Rearrangement of β-Chloro *N*-Oxides to Hydroxylamines: Opening of the Oxazetidinium Intermediate by Different Nucleophiles†

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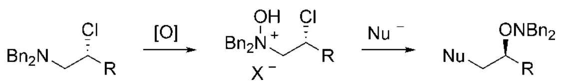
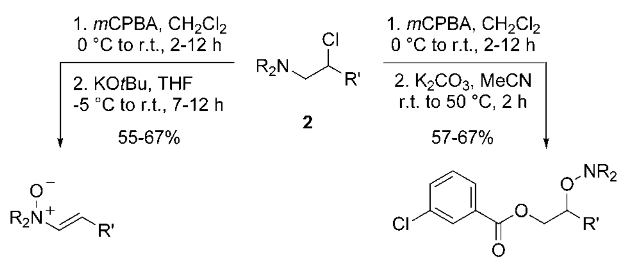


The rearrangement of β-chloro *N*-oxides to hydroxylamines is stereospecific in accord with the presence of a cyclic oxazetidinium intermediate. The latter opens with a range of nucleophiles (carboxylates, cyanide, azide, and thiols).

During investigations on efficient routes toward enamine *N*-oxides **1**, we recently delineated a novel type of rearrangement for *N*-oxides of the β-chloroamines **2** to alkoxyamines **3** (Scheme 1).[1] This kind of rearrangement was briefly described by Owari[2] in 1953 and has only subsequently been observed serendipitously by Denny[3] in the synthesis of the anticancer agent chlorambucil and by Morimoto[4] during the synthesis of erythromycin derivatives. It offers high potential to allow very significant increases in molecular diversity, if a single-pot reaction and a range of nucleophiles could be used compared to multistep synthesis.

SCHEME 1. Enamine *N*-Oxides and Hydroxylamines from β-Chloroamines



Mechanistically the "Owari-rearrangement" should proceed via stereospecific ring closure to the four-membered cycle **4**. This is opened by a nucleophile derived from the oxidation conditions, e.g., benzoate (Figure 1). Intermediate **4** had been suggested by Owari, but no investigation of the proposed stereospecifity of the reaction has been carried out. In 1960 Ishidate[5] claimed to have found an example of intermediate **4** in the urine of dogs after the corresponding β-amino chloride had been given intravenously. The Owari-rearrangement can be seen in connection to the allylic [2,3]-Meisenheimer rearrangement. However, the mechanism for the formation of **4** is distinctly different from the [2,3]-Meisenheimer rearrangement, in which the *N*-oxide attacks an sp^2-carbon and which proceeds via a five-membered transition state.[6]

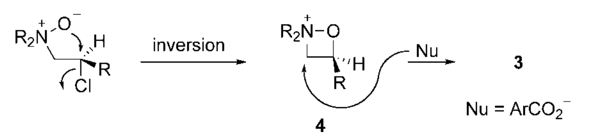
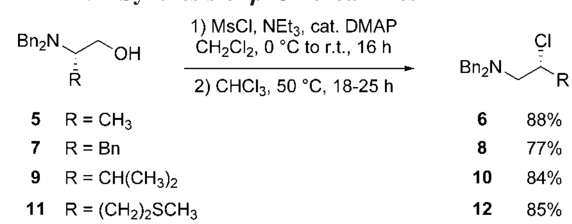


FIGURE 1. Four-membered-ring oxazetidinium intermediate in the Owari-rearrangement.

To investigate the stereospecificity of the Owari-rearrangement we synthesized enantiomerically pure β-chloroamines starting from dibenzylated alaninol, phenylalaninol, valinol, and methioninol, respectively. After treatment with mesylchloride for 16 h, the crude material contained mixtures of the corresponding primary and secondary chlorides (ratios 2:1 to 4:1). Equilibration in chloroform at 50 °C for 18−25 h yielded the required secondary β-chloroamines **6**, **8**, **10**, and **12** in 77−88% (Scheme 2).[7] These contained only traces of the corresponding primary chloride at a level (0−3%) that did not interfere with our subsequent Owari-rearrangement trials.

SCHEME 2. Synthesis of β-Chloroamines



Using β-chloroamine **6** we optimized the reaction conditions for the Owari-rearrangement in order to make it a one-pot procedure and to increase the yield (Scheme 3). We chose triethylamine (10 equiv) instead of potassium carbonate as base, so that it was not necessary to change the solvent after the oxidation step. Triethylamine also reacted as a trap for any excess oxidant. We found that with 1.5 equiv of *m*CPBA reaction times of 30−40 min at 0 °C are optimal for the oxidation to the *N*-oxide. For the subsequent rearrangement 2.5−3 h at 0 °C is sufficient for complete conversion. It is important to add the β-chloroamine to a solution of the peracid

† Dedicated to Prof. Hans-Ulrich Reissig on the occasion of his 60th birthday.
(1) Bernier, D.; Blake, A.; Woodward, S. *J. Org. Chem.* **2008**, *73*, 4229–4232.
(2) Owari, S. *Chem. Pharm. Bull.* **1953**, *1*, 353–357.
(3) Tercel, M.; Wilson, W. R.; Denny, W. A. *J. Med. Chem.* **1995**, *38*, 1247–1252.
(4) Morimoto, S.; Adachi, T.; Watanabe, Y.; Omura, S. *Heterocycles* **1990**, *31*, 305–319.
(5) Ishidate, M.; Tsukagoshi, S. *Chem. Pharm. Bull.* **1960**, *8*, 87–89.
(6) Kleinschmidt, R. F.; Cope, A. C. *J. Am. Chem. Soc.* **1944**, *66*, 1929–1933. For a review on reactions of amine *N*-oxides see: Albini, A. *Synthesis* **1993**, 263–277.
(7) The transformation from **7** to **8** is known to proceed in a stereospecific manner: Weber, K.; Kuklinski, S.; Gmeiner, P. *Org. Lett.* **2000**, *2*, 647–649.

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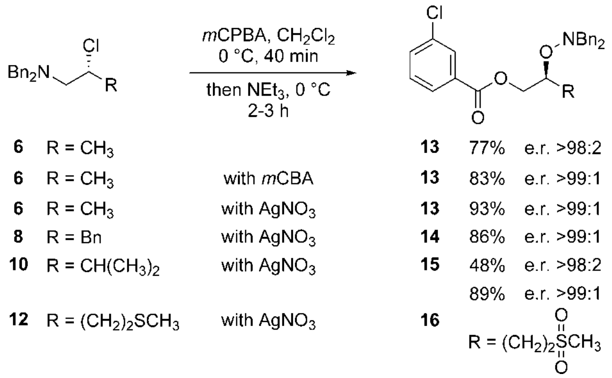
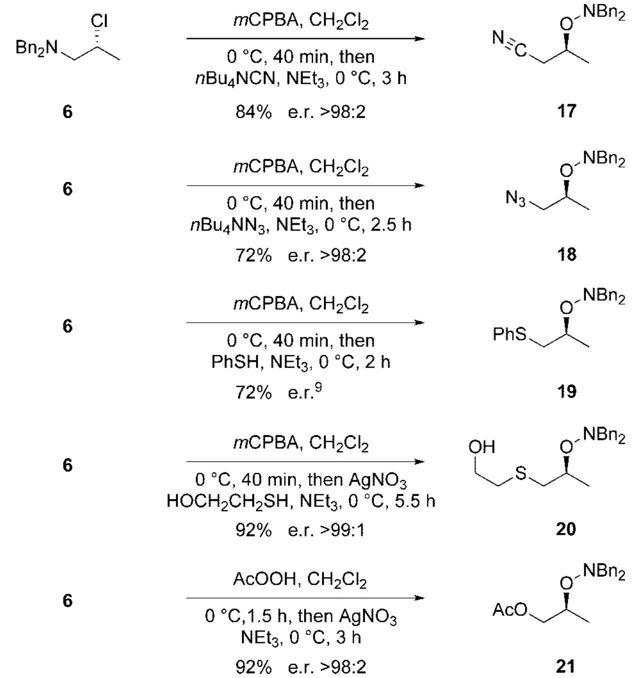
SCHEME 3. Owari-Rearrangement of Enantiomerically Pure β-Chloroamines



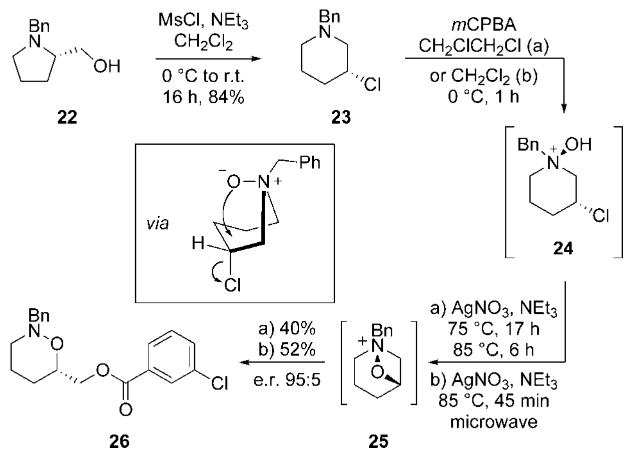
to ensure that an excess of acid is present, protonating all of the *N*-oxide formed. In the reverse addition mode, the β-chloroamine itself can act as a base promoting rearrangement and thus exposing the product to *N*-oxidation. Using the optimal procedure we isolated the hydroxylamine **13** in enantiomerically pure form in 77% yield (Scheme 3). The chloride reacted as a competing nucleophile to the *m*-chlorobenzoate and 21% of the corresponding byproduct was formed. Deliberate addition of excess *m*-chlorobenzoic acid (*m*CBA, 3 equiv) led to 83% of benzoate **13** and 13% of the corresponding chloride. The formation of the chloride product could be suppressed by the addition of $AgNO_3$ (1.05 equiv) and **13** was isolated in 93% yield. The equivalent Owari-rearrangement of phenylalanine derived β-chloroamine **8** also proceeded smoothly. With β-chloroamine **10**, which has a substituent in the α-position to the chloride, the reaction was more problematic, presumably because of steric hindrance. Compound **15** was formed in only 48% yield and was difficult to purify. Methionine derived β-chloroamine **12** could easily be converted to the triply oxidized and rearranged compound **16** in 89% yield. This represents an interesting transformation, as three new functionalities (benzoate, hydroxylamine, and sulfone) are generated in a single step.

We have used our improved procedure to allow the incorporation of other, non-benzoate, nucleophiles. As the oxidation is carried out with *m*CPBA, the new nucleophiles have to be superior to *m*-chlorobenzoate. Tetrabutylammonium salts of cyanide and azide were selected because of their high nucleophilicity and their good solubility in dichloromethane. The addition of 3 equiv of tetrabutylammonium cyanide gave the corresponding cyanide **17** in 84% yield (Scheme 4). The benzoate **13** was found as a byproduct in 7% yield. An excess of tetrabutylammonium azide (3 equiv) yielded 72% of β-azidoalkoxyamine **18** and 15% of benzoate **13**. With thiophenol and 2-thioethanol as nucleophiles, no benzoate **13** was detected as a byproduct. Phenylthioether **19** was isolated in 72% yield, whereas thioether **20** was easily obtained in 92% yield. When we used peracetic acid as oxidant, the time for the oxidation step was longer, presumably due to the more acidic reaction mixture: we employed 28 wt % AcOOH in AcOH, whereas the *m*CPBA in the previous described reactions was 75 wt % in *m*CBA.[8] β-Acetoxyalkoxyamine **21** was isolated in 92% yield. We could prove the enantiopurity of compounds **13**−**18**, **20**, and **21** by chiral HPLC,[9] indicating for the first time that the chemistry of Figure 1 is completely stereospecific. An attempt to observe **4** by following the reaction from the *N*-oxide of **6** to **13** at −60 °C via ^{13}C NMR spectroscopy was unsuccessful. We saw only signals of the *N*-oxide of **6** and smooth formation of **13**.

SCHEME 4. Owari-Rearrangements with Non-Benzoate Nucleophiles



SCHEME 5. Synthesis of oxazane 24 via Owari-rearrangement.



As significant ring strain might be expected in the formation of **4** we were interested to probe such effects by attempted formation of a bicyclic analogue. A suitable precursor was prepared in one step from benzylated prolinol (**22**) according to the procedure described in Scheme 2 (Scheme 5). Here no equilibration was necessary, as the proton NMR spectrum of the crude compound **23** did not show the presence of any isomer. The oxidation of **23** yielded **24** as a single isomer, and the configuration could be proven by NOE analyses of the crude compound. For the Owari-rearrangement it was necessary to

(8) The purity of the peracids were determined according to a procedure described in the following: Woodward, S. in *Transition Metals in Organic Synthesis—A Practical Approach*; Gibson, S. E., Ed.; Oxford University Press: Oxford, UK, 1997; p 7.

(9) For phenylthioether **19** we could not find conditions for complete baseline separation of the racemic compound. However, the enantiomeric ratio is very high, as we do not see any shoulder of the minor enantiomer.

heat the reaction mixture for several hours at 75−85 °C in dichloroethane, or at 85 °C (internal sensor temperature) for 45 min in CH_2Cl_2 in a microwave. We isolated oxazane **26** in 40% and 52% yields respectively from these two approaches both with an enantiomeric ratio of 95:5. Neither the benzylated prolinol **22** nor the chloropiperidine **23** employed showed enantiomeric ratios higher than 95:5. Therefore we can conclude that the Owari-rearrangment is stereospecific even when the intermediate **4** suffers considerable ring strain, such as **25**. The lower yield might be explained by the unfavored boat-like transition state shown in Scheme 5. Intermediate **26** is a surrogate of 5,6-dihydroxyhexamine that has found use in target synthesis.[10]

In conclusion we have optimized the conditions for Owari-type rearrangement with a variety of external nucleophiles. In addition we have for the first time proved the stereospecifity of this rearrangement and developed a new access to enantiomerically pure β-cyano-, β-azido-, β-thio, and β-aceto hydroxylamines.

Experimental Section

Procedure for the Preparation of β-Chloroamines: (2*R*)-*N*,*N*-Dibenzyl-2-chloropropan-1-amine (6). To a solution of the β-amino alcohol **6** (1.15 g, 4.52 mmol), NEt_3 (1.88 mL, 13.6 mmol), and a catalytic amount of DMAP (14 mg, 0.11 mmol) in CH_2Cl_2 (10 mL) was added MsCl (0.70 mL, 9.0 mmol) at 0 °C. Stirring was continued for 6 h at this temperature and then at rt overnight. The reaction mixture was diluted with EtOAc then washed with brine and the solvent was removed in vacuo. The proton-NMR spectrum of the crude material showed a 3.6:1 mixture of the desired secondary chloride and the corresponding primary chloride. Equilibration in $CHCl_3$ (10 mL) at 50 °C for 20 h and subsequent flash-chromatography (silica gel, petrol 40−60 °C/NEt_3 20:0.4) yielded a 97:3 mixture of compound **6** and the corresponding primary chloride as a colorless oil, which crystallized after 1 h in the fridge (1.13 g, 91%, compound **6**: 88%). Mp 47−48 °C; $[\alpha]^{27}_D$ −18.1 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.41 (d, J = 6.7 Hz, 3 H, 3-H), 2.63 (dd, J = 7.6, 13.3, 1 H, 1-H), 2.77 (dd, J = 6.2, 13.3 Hz, 1 H, 1-H), 3.56 (d, J = 13.7 Hz, 2 H, CH_2Ph), 3.68 (d, J = 13.6 Hz, 2 H, CH_2Ph), 4.00 (qdd, $J \approx$ 6.5, 6.5, 7.6 Hz, 1 H, 2-H), 7.26−7.32 (m, 2 H, Ar), 7.34−7.44 (m, 8 H, Ar) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 23.1 (q, C-3), 55.5 (d, C-2), 59.1 (t, CH_2Ph), 62.0 (t, C-1), 127.1, 128.2, 128.9 (3 d, Ar), 139.1 (s, Ar) ppm; IR (ATR) ν 3060−2810 (C=CH, C−H), 1495, 1450 (C=C) cm^{-1}; HRMS (pos. ESI) $C_{17}H_{20}ClN\cdot H^+$ calcd 274.1363, found 274.1353. Anal. calcd for $C_{17}H_{20}ClN$ (273.8): C 74.57, H 7.36, N 5.12. Found: C 74.45, H 7.38, N 5.18.

(10) For example: Takahata, H.; Ihara, K.; Kubota, M.; Momose, T. *Heterocycles* **1997**, *46*, 349–356.

Procedure for the Owari-Rearrangement: (2*S*)-2-(Dibenzylaminooxy)propyl 3-Chlorobenzoate (13). To a solution of *m*CPBA (75 wt %, 93 mg, 0.41 mmol) in CH_2Cl_2 (1.5 mL) was added a solution of β-chloroamine **6** (75 mg, 0.27 mmol) in CH_2Cl_2 (2.5 mL) at 0 °C. After 30 min $AgNO_3$ (48 mg, 0.28 mmol) and NEt_3 (0.37 mL, 2.7 mmol) were added. Stirring was continued for 3 h at 0 °C, then the solvent was removed under reduced pressure. Flash-chromatography (silica gel, petrol 40−60 °C/NEt_3 20:0.04) afforded 103 mg (93%) of compound **13** as a colorless oil. $[\alpha]^{22}_D$ −27.8 (*c* 1.54, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.97 (d, J = 6.5 Hz, 3 H, 3-H), 3.66 (ddq, J = 4.2, 4.5, 6.5 Hz, 1 H, 2-H), AB-system (δ_A = 3.85, δ_B = 3.88, J_{AB} = 13.0 Hz, 4 H, CH_2Ph), ABX-system (δ_A = 4.07, δ_B = 4.10, J_{AB} = 11.5 Hz, J_{AX} = 4.5 Hz, J_{BX} = 4.2 Hz, 2 H, 1-H), 7.21−7.31 (m, 6 H, Ar), 7.33−7.38 (m, 5 H, Ar), 7.52 (ddd, J = 1.1, 2.1, 7.9 Hz, 1 H, Ar), 7.86 (ddd, J = 1.1, 1.6, 7.9 Hz, 1 H, Ar), 7.95 (ddd, J = 0.4, 1.6, 2.1 Hz, 1 H, Ar) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.0 (q, C-3), 62.8 (t, CH_2Ph), 66.7 (t, C-1), 75.2 (d, C-2), 127.4, 127.7, 128.2, 129.55, 129.66, 129.72 (6 d, Ar), 132.0 (s, Ar), 132.9 (d, Ar), 134.4, 137.5 (2 s, Ar), 165.1 (s, C=O) ppm; IR (ATR) ν 3030−2840 (C=CH, C−H), 1725 (C=O), 1575, 1495 (C=C) cm^{-1}; HRMS (pos. ESI) $C_{24}H_{24}ClNO_3\cdot H^+$ calcd 410.1523, found 410.1515; enantiomeric ratio >99:1 (determined by chiral HPLC, column OD, hexane/*i*PrOH 99:1, flow 0.5 mL/min, minor enantiomer: 16.1 min, major enantiomer: 17.3 min). Anal. calcd for $C_{24}H_{24}ClNO_3$ (409.9): C 70.32, H 5.90, N 3.42. Found: C 70.12, H 5.91, N 3.19.

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Supporting Information Available: Experimental and analytical details and copies of ^1H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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