Monatsh Chem 139, 663–667 (2008)
DOI 10.1007/s00706-007-0820-1
Printed in The Netherlands

Monatshefte für Chemie
Chemical Monthly

Regio- and stereoselective synthesis of functionalized oxazolidin-2-ones from the reaction of α-epoxyketones with urea

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Received 21 September 2007; Accepted 30 September 2007; Published online 21 April 2008

Abstract A regio- and stereoselective synthesis of functionalized 4,5-disubstituted oxazolidin-2-ones is reported with moderate to good yields from the reaction of α-epoxyketones with urea in the presence of *p*-toluenesulfonic acid as the catalyst.

Keywords Regioselective; Stereoselective; α-Epoxyketones; Oxazolidin-2-ones; Heterocycles.

Introduction

Functionalized chiral oxazolidin-2-ones (*Evans*' chiral auxiliaries) have often been used as versatile chiral synthons in asymmetric syntheses of biologically active compounds or their synthetic intermediates. They are chiral auxiliaries in many important asymmetric syntheses [1] and used as interesting biologically active compounds themselves [2]. Owing to the potent activity of oxazolidin-2-ones, considerable attention has been focused on their synthesis [3]. They are generally prepared from chiral 1,2-amino alcohols or their precursors chiral α-amino-acids with a carbonyl source, such as phosgene [4] (or diphosgene) and dialkyl carbonates [5] (or alkyl chloroformates). Also, intramolecular nitrene insertion of alkyl azidoformates has been reported [6]. It is still important that effective methods to synthesize or to modify such compounds are developed and exploitation of non-toxic molecules and simple reagents with good reaction yields could be of interest.

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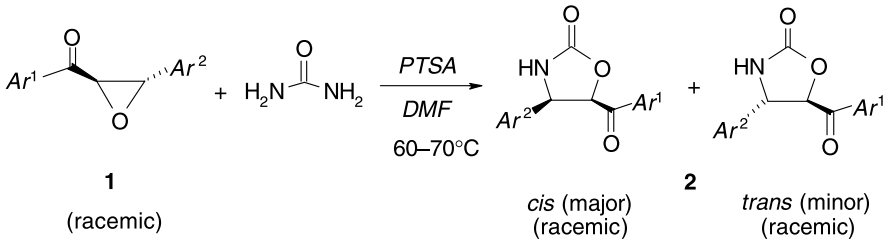
Results and discussion

Here, we wish to report an easy strategy, which allows the regio- and stereoselective preparation of 4,5-disubstituted oxazolidin-2-ones **2**, based on the reaction of the α-epoxyketones **1** with urea as promising starting materials, in the presence of a catalytic amount of *p*-toluenesulfonic acid (*PTSA*) in *DMF* (Scheme 1). The results are summarized in Table 1.

As shown in Table 1, the majority of the prepared and isolated compounds are *cis*-isomers. Furthermore, we found that when electron-donating groups are present on Ar^2, both of the reaction rates and the reaction yields increase; however, electron-withdrawing groups on Ar^2 cause no reaction. The plausible mechanisms are proposed in Scheme 2. It seems that in an acid mediated in a polar solvent, such as *DMF*, the acid mediated reaction begins with the formation of transition state **3** (Path A). Ring opening of **3** followed by rotation of the C_α–C_β bond produces the intermediate **4**. Cyclization of **4** under the same reaction conditions leads to the synthesis of the *cis*-oxazolidin-2-ones **2**. The *trans*-isomers might be obtained through the formation of the



Scheme 1

Table 1 Reaction of α-epoxyketones **1a**–**1l** with urea in the presence of *PTSA* in *DMF*

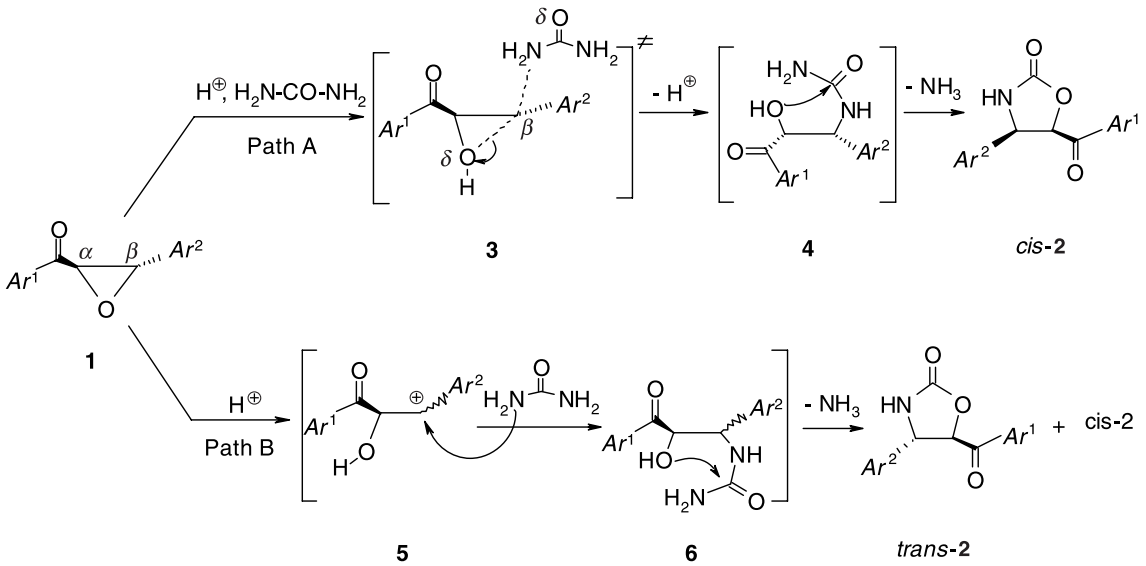
	Ar^1	Ar^2	Time/ h	Conversion/ %[a]	Yield **2**/ %[b]	
					cis	*trans*
a	*Ph*	*Ph*	5	82	45	24
b	*Ph*	4-*Me*	4	100	56	20
c	4-*Me*	4-*Me*	4	100	80	–
d	4-*Me*O	*Ph*	5	80	73	trace
e	4-*Me*O	4-*Me*O	3	100	77	–
f	4-Br	*Ph*	5	85	60	trace
g	*Ph*	3-*Me*	4	85	74	trace
h	*Ph*	2-*Me*O	3	84	55	trace
i	4-*Me*	2-*Me*O	3	90	68	–
j	*Ph*	2-Cl	7	–	–	–
k	*Ph*	3-NO_2	7	–	–	–
l	4-*Me*	4-NO_2	7	–	–	–

[a] Based on consumed α-epoxyketones. [b] Isolated yield based on consumed α-epoxyketones

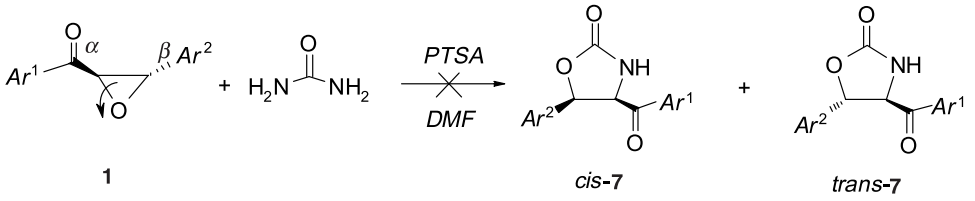
open-carbocation **5** and cyclization of the intermediate **6** (Path B). Since the major products are *cis*-isomers, formation of the transition state **3** through the pathway A is the more liable route for carrying out the reaction. The results also show regioselectivity on the C_β atom. In fact, in the absence of an acid catalyst, nucleophilic attack may occur on both C_α and C_β atoms of an α-epoxyester [7], however, in the case of α-epoxyketones, C_β is more reactive than C_α against nucleophiles and in acid catalyst solution which ring opening of epoxides achieves through cation formation, C_β–O bond breaking is liable for beginning and progression of the reaction. Thus, the reactions are carried out with high regioselectivity in acidic solution and no **7** is obtained (Scheme 3). Besides, instability of the C_β-cation in the presence of electron-withdrawing groups on Ar^2, causes no reaction to occur.

The reactions were carried out in *DMF* as an excellent polar-aprotic solvent. It is water miscible, therefore, in the work-up process, it is simple to remove the solvent, the residual urea, and *PTSA* by washing of the reaction mixture in water.

The identification and characterization of the products were carried out by means of their physical and spectroscopic data. The IR spectra of compounds



Scheme 2



Scheme 3

2 in comparison with the α-epoxyketones **1** show a CO-stretching of carbamate carbonyl in about $\bar{\nu} = 1740–1725\,cm^{-1}$ and a shift of the CO-stretching of the ketone carbonyl to higher frequency due to the ring expansion and loss of the epoxide ring strain.

The stereochemistry of the major products was identified as *cis*. Based on our previous investigation on the synthesis of 1,3-dioxolanes [8] from **1**, the coupling-constants of C^4–H and C^5–H in the *cis*-isomer are larger than of those in the *trans*-isomer. Also, in *cis*-orientation, C^4–H and C^5–H (especially C^4–H) appear in lower field in comparison with those in *trans*-orientation, because of the anisotropic effect of C^4-aryl and C^5-aroyl groups. It also was observed that the NH-signal in ^{1}H NMR appears in $\delta = 3.5–4.2$ instead of 6–7 ppm. It can be confirmed by exchange of the NH-proton in the presence of D_2O, which causes disappearance of the NH-signal. Probably, the aryl group in the C^4-position is perpendicular to the NH-bond; thus, the shielding effect of the aryl group causes the NH-signal to appear at higher field. Two CO-peaks are observed in the ^{13}C NMR spectrum at about $\delta = 197$ and 165–160 ppm related to ketone and carbamate carbonyl groups. Also, in all cases molecular ion-peaks with low abundances appear in the mass spectra.

In conclusion, a simple synthesis route is described for the regio- and stereoselective synthesis of functionalized oxazilidine-2-ones with moderate to good yields from the reaction of α-epoxyketones with urea in the presence of *PTSA* as catalyst. The reactions were carried out under mild conditions and in one-pot without separation and purification of the intermediates.

Experimental

Melting points were measured with an Electrothermal 9100 apparatus. IR spectra were measured with a Shimadzu IR-460 spectrometer. NMR spectra were recorded with a Bruker DRX-250 AVANCE instrument (250.1 MHz for ^{1}H and 62.9 MHz for ^{13}C). Chemical shifts are given in ppm (δ) relative to internal *TMS*, and coupling constants *J* are reported in Hz. Mass spectra were recorded with a Finnigan-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. The synthesis of the α-epoxyketones was achieved by using the published method [9].

General reaction procedure

In a 10 cm^3 round bottom flask, 1 mmol α-epoxyketones **1a**–**1i** was dissolved in 2 cm^3 of *DMF* and 0.1 mmol *PTSA* was added. To this solution, 0.15 g urea (2.5 mmol) was added and the mixture was heated at 60–70 °C for the times indicated in Table 1. The mixture was washed with cold-water (three times) to remove solvent and the residues of urea and *PTSA*. The products were separated and purified by thin-layer chromatography on 20×20 plates of silicagel 60 GF_{254} with *n*-hexane/*Et*OA*c* as eluent.

cis-5-Benzoyl-4-phenyloxazolidin-2-one (*cis*-**2a**, $C_{16}H_{13}NO_3$)
IR (liquid film): $\bar{\nu} = 3465$ (NH), 1726 (CO-carbamate), 1687 (CO-ketone) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 8.51$ (d, $^3J_{HH} = 7.2$ Hz, 2H–*Ar*), 8.04 (dd, $^3J_{HH} = 7.8$, 7.0 Hz, 2H–*Ar*), 7.78–7.70 (m, 4H–*Ar*), 7.55 (dd, $^3J_{HH} = 7.5$, $^4J_{HH} = 1.6$ Hz, 2H–*Ar*), 6.76 (d, $^3J_{HH} = 2.8$ Hz, C^5–H), 6.09 (d, $^3J_{HH} = 2.8$ Hz, C^4–H), 4.17 (bs, NH) ppm; ^{13}C NMR (69.2 MHz, $CDCl_3$): $\delta = 197.8$, 160.9, 135.1, 134.2, 133.5, 129.7, 129.4, 129.3, 128.6, 127.9, 78.2, 75.4 ppm; MS (EI): m/z (%) = 267 ($M^{+\bullet}$, 5), 239 (9), 224 (10), 223 (8), 208 (19), 105 (100), 77 (62).

trans-5-Benzoyl-4-phenyloxazolidin-2-one (*trans*-**2a**, $C_{16}H_{13}NO_3$)
IR (liquid film): $\bar{\nu} = 3456$ (NH), 1721 (CO-carbamate), 1686 (CO-ketone) cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 8.04$ (dd, $^3J_{HH} = 6.7$, $^4J_{HH} = 1.6$ Hz, 2H–*Ar*), 7.57 (dd, $^3J_{HH} = 8.0$, 7.5 Hz, 2H–*Ar*), 7.27–7.24 (m, 4H–*Ar*), 7.08 (dd, $^3J_{HH} = 7.5$ Hz, $^4J_{HH} = 1.6$ Hz, 2H–*Ar*), 6.29 (d, $^3J_{HH} = 2.0$ Hz, C^5–H), 5.62 (d, $^3J_{HH} = 2.0$ Hz, C^4–H), 3.68 (bs, NH) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 197.3$, 160.4, 134.7, 133.8, 133.0, 129.3, 128.9, 128.9, 128.1, 127.4, 76.6, 75.0 ppm; MS (EI): m/z (%) = 267 ($M^{+\bullet}$, 3), 239 (8), 224 (7), 223 (5), 208 (15), 105 (100), 77 (72).

cis-5-Benzoyl-4-(4-methylphenyl)oxozolidin-2-one (*cis*-**2b**, $C_{17}H_{15}NO_3$)
IR (liquid film): $\bar{\nu} = 3445$ (NH), 1727 (CO-carbamate), 1686 (CO-ketone) cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 8.03$ (dd, $^3J_{HH} = 8.0$ Hz, $^4J_{HH} = 1.5$ Hz, 2H–*Ar*), 7.70 (dd, $^3J_{HH} = 7.2$ Hz, $^4J_{HH} = 1.5$ Hz, 1H–*Ar*), 7.58 (dd, $^3J_{HH} = 8.0$, 7.2 Hz, 2H–*Ar*), 7.05 (d, $^3J_{HH} = 8.0$ Hz, 2H–*Ar*), 6.96 (d, $^3J_{HH} = 8.0$ Hz, 2H–*Ar*), 6.25 (d, $^3J_{HH} = 3.0$ Hz, C^5–H), 5.61 (m, C^4–H), 3.67 (d, $^3J_{NH} = 6.5$ Hz, NH), 2.31 (s, CH_3) ppm; ^{13}C NMR

($CDCl_3$): $\delta = 197.4$, 160.4, 138.8, 134.6, 133.7, 129.9, 129.2, 128.8, 127.4, 126.4, 76.7, 75.0, 21.2 ppm; MS (EI): m/z (%) = 281 ($M^{+\bullet}$, 4), 253 (4), 237 (13), 222 (15), 105 (100), 91 (67), 77 (31).

trans-5-Benzoyl-4-(4-methylphenyl)oxozolidin-2-one (*trans*-**2b**, $C_{17}H_{15}NO_3$)
IR (liquid film): $\bar{\nu} = 3460$ (NH), 1719 (CO-carbamate), 1686 (CO-ketone) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 7.90$ (dd, $^3J_{HH} = 8.2$ Hz, $^4J_{HH} = 1.5$ Hz, 2H–*Ar*), 7.53 (dd, $^3J_{HH} = 7.7$, $^4J_{HH} = 1.5$ Hz, 1H–*Ar*), 7.33 (d, $^3J_{HH} = 8.2$ Hz, 2H–*Ar*), 7.28 (d, $^3J_{HH} = 7.7$ Hz, 2H–*Ar*), 7.16 (d, $^3J_{HH} = 8.0$ Hz, 2H–*Ar*), 6.17 (d, $^3J_{HH} = 2.5$ Hz, C^5–H), 5.33 (m, C^4–H), 3.89 (bs, NH), 2.33 (s, CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 198.1$, 159.4, 138.6, 134.3, 133.4, 129.2, 129.0, 128.6, 127.0, 126.4, 75.4, 75.3, 21.2 ppm; MS (EI): m/z (%) = 281 ($M^{+\bullet}$, 5), 253 (6), 237 (10), 222 (9), 105 (100), 91 (77), 77 (23).

cis-5-(4-Methylbenzoyl)-4-(4-methylphenyl)oxozolidin-2-one (*cis*-**2c**, $C_{18}H_{17}NO_3$)
Mp 93–95 °C from *n*-hexane. IR (KBr): $\bar{\nu} = 3375$ (NH), 1736 (CO-carbamate), 1679 (CO-ketone) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 8.00$ (d, $^3J_{HH} = 7.8$ Hz, 2H–*Ar*), 7.36 (d, $^3J_{HH} = 7.8$ Hz, 2H–*Ar*), 7.25 (d, $^3J_{HH} = 5.5$ Hz, 2H–*Ar*), 7.09 (d, $^3J_{HH} = 5.5$ Hz, 2H–*Ar*), 6.14 (d, $^3J_{HH} = 3.0$ Hz, C^5–H), 5.72 (dd, $^3J_{NH} = 7.2$ Hz, $^3J_{HH} = 3.0$ Hz, C^4–H), 3.65 (d, $^3J_{NH} = 7.2$ Hz, NH), 2.47, 2.16 (2s, $2CH_3$) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 197.2$, 166.2, 145.7, 133.7, 131.3, 129.9, 129.1, 128.6, 128.0, 127.5, 77.2, 75.0, 21.9, 19.3 ppm; MS (EI): m/z (%) = 295 ($M^{+\bullet}$, 3), 267 (1), 236 (5), 150 (21), 119 (100), 105 (14), 91 (77), 77 (23).

cis-5-(4-Methoxybenzoyl)-4-phenyloxozolidin-2-one (*cis*-**2d**, $C_{17}H_{15}NO_4$)
IR (liquid film): $\bar{\nu} = 3455$ (NH), 1720 (CO-carbamate), 1673 (CO-ketone) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 8.06$ (d, $^3J_{HH} = 7.0$ Hz, 2H–*Ar*), 7.30 (d, $^3J_{HH} = 8.2$ Hz, 2H–*Ar*), 7.26 (d, $^3J_{HH} = 7.5$ Hz, 2H–*Ar*), 7.11 (dd, $^3J_{HH} = 7.2$, $^4J_{HH} = 1.5$ Hz, 1H–*Ar*), 7.08 (d, $^3J_{HH} = 7.0$ Hz, 2H–*Ar*), 6.28 (d, $^3J_{HH} = 2.5$ Hz, C^5–H), 5.56 (bs, C^4–H), 3.93 (s, OCH_3), 3.75 (bs, NH) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 195.3$, 164.7, 160.5, 133.8, 129.9, 129.3, 128.9, 128.1, 127.5, 114.5, 76.8, 74.6, 55.7 ppm; MS (EI): m/z (%) = 297 ($M^{+\bullet}$, 1), 254 (27), 253 (7), 135 (100), 107 (17), 105 (18), 77 (44).

cis-5-(4-Methoxybenzoyl)-4-(4-methoxyphenyl)oxozolidin-2-one (*cis*-**2e**, $C_{18}H_{17}NO_5$)
IR (liquid film): $\bar{\nu} = 3450$ (NH), 1719 (CO-carbamate), 1676 (CO-ketone) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 8.07$ (d, $^3J_{HH} = 8.5$ Hz, 2H–*Ar*), 7.05–7.00 (m, 4H–*Ar*), 6.77 (d, $^3J_{HH} = 8.5$ Hz, 2H–*Ar*), 6.23 (d, $^3J_{HH} = 3.0$ Hz, C^5–H), 5.54 (dd, $^3J_{NH} = 6.5$, $^3J_{HH} = 3.0$ Hz, C^4–H), 3.94 and 3.77 (2s, $2CH_3O$), 3.88 (d, $^3J_{NH} = 6.5$ Hz, NH) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 196.1$, 164.7, 160.5, 131.3, 128.9, 126.5, 125.1, 118.7, 114.5, 113.5, 77.2, 74.6, 55.6, 55.2 ppm; MS (EI): m/z (%) = 284 ($M^{+\bullet}$-HNCO, 5), 283 (4), 177 (13), 135 (100), 107 (47), 92 (41), 77 (35).

cis-5-(4-Bromobenzoyl)-4-phenyloxozolidin-2-one (*cis*-**2f**, $C_{16}H_{12}BrNO_3$)
IR (liquid film): $\bar{\nu} = 3205$ (NH), 1742 (CO-carbamate), 1684 (CO-ketone) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 7.41$, 7.36 (2d, $^3J_{HH} = 8.5$ Hz, 4H–*Ar*), 7.17–7.11 (m, 5H–*Ar*), 6.31 (d, $^3J_{HH} = 3.0$ Hz, C^5–H), 5.55 (bs, C^4–H), 3.84 (bs, NH) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 196.0$, 164.2, 132.3, 131.1, 129.9, 129.1, 128.7, 128.1, 127.6, 126.9, 77.0, 74.5 ppm; MS (EI): m/z (%) = 347 ([$M^{+\bullet} + 2$], 2), 345 ($M^{+\bullet}$, 2), 304 (8), 302 (7), 185 (100), 183 (98), 104 (53), 77 (45).

Acknowledgements

We are grateful to the University of *Kurdistan* Research Council for the partial support of this work.

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