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The 'non-oxidative' chloro-Pummerer reaction: a highly stereoselective entry to β-chloro amines and aziridines

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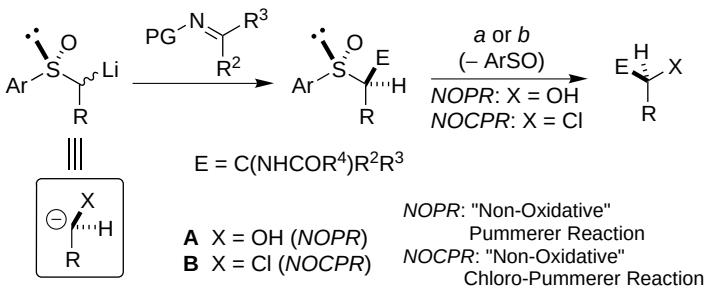
Abstract—Enantiomerically pure α-Li alkyl-sulfoxides can be used as chiral α-chloroalkyl carbanions with *N*-protected imines by means of the 'non-oxidative' chloro-Pummerer reaction (NOCPR). This novel methodology allows for a one-pot displacement of a sulfinyl group by chlorine from *N*-alkoxycarbonyl β-sulfinylamines derived from aryl, fluoroalkyl and alkyl imines, with clean stereoinversion at carbon. Several 1,2-chloroamines produced via NOCPR were transformed into the corresponding aziridines.

1. Introduction

In spite of its extensive use in asymmetric synthesis, the potential of the sulfinyl group as a chiral auxiliary is hitherto partially unexploited.[1] In fact, the lack of methods for removing a sulfinyl group from a stereogenic centre while preserving the stereochemical information is detrimental to its ability to give rise to excellent 1,2-induction in C–C bond-forming reactions.[2,3] Recently, we reported on a stereospecific intramolecular variant of an 'interrupted' Pummerer reaction,[4] the 'non-oxidative' Pummerer reaction (NOPR), which allows for a one-pot replacement of a sulfinyl group with hydroxyl in a stereospecific S_N2-fashion (Schemes 1 and 2).[5] This protocol enabled us and others to transform a wide range of β-sulfinyl amines *N*-monoprotected as amides or carbamates, which are nowadays easily accessible intermediates, into the corresponding β-amino alcohols with high yields and total stereocontrol.[2c,6] Thus, α-lithiated sulfoxides could be successfully used as synthetic equivalents of chiral α-hydroxy-carbanions **A** (Scheme 1) with non-enolizable imines (R^3 = aryl, fluoroalkyl).[7,8] In this communication we report the 'non-oxidative' chloro-Pummerer reaction (NOCPR), a new methodology which extends the spectrum of applicability of α-lithium sulfoxides to synthetic equivalents of chiral α-chloro-carbanions **B** (Scheme 1). A further progress presented in this paper is the extension of the 'non-oxidative' Pummerer chemistry to enolizable imines (R^2 or R^3 = alkyl). In fact, the NOCPR allows for a clean S_N2 displacement of an arylsulfinyl group by chlorine under Swern-type conditions from *N*-alkoxycarbonyl α-alkyl, α-fluoroalkyl, and α-aryl β-sulfinyl amines.[9] This provides a general and efficient entry to a wide range of enantiomerically pure vicinal chloroamine derivatives,



Scheme 1. (a) (NOPR): $(CF_3CO)_2O$, *sym*-collidine, then H_2O/K_2CO_3, $NaBH_4$; (b) (NOCPR): $(COCl)_2$, then MeOH, $NaBH_4$.

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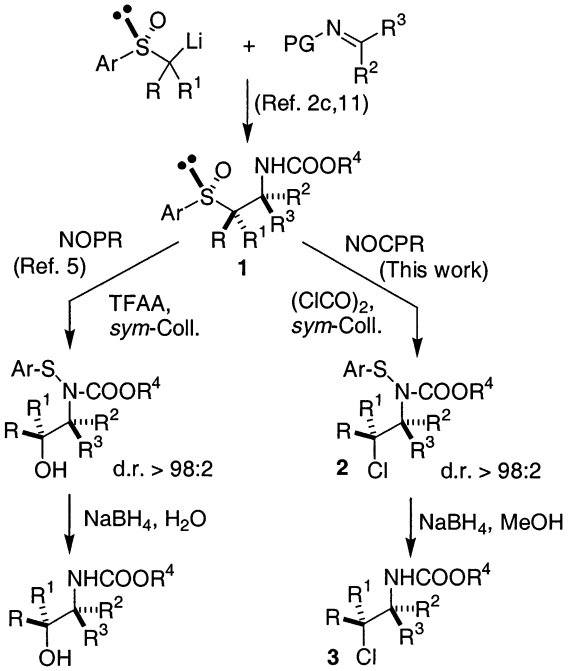


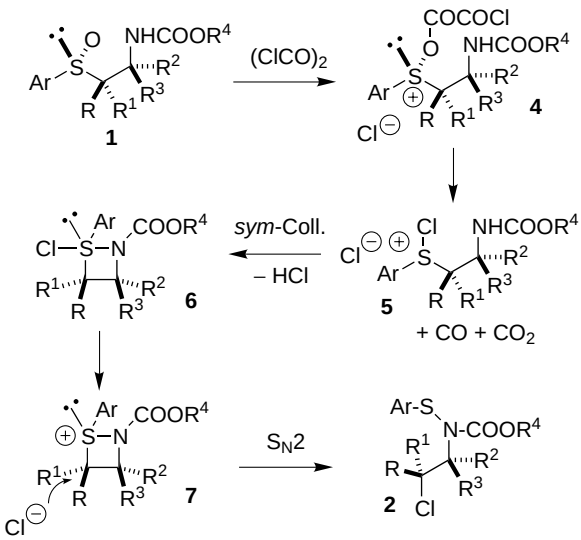
Scheme 2.

which are important building blocks in modern organic and medicinal chemistry.[10]

2. Results and discussion

Treatment of a set of representative *N*-alkoxycarbonyl β-sulfinyl amines **1**, having known stereochemistry (Scheme 1 and Table 1),[11,12] with oxalyl chloride (1.5 equiv.) in the presence of *sym*-collidine (3 equiv., CH_2Cl_2, −50°C) resulted in a fast and stereoselective rearrangement to the β-chloro sulfenamides **2**. In this process, the sulfinyl group undergoes deoxygenation and migration to the β-nitrogen, while a new C–Cl bond is formed with inversion of configuration. This point is demonstrated for the transformations of **1e–k** into **2e–k** (entries 5–10), which took place with a degree of stereoselection >98:2.[13] Intermediates **2**, which can be isolated by flash chromatography (FC) (see entry 1), were diluted with methanol and then treated in situ with an excess of $NaBH_4$ (about 5 equiv.), providing the final β-chloro amines **3** as single diastereomers (entries 5–10), isolated in good to excellent overall yields by FC. The NOCPR is generally applicable to β-sulfinyl amines **1** *N*-monoprotected as carbamates, including fluoroalkyl, aryl (**1c**,**d**), alkyl (**1j**,**k**),[12] and sterically congested/densely functionalized structures such as **1e**,**g**. It is worth noting that epimerization by double displacement (Cl^- displaces Cl^-), which is a potential side-reaction, was never observed. Addition of $(COCl)_2$ in the presence of *sym*-collidine is crucial for achieving high yields of **3**, because, in the absence of a base, oxalyl chloride was able to deoxygenate competitively the sulfoxides **1** to the corresponding sulfides.[14]

The mechanism of the NOCPR is very likely to be as shown in Scheme 3, consistently with the proposed outcome of the Swern reaction, and in analogy with the mechanism of the NOPR, which has been recently investigated in detail.[15] One equiv. of oxalyl chloride acylates the sulfinyl oxygen of **1** providing the salt **4**, which decomposes into **5** by loss of CO and CO_2. Then, a molecule of HCl is removed by *sym*-collidine and the



Scheme 3.

Table 1. Synthesis of β-chloro-amines via NOCPR[a]

Entry	Prod.	R	R^1	R^2	R^3	Yield (%)
1	**2a**	H	H	H	CHF_2	82
2	**3b**	H	H	H	$CClF_2$	85
3	**3c**	H	H	H	3-F-C_6H_4	>98
4	**3d**	H	H	H	PMP[b]	>98
5	**3e**	CH_3	H	CF_3	CO_2Me	60
6	**3f**	H	Ph	H	CF_3	65
7	**3g**	Ph	H	CF_3	CO_2Et	72
8	**3h**	Allyl	H	H	CF_3	87
9	**3j**	CH_3	H	H	C_2H_5	75
10[c]	**3k**	H	Allyl	*i*-Bu	H	68

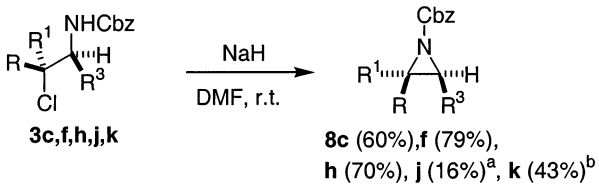
[a] Ar = *p*-Tol except for entry 1, where Ar = 1-naphthyl; R^4 = Bn except for entry 5, where R^4 = Et.
[b] PMP = 4-MeO-C_6H_4.
[c] A *p*-tolylsulfinyl group having (*S*)-configuration was used.

sulfur cation is intercepted by the adjacent carbamic nitrogen atom, producing the intermediate cyclic four membered σ-sulfurane **6**.

Dissociation of the latter into an ion-pair **7** triggers its recombination via S_N2-type attack of the generated chloride anion to the sulfur-substituted stereogenic carbon, which produces the final β-chloro sulfenamide **2**. Release of the four-membered ring strain in **6** is likely to play a significant role, favoring a fast, stereocontrolled displacement. It is more than likely that deoxygenation of **1** to the corresponding sulfides, a side-reaction observed when oxalyl chloride is used without *sym*-collidine (see above), involves formation of Cl_2 from **5** when it cannot be rapidly transformed into **6** by action of the base.[9b]

Among the possible derivatives of vicinal chloroamines, aziridines constitute a valuable class of compounds both for their pharmaceutical properties and synthetic versatility.[16] Treatment of **3c**,**f**,**h**,**j**,**k** with NaH (1.5 equiv.) (Scheme 4) afforded the enantiomerically pure *N*-Cbz aziridines **8c**,**f**,**h**,**j**,**k** in good yields.[17]

In summary, the disclosure of the NOCPR opens up a straightforward route to enantiomerically pure, stereodefined β-chloro amines and some important derivatives like aziridines, and extends the applicability of sulfoxides in asymmetric synthesis. We are currently working toward the development of NOCPR and NOPR-based sulfoxide reagents for solution and solid-phase synthesis to be used as chiral α-chloro and α-hydroxy-alkyl anion equivalents.[18]



3c,f,h,j,k

8c (60%),**f** (79%),
h (70%), **j** (16%)[a], **k** (43%)[b]

Scheme 4. (a) Unreacted **3j** recovered in nearly quantitative yield after 48 hours. (b) Unreacted **3k** recovered in 35% yield after 2 hours.

Acknowledgements

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12. Compounds **1j**,**k** were obtained by condensation (THF, −70°C) of lithiated (*R*)-ethyl and (*S*)-3-butenyl *p*-tolylsulfoxides with Cbz-N=$CHCH_2CH_3$ and Cbz-N=$CHCH_2CH(CH_3)_2$, respectively, prepared according to the method of Mecozzi and Petrini: Mecozzi, T.; Petrini, M. *J. Org. Chem.* **1999**, *64*, 8970–8972. Full details about this topic, including configuration assignment to **1j**,**k**, will be reported in a forthcoming full paper.
13. No minor diastereomers of **3** could be either detected by 500 MHz ^{1}H NMR analysis of the crude reaction mixtures, or isolated by FC.
14. Deoxygenation of sulfoxides **1** to the corresponding sulfides took place quantitatively also in the case of attempted 'non-oxidative' bromo-Pummerer reaction, namely upon treatment of **1** with oxalyl bromide under the optimized NOCPR conditions.
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17. (a) In contrast, the sterically congested β-chloro-amine **3g** did not afford the corresponding aziridine under the same conditions; (b) The relative configurations of aziridines **8f**,**h**,**k** were unambiguously determined by NOE experiments. For example, irradiation of the CF_3 group of **8h** produced 1.5 and 2.0% heteronuclear NOE enhancements on the diastereotopic CH_2 allylic protons in *cis* position (R = allyl), and only 0.5% on the aziridine ring proton (R^1 = H) *trans* to the trifluoromethyl; (c) The stereochemistry of **8j** was assigned by comparison of its ^{1}H NMR and polarimetric analyses with those described by García Ruano et al. in Ref. 6a.
18. **Experimental.** *The non-oxidative 'chloro-Pummerer reaction'. General procedure*. To a solution of *N*-alkoxycarbonyl β-sulfinylamine **1** (1 equiv.) and *sym*-collidine (3 equiv.) in dry CH_2Cl_2 at −50°C, under a nitrogen atmosphere, neat oxalyl chloride (1.5 equiv.) was added dropwise. After complete consumption of the starting material (TLC) the reaction was allowed to reach room temperature, diluted with MeOH and then an excess of $NaBH_4$ (ca. 5 equiv.) was added portion-wise. After consumption of the intermediate sulfenamide **2** (TLC), the reaction was quenched with saturated solution of NH_4Cl and extracted with AcOEt. The collected organic layers were dried on anhydrous Na_2SO_4, filtered and the solvent removed in vacuo. Purification of the crude by FC afforded the corresponding β-chloro amine **3**.