Regio- and Chemoselective Synthesis of 5-Aroyl-*NH*-1,3-oxazolidine-2-thiones

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A one-pot synthesis of 5-aroyl-*NH*-1,3-oxazolidine-2-thiones by a regio- and chemoselective reaction of α-epoxyketones with thiourea or sodium thiocyanate in the presence of *p*-toluenesulfonic acid as catalyst in tetra-*n*-butylammonium chloride is described.

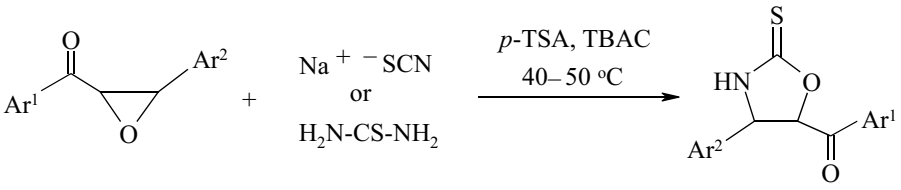
Key words: *NH*-Oxazolidine-2-thiones, Chemoselective Reaction, Regioselective Reactions, One-pot Synthesis, Ionic Liquid

Introduction

1,3-Oxazolidine-2-thiones are known as an important class of heterocycles having significant biological and pharmacological activities [1]. They have wide applications as chiral auxiliaries in asymmetric syntheses [2 – 11] and play a vital role as starting materials for further transformations in organic syntheses [12 – 14]. Although a number of emerging methods are available to build up these heterocycles [15 – 17], few synthetic routes have been reported for functionalized *NH*-1,3-oxazolidine-2-thiones. The simple 1,3-oxazolidine-2-thiones are generally prepared by thiocarbonylation of β-amino alcohols with CS_2 [18 – 21] and by the reaction of thiocyanic acid with α-hydroxyketonens [22, 23]. In this protocol, an expedient method is described for the synthesis of a number of 5-aroyl-*NH*-1,3-oxazolidine-2-thiones by the reaction of α-epoxyketones with thiourea or sodium thiocyanate under mild conditions.

Results and Discussion

Since one of the most important features in the chemistry of 1,3-oxazolidine-2-thiones is their use in design and synthesis of organic compounds, the presence of chemically active functional groups at C-4 or C-5 position can affect the reactivity and expand their applications. Thus, with the aim of extending synthetic methods, herein, we disclose the regio- and chemoselective reaction of α-epoxyketones **1** with thiourea or sodium thiocyanate for the synthesis of title compounds **2**. The reactions were carried out in the presence of a catalytic amount of *p*-toluenesulfonic acid (*p*-TSA) in tetra-*n*-butylammonium chloride (TBAC)



1 **2**

Scheme 1.

Table 1. Synthesis of the 5-aroyl-*NH*1,3-oxazolidine-2-thiones **2** from the reaction of α-epoxyketones **1** (1 mmol) with NaSCN (1.3 mmol) or H_2NCSNH_2 (1.3 mmol) in the presence of *p*-TSA (0.1 mmol) in TBAC.

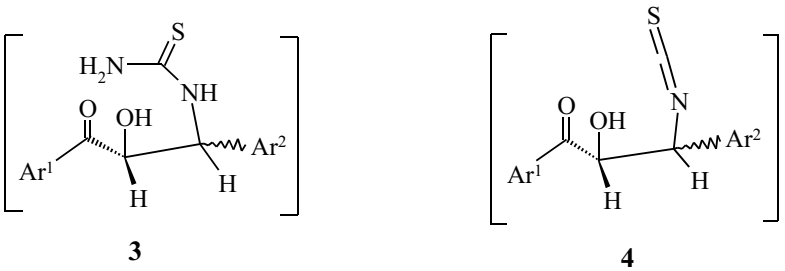
Entry	Ar^1	Ar^2	Product	A[a] B[b]	Time (h)	Conversion (%)[c]	Yield (%)[d]	Ratio[e]	
								cis	*trans*
1	Ph	Ph	**2a**	A	2.5	80	60	54	46
				B	1.5	>90	60	54	46
2	Ph	4-MePh	**2b**	A	2	85	63	60	40
				B	1	>90	65	56	44
3	4-MePh	4-MePh	**2c**	A	2	80	65	58	42
				B	1	>90	68	53	47
4	4-ClPh	Ph	**2d**	A	5	85	55	60	40
				B	3	75	58	59	41
5	4-ClPh	4-MePh	**2e**	A	2	75	65	54	46
				B	1	80	65	54	46
6	2-MePh	4-MeOPh	**2f**	A	1	>90	55	28	72
				B	0.5	75	55	28	72
7	4-MeOPh	Ph	**2g**	A	2.5	>90	62	65	35
				B	1.5	>90	60	67	33
8	Ph	2-ClPh	**2h**	A	5	trace	–	–	–
				B					
9	Ph	3-NO_2Ph	**2i**	A	5	0	–	–	–
				B					
10	4-MePh	4-NO_2Ph	**2j**	A	5	0	–	–	–
				B					

[a] Reaction with NaSCN; [b] reaction with H_2NCSNH_2; [c] based on consumed α-epoxyketone; [d] isolated yield based on consumed α-epoxyketones; [e] estimated from ^{1}H NMR spectra.

as solvent (Scheme 1). Results are summarized in Table 1.

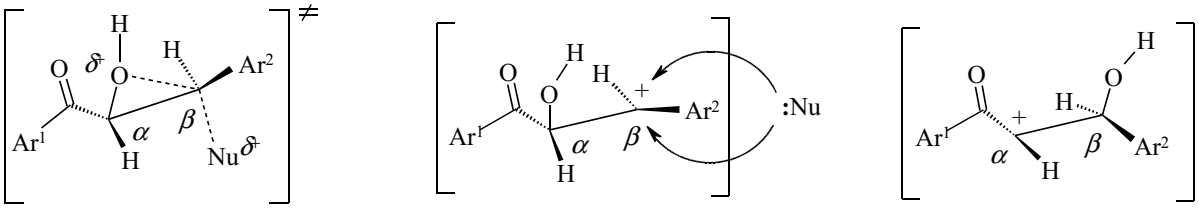
Plausible intermediates are proposed in Fig. 1. Although we made no attempts to characterize the produced intermediates, it is reasonable to assume that in an acid present in a polar solvent such as TBAC, the reaction begins with initial addition of thiourea or sodium thiocyanate to the α-epoxyketones **1** and formation of intermediates **3** and **4**, respectively. Fast cyclization of **3** or **4** under the reaction conditions leads to the *NH*-oxazolidine-2-thiones **2**. The removal of NH_3 from **3** was confirmed using wet litmus paper.

The stereoselectivity of the reactions depends on the rate of formation and stability of the C^{β} carbocation (Fig. 2). Formation of transition state **5** in the beginning of the reaction pathway increases



3 **4**

Fig. 1.



5 **6** **7**

Fig. 2.

the stereoselectivity; however, formation of carbocation **6** reduces the stereoselectivity. This may be affected by solvent and substituent effects on the Ar^2 group [24 – 26]. It seems that in the ionic liquid TBAC, the carbocations **6** are better formed, and thus the oxazolidine-2-thiones **2** are obtained with less stereoselectivity. Furthermore, we observed no reaction when electron-withdrawing groups are on Ar^2 (Table 1, entries 8 – 10). Since the C^{α} cation **7** is too unstable [24 – 26], only the C^{β}-O bond breaking (intermediate **6**) is liable for the regioselective beginning and progression of the reaction. All the reactions proceeded with high chemoselevtivity, and the carbonyl groups of the ketones in α-epoxyketones **1** remained without any changes.

The ionic liquid TBAC was used as an excellent green solvent. It is water miscible, therefore, in the work-up process, it is simple to remove the solvent, the residual thiourea or NaSCN and *p*-TSA by washing of the reaction mixture with water.

The identification and characterization of the products were deduced from their physical and spectroscopic data. The IR spectra of compounds **2** show the CS stretching of the thiocarbamate moiety as weak peaks at 1200 – 1080 cm^{-1}. In the ^1H NMR spectra, the coupling constants H^4-H^5 ($^3J_{HH}$) are in the range 7.5 – 8.5 Hz and 3.5 – 5.0 Hz for *cis* and *trans* isomers respectively. Also, the CO and CS groups are observed at about $\delta = 197$ and 185 – 167 ppm, respectively in the ^{13}C NMR spectra. Molecular ion peaks with low abundances appear in the mass spectra.

Conclusion

In conclusion, an expedient approach is described for the synthesis of functionalized 4,5-disubstituted *NH*-oxazolidine-2-thiones from the reaction of α-epoxyketones **1** with thiourea or sodium thiocyanate in TBAC and in the presence of *p*-TSA as catalyst. All the reactions were carried out under mild conditions, in a one-pot reaction and without the need of separation and purification of the intermediates. The products were obtained in moderate to good yields with high regio- and chemoselectivities.

Experimental Section

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 ^1H 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 an Agilent-5975C mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer. The synthesis of the α-epoxyketones **1** was achieved using the published method [27].

General reaction procedure: In a 10 mL round-ballon flask, α-epoxyketones **1** (1 mmol) were mixed with TBAC (0.5 g) and *p*-TSA (0.02 g, 0.1 mmol). To this mixture, thiourea or sodium thiocyanate (0.1 g, 1.3 mmol) was added, and the mixture was heated at 40 – 50 °C for the period indicated in Table 1. Then the mixture was washed three times with cold water to remove the solvent, the residual thiourea or sodium thiocyanate, and *p*-TSA. The products were separated and purified by thin-layer chromatography on 20 × 20 cm^2 plates of silica gel 60 GF_{254} with *n*-hexane-EtOAc as eluent.

*5-Benzoyl-4-phenyloxazolidine-2-thione (mixture of cis- and trans-**2a**)*

IR (film): $\bar{\nu}$ (cm^{-1}) = 3445 (NH), 1684 (CO-ketone), 1187 (CS). – ^1H NMR (250 MHz, $CDCl_3$): $\delta = 8.02$ (d, $^3J_{HH} = 7.5$ Hz, 2 H – Ar), 7.87 (dd, $^3J_{HH} = 7.5$ Hz, $^3J_{HH} = 8.0$ Hz, 2 H-Ar), 7.63 (t, $^3J_{HH} = 7.5$ Hz, 2 H-Ar),

7.53 – 7.16 (m, 12 H-Ar), 5.55 (bs, *trans*-C^5H), 5.37 (d, $^3J_{HH} = 5.2$ Hz, *trans*-C^4H), 5.28 (d, $^3J_{HH} = 8.2$ Hz, *cis*-C^5H), 5.14 (d, $^3J_{HH} = 8.2$ Hz, *cis*-C^4H), 3.36 (bs, 2 NH) ppm. – ^{13}C NMR (69.2 MHz, $CDCl_3$): $\delta = 194.5$, 192.5, 172.1, 172.1, 139.1, 138.9, 134.6, 134.4, 134.2, 134.0, 129.1, 128.9, 128.8, 128.7, 128.4, 127.2, 126.8, 128.2, 128.0, 76.9, 73.1, 63.2, 61.4 ppm. – Anal. for $C_{16}H_{13}NO_2S$ (283.35): calcd. C 67.82, H 4.62, N 4.94; found C 67.88, H 4.65, N 4.92.

*5-(4-Methylbenzoyl)-4-phenyloxazolidine-2-thione (mixture of cis- and trans-**2b**)*

IR (film): $\bar{\nu}$ (cm^{-1}) = 3475 (NH), 1683 (CO-ketone), 1200 (CS). – ^1H NMR (250 MHz, $CDCl_3$): $\delta = 8.02$ (d, $^3J_{HH} = 7.5$ Hz, 2 H-Ar), 7.87 (d, $^3J_{HH} = 7.5$ Hz, 2 H-Ar), 7.68 – 7.05 (m, 14 H-Ar), 5.52 (d, $^3J_{HH} = 3.8$ Hz, *trans*-C^5H), 5.25 – 5.21 (m, C^4H and C^5H), 5.13 (d, $^3J_{HH} =$ 8.2 Hz, *cis*-C^4H), 3.40 (bs, 2 NH), 2.35 and 2.29 (2 s, 2 CH_3) ppm. – ^{13}C NMR (69.2 MHz, $CDCl_3$): $\delta = 194.5$, 194.2, 172.5, 170.8, 138.4, 134.7, 134.3, 134.1, 134.1, 129.2, 129.1, 129.0, 129.0, 128.9, 128.8, 128.7, 127.9, 127.1, 126.8, 74.5, 73.2, 63.0, 61.5, 21.2, 21.1 ppm. – Anal. for $C_{17}H_{15}NO_2S$ (297.37): calcd. C 68.66, H 5.08, N 4.71; found C 68.70, H 5.10, N 4.70.

*5-(4-Methylbenzoyl)-4-(4-methylphenyl)oxazolidine-2-thione (mixture of cis- and trans-**2c**)*

IR (film): $\bar{\nu}$ (cm^{-1}) = 3445 (NH), 1600 (CO-ketone), 1179 (CS). – ^1H NMR (250 MHz, $CDCl_3$): $\delta = 7.92$ (d, $^3J_{HH} = 7.5$ Hz, 2 H-Ar), 7.79 (d, $^3J_{HH} = 7.5$ Hz, 2 H-Ar), 7.40 – 7.12 (m, 10 H-Ar), 7.05 (s, 2 H-Ar), 5.55 (s, *trans*-C^5H), 5.32 – 5.29 (m, *cis*-C^5H), 5.25 – 5.22 (m, *trans*-C^4H), 5.12 – 5.09 (m, *cis*-C^4H), 3.69 (bs, NH), 3.27 (bs, NH), 2.46, 2.43, 2.36 and 2.31 (4 s, 4 CH_3) ppm. – ^{13}C NMR (69.2 MHz, $CDCl_3$): $\delta = 197.0$, 194.2, 176.0, 75.5, 145.7, 145.4, 138.4, 138.3, 136.2, 136.1, 132.1, 132.0, 129.8, 129.5, 129.2,129.1, 128.8, 127.9, 127.1, 126.7, 74.6, 73.1, 63.2, 61.2, 29.6, 21.7, 21.2, 21.1 ppm. – Anal. for $C_{18}H_{17}NO_2S$ (311.40): calcd. C 69.42, H 5.50, N 4.50; found C 69.47, H 5.52, N 4.52.

*5-Benzoyl-4-(4-chlorophenyl)oxazolidine-2-thione (mixture of cis- and trans-**2d**)*

IR (film): $\bar{\nu}$ (cm^{-1}) = 3420 (NH), 1682 (CO-ketone), 1089 (CS). – ^1H NMR (250 MHz, $CDCl_3$): $\delta = 7.95$ (d, $^3J_{HH} = 8.5$ Hz, 2 H-Ar), 7.78 (d, $^3J_{HH} = 8.2$ Hz, 2 H-Ar), 7.54 – 7.07 (m, 14 H-Ar), 5.46 (m, *trans*-C^5H), 5.32 (m, *cis*-C^5H), 5.23 (d, $^3J_{HH} = 4.0$ Hz, *trans*-C^4H), 5.08 (d, $^3J_{HH} =$ 8.5 Hz, *cis*-C^4H), 4.14 and 3.72 (2 bs, 2 NH) ppm. – ^{13}C NMR (69.2 MHz, $CDCl_3$): $\delta = 196.9$, 193.5, 172.0, 169.0, 140.9, 140.8, 140.7, (2 C), 138.9, 135.5, 133.9, 132.8, 131.5, 130.4, 130.1, 129.9, 129.3, 129.1, 128.9, 128.5, 128.3, 127.9, 127.2, 125.8, 76.7, 74.7, 63.1, 60.3 ppm. – Anal. for $C_{16}H_{12}ClNO_2S$ (317.79): calcd. C 60.47, H 3.81, N 4.41; found C 60.51, H 3.80, N 4.43.

*4-(4-Chlorophenyl)-5-(4-methylbenzoyl)oxazolidine-2-thione (mixture of cis- and trans-**2e**)*

IR (film): $\bar{\nu}$ (cm^{-1}) = 3290 (NH), 1605 (CO-ketone) 1089 (CS). – ^1H NMR (250 MHz, $CDCl_3$): $\delta = 7.96$ (d, $^3J_{HH} = 7.5$ Hz, 2 H-Ar), 7.81 – 7.69 (m, 2 H-Ar), 7.52 – 7.32 (m, 6 H-Ar), 7.20 – 7.03 (m, 6 H-Ar), 5.61(d, $^3J_{HH} = 7.5$ Hz, *cis*-C^5H), 5.52 – 5.47 (m, *trans*-C^5H), 5.30 (d, $^3J_{HH} =$ 6.0 Hz, *trans*-C^4H), 5.17 (d, $^3J_{HH} = 7.5$ Hz, *cis*-C^4H), 3.19 (bs, 2 NH), 2.47 and 2.32 (2 s, 2 CH_3) ppm. – ^{13}C NMR (69.2 MHz, $CDCl_3$): $\delta = 193.2$, 190.1, 168.0, 167.0, 141.4, 140.3, 137.3, 136.4, 130.7, 130.5, 130.4, 130.2(2 C), 129.2, 128.7, 128.4, 127.9, 126.4, 126.2, 125.8, 75.0, 70.2, 69.9, 60.5, 24.0, 21.3 ppm. – EI-MS (70 eV): m/z (%) = 333 [($M^+ + 2$), 2], 331 (M^+, 5), 274 (8), 272 (18), 258 (12), 256 (31), 141 (38), 139 (100), 91 (34). – Anal. for $C_{17}H_{14}ClNO_2S$ (331.82): calcd. C 61.65, H 4.25, N 4.22; found C 61.70, H 4.23, N 4.21.

*5-(4-Methoxybenzoyl)-4-(2-methylphenyl)oxazolidine-2-thione (mixture of cis- and trans-**2f**)*

IR (film): $\bar{\nu}$ (cm^{-1}) = 3420 (NH), 1682 (CO-ketone), 1089 (CS). – ^1H NMR (250 MHz, $CDCl_3$): $\delta =$ 7.94 – 7.90 (m, 2 H-Ar), 7.82 – 7.75 (m, 1 H-Ar), 7.63 – 7.55 (m, 1 H-Ar), 7.45 – 7.31 (m, 10 H-Ar), 6.96 – 6.87 (m, 2 H-Ar), 5.47 (d, $^3J_{HH} = 5.2$ Hz, *trans*-C^5H), 5.31 (d, $^3J_{HH} = 5.2$ Hz, *trans*-C^4H), 5.22 (d, $^3J_{HH} = 8.0$ Hz, *cis*-C^5H), 5.08 (d, $^3J_{HH} = 8.0$ Hz, *cis*-C^4H), 3.87 and 3.82 (2 s, 2 OCH_3), 3.87 and 3.73 (2 bs, 2 NH), 2.43 and 2.40 (2 s, 2 CH_3) ppm. – ^{13}C NMR (69.2 MHz, $CDCl_3$): $\delta = 193.3$, 191.3, 186.5, 186.4, 160.1, 160.0, 137.4, 137.3, 136.9, 136.7, 129.7, 129.5, 128.7, 128.6, 128.2, 128.1, 127.5, 127.4, 126.7, 126.5, 115.5, 115.4, 90.8, 88.1, 64.8, 64.5, 55.2, 55.1, 19.2, 19.1 ppm. – EI-MS (70 eV): m/z (%) = 268 (32), 252 (40), 135 (100), 107 (17), 91 (28). – Anal. for $C_{18}H_{17}NO_3S$ (327.40): calcd. C 66.03, H 5.23, N 4.28. found C 66.09, H 5.25, N 4.30.

*5-Benzoyl-4-(4-methoxyphenyl)oxazolidine-2-thione (mixture of cis- and trans-**2g**)*

IR (film): $\bar{\nu}$ (cm^{-1}) = 3445 (NH), 1671 (CO-ketone), 1169 (CS). – ^1H NMR (250 MHz, $CDCl_3$): $\delta = 8.00$ (d, $^3J_{HH} = 8.5$ Hz, 2 H-Ar), 7.93 – 7.85 (m, Hz, 2 H-Ar), 7.50 – 7.19 (m, 10 H-Ar), 6.95 (d, $^3J_{HH} =$ 8.5 Hz, 4 H-Ar), 5.36 (d, $^3J_{HH} = 5.0$ Hz, *trans*-C^5H), 5.25 (d, $^3J_{HH} = 8.0$ Hz, *cis*-C^5H), 5.20 (d, $^3J_{HH} = 5.0$ Hz, *trans*-C^4H), 5.09 (d, $^3J_{HH} =$ 8.0 Hz, *cis*-C^4H), 3.91 and 3.89 (2 s, 2 OCH_3), 3.73 and 3.41 (2 bs, 2 NH) ppm. – ^{13}C NMR (69.2 MHz, $CDCl_3$): $\delta = 196.0$, 194.0, 166.5, 165.0, 139.2, 139.0, 131.6, 131.2, 130.9, 128.8, 128.5, 128.2, 128.1, 127.2, 126.8, 114.3, 114.1,

74.9, 73.0, 63.5, 61.0, 57.3, 55.6 ppm. – EI-MS (70 eV): m/z (%) = 313 (M^+, 5), 254 (34), 135 (100), 107 (27), 105 (25). – Anal. for $C_{17}H_{15}NO_3S$ (313.37): calcd. C 65.16, H 5.50, N, 4.47; found C 65.12, H 5.48, N 4.48.

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