ORGANIC LETTERS

2008
Vol. 10, No. 2
305−308

Thermal Rearrangement of 2-Bromooxazolines to 2-Bromoisocyanates

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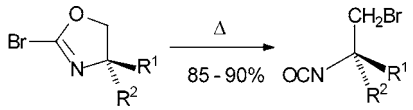
Received November 18, 2007

ABSTRACT



R^1 = Me, R^2 = Me
R^1 = H, R^2 = *i*Pr, Ph

A unprecedented thermally induced rearrangement of 2-bromo-4-substituted oxazolines into 2-bromoisocyanates with high selectivity has been observed. Isolated yields of 85–90% were obtained with 2-bromo-4-phenyloxazoline, 2-bromo-4-isopropyloxazoline, or 2-bromo-4,4-dimethyloxazoline. In addition, chiral aziridinecarboxamides or 2-aminooxazolines could be selectively obtained from the corresponding 2-bromo isocyanate depending on reaction conditions.

General interest in the synthesis and reactivity of oxazolines is reflected in the extensive work published on the subject matter during past decades.[1] Oxazolines are useful intermediates in the synthesis of many classes of compounds;[2] in particular, they can be used as protecting or activating groups. Oxazoline units can ring-open under certain conditions, by way of electrophilic attack,[3] acidolysis,[4] glycolysis,[5] Wittig rearrangement,[6] or transition-metal-promoted rearrangement.[7] Ring-opening polymerization of 2-oxazolines is also the focus of current interest.[8] The introduction of a chiral center within the oxazoline ring leads to versatile synthons for asymmetric synthesis and for the development of ligands in catalysis.[9,10] These chiral enantiopure materials are readily accessible in a few steps from α-amino acids.

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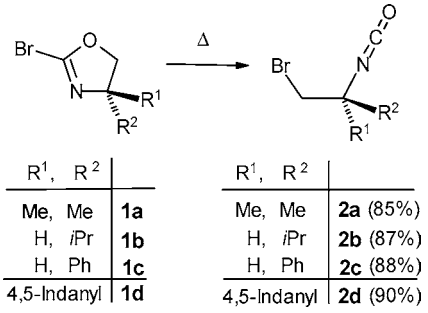
10.1021/ol7027509 CCC: $40.75
Published on Web 12/23/2007

In the course of the development of new ligands for asymmetric catalysis, we have shown that 2-bromooxazolines may be used as key reagents in the synthesis of 1,1,1-tris-(oxazolinyl)ethane ("trisox") ligands[11] as well as oxazolinyl-*N*-heterocyclic carbenes.[12] 2-Bromooxazolines, which were first reported by Meyers and Novachek,[13] are readily prepared by direct lithiation of the 2*H*-oxazoline[14] followed by reaction with 1,2-dibromo-1,1,2,2-tetrafluoroethane as electrophilic brominating agent. Upon investigating the reactivity of these heterocycles (**1a**−**d**), we have discovered that they are thermally sensitive and that a rearrangement occurs to the respective 2-bromoisocyanates (**2a**−**d**) (Scheme 1). This has

Scheme 1. Thermal Rearrangement of 2-Bromooxazolines to 2-Bromoisocyanates (Yields in Parentheses)



R^1, R^2	
Me, Me	**1a**
H, *i*Pr	**1b**
H, Ph	**1c**
4,5-Indanyl	**1d**

R^1, R^2	
Me, Me	**2a** (85%)
H, *i*Pr	**2b** (87%)
H, Ph	**2c** (88%)
4,5-Indanyl	**2d** (90%)

prompted a more detailed study of this unprecedented rearrangement which we report in this work along with the use of these compounds as synthons for the preparation of chiral aziridines or 2-aminooxazolines.

The 2-bromooxazoline derivatives can be kept in THF solution at −30 °C for a few days. However, over time the formation of a new product is observed, a process which can be monitored by ^{1}H NMR spectroscopy. As shown in the proton NMR spectra displayed in Figure 1, 2-bromo-4-phenyloxazoline (**1c**, top) is selectively and completely converted into a new product (**2c**, bottom) by heating the solution at 90 °C for 2 days. A GC−MS analysis of the reaction mixture confirmed the high selectivity of the reaction and revealed that the molecular weight of the new product is unchanged with respect to the reactant, suggesting that a rearrangement had occurred. In the IR spectrum, the characteristic stretching band of an isocyanate ($\nu_{C=N}$ = 2265 cm^{-1}) is observed. The ^{1}H, ^{13}C, and ^{15}N NMR as well as the analytical data confirmed the formation of a 2-bromoisocyanate.

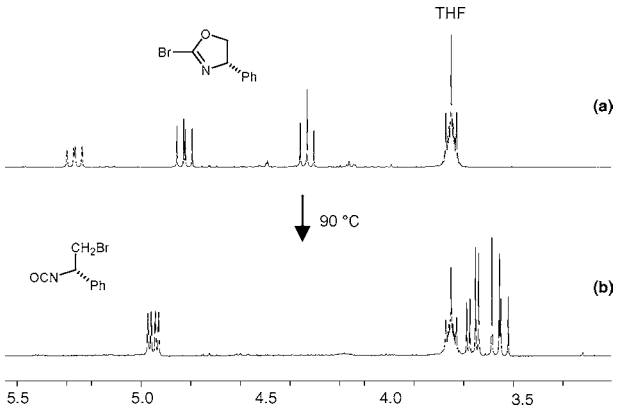
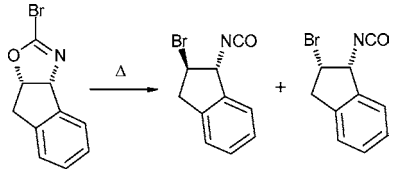


Figure 1. ^{1}H NMR spectra ($CDCl_3$, 300 MHz) of (a) (4*R*)-2-bromo-4-phenyloxazoline **1c**; (b) after heating 90 °C for 2 days.

The same behavior was observed with the 2-bromo-4-substituted oxazolines **1a**−**c**. Among all substrates studied, the (4R,5S)-2-bromo-4,5-indanediyloxazoline (**1d**) was found to be the least stable derivative,[15] and suitable crystals of the product **2d** for an X-ray diffraction study were obtained (Scheme 2 and Figure 2), thus establishing the details of the

Scheme 2. Diastereoselective Conversion of the (4*R*,5*S*)-2-Bromo-4,5-indandiyloxazoline **1d** into 2-Bromo-1-isocyanato-2,3-dihydro-1*H*-indene **2d** (Neat, 25 °C, 5 min)



> 95 : 5

molecular structure of the compound.[16]

The X-ray analysis confirmed the ring-opening of the oxazoline and the formation of a 2-bromoisocyanate. In this particular case, the rearrangement of the heterocycle induces the inversion of the absolute configuration of the carbon C(2), and only one diastereomeric form was observed in the crystal. Moreover, the ^{1}H NMR spectrum of the crude product established a dr of 95:5 and, thus, the high stereoselectivity of the rearrangement (Scheme 2).

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(15) A low yield was obtained in the synthesis of the trisoxazoline ligand 1,1,1-tris[(4*R*, 5*S*)-4,5-indandiyloxazolin-2-yl]ethane; see: Foltz, C.; Enders, M.; Bellemin-Laponnaz, M.; Wadepohl, H.; Gade, L. H. *Chem. Eur. J.* **2007**, *13*, 5961. The fast rearrangement of the bromooxazoline would explain this result. For the other bromooxazolines, which require higher temperatures to form the respective β-bromo isocyanates higher yields were consequently obtained in the coupling reaction.

(16) Crystal data: (1*R*,2*R*)-2-bromo-1-isocyanato-2,3-dihydro-1*H*-indene $C_{10}H_8BrNO$, orthorhombic, space group $P2_12_12_1$, a = 7.8071(10) Å, b = 8.0417(10) Å, c = 14.2852(18) Å, V = 896.9(2) Å^3, Z = 4, μ = 4.537 mm^{-1}, t_{max}/t_{min} = 0.5494/0.3967, F_{000} = 472. Reflections measured: 7904, independent: 3010 [R_{int} = 0.034], index ranges $-11 \le h \le 11$, $0 \le k \le 11$, $0 \le l \le 21$, θ range 2.9−32°. Final R values [$I > 2\sigma(I)$]: R1 = 0.0314, wR2 = 0.0681, GoF = 1.015.

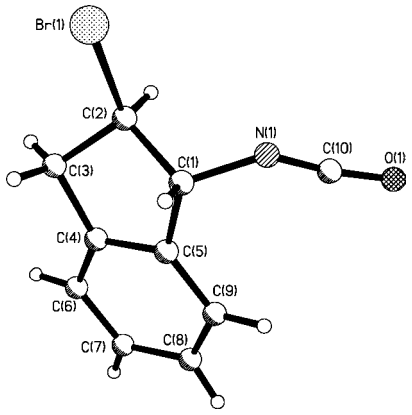


Figure 2. Molecular structure of (1*R*,2*R*)-2-bromo-1-isocyanato-2,3-dihydro-1*H*-indene **2d**.[16] Selected bond lengths (Å) and angles (deg): C(1)−C(2) 1.537(3), C(1)−N(1) 1.446(3), N(1)−C(10) 1.183(4), C(10)−O(1) 1.182(3), C(2)−Br(1) 1.949(2), N(1)−C(1)−C(2) 112.0(2), C(1)−N(1)−C(10) 140.5(3), N(1)−C(10)−O(1) 172.5(3). Torsion angle Br(1)−C(2)−C(1)−N(1) −79.7(2).

The rate of the rearrangement depends on the substitution pattern of the oxazoline with the stability decreasing in the order *i*Pr ≫ Bn ≈ Me_2 ≫ Ph > Ind. No conversion was observed upon exposure of the 2-bromooxazolines to radical initiators such as 2,2′-azobis(4-methoxy-2,4-dimethylvaleronitrile) (V70) and 2,2′-azobis(isobutyronitrile) (AIBN) or to UV radiation, ruling out a radical mechanism. Monitoring the conversion of the 2-bromo-4,4-dimethyloxazoline by ^{1}H NMR spectroscopy at 60 °C at different concentrations gave the sequence of conversion curves displayed in Figure 3.

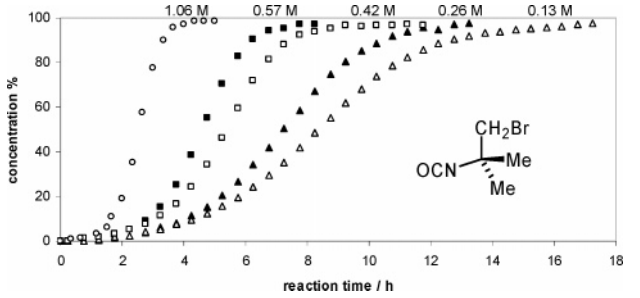


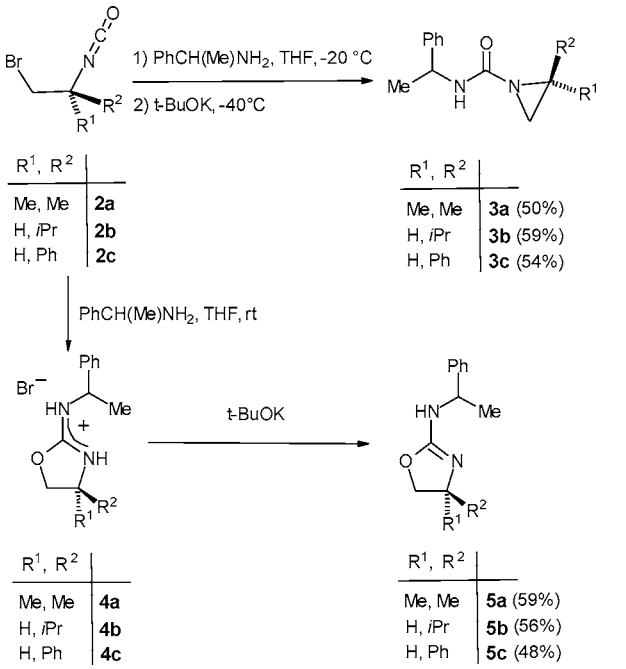
Figure 3. Conversion of 2-bromo-4,4′-dimethyloxazoline **1a** in 1-bromo-2-isocyanato-2-methylpropane **2a** as a function of time at different concentrations (followed by ^{1}H NMR in THF-d_8 at 60 °C).

Their sigmoidal shape suggests autocatalysis by the product, and the concentration dependence indicates that overall reaction is not of first order with respect to the concentration of bromooxazoline. A detailed mechanistic study is underway and will be reported elsewhere. However, the involvement of bromide ions liberated in the course of the transformation is suggested by the observation that the addition of 1 equiv of Bu_4NBr into a solution of 2-bromo-4,4′-dimethyloxazoline considerably accelerates the reaction ($t_{1/2}$ = 0.5 h vs $t_{1/2}$ = 4.5 h at 60 °C and C = 0.57 mol·L^{-1}, see the Supporting Information).

In view of the selectivity of the rearrangements, we prepared the 2-bromoisocyanates on a millimolar scale for a first study into their reactivity.[17] Various applications of α-functionalized isocyanates in the synthesis of new compounds are reported in the literature, such as benzimidazole derivatives,[18] oxazolinylpyperazine derivatives,[19] oxazoloquinazolines,[20] 2-amino-2-oxazolines,[21] fullerene derivatives,[22] and 1-amidino-2-imidazolidinones.[23] Since the stereogenic center in the 4 position is not affected by the rearrangement of the bromooxazoline, an interesting application appeared to be their use for the determination of the enantiomeric excess of primary or secondary amines. To probe this, the enantiomerically pure isocyanates **2a**−**c** were reacted with (*S*)-1-phenylethylamine or *rac*-phenylethylamine.[24]

Depending on experimental conditions, the reaction of the 2-bromo isocyanate with phenylethylamine and a base led selectively to aziridinecarboxamides **3a**−**c** or the *O*-cyclized 2-aminooxazolines **5a**−**c** (Scheme 3). The first reaction

Scheme 3. Formation of Aziridinecarboxamide **3**, Protonated Aminooxazoline **4**, and Aminooxazoline **5** (Yields in Parentheses)



intermediates in these transformations are β-bromourea derivatives, which are formed by nucleophilic attack of the amine and which may be detected at low temperature by NMR spectroscopy (see the Supporting Information). Adding the base *t*-BuOK at low temperature (−20 °C) led selectively to the aziridinecarboxamides **3a**−**c**.[25] On the other hand, carrying out the reaction at room temperature gave the protonated aminooxazolines **4a**−**c** which were converted to

the corresponding amino-oxazolines **5a**−**c** by subsequent addition of the base.

The formation of the aziridines **3a**−**c** was confirmed by an X-ray diffraction analysis of the (*S*)-2-isopropyl-*N*-((*S*)-1-phenylethyl)aziridine-1-carboxamide (**3b**).[26] Its molecular structure is depicted in Figure 4 along with selected bond lengths and angles. Identification of products **4a**−**c** and **5a**−**c** proved to be not trivial since the ^{1}H and ^{13}C {^{1}H} NMR spectroscopic data did not allow the distinction between the possible formation of imidazolidinones or aminooxazolines. An unambiguous assignment has been achieved by ^{15}N NMR spectroscopy along with a theoretical modeling of the ^{15}N NMR chemical shifts.[27] Several isomers of the parent compound **5** ($R^1 = R^2 = H$) have been calculated. As expected, the 2-imidazolidinone is the thermodynamically favored isomer. However, its calculated ^{15}N chemical shifts (δ 88 and 118 ppm) do not match with the experminental shifts for **5a**−**c** (δ 77.6−79.8 and 160.0−176.7 ppm). The latter values are in agreement with the data calculated for the aminooxazoline isomers (δ 76−95 and 156−179 ppm). In addition, the infrared data confirm the formation the aminooxazoline. The infrared spectra of the three derivatives of **5a**−**c** show a strong absorption between 1672 and 1687 cm^{-1} which is assigned to the $\nu_{C=N}$ stretching mode of the oxazoline.[28] Addition of HCl (2 M solution in diethylether) to **5a**−**c** in chloroform-d_1 led to the reformation of **4a**−**c** and confirmed their fomulation as protonated aminooxazolines.

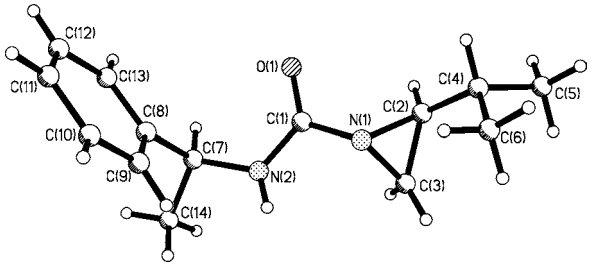


Figure 4. Molecular structure of (*S*)-2-isopropyl-*N*-((*S*)-1-phenylethyl)aziridine-1-carboxamide **3b**. Selected bond lengths (Å) and angles (deg): C(1)−O(1) 1.228(3), C(1)−N(2) 1.342(3), C(1)−N(1) 1.408(3), C(2)−N(1) 1.456(3), C(2)−C(3) 1.485(3), C(3)−N(1) 1.469(3), N(2)−C(1)−N(1) 113.25(18), N(1)−C(2)−C(3) 59.94(15), N(1)−C(3)−C(2) 59.06(15), C(2)−N(1)−C(3) 61.00-(15), C(1)−N(1)−C(2) 118.87(18), C(1)−N(1)−C(3) 119.14(19).

The potential of using the transformations described above for the determination of the enantiomeric excess of chiral amines was probed by reaction **2b** with *rac*-phenylethylamine. The formation of either the 2-aminooxazoline (**5b**) or the carbamoyl-aziridine (**3b**) enabled the determination of the enantiomeric excess of the amine by ^{1}H NMR spectroscopy by integration of the completely assigned and the well-separated signals of the two diastereoisomers.

In conclusion, we have found that 2-bromo-4-substituted oxazolines, which are readily prepared from 2*H*-oxazolines, undergo an unprecedented thermal rearrangement to their corresponding 2-bromoisocyanates with high selectivity. Their availablity in good yields may render them key synthetic intermediates in a variety of organic transformations.

Acknowledgment. We thank the Deutsche Forschungsgemeinschaft (SFB 623, Project B6), the Deutsch-Französische Hochschule (DFH), and the CNRS (France) for funding and Prof. D. G. Blackmond for helpful comments.

Supporting Information Available: Experimental details and spectroscopic/analytical data for all new compounds and crystal data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Alternatively, such 2-bromo isocyanates can be obtained from the rearrangement of N-halogenated β-lactams in the presence of olefins or alkynes or from the dehydrochlorination of compounds such as RNHCOCl in the presence of H_2O and HCl. See, for example: (a) Kampe, K. D. *Tetrahedron Lett.* **1969**, *2*, 117. (b) Farbwerke Hoechst A.-G. Patent FR 1565226, 1969. (c) Kampe, K. D. Patent DE 1930329, 1970. (d) Kampe, K. D. *Justus Liebigs Ann. Chem.* **1971**, *752*, 142. (e) Koenig, K. H.; Rohr, W.; Fischer, A. Patent DE 2045907, 1972. (f) Koenig, K. H.; Zanker, F.; Mangold, D. Fischer, A. Patent DE 2045906, 1972. (g) Zanker, F. Patent DE 2156761, 1972.

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(20) Kampe, K. D. Patent DE 2252122, 1973.

(21) (a) Kampe, K. D. *Justus Liebigs Ann. Chem.* **1974**, *4*, 593. (b) Kampe, K. D.; Babej, M.; Kaiser, J. Patent DE 2253554, 1974.

(22) Kampe, K. D. Patent EP 653424, 1995.

(23) Kulitzscher, B.; Sommer, C.; Kammermeier, B. Patent DE 19502790, 1996.

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(25) In a more classical way, such compounds may be obtained by direct reaction of the aziridine with the isocyanate; see, for examples: (a) Kostyanovskii, R. G.; Zakharov, K. S.; Zarinova, M.; Rudchenko, V. F. *Izvest. Akad., Nauk SSSR, Ser. Khim.* **1975**, *4*, 875. (b) Araki, T.; Nagata, K.; Tsukube, H. *J. Polym. Sci. Polym. Chem. Ed.* **1979**, *17*, 731. (c) Fishbein, P. L.; Harold, K. *J. Med. Chem.* **1987**, *30*, 1767.

(26) (*S*)-2-Isopropyl-*N*-((*S*)-1-phenylethyl)aziridine-1-carboxamide $C_{14}H_{20}N_2O$, orthorhombic, space group $P2_12_12_1$, $a = 5.1912(7)$ Å, $b = 11.6401(15)$ Å, $c = 21.277(3)$ Å, $V = 285.7(3)$ Å^3, $Z = 4$, $\mu = 0.076$ mm^{-1}, $t_{max}/t_{min} = 0.8624/0.7746$, $F_{000} = 504$. Reflections measured: 10195, independent: 1931 [$R_{int} = 0.067$], index ranges $0 \le h \le 7$, $0 \le k \le 15$, $0 \le l \le 28$, θ range 1.9−29°. Final R values [$I > 2\sigma(I)$]: R1 = 0.0429, wR2 = 0.0961, GoF = 1.015.

(27) Three isomers of **5** and the corresponding 2-imidazolidinone derivative were calculated. For details of the computational study, see the Supporting Information.

(28) Aminooxazolines display a vibrational band between 1655 and 1687 cm^{-1} depending on the substituents, whereas those of imidazolidinones are observed between 1684 and 1716 cm^{-1}; see ref 24 and: Kim, T. H.; Lee, N.; Lee, G.-J.; Kim, J. N. *Tetrahedron* **2001**, *57*, 7137.