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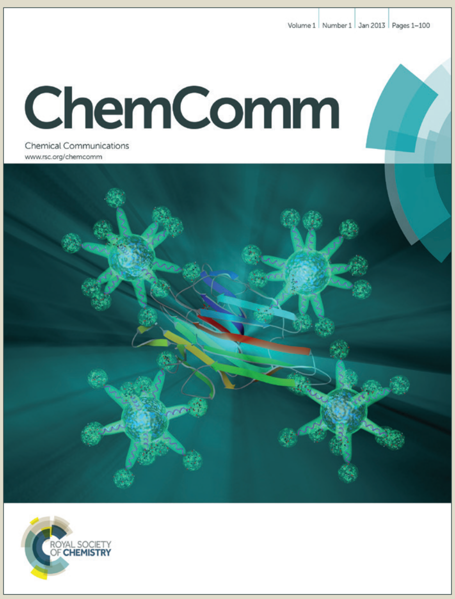

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ARTICLE TYPE

Stereochemical Aspects and Synthetic Scope of the S_Hi at the Sulfur Atom. Preparation of Enantiopure 3-Substituted 2,3-Dihydro-1,2-Benzoisothiazole 1-Oxides and 1,1-Dioxides

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Intramolecular homolytic substitution (S_Hi) on the sulfur atom at acyclic N-(*o*-bromobenzyl)sulfinamides takes place with a complete inversion of the configuration and provides an excellent tool to connect N-*tert*-butanesulfinylimines with enantiopure 3-substituted benzo-fused sulfinamides (1,2-benzoisothiazoline 1-oxides) and the related pharmacologically relevant sulfonamides.

Key words: Cyclic enantiopure 3-substituted benzosulfinamides, enantiopure 3-substituted benzosultams, intramolecular homolytic substitution at the sulfur atom, N-*tert*-butanesulfinylimines

Intramolecular homolytic substitution (S_Hi) reactions have been successfully used to prepare heterocyclic systems.[1] Those involving the sulfur atom have a special relevance because of the synthetic and pharmacological usefulness of sulfinamides[2] and sulfonamides.[3] One of the most interesting reactions in this field is the cyclization of *o*-bromoaryl sulfinamide **1** into the corresponding cyclic sulfinamide **2** under radical conditions[4] (Scheme 1a), mainly due to its stereochemical course and the possibility of using **2** as precursor of chiral sulfonamides. Concerning the first aspect, the inversion of the sulfur configuration at **1** was assumed on the base of the behavior of sulfoxides[5] and sulfinates,[6] but it was not unambiguously proven (the absolute configuration of **2** was never established). ROBH and HLYP/6-31++G(d,p) calculations suggest this inversion to occur via hypervalent intermediates[7,8] (**A** in Scheme 1a), susceptible of giving pseudorotation processes prior to its dissociation. It would explain the slight racemization observed in the formation of **2** (94% ee) from optically pure **1**.[6] On the other hand, the synthetic interest of the S_Hi reaction to prepare unsubstituted benzosulfinamides and benzosulfonamides (Scheme 1a) is rather low, because it only provides products lacking of substituents at the benzylic position. On the contrary, C-3

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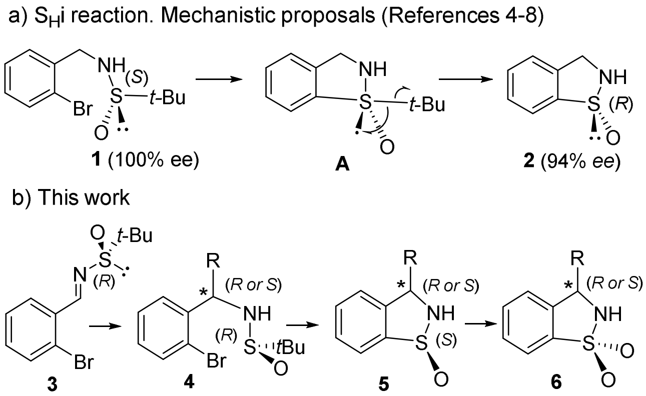


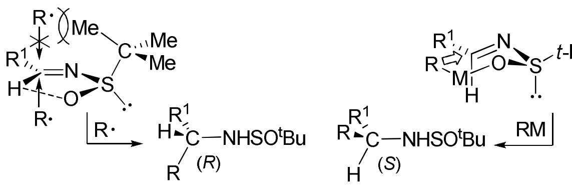
Scheme 1. Antecedents of S_Hi reaction at the sulfur atom and goal of this work.

substitution is synthetically important since it is present at compounds exhibiting pharmacological activity (often associated to the absolute configuration at C-3[9]) or valuable as chiral auxiliaries.[10]

At this point, we reasoned that a general method to obtain enantiomerically pure sulfinamides **5** and sulfonamides **6**, bearing substituents at C-3, would be that indicated in Scheme 1b, starting from the N-*tert*-butanesulfinylimines **3**. They can be transformed with a complete control of the stereoselectivity into **4**,[2b,11] which would evolve into **5** under radical reaction conditions. As additional interest, the use of **4** as starting materials in S_Hi reactions would provide unequivocal evidences of their stereochemical course (inversion or retention), due to the diastereomeric character of the obtained sulfinamides **5**. Moreover, substituents at C-3 could slow down the pseudorotation process in hypervalent structures, thus avoiding the observed racemization. The synthetic sequence shown in Scheme 1b represent an interesting alternative to the methods used in the preparation of benzosultams **6** so far, mainly based on the chemical manipulation of saccharin.[12]

In this paper, we report the synthesis of the enantiomerically pure acyclic *o*-bromophenylsulfinamides **4** from the corresponding *N*-*tert*-butanesulfinylimines **3** and the results obtained in their radical cyclization to form 3-substituted benzo-fused sulfinamides **5** and their further oxidation into the related sulfonamides **6** (Scheme 1b).

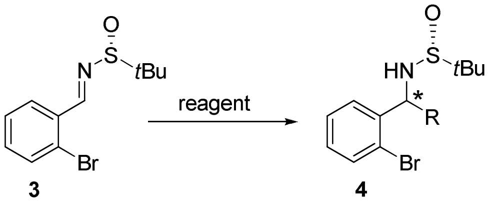
Acyclic sulfinamides **4** with *R* and *S* configuration at the benzylic carbon[13] were prepared from (*R*)-*N*-*tert*-butanesulfinylimine **3** using reactions with a different stereochemical course. Nucleophilic additions of different organometallics reagents, involving intramolecular transfer of the organyl residues from intermediate species with the metal associated to the sulfinyl oxygen,[14] provide different diastereoisomers to those resulting in the radical additions,[11,15] which are intermolecular processes with the reagent approaching to the less hindered face of **3** adopting its most stable conformation (Scheme 2).



Scheme 2. Stereochemical course of nucleophilic and radical additions to *N*-*tert*-butanesulfinylimines.

The results obtained in the synthesis of sulfinamides **4a-i** are depicted in Table 1. Alkyl residues (Et, iPr, Cy, and *t*-Bu) were introduced with very good yields and complete control of the configuration (>99% *de*) from alkyl iodides under radical conditions[11,16] (Et_3B/O_2 in the presence of Bu_3SnH and Lewis acid activation) to attain sulfinamides (R,R_S)-**4a-d** (Table 1, entries 1-4).

Table 1. Synthesis of sulfinamides **4**



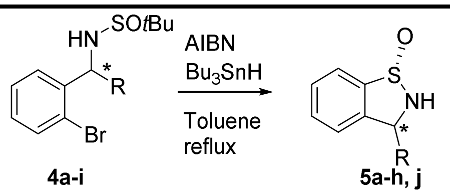
Entry	Reagent	Compound (yield %)[a]	dr[b]	[c]
1	EtI-Et_3B/O_2[d]	**4a** (80)	>99:1	R,R_S
2	*i*PrI-Et_3B/O_2[d]	**4b** (91)	>99:1	R,R_S
3	CyI-Et_3B/O_2[d]	**4c** (90)	>99:1	R,R_S
4	*t*BuI-Et_3B/O_2[d]	**4d** (75)	>99:1	R,R_S
5	PhMgBr	**4e** (90)	92:8	S,R_S
6	3-TBSOCH$_2$C$_6$H$_4$MgBr	**4f** (93)	95:5	S,R_S
7	Me$_2$PhSiCH$_2$MgCl	**4g** (94)	>99:1	R,R_S
8	*t*BuO$_2$CCH$_2$ZnBr	**4h** (97)	>99:1	S,R_S
9	TMSCN/Y(OTf)$_3$	**4i** (90)	96:4	R,R_S

[a] Isolated yield. [b] Determined by ^{1}H NMR. [c] Absolute configuration . [d] In the presence of $BF_3{\cdot}OEt_2$-Bu_3SnH (See SI).

Sulfinamides (S,R_S)-**4** with the opposite configuration at the benzylic carbon (**4g** and **4i** have R,R_S configuration because the prelation order of the groups) were obtained with different nucleophiles. Grignard reagents were used for introducing Ph (**4e**), 3-TBSOCH$_2$C$_6$H$_4$ (**4f**), and CH$_2$SiPhMe$_2$ (**4g**) groups in a highly stereoselectivity manner (entries 5-7), whereas Reformatsky reagent allowed to insert the *tert*-butyl bromoacetate residue present in **4h** (entry 8). Finally, *N*-sulfinyl α-aminonitrile **4i** was obtained under Strecker reaction conditions (entry 9)**.** Configurations assigned in Table 1 to **4a-i** are based on the well established stereochemical course of the different reactions used in their preparation, confirmed by chemical correlation (See SI).

Homolytic cyclizations of compounds **4** were performed in refluxing toluene in the presence of AIBN and Bu_3SnH. The chiral cyclic 3-substituted benzo-fused sulfinamides **5** were obtained in good yields with complete stereocontrol (Table 2). The presence of functional groups like OTBS (**4f**), SiR$_3$ (**4g**) and even CO$_2$*t*Bu (**4h**) has not any influence on the reaction course (entries 6-8), whereas the reaction of **4i** (entry 9) was unsucessfull because the intramolecular addition of the *ortho* aryl radical to the CN group (5-*endo-dig*)[17] is faster. Reduction of the CN group at **4i** with BH_3, and further protection of the resulting amino group, gives the sulfinamide **4j** (entry 10), which satisfactorily evolves into the cyclic sulfinamide **5j** under radical conditions.[18]

Table 2. Homolytic cyclization of sulfinamides **4**



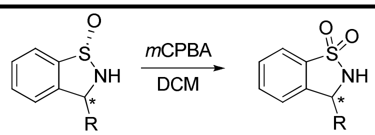
Entry	R	Yield[a] (%)	de[b] ([c])
1	Et (**4a**)	78 (**5a**)	>98 (R,S_S)
2	*i*Pr (**4b**)	96 (**5b**)	>98[d] (R,S_S)
3	Cy (**4c**)	76 (**5c**)	>98 (R,S_S)
4	*t*Bu (**4d**)	74 (**5d**)	>98 (R,S_S)
5	Ph (**4e**)	76 (**5e**)	>98 (S,S_S)
6	3-TBSOCH$_2$C$_6$H$_4$ (**4f**)	86 (**5f**)	>98 (S,S_S)
7	CH$_2$SiPhMe$_2$ (**4g**)	66 (**5g**)	>98 (R,S_S)
8	CH$_2$CO$_2$*t*Bu (**4h**)	73 (**5h**)	>98 (S,S_S)
9	CN (**4i**)	-	-
10	CH$_2$NHBOC (**4j**)	78 (**5j**)	>98 (R,S_S)

[a] Isolated yield. [b] Determined by ^{1}H NMR. [c] Configuration .[d] Determined by HPLC analysis.

The absolute configuration of benzo-fused sulfinamide **5b** was established as (R,S_S) by X-ray diffraction studies.[19] Taking into account the (R,R_S) configuration of the precursor **4b**, we can unequivocally state that the S_Hi has taken place with a complete inversion of the configuration at the sulfur atom. The exclusive formation of only one diastereoisomer, indicates that cyclization occurs with complete inversion, regardless the carbon configuration of the starting sulfinamide (Table 2). This result constitutes the first experimental evidence supporting this assertion. On the other hand, the absence of epimerization in the reactions at Table 2 contrasts with the slight racemization observed in the conversion of the unsubstituted compound **1** into **2** at Scheme 1a, attributed to a pseudorotation process at intermediate **A**. This fact suggests that the presence of substituents at C-3 slowed down or hindered the pseudorotation, probably due to steric factors.

Once established that S_Hi of the acyclic sulfinamides provides an excellent method to prepare enantiopure cyclic sulfinamides **5a-h**,**j**, we studied their oxidation with *m*CPBA (it preserves the configuration at C-3) in order to obtain benzosultams **6a-h,j**, with the results indicated in Table 3. Almost quantitative yields were obtained in all cases and the optical purity and the configurational assignment of these compounds was confirmed by comparison of their $[\alpha]_D$ values with those previously reported. Compounds **6j** can be easily deprotected into the 3-aminomethyl derivative **6k,** potentially useful as coordinating ligand (see SI).

Table 3. Synthesis of benzo-fused sulfonamides **6**.



5a-h, j → **6a-h, j**

Entry	R	Yield (%)
1	Et (**5a**)	98, (*R*)-**6a**
2	*i*Pr (**5b**)	96, (*R*)-**6b**
3	Cy (**5c**)	98, (*R*)-**6c**
4	*t*Bu (**5d**)	97, (*R*)-**6d**
5	Ph (**5e**)	90, (*S*)-**6e**
6	3-TBSOCH$_2$C$_6$H$_4$ (**5f**)	91, (*S*)-**6f**
7	CH$_2$SiPhMe$_2$ (**5g**)	92, (*R*)-**6g**
8	CH$_2$CO$_2$*t*Bu (**5h**)	90, (*S*)-**6h**
9	CH$_2$NHBOC (**5j**)	99, (*R*)-**6j**

At this point, it is interesting the comparison of our method to obtain enantiopure benzosulfonamides (three steps from *N*-*t*ert-butanesulfinylimine **3**, Scheme 1b), with the mostly used procedure so far, consisting in the addition of organometallic reagents to saccharin, followed by catalytic asymmetric reduction, with hydrogen (usually requiring autoclave) or hydrogen transfer reagents (affording rather moderated *ee* with 3-aryl derivatives). Fixing the attention on the pharmacological important[20] enantiomerically pure compounds **6e, 6f** and **6h**, they were respectively prepared from **3** in 62%, 73% and 64% overall yields, whereas 63% (**6e**),[9b,21] 47% (**6f**),[9b,21a] and 25% (**6h**)[12c] yields were obtained starting from saccharin. These data suggest that our procedure constitutes a valuable alternative to prepare 3-substituted benzosultams **6**.

In summary, we describe a very efficient method to obtain enantiopure 3-substituted benzosulfinamides **5** and sulfonamides **6** from *N-tert*-butanesulfinylimines **3**. Moreover, we have unequivocally established that the S_Hi reactions occur with complete inversion of the sulfur configuration and that the presence of α-substituents in *ortho*-bromobenzyl sulfinamides **4** precludes the racemization at the sulfur atom, thus providing enantiopure 3-substituted cyclic benzosulfinamides **5**.

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