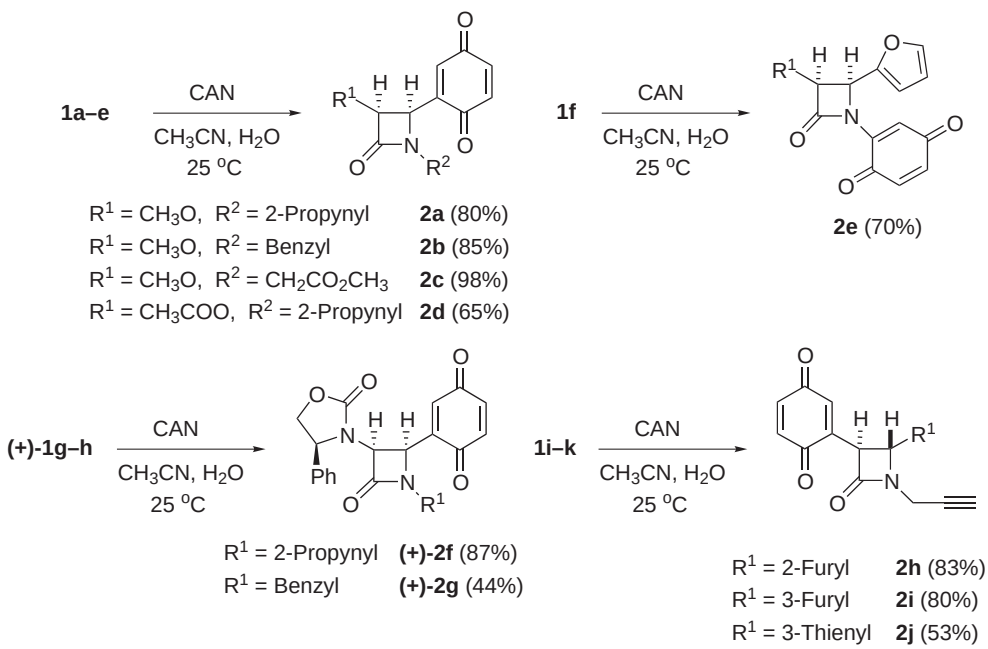
Table 1. Synthesis of 2,5-dimethoxyphenyl β-lactams **1a–k** via ketene–imine cycloaddition[a]



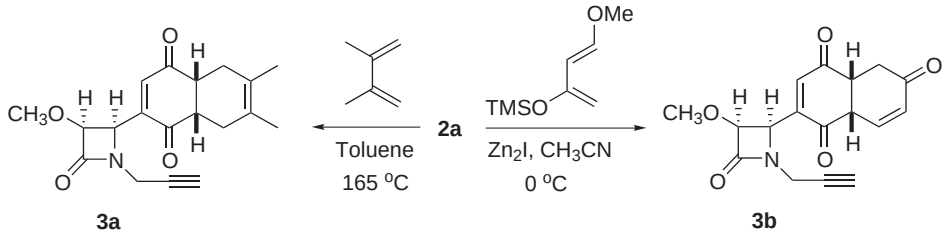
1a–k

Entry	R^1	R^2	R^3	X	β-Lactam	*cis*/*trans* ratio[b]	Yield (%)[c]
1	CH_3O	Ar	2-Propenyl	Cl	**1a**	100:0	99
2	CH_3O	Ar	2-Propynyl	Cl	**1b**	100:0	85
3	CH_3O	Ar	Benzyl	Cl	**1c**	100:0	87
4	CH_3O	Ar	$CH_2CO_2CH_3$	Cl	**1d**	100:0	76
5	CH_3COO	Ar	2-Propynyl	Cl	**1e**	100:0	90
6	CH_3O	2-Furyl	Ar	Cl	**1f**	100:0	52
7	Ox	Ar	2-Propynyl	OH	(+)-**1g**	100:0	50
8	Ox	Ar	Benzyl	OH	(+)-**1h**	100:0	92
9	Ar	2-Furyl	2-Propynyl	Cl	**1i**	0:100	50
10	Ar	3-Furyl	2-Propynyl	Cl	**1j**	0:100	54
11	Ar	3-Thienyl	2-Propynyl	Cl	**1k**	0:100	47

[a] Ar, 2,5-dimethoxyphenyl; Ox, (*S*)-4-phenyl-2-oxooxazolidin-3-yl.
[b] Determined by integration of well-resolved signals in the ^1H NMR spectra of crude reaction mixtures prior to purification.
[c] Yield of pure, isolated product with correct analytical and spectral data.



Scheme 1.



Scheme 2.

approaches the less hindered face in the transition state.

In conclusion, to the best of our knowledge, this is the first example of the preparation of hybrid products containing the pharmacologically relevant subunits of β-lactam and quinone. The extension of this methodology to the preparation of novel, differently substituted polycyclic β-lactams is currently under investigation in our laboratories.

Acknowledgements

Support for this work by the DGES-MEC (Project PB96-0565) is gratefully acknowledged.

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11. A solution of CAN (688 mg, 1.26 mmol) in 1.2 mL of aqueous acetonitrile (CH_3CN/H_2O 3:1) was added dropwise over 3 min to a solution of the appropriate 2,5-dimethoxyphenyl substituted β-lactam **1** (0.55 mmol) in acetonitrile (3 mL) at room temperature. The reaction mixture was stirred for another 10 min and then extracted with ethyl acetate. The combined organic layers were washed with brine, dried ($MgSO_4$), concentrated under reduced pressure and, after flash chromatography, compounds **2** were obtained.
12. All new compounds were fully characterized by ^1H NMR, ^{13}C NMR, MS, and IR and gave the correct elemental analyses. Representative data are given for compound **2a**: ^1H NMR ($CDCl_3$): δ 2.24 (t, 1H, $J=2.5$ Hz), 3.30 (s, 3H), 3.85 and 4.32 (dd, each 1H, $J=17.8$, 2.7 Hz), 4.77 (d, 1H, $J=5.1$ Hz), 5.06 (dd, 1H, $J=5.1$, 1.2 Hz), 6.73 (dd, 1H, $J=2.4$, 1.2 Hz), 6.81 (d, 2H, $J=1.5$ Hz). ^{13}C NMR ($CDCl_3$): δ 186.7, 186.6, 166.6, 141.8, 136.9, 133.5, 86.7, 75.5, 74.1, 59.6, 55.9, 30.6. IR ($CHCl_3$, cm^{-1}): ν 1747, 1660. MS (EI), m/z: 246 (M^++1, 23), 245 (M^+, 100). Anal. calcd for $C_{13}H_{11}NO_4$: C, 63.67; H, 4.52; N, 5.71. Found: C, 63.57; H, 4.54; N, 5.75.
13. The assignment of the *cis*-stereochemistry to β-lactams **1a–h** was based on the observed coupling constants of about 5.0 Hz for methine protons H3 and H4, whereas the *trans*-stereochemistry of the 2-azetidinones **1i–k** was consistent with methine coupling constants of ca. 2.0 Hz in their ^1H NMR spectra.
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15. Cycloadduct **3b** was analyzed by the ^1H NMR spectrum of the crude reaction mixture. Unfortunately, this cycloadduct could not be fully characterized because of its instability under the chromatographic conditions applied.