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The *tert*-Butyl Sulfoximine Group as an Effective *Ortho*-Director of Lithiation: *Ortho*-Metallated S-(*tert*-Butyl)-S-Phenylsulfoximines

V. Levacher[a]*, B. Langer Eriksen[b], M. Begtrup[b], G. Dupas[a], G. Quéguiner[a], J. Duflos[a] and J. Bourguignon[a]

[a]*Laboratoire de Chimie Organique Fine et Hétérocyclique associé au CNRS IRCOF-INSA, rue Tesnières, B.P 08 F-76131, Mont Saint Aignan Cedex (France)*

[b]*Department of Medicinal Chemistry, Royal Danish School of Pharmacy, Universitetsparken 2 DK-2100 Copenhagen (Denmark)*

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Abstract

The readily available *S*-(*tert*-butyl)-N-(trimethylsilyl)-S-phenylsulfoximine was prepared from *S*-methyl-N-(trimethylsilyl)-S-phenylsulfoximine *via* lithiation-methylation sequences. The reaction with n-butyllithium in THF at -78°C afforded the corresponding *ortho*-lithiated species which could be trapped with different electrophiles in good yields. Addition of benzaldehyde proceeded with a modest diastereoselectivity (de=52%).

keywords: Sulfoximine; Ortho-lithiation; Diastereoselection

The directed *ortho*-lithiation reaction is a very powerful method for the functionalization of aromatic compounds and synthesis of polysubstituted homoaromatic and heteroaromatic compounds [1-2]. A great variety of *ortho*-directing groups have been used with success. Among them, sulfoxide [3-4] and sulfone [5] were found to be powerfull *ortho*-directors. Sulfoximines, the chiral aza analogue of sulfones, have gained widespread use in asymmetric synthesis as chiral auxiliaries [6-10] and chiral ligands for transition metals [11-15]. To the best of our knowledge, only two reports have mentioned the ability of aryl sulfoximines to undergo *ortho*-lithiation [16,17] but the application of sulfoxime groups as an *ortho*-director has not been developed. Based on these results, we synthesised arylsulfoximines **3** in order to study the ability of the sulfoximine group as an *ortho*-director in lithiation.

* *E-mail: vlevache@ircof.insa-rouen.fr*
Fax +33(0)235522962

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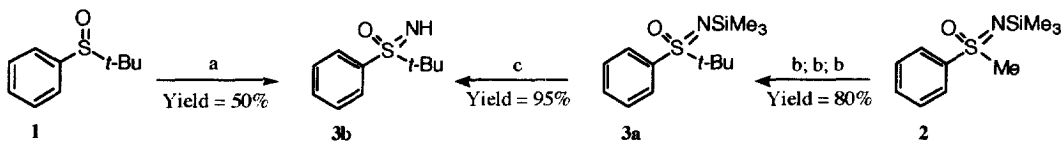
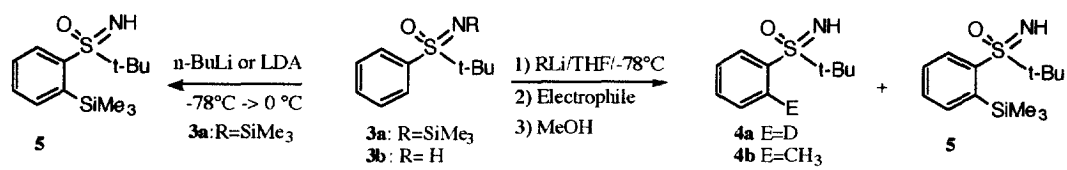
As described previously for the preparation of *S*-methyl-*S*-phenylsulfoximine [18], oxidative imination of *tert*-butyl phenylsulfoxide **1** with NaN_3 failed. However **1** could be iminated by *O*-mesitylsulfonylhydroxylamine (MSH) [19, 20] to give *S*-(*tert*-butyl)-*S*-phenylsulfoximine **3b** in 50% yield. Higher yields of **3** were obtained by repeated lateral lithiation of *S*-methyl-*N*-trimethylsilyl-S-phenylsulfoximine **2** [21] followed by quenching with MeI. Three lithiation-methylation cycles performed in the same pot followed by methanolysis of the silyl group[1] furnished the desired sulfoximine **3b** in 80% overall yield (Scheme 1).

Scheme 1: Preparation of sulfoximes **3**. a: MSH /CH_2Cl_2 b: n-BuLi (1eq) /THF/ 0°C; CH_3I c: MeOH / 2h / rt.



The *ortho*-lithiation of **3a** was first conducted using *n*-BuLi in THF at -78 °C. Under these conditions, a lithiation time of 10 min followed by quenching of the *ortho*-lithiated sulfoximine **3a** with MeOD and desilylation provided the 2-[^{2}H]-phenylsulfoximine **4a** in almost quantitative yield (Table 1; entry 1).[1] It is noteworthy that minor amounts of by-product **5** were observed as a result of silyl migration in the intermediate *ortho*-lithiated sulfoximine **3a** (Scheme 2).

Scheme 2: *Ortho*-lithiation of sulfoximines **3a** and **3b**



Smooth and complete conversion to **5** was observed when *ortho*-lithiated **3a** was warmed to 0°C during 30 min in the absence of electrophiles (Table 1, entry 3). LDA did not deprotonate **3a** at -78°C but produced **5** in 95% yield when the lithiation was conducted at higher temperatures (Table 1; entry 4). When sulfoximine **3b** was subjected to *ortho*-lithiation in the presence of 3 eq of n-BuLi at -78°C for 1 hour followed by action of methyl iodide, **4b** was obtained in 50% yield (Table 1; entry 5). The yield did not increase when the lithiation was performed at higher temperatures (Table 1; entry 6). The highest yields of **4b** (78-90%) were achieved when using *sec*-BuLi for the lithiation (Table 1; entries 7 and 8).

Table 1: *ortho*-Lithiation of sulfoximines **3a** and **3b**

Entry	Sulfoximine	RLi (eq)	Temperature	Electrophile	E	Product	Yield[a]
1	**3a**	*n*-BuLi (1.2)	-78 °C	MeOD	D	**4a**	95%[b]
2	**3a**	*n*-BuLi (1.2)	-78 °C	CH_3I	CH_3	**4b**	90%
3	**3a**	*n*-BuLi (1.2)	-78°C -> 0 °C	-	$SiMe_3$	**5**	95%
4	**3a**	LDA (1.5)	-78°C -> 0 °C	-	$SiMe_3$	**5**	95%
5	**3b**	*n*-BuLi (3)	-78°C	CH_3I	CH_3	**4b**	50%
6	**3b**	*n*-BuLi (3)	0°C	CH_3I	CH_3	**4b**	55%
7	**3b**	*sec*-BuLi (3)	-78 °C	CH_3I	CH_3	**4b**	78%
8	**3b**	*sec*-BuLi (3)	0 °C	CH_3I	CH_3	**4b**	90%

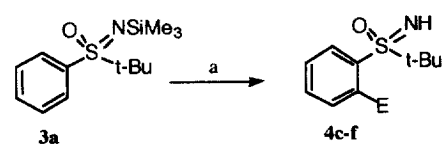
[a] Isolated yields. All conpounds were fully caracterized by ^{1}H-NMR and ^{13}C-NMR.

[b] ^{1}H-NMR analysis indicates a deuterium incorporation > 95%.

When the *ortho*-lithiated sulfoximime **3a** was treated with various electrophiles, the corresponding *ortho*-functionalized sulfoximines **4c-f** were formed in fair to excellent yields (Table 2; entries 1-4).[2] Benzaldehyde was selected as prochiral electrophile in order to investigate the potential of the chiral *ortho*-directing group for asymmetric induction.[3] Using *n*-BuLi in THF benzaldehyde afforded **4f** in 60% yield, in a 50:50 diastereomeric mixture (Table 2; entry 4).

Table 2: Lithiation of sulfoximine **3a** and subsequent addition of various electrophiles. a: *n*-BuLi/-78°C/THF/10 min; Electrophile / -78°C/1 h; NH_4Cl/H_2O; MeOH/r.t./2 h.

Entry	Electrophile	E	Product	Yield[a]
1	C_2Cl_6	Cl	**4c**	76%
2	I_2	I	**4d**	75%
3	Me_2S_2	SMe	**4e**	95%
4	PhCHO	PhCHOH	**4f**	60%



3a **4c-f**

In attempts to improve the stereoselectivity different reaction conditions were investigated (Table 3). Addition of TMEDA improved the diastereoselectivity slightly (Table 3; entry 1). When the reaction was conducted in toluene or Et_2O using *n*-BuLi, the starting material was recovered in almost quantitative yield.

Table 3: *ortho*-Lithiation of sulfoximine **3a** and subsequent addition of benzaldehyde under various conditions[a]

Entry	Solvent	RLi	TMEDA	Product	Yield	de[b]
1	THF	*n*-BuLi	1.2 eq	**4f**	60%	25%
2	Et_2O	*n*-BuLi	1.2 eq	**4f**	60%	40%
3	Toluene	*n*-BuLi	1.2 eq	**4f**	60%	40%
4	Toluene	*sec*-BuLi	1.2 eq	**4f**	60%	50%

[a] All reactions were conducted at -78°C in the presence of 1.2 eq of alkyllithuium

[b] Determined by 200 MHz ^{1}H NMR analysis of the crude product

Addition of TMEDA promoted the reaction in toluene and Et_2O leading to **4f** in 60% isolated yield and 40% de (Table 3; entries 2,3). The best result in terms of diastereoselecty was obtained using *sec*-BuLi/TMEDA in toluene, yielding **4f** in 50% de (Table 3; entry 4).

In summary, we have established that *S*-(*tert*-butyl)-*S*-phenylsulfoximines **3a** and **3b** undergo *ortho*-lithiation under mild conditions and in good yields providing simple access to *ortho*-functionalized *tert*-butyl phenylsulfoximines. Work is in progress to extend the *ortho*-metallation of phenylsulfoximines to other aromatic rings and further to develop the use of this chiral *ortho*-director of lithiation in asymmetric synthesis.[3]

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[1] All sulfoximines were isolated after desilylation. The free sulfoximines were obtained in 95% yield, simply by stirring the crude reaction mixture in MeOH for 2 hours. See ref. [21].

[2] Typical procedure of lithiation: To a stirred solution of **3a** (200 mg, 0.71 mmol) in dry THF (3 mL) cooled to -78 °C was added under Ar a solution of butyllithium in hexane (340 µL, 2.5 M, 0.85 mmol). After the solution was stirred at this temperature for 10 min, C_2Cl_6 (237 mg, 1 mmol) was added and the solution stirred at -78 °C for a further 1 hour. After treatment with saturated aqueous NH_4Cl (20 mL), and extraction with CH_2Cl_2 (2 x 20 ml), the organic layer was dried over $MgSO_4$ and evaporated under vacuum affording a slightly yellow oil. After methanolysis of the silyl group in MeOH for 2 hours at room temperature, the crude product was purified by chromatography on silica gel (eluent EtOAc) to yield 126 mg (76%) of free sulfoximine **4c** as a white solid. NMR data: Compound **4c** ^{1}H NMR ($CDCl_3$) δ 8.13 (d, 1H, *J*=7.5 Hz); 7.85; 7.50-7.30 (m, 3H); 2.70 (br s, 1H); 1.40 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 136.05; 135.21; 134.67; 133.89; 132.72; 126.87; 62.53; 24.10.

[3] Enantiomerically pure *S*-methyl-*S*-phenylsulfoximine, precursor of **3a** and **3b** is readily available *via* the resolution of racemic *S*-methyl-*S*-phenylsulfoximine with (+)-10-camphorsulfonic acid. See ref. [22].

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