Pergamon

Tetrahedron Letters 43 (2002) 6537–6540

TETRAHEDRON LETTERS

An umpolung sulfoxide reagent as α-hydroxy and α-chloro benzyl carbanion equivalents

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Received 28 June 2002; accepted 16 July 2002

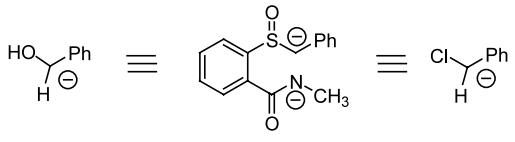
Abstract—*ortho*-[(*N*-Methyl)carbamoyl]phenyl benzyl sulfoxide is used as a synthetic equivalent of α-hydroxy and α-chloro benzyl carbanions by means of a two-step sequence involving (1) highly stereoselective α-*C*-alkylation with alkyl bromides, and (2) displacement of the sulfinyl group by an OH or a Cl under Pummerer or chloro-Pummerer conditions, respectively. The sulfinyl auxiliary can be effectively regenerated and recycled. © 2002 Elsevier Science Ltd. All rights reserved.

The use of umpolung synthetic equivalents of α-hydroxy and α-chloro carbanions not stabilized by an additional electron-withdrawing group (as in the case of α-alkoxy/α-Cl-enolates, or metallated cyanohydrins) is still uncommon in organic synthesis, and relatively few examples of these potentially powerful synthetic tools are extant in the literature.[1]

Recently, we demonstrated that enantiopure α-Li sulfoxides can be used as chiral α-hydroxy and α-chloro carbanion equivalents with alkyl and aryl imines,[2] by means of a two-step procedure based on: (1) C–C bond forming reaction leading to β-sulfinyl-amines, (2) 'non-oxidative' Pummerer reaction (NOPR)[3] or chloro-Pummerer reaction (NOCPR)[4] which allow for replacing the sulfinyl auxiliary by an OH or a Cl atom, respectively, with an S_N2-like pathway (stereoinversion at carbon). This strategy was exploited by us and others for the stereoselective synthesis of biologically important β-amino-alcohols, such as statine,[3] and its trifluoromethyl (Tfm) analog,[5] Tfm-analogs of ephedra alkaloids,[6] several phenyl-glycinols,[7] β-chloro-amines and aziridines.[4] As an extension of this synthetic concept, we commenced a project aimed at developing sulfoxide reagents to be used as α-hydroxy and α-chloro carbanion equivalents of broader scope. Herein, we describe the use of bis-lithiated sulfoxide **1a** as α-hydroxy and α-chloro benzyl carbanion equivalents for the synthesis of benzyl-carbinols and -chlorides (Fig. 1).

In our strategy (Scheme 1) *C*-alkylation of an *ortho*-[(*N*-alkyl)carbamoyl]phenyl sulfoxide **1** with an alkyl halide was planned to give the α-alkyl sulfoxide **2**. Next, we expected that treatment of **2** under Pummerer or chloro-Pummerer conditions could give rise to NOPR- or NOCPR-like outcomes, that is formation of the corresponding alcohol (**3**) or chloride (**4**). Recycling benzisothiazolone co-product **5** by re-conversion into the starting sulfoxide **1** was conceived as an advantage in terms of atom economy. As shown below, this strategy turned out to be successful only in the case of benzyl sulfoxide **1a** (R^1 = Ph). In fact, α-alkyl sulfoxides **2** obtained from **1a** (step 1) underwent the desired transformations into **3** and **4** (step 2), whereas in general substrates **2** did not display NOPR- or NOCPR-like reactivity.

The preparation of racemic sulfoxides **1** (Scheme 2) started with *S*-alkylation of thiosalicylic acid by BnBr, *n*-PrBr or MeI, affording the *ortho*-carboxy sulfides **6**, which were transformed into the amides **7** by coupling with CH_3NH_2 or $(CH_3)_2NH$, and oxidized with MCPBA to **1a–d** in good overall isolated yields (Table 1).



C,N-bis-lithiated (±)-**1a**

Figure 1. The new umpolung synthon.

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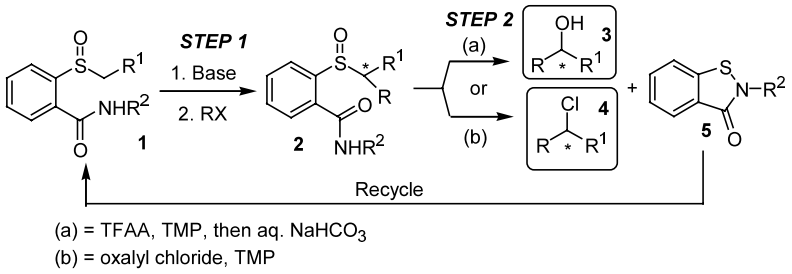
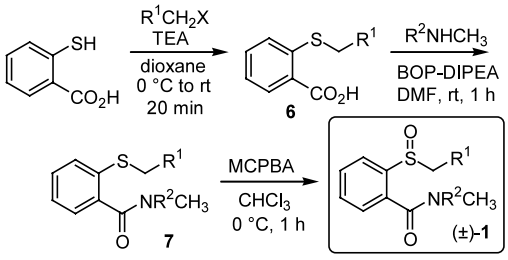
PII: S0040-4039(02)01435-1



Scheme 1. Planned synthetic strategy.



Scheme 2. Preparation of sulfoxides **1**.

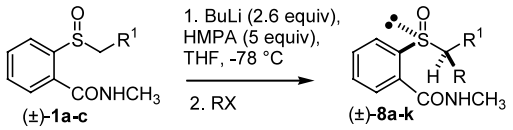
Table 1. Preparation of sulfoxides **1**

Product	X	R^1	R^2	Yield (%)[a]
1a	Br	Ph	H	82
1b	Br	Et	H	81
1c	I	H	H	77
1d	Br	Ph	Me	84

[a] Overall isolated yield from thiosalicylic acid.

Treatment of benzyl sulfoxide **1a** (Scheme 3) with 2.6 equiv. of BuLi,[8,9] in the presence of 5 equiv. of HMPA (THF, −78°C), followed by addition of alkyl bromides (Table 2) afforded the products **8a**,**c**–**f** with good to excellent yields and high diastereoselectivity. Lower diastereoselectivity was achieved with allyl and benzyl bromides (products **8b** and **8g**, respectively). Except for MeI, which gave rise to a mixture of *C*- and *N*-methylated products, all the reactions occurred with high site-selectivity in favor of the *C*-alkylation.[10] The stereochemistry of the main diastereomer **8e** was assessed by single-crystal X-ray diffraction,[11] and the configurations of the other main benzyl diastereomers **8a**–**g** were confidentially assigned on the basis of spectroscopic and physical analogies with **8e**.

Lithiated *n*-propyl sulfoxide **1b** reacted with several halides as well, affording effectively the corresponding products, such as **8h**,**i**. Unfortunately, the latter were invariably formed with low stereocontrol as mixtures of the two diastereomers.[12,13] Also the lithiated α-unsubstituted sulfoxide **1c** ($R^1 = H$) smoothly afforded *C*-alkylated products such as **8j**,**k**. No reaction took place with the *N*,*N*-dimethylamide **1d** (*n*-BuLi/HMPA, THF), suggesting that the *ortho* *N*-lithiated amide function plays a key role. Further support to this hypothesis came from the observation that benzyl *p*-tolylsulfoxide was unreactive with *n*-Hex-Br under the same conditions, whereas using LDA as base afforded in modest yield and no stereocontrol both diastereomers of 1-phenyl-1-(*p*-tolylsulfinyl)heptane.



Scheme 3. Step 1: alkylation of racemic **1**.

Step 2 (see Scheme 1), namely the Pummerer processes, were investigated next. Several authors previously reported that *N*-monosubstituted *ortho*-carbamoylarylsulfoxides undergo an 'interrupted' Pummerer reaction[14] upon treatment with certain electrophiles,[15] providing benzisothiazolones and esters (with Ac_2O/H_2SO_4 or trichloroacetic anhydride) or chlorides (with $SOCl_2$, diphosgene or AcCl) as co-products. As we expected, treatment of dichloromethane (DCM) solutions of the three benzyl sulfoxides **8a**,**c**,**d** (Scheme 4 and Table 3) under NOPR conditions [TFAA/TMP (2,4,6-trimethylpyridine), then aq. $NaHCO_3$] afforded in good yields the secondary benzylic carbinols **9a**–**c**, along with the benzisothiazolone co-product **5a**.[16a,b]

Non-benzylic sulfoxides ($R^1 \neq Ph$) such as **8i**,**j** failed to give the corresponding alcohols, affording mixtures of conventional 'Pummerer products'.[17] Concerning the chloro-Pummerer reaction, **1a** was already known to give high yields of benzyl chloride **10a** upon treatment with $SOCl_2$.[15a] We found that the NOCPR conditions (oxalyl chloride, TMP, DCM, −50°C) work well on secondary ($R \neq H$) benzyl sulfoxides **8a**,**c**,**d**, affording the benzyl chlorides **10b**–**d** together with **5a**. In this case too, non-benzylic sulfoxides **8j**,**k** did not react under NOCPR conditions (overnight).[16c]

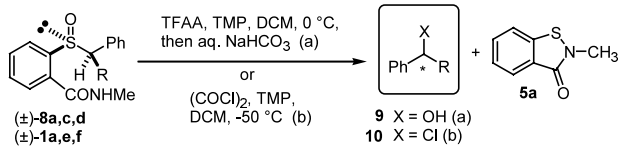
The co-product **5a** could be reduced by $NaBH_4$ in excess to the thiol **11** (Scheme 5), which was reconverted to the starting sulfide **7a** by *S*-benzylation (ca. 80% overall).

A likely mechanism for these Pummerer reactions is shown in Scheme 6 for the model substrate **8a**. Acylation of the sulfinyl oxygen by TFAA or $(COCl)_2$[18] followed by removal of TFA or HCl by TMP, and interception of the transient sulfur cation by the *ortho*-carbamoyl nitrogen provides the sulfurane intermediate **12**. The latter undergoes fragmentation (S–X and C–S

Table 2. Step 1: alkylation of racemic **1**

Substr.	Prod.	R^1	RX	D.e. (%)[c]	Yield (%)[d]
1a	**8a**	Ph	$(CH_3)_2CH(CH_2)_2Br$	94	92
1a	**8b**	Ph	$CH_3CH{=}CHCH_2Br$	66	79
1a	**8c**	Ph	$Ph(CH_2)_3Br$	94	74
1a	**8d**	Ph	$CH_2{=}CH(CH_2)_3Br$	92	95
1a	**8e**	Ph	$CH_3(CH_2)_4Br$	88	69
1a	**8f**	Ph	$CH_3(CH_2)_2Br$	92	74
1a	**8g**	Ph	$PhCH_2Br$	58	96
1a	**8g**[b]	Ph	$PhCH_2Br$	<5	70
1b	**8h**[a]	Et	$CH_3(CH_2)_5Br$	<5	60
1b	**8i**[a]	Et	$(4\text{-MeO-}C_6H_4)CH_2Cl$	32	70
1c	**8j**	H	$Ph(CH_2)_3Br$	–	62
1c	**8k**	H	$(2,6\text{-}Cl_2\text{-}C_6H_3)CH_2Br$	–	85

[a] Stereochemistry not assigned.
[b] LDA was used instead of *n*-BuLi/HMPA.
[c] Measured by HPLC/^{1}H NMR.
[d] Overall isolated yield.

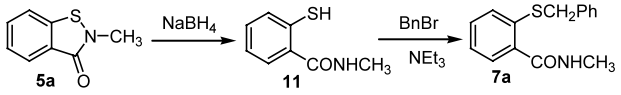


Scheme 4. Step 2: Pummerer and chloro-Pummerer reactions.

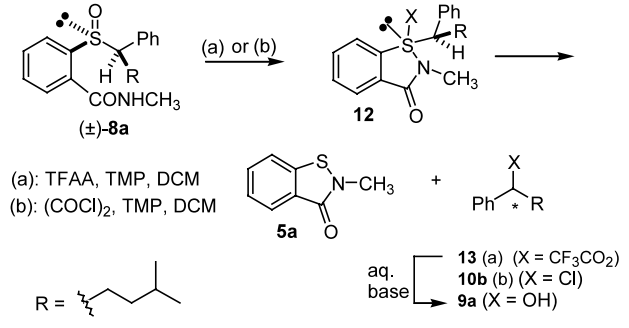
Table 3. Step 2: Pummerer and chloro-Pummerer reactions

Substr.	Prod.	X	R	Yield (%)
8a	**9a**	OH	$(CH_2)_2CH(CH_3)_2$	73
8c	**9b**	OH	$(CH_2)_3Ph$	86
8d	**9c**	OH	$(CH_2)_3CH{=}CH_2$	58[a]
1a	**10a**	Cl	H	99[b,c]
8a	**10b**	Cl	$(CH_2)_2CH(CH_3)_2$	71
8c	**10c**	Cl	$(CH_2)_3Ph$	90
8d	**10d**	Cl	$(CH_2)_3CH{=}CH_2$	60

[a] Trichloroacetic anhydride used instead of TFAA.
[b] See Ref. 15a.
[c] $SOCl_2$ or AcCl in DCM at reflux were used.



Scheme 5. Recycle of the co-product **5a**.



Scheme 6. Proposed mechanism of the Pummerer reactions.

bonds breaking leading to **5a**) and recombination (formation of a new X–C bond) affording either the benzyl alcohol **9a** (after hydrolysis of the trifluoroacetate **13**) or the benzyl chloride **10b**. The pattern of reactivity of sulfoxides **1** (see also Ref. 16a) and **8** under both Pummerer and chloro-Pummerer conditions suggests that fragmentation of **12** should involve the formation of a benzyl carbocation intermediate and a counteranion ($CF_3CO_2^-$ or Cl^-), which then undergo recombination.

In perspective, the high stereoselectivity of the *C*-alkylation of racemic sulfoxide reagent **1a** (step 1) may represent a key factor for the development of an asymmetric version of this methodology, whose success will also rely on the preparation of highly enantiomerically enriched **1a**, as well as on the development of stereocontrolled conditions for performing the Pummerer and chloro-Pummerer reactions (step 2). These issues are presently under active investigation, together with the extension of this strategy to other α-OH and α-Cl-carbanions, and its use in the synthesis of more complex structures of biological interest.

Acknowledgements

MURST Cofin 2000 and CNR are gratefully acknowledged for financial support.

References

1. For a review, see: (a) Cheshire, D. R. In *Comprehensive Organic Synthesis*; Trost, B. A., Ed.; Pergamon: New York, 1991; Vol. 3, pp. 193–205. See also: (b) Fernández-Megía, E.; Ley, S. V. *Synlett* **2000**, 455–458 and references cited therein; (c) Linderman, R. J.; Ghannam, A. *J. Am. Chem. Soc.* **1990**, *112*, 2392–2398; (d) Deiters, A.; Fröhlich, R.; Hoppe, D. *Angew. Chem., Int. Ed.* **2000**, *39*, 2105–2107.

2. Zanda, M.; Bravo, P.; Volonterio, A. In *Asymmetric Fluoro-Organic Chemistry: Synthesis, Applications, and Future Directions*; Ramachandran, P. V., Ed.; ACS Symposium Series 746; American Chemical Society: Washington, DC, 1999; pp. 127–141.
3. Pesenti, C.; Bravo, P.; Corradi, E.; Frigerio, M.; Meille, S. V.; Panzeri, W.; Viani, F.; Zanda, M. *J. Org. Chem.* **2001**, *66*, 5637–5640 and references cited therein.
4. Volonterio, A.; Bravo, P.; Pesenti, C.; Zanda, M. *Tetrahedron Lett.* **2001**, *42*, 3985–3988.
5. Bravo, P.; Corradi, E.; Pesenti, C.; Vergani, B.; Viani, F.; Volonterio, A.; Zanda, M. *Tetrahedron: Asymmetry* **1998**, *9*, 3731–3735.
6. Bravo, P.; Farina, A.; Kukhar, V. P.; Markovsky, A. L.; Meille, S. V.; Soloshonok, V. A.; Sorochinsky, A. E.; Viani, F.; Zanda, M.; Zappalà, C. *J. Org. Chem.* **1997**, *62*, 3424–3425.
7. (a) García Ruano, J. L.; Alcudia, A.; del Prado, M.; Barros, D.; Maestro, M. C.; Fernández, I. *J. Org. Chem.* **2000**, *65*, 2856–2862; (b) Bravo, P.; Capelli, S.; Crucianelli, M.; Guidetti, M.; Markovsky, A. L.; Meille, S. V.; Soloshonok, V. A.; Sorochinsky, A. E.; Viani, F.; Zanda, M. *Tetrahedron* **1999**, *55*, 3025–3040.
8. To our knowledge the α-*C*-alkylation of *ortho*-carbamoyl-aryl alkyl sulfoxides has not been reported previously. For some reviews on the alkylation of metallated sulfoxides, see: (a) Procter, D. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 835–871; (b) Solladié, G. In *Houben-Weyl: Methods in Organic Synthesis*; Müller, E., Ed.; Thieme: Stuttgart, 1995; Vol. E21b, pp. 1793–1815; (c) Walker, A. J. *Tetrahedron: Asymmetry* **1992**, *3*, 961–998; (d) Carreño, M. C. *Chem. Rev.* **1995**, *95*, 1717–1760.
9. (a) *n*-BuLi was titrated according to: Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1979–1980. Using less than 2.6 equiv. of BuLi the reactions were incomplete; (b) *General procedure for the synthesis of compounds **8a–k***. To a cooled solution of **1a** (1.83 mmol, 500 mg) and dry HMPA (9.15 mmol, 1.60 mL) in dry THF (29 mL) was added dropwise, at −70°C and under an argon atmosphere, a 2.5 M solution of *n*-BuLi (4.77 mmol, 1.90 mL). After 10 min, at −78°C 3-methyl-1-bromo-butane (2.01 mmol, 0.252 mL) was added. After the reaction was complete (TLC monitoring), saturated aqueous NH_4Cl was added, the temperature raised to rt and the solution extracted with AcOEt. The collected organic layers were dried over anhydrous Na_2SO_4, filtered and the solvent evaporated in vacuo. The residue was purified by flash-chromatography to give **8a** (1.68 mmol, 577 mg) in 92% yield.
10. No reaction was observed in the following cases: without HMPA, replacing HMPA with TMEDA, or replacing BuLi with LDA, except in the case of BnBr which led to **8g** with low stereocontrol (see Table 2).
11. The crystal structure of **8e** will be published in a full paper.
12. The dramatic stereoselectivity difference between **1a** and **1b** suggests that electronic effects depending on the nature of the α-substituent R^1 are likely to play a key role in the transition state.
13. Some alkyl halides, such as isobutyl-bromide and 2-bromomethyl-dioxolane reacted very sluggishly with α-substituted sulfoxides **1a**,**b**.
14. Xia, M.; Chen, S.; Bates, D. K. *J. Org. Chem.* **1996**, *61*, 9289–9292 and references cited therein.
15. (a) Uchida, Y.; Oae, S. *Gazz. Chim. Ital.* **1987**, *117*, 649–654 and references cited therein; (b) Walter, W.; Krische, B. *Liebigs Ann. Chem.* **1980**, 14–27; (c) Cipollina, J. A.; Ruediger, E. H.; New, J. S.; Wire, M. E.; Shepherd, T. A.; Smith, D. W.; Yevich, J. P. *J. Med. Chem.* **1991**, *34*, 3316–3328; (d) Wright, S. W.; Abelman, M. M.; Bostrom, L. L.; Corbett, R. L. *Tetrahedron Lett.* **1992**, *33*, 153–156; (e) For a highly stereoselective lactonization with displacement of a sulfinyl group under Pummerer-type conditions, see: Casey, M.; Manage, A. C.; Murphy, P. J. *Tetrahedron Lett.* **1992**, *33*, 965–968.
16. (a) Ancillary experiments showed that, in line with a carbocationic mechanism, the primary *ortho*-[(*N*-methyl)carbamoyl]phenyl sulfoxide **1e** having an electron-rich R^1=4-MeO-C_6H_4 afforded good yield of 4-MeO-$C_6H_4CH_2OH$ under NOPR conditions, whereas sulfoxide **1f** having R^1=4-Me-C_6H_4 reacted sluggishly producing low yield of 4-Me-$C_6H_4CH_2OH$, and **1g** with rather electron-poor R^1=4-Br-C_6H_4 gave no 4-Br-$C_6H_4CH_2OH$ at all; (b) *General procedure for the Pummerer reaction*. To a cooled solution of **8a** (0.23 mmol, 80 mg) and TMP (0.70 mmol, 93 μL) in dry DCM (3 mL) was added neat TFAA (1.16 mmol, 164 μL) at 0°C and under an argon atmosphere. The temperature was allowed to reach rt and the reaction was stirred until complete disappearance of the starting material (TLC). The organic solvent was evaporated, the residue diluted with MeOH and water, then an excess of solid K_2CO_3 was added until basic pH was reached. The mixture was extracted with AcOEt, the collected organic layers dried over anhydrous Na_2SO_4, filtered, and the solvent evaporated in vacuo. The residue was purified by flash-chromatography to give **9a** (0.17 mmol, 30 mg) in 73% yield and **5** (0.20 mmol, 33 mg, 87%); (c) *General procedure for the chloro-Pummerer reaction*. To a cooled solution of **8a** (0.24 mmol, 83 mg) and TMP (0.73 mmol, 96 μL) in dry DCM (3 mL) was added neat oxalyl chloride (0.36 mmol, 32 μL) at −50°C and under an argon atmosphere. After complete disappearance of the starting material (TLC), the reaction was quenched with 1N HCl, the temperature raised to rt and the mixture extracted with DCM. The collected organic layers were dried on anhydrous Na_2SO_4, filtered and the solvent evaporated in vacuo. The residue was purified by flash-chromatography to give **10b** (0.17 mmol, 33 mg) in 71% yield and 5 (0.22 mmol, 36 mg, 92%).
17. Details on these products will be published in a forthcoming full paper.
18. In this case, 1 equiv. of both CO and CO_2 are produced, in analogy with the outcome of the Swern reaction.