Organic LETTERS

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S-Trifluoromethyl Sulfoximine as a Directing Group in *Ortho*-Lithiation Reaction toward Structural Complexity

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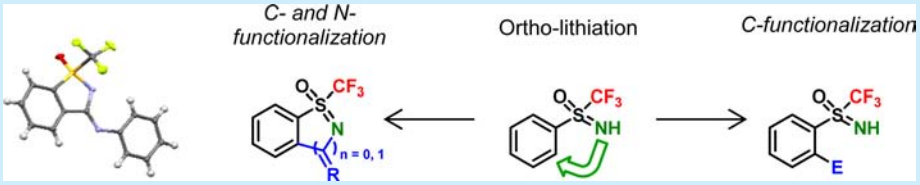
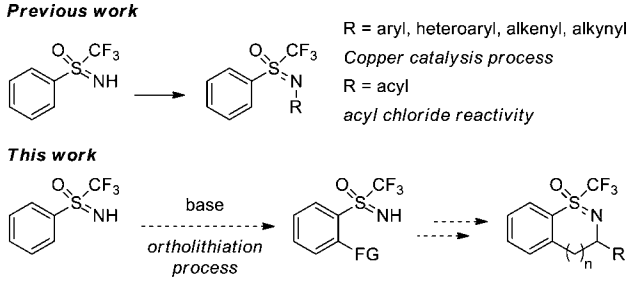
Supporting Information



ABSTRACT: The first use of the NH *S*-trifluoromethyl sulfoximine as an *ortho* directing group is described for the functionalization of the aryl group bonded to the sulfur atom. Various electrophiles (halogen, carbon, oxygen, sulfur, boron, etc.) are introduced on the aromatic ring. Cyclic *S*-trifluoromethyl sulfoximines are synthesized either with properly chosen electrophiles or by structural adjustment of *o*-azido sulfoximines. Fluorinated analogues of prazosin are also prepared.

The *S*-perfluoroalkyl sulfoximines are very particular and underrepresented members of a peculiar family of chiral hexavalent sulfur compounds.[1] Recent years have nevertheless witnessed noteworthy developments that have proven that fluorinated sulfoximines are key reagents for the late introduction of a perfluoroalkyl moiety in organic molecules. Their structural modularity, particularly thanks to the *N*-functionalization, allowed their use as efficient carriers of various perfluoroalkyl entities (from mono- to trifluoromethyl) through electrophilic,[2] nucleophilic,[3] and more recently, radical pathways.[4] Beyond these widespread applications, other utilities have been also proposed. Their high electron-withdrawing capabilities[5] made them efficient substituents for liquid crystals[6] and fluorescent materials.[7] Lastly, very little research work has been devoted to the properties of *S*-perfluoroalkyl sulfoximines in life science.[8] This increasing interest for this promising sulfur group was concomitant with ways to improve its preparation. Until recently, their synthesis was indeed quite cumbersome. The fluorine-induced tamed reactivity of the sulfur atom actually made the classical synthesis of nonfluorinated sulfoximines ineffective. The seminal works of Shreeve[9] in the early 1970s and then those of Yagupol'skii[10] were followed by a latency period until a recent renewal of the chemistry of the *S*-perfluoroalkyl sulfoximines.[11] In our laboratory, a straightforward methodology for the preparation of *S*-perfluoroalkylated NH sulfoximines was developed.[12] Extensive studies devoted to the *N*-functionalization were carried out. The copper-catalyzed *N*-arylation[13] or *N*-alkenylation[14] as well as the acylation[15] of the free sulfoximines was then explored (Scheme 1). A very important remaining challenge was the late introduction of functional groups (FG) on the aromatic part. This would open the door to the convergent synthesis of unknown sulfoximines starting from the simple *S*-phenyl *S*-trifluoromethyl sulfoximine. In this paper, the use of NH *S*-trifluoromethyl sulfoximines as an *ortho* directing group is described for the very first time. A tool for the synthesis of a wide range of new structurally diverse compounds as well as cyclic sulfoximines is disclosed. As an illustration, the synthesis of fluorinated analogues of a drug, prazosin, is also detailed.

Scheme 1. Synthetic Routes to Various *S*-Perfluorinated Sulfoximines



The *ortho*-metalation of (hetero)arenes followed by quench with an electrophile is a very powerful synthetic method of functionalization of aromatic structures.[16] Compared to the classical electrophilic substitution, this methodology offers the major advantage of a total regio-stereoselectivity thanks to the

Received: August 25, 2016
Published: September 28, 2016

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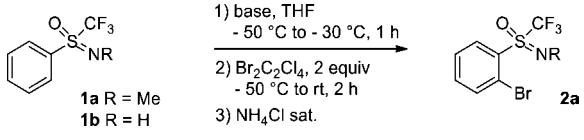
DOI: 10.1021/acs.orglett.6b02548
Org. Lett. 2016, 18, 5102–5105

directing metalating group (DMG). The latter often decreases the pK_a of the adjacent proton through inductive effects and also participates in the coordination of the lithium with the formation of a stable aryllithium complex. This implies the presence of at least one heteroatom. An impressive number of DMGs were utilized in this transformation and classified. Among the DMGs having the strongest effect, sulfones, amides, and sulfonamides were the best candidates. Surprisingly very few examples were described with sulfoximines as DMG[17] and, to the best of our knowledge, none with *S*-perfluoroalkyl sulfoximines. We were, however, fully convinced of the interest of these groups because of the presence of chelating heteroatoms associated with high electron-withdrawing properties. The evaluation the *S*-trifluoromethyl sulfoximines as DMG was then undertaken. Inspired by the scarce results in nonfluorinated series which led to better reactivity with *N*-protected sulfoximines,[17a,b] the ortholithiation of the *N*-methylated compound **1a** was first attempted (Table 1).

Table 1. Optimization of the *N*-Substitution of the Sulfoximine for the *Ortho*-Lithiation Reaction



entry	compound	base	equiv	conv[a] (%)	yield (%)
1	**1a**	*n*-BuLi	1	0	*b*
2	**1a**	*n*-BuLi	2	0	*b*
3	**1a**	*n*-BuLi	3	100	*c*
4	**1b**	*n*-BuLi	1	0	*c*
5	**1b**	*n*-BuLi	2	21	14
6	**1b**	*n*-BuLi	2.5	51	41
7	**1b**	*n*-BuLi	3	100	95
8	**1b**	LDA	3	23	8
9	**1b**	LTMP	3	30	12

[a]Determined by ^{19}F NMR. [b]Starting material was recovered unchanged. [c]All of the sulfoximine was decomposed.

Classical *n*-BuLi was chosen as the base with $Br_2C_2Cl_4$ as the electrophilic source of bromine.[18] The use of 1 or 2 equiv of base resulted in no conversion, even at −50 °C, with the starting material being totally recovered (entries 1 and 2). A third equivalent led to a total degradation of the molecule **1a**. This result is not so surprising knowing that the *S*-perfluoroalkyl sulfoximines are quite sensitive to nucleophiles which can be true with *n*-BuLi.[19] Müller et al. have successfully crystallized the anion resulting from the deprotonation of *S*-ethyl *N*-methyl phenylsulfoximine.[20]

The dilithiated sulfoximine **A** (Figure 1) was observed as part of the cluster structure. With the *N*-methyl *S*-trifluoromethyl sulfoximine **1a**, the same type of structure **B** could be proposed. In our case, either the deprotonation did not occur or the complex with 2 equiv of *n*-BuLi was stabilized by the CF_3 group and therefore unreactive. The additional third equivalent of base probably attacks on the sulfur center, generating the degradation of our substrate. Fortunately, a fully reversed situation with NH sulfoximine **1b** was observed. The first equivalent of *n*-BuLi is, of course, necessary for the initial deprotonation of the NH function. The formation of a nitrogen anion is then crucial for the desired *ortho*-activation process. This anion could increase the chelation with this atom by the complex-induced proximity effect (CIPE)[16c] (see structure **C**) and facilitate the ortholithiation process with the second additional equivalent of base (Table 1, entry 5). This positive result is proof of the participation of the nitrogen versus the oxygen of the sulfoximine group. Additional quantities of *n*-BuLi are then necessary for the total completion of the reaction conversion and to afford a quantitative yield of *o*-bromosulfoximine **2a** (entries 6 and 7). The use of other bases was deleterious to the yield (entries 8 and 9).

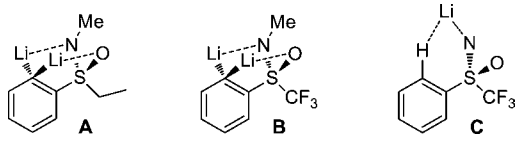
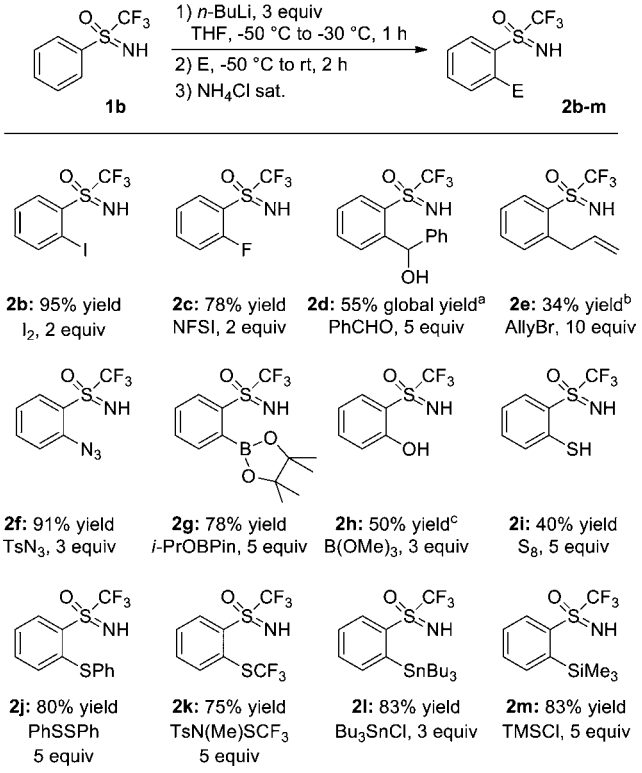


Figure 1. Structure of Müller's monoanionic sulfoximine A and the suggested dianionic perfluorinated analogue B.

The scope of this transformation was next assessed using the conditions previously developed (*n*-BuLi 3 equiv at −50 °C) (Scheme 2).

Scheme 2. *Ortho*-Lithiation of NH-Free Trifluoromethylated Sulfoximine



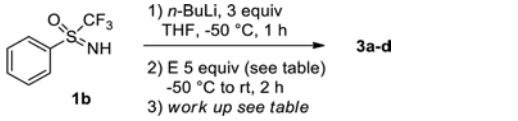
[a]Two diastereoisomers were isolated with, respectivel,y 34% and 21% yields (ed = 24%). [b]Contaminated by an inseparable side compound of unidentified structure. [c]Followed by a treatment by H_2O_2/CH_3CO_2H.

Providing an adaptation of the number of equivalents of the electrophile (see Scheme 2), our conditions proved very efficient whatever its nature. In the same manner as bromine, two other halogens, iodine and fluorine (compounds **2b** and **2c**), can be introduced in very good yield. The reaction with benzaldehyde gave rise to the alcohol **2d**, and the reaction with allyl bromide led to compound **2e**. The *ortho* introduction of an

DOI: 10.1021/acs.orglett.6b02548
Org. Lett. 2016, 18, 5102−5105

azido group as well as a pinacol borane moiety proved successful to the synthesis of the sulfoximines **2f** and **2g**. This last result opened the door to the formation of a phenolic compound **2h** with $B(OMe)_3$ as electrophile followed by a classical treatment with hydrogen peroxide. Thiolation was realized in one step with the simple use of S_8. Phenyl thioether **2j** and trifluoromethyl thioether **2k** were synthesized in high yield with, respectively, diphenyl disulfide and Billard's electrophilic trifluoromethylating reagent[21] (BB23). Stannylation with Bu_3SnCl gave rise to the sulfoximine **2l** and silylation with TMSCl to **2m**. No trace of *N*-alkylation was detected in the previous examples with the exception of the last one, where a small amount of a disilylated sulfoximine was detected in the crude mixture. Its isolation was not possible due to the instability of the nitrogen silyl bond toward hydrolysis leading to the sole formation of molecule **2m**. Nevertheless, this result prompted us to search for particular electrophiles able to react on both carbon and nitrogen nucleophilic positions.To our delight, phenyl isocyanate was the first good candidate to achieve this challenge (Table 2, entry 1).

Table 2. *Ortho*-Lithiation and Concomitant *N*-Alkylation



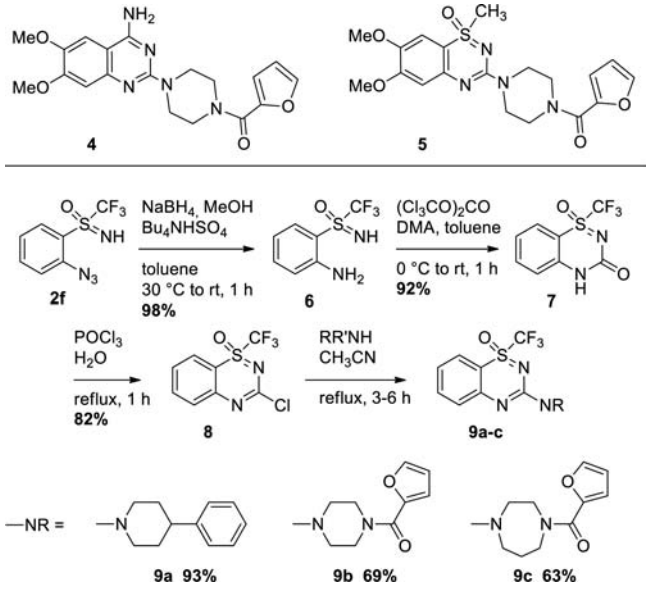
entry	electrophile and work-up	yield (%)	compound	crystal structure
1	2) PhNCS 3) NH_4Cl sat.	77	**3a**	
2	2) C_6F_6 3) NH_4Cl sat. 4) K_2CO_3 CH_3CN, rt 12 h	56	**3b**	
3	2) DMF 3) NH_4Cl sat.	93[a]	**3c**	
4	2) DMF 3) H_2O	92[b]	**3d**	

[a]Isolated as a mixture of diastereoisomers, ed = 50%. [b]Isolated as a mixture of diastereoisomers, ed = 72%.

Its reaction with the anion of **1b**, formed under the previous standard conditions, allowed the preparation of the cyclic sulfoximine **3a** as a single diastereomer in 77% yield. No other fluorinated molecule was detected in the crude mixture or isolated. The cyclization may occur during the final treatment by NH_4Cl. The structure of this very original sulfoximine **3a** has been secured by X-ray analysis. The use of hexafluorobenzene as electrophile led to an almost inseparable mixture of starting material and *o*-pentafluorophenyl sulfoximine (3/7) (see the SI). Fortunately, the treatment of the crude mixture by potassium carbonate enabled the full cyclization of the intermediate, giving rise to tricyclic sulfoximine **3b** in good yield (entry 2). Delightfully, DMF employed as electrophile delivered two different new bicyclic derivatives, both in excellent yield, depending on the final treatment of the reaction. Our standard workup by NH_4Cl produced the hydroxyl compound **3c**, whereas a neutral hydrolysis with water gave rise to the dimethylamino sulfoximine **3d**. Once again, the cyclization may occur during the treatment and not by an intramolecular attack of the lithium amide.[22]

Encouraged by these results, our methodology has been applied to the preparation of an *S*-trifluoromethyl sulfoximine analogue of prazosin **4**, a drug used to treat high blood pressure, anxiety, and post-traumatic stress disorder (Scheme 3). This last part of our study was geared toward increasing

Scheme 3. Preparation of Sulfoximine Analogues of Hypertensive Prazosin



interest for the sulfoximines in the life sciences.[23] In the early 1980s, Dillard et al. prepared an analogue (**5**) of prazosin **4** by replacing the amidine function by a cyclic sulfoximine.[24] This new molecule **5** exhibited better activity for reduction of blood pressure. This enhancement proved the efficiency of the sulfoximine group for the life sciences.

Following the synthetic route of Dillard and starting from the azido compound **2f**, an *S*-trifluoromethyl sulfoximine analogue of the cyclic skeleton of prazosin **4** was synthesized (Scheme 3). Reduction of the azido function of the sulfoximine **2f** occurred smoothly under phase-transfer catalysis. The resulting aminosulfoximine **6** is cyclized to sulfoximine urea **7** ,which is further chlorinated into derivative **8**. Lastly, this halogen atom is displaced by amines to give rise to three analogues of prazosin **9a−c**.

To conclude, the palette of functionality of the NH *S*-trifluoromethyl sulfoximines was enlarged. The NH *S*-trifluoromethyl sulfoximines are excellent moieties for *ortho*-metalation reactions with participation of the nitrogen atom. Many different types of electrophiles proved to be compatible with this transformation and allowed the introduction of a rich panel of functional groups. Previously unseen cyclic sulfox-

DOI: 10.1021/acs.orglett.6b02548
Org. Lett. 2016, 18, 5102−5105

imines were synthesized as well as analogues of a bioactive compound. Extension of this methodology to gain structural diversity, valorization of compounds **2**, as well as comprehensive mechanistic studies are currently in development in our group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02548.

Detailed experimental procedures and spectral data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

T.-N.L. is grateful to the Vietnamese government, specifically the National Institute of Medicinal Materials in Hanoi, for a doctoral fellowship (Program 322). We warmly acknowledge Thierry Billard (ICBMS CNRS Lyon) for a generous gift of its reagent BB13, François Metz (Rhodia-Solvay Company) for the gift of chemicals, and Loïc Pantaine (ILV Versailles) for the improvement of the English. We thank the CNRS and the French Fluorine Network (GIS Fluor).

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DOI: 10.1021/acs.orglett.6b02548
Org. Lett. 2016, 18, 5102–5105