Sulfinimidate Esters as an Electrophilic Sulfinimidoyl Motif Source: Synthesis of *N*-Protected Sulfilimines from Grignard Reagents

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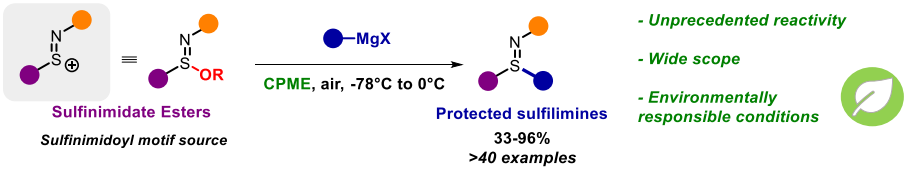
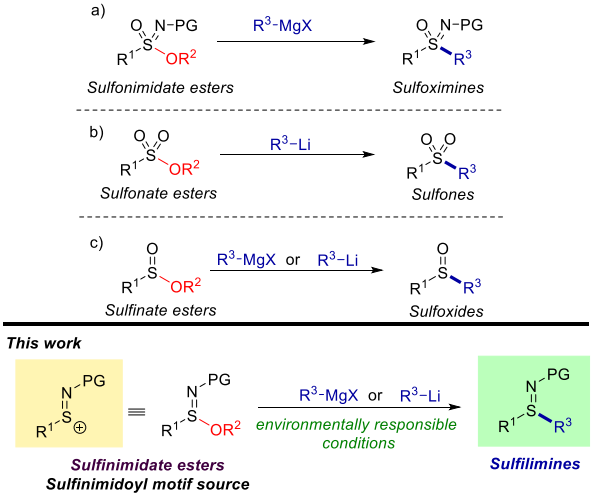


ABSTRACT In this work we investigated, for the first time, the reactivity of sulfinimidate esters as electrophilic sulfinimidoyl motif source. The reaction of such sulfinimidate esters with Grignard reagents enables the preparation of protected sulfilimines in high yields and with a remarkable structural variability. Moreover, the transformation can be performed in CPME (cyclopentyl methyl ether) as a green solvent under environmentally responsible conditions.

Sulfilimines, the aza-analogues of sulfoxides, are highly valuable compounds in medicinal chemistry where are employed as sulfoximines precursors.[1] Most of the synthetic tactics for their preparation rely in the imidation of thioethers with a wide range of nitrogen sources such as azides,[2] iminoiodinanes,[3] oxaziridines,[4] and *O*-activated N-alkoxycarbonyl hydroxylamines.[5] Otherwise, sulfilimines are accessible from sulfoxides using Burgess-type reagents,[6] and from sulfinylamines as recently reported by Willis.[7] Due to the growing interest in accessing biologically relevant sulfur-based structural motifs,[1,8] several advances on the reactivity of sulfur functionalities have been reported during the past decade.[9,10] As an example, Stockman disclosed the electrophilic character of sulfonimidates in reactions with organometallic reagents (Scheme 1, a).[11] In detail, the reaction of Grignard reagents with sulfonimidates resulted in the stereospecific preparation of sulfoximines via the formation of a new S-C bond, by a formal susbtitution of the alkoxy group linked to the sulfur (VI) atom.[12] Similarly, attack of organometals to sulfonates and sulfinates esters enabled the preparation of sulfones and sulfoxides respectively, again by breaking an S-OR bond through a formal nucleophilic substitution reaction (Scheme 1, b and c).[13,14] We recently described the synthesis of hardly accessible sulfinimidate esters and sulfinamidines through a nitrogen transfer to sulfenamides.[15] Nevertheless, the reactivity of sulfinimidate esters was not investigated at that time. To fill this gap, inspired by Stockman's report on the nucleophilic substitution at the sulfur atom using organometallic reagents, we decided to investigate the reactivity of sulfinimidate esters with Grignard reagents. With our delight, we disclosed the unprecedented electrophilic character of these neglected sulfur (IV) derivatives, which act as sulfinimidoyl motif sources. Herein, we therefore report a still unexplored synthesis of protected sulfilimines that could be executed under environmentally responsible conditions.

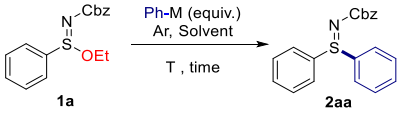
Scheme 1. S-OR bond cleavage on sulfonimidate, sulfonate and sulfinate esters by using organometallic reagents



We began our investigation by exploring the reaction of sulfinimidate ester **1a** with phenyllithium. The first attempt to prepare sulfilimine **2aa** with 1.5 equivalents of organolithium at -78°C in dry THF, and a reaction time of 45 minutes failed (Table 1, entry 1). However, we observed complete conversion of **1a**, resulting in a complex reaction mixture. With our delight, under different reaction conditions (1.1 equivalents of phenyllithium and 5 minutes reaction time), sulfilimine **2aa** could be

obtained in 51% yield (Table 1, entry 2). The reaction time was found to strongly affect the yield of this process, and the best performance was observed by quenching the reaction with methanol after 20 seconds (Table 1, entry 3). With these preliminary results in hand, we decided to explore the use of phenylmagnesium bromide as organometallic reaction partner. According to literature reports,[11] as first approach we employed 5 equivalents of Grignard reagent and 45 minutes of reaction time obtaining **2aa** in 73% yield (Table 1, entry 6). Moreover, reducing the amount of nucleophile (1.1 equivalents of Grignard reagent) and quenching the reaction after 5 minutes afforded **2aa** in 94% yield, (Table 1, entry 7). Next, we tested the reaction adopting environmentally responsible solvents such as 2-MeTHF and CPME (cyclopentyl methyl ether). However, both solvents were found suitable for the transformation (Table 1, entries 8 and 9), and interestingly, sulfilimine **2aa** could be prepared in excellent yield at 0°C and using open-flask conditions (Table 1, entry 9). The low affinity for water of CPME promoted it as the solvent of choice for conducting moisture sensitive reactions.[16]

Table 1. Optimization study of the reaction of sulfinimidate ester 1a with PhLi or PhMgBr

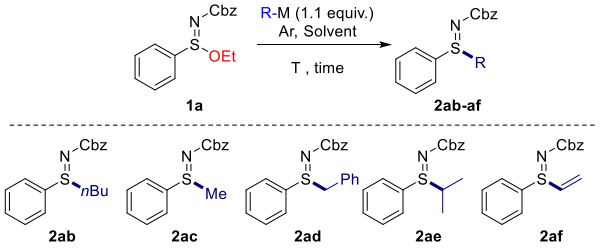


Entry	Solvent	Ph-M (equiv.)	T (°C)	time	2aa (yield %)[a]
1	THF	PhLi (1.5)	-78	45 min	-
2	THF	PhLi (1.1)	-78	5 min	51
3	THF	PhLi (1.1)	-78	20 sec	74
4	THF	PhLi (1.1)	-78	5 sec	67
5	CPME	PhLi (1.1)	-78	20 sec	48
6	THF	PhMgBr (5.0)	-78	45 min	73
7	THF	PhMgBr (1.1)	-78	5 min	94
8	2-MeTHF	PhMgBr (1.1)	-78	5 min	94
9[b]	**CPME**	**PhMgBr (1.1)**	**0**	**5 min**	**95 (89)**[c]

a) NMR yields calculated by using dibromomethane as the internal standard; b) Under air; c) Yield of isolated product.

Subsequently, the use of alkyl organometallics was explored. Similarly, the use of *n*BuMgCl enabled the preparation of the corresponding sulfilimine **2ab** in higher yield with respect to *n*BuLi (Table 2, entries 1 and 2). Next, sulfinimidate ester **1a** was reacted with MeMgBr and BnMgCl at -78°C in CPME, affording products **2ac** and **2ad** in 81% and 71% yields respectively (Table 2, entries 3 and 8). It seemed that the reaction with alkyl Grignard reagents could suffer from selectivity issues, and *N*-protected *S*-phenyl-*S*-alkylsulfilimines **2ab-af** were obtained in slightly lower yields compared to the use of PhMgBr furnishing **2aa**. In addition, the reaction of **1a** with MeMgBr in either 2-MeTHF or CPME afforded the product **2ac** in good yield (Table 2, entries 4 and 6), while the reaction of BnMgCl with **1a** afforded a complex mixture at 0 °C (Table 2, entry 7). The expected S-benzylated product **2ad** was obtained in 71% yield running the reaction at -78 °C (Table 2, entry 8).

Table 2. Optimization study of the reaction conditions with RM organometals



Entry	Solvent	R-M	time	T (°C)	2 Yield (%)[a]
1	THF	*n*BuLi	20 sec	-78	**2ab** (55)
2[b]	CPME	*n*BuMgCl	5 min	-78	**2ab** (67)[c]
3[b]	CPME	MeMgBr	5 min	-78	**2ac** (81)[c]
4[b]	CPME	MeMgBr	5 min	0	**2ac** (66)
5	2Me-THF	MeMgBr	5 min	-78	**2ac** (78)
6	2Me-THF	MeMgBr	5 min	0	**2ac** (70)
7[b]	CPME	BnMgCl	5 min	0	-
8[b]	CPME	BnMgCl	5 min	-78	**2ad** (71)[c]
9[b]	CPME	*i*PrMgCl	5 min	-78	**2ae** (86)[c]
10	CPME	CH_2=CHMgBr[d]	2 h	-78 - r.t.	**2af** (60)[c]
11	THF	PhC≡CMgCl	5 min	0°C	-
12	THF	PhC≡CLi	3h	0°C	-
13	CPME	PhC≡CLi	72h	r.t.	-

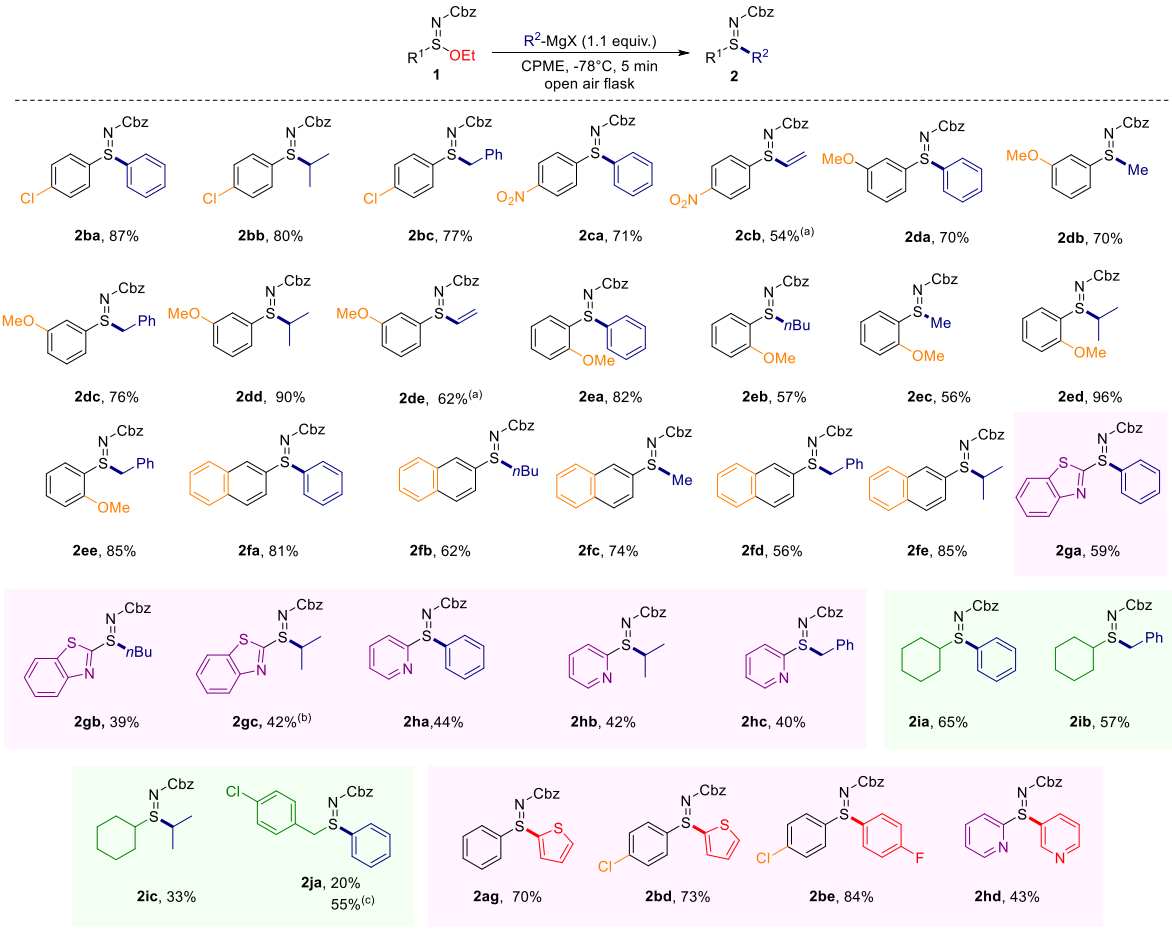
a) NMR yields calculated by using dibromomethane as the internal standard; b) Under air; c) Yield of isolated product; d) 2.1 equivalents of Grignard reagent used.

Performing the reaction at -78°C with *i*PrMgBr as a secondary organomagnesium reagent, sulfilimine **2ae** was obtained in 86% yield (Table 2, entry 9). In striking contrast to other Grignard reagents, vinylmagnesium bromide was found less reactive. In fact, the reaction required 2 equivalents of nucleophile and higher temperature (i.e. 25 °C), affording product **2af** in 60% yield (Table 2, entry 10). Next, the addition of an alkynyl organometallic reagent was explored. Unfortunately, the nucleohilic substitution did not occur when both lithium and magnesium phenylacetylides were added to sulfinimidate **1a** at different reaction temperatures. (Table 2, entries 11-13). This reactivity study clearly showed that C*sp3* and C*sp2* Grignard reagents are the suitable reaction partners for this process.

The scope of the reaction was further explored using a collection of sulfinimidate esters **1b-j** (see Supporting Information), furnishing a library of *N*-protected sulfilimines with wide structural variability. The results of this investigation are shown in Scheme 2. According to the reactivity study (Table 2), the reactions with several Grignard reagents were conducted at low temperature (-78°C), in CPME as the solvent, and using open-air flasks. First, the effect of substituents on the phenyl ring of sulfinimidate esters was explored. The presence of a chlorine in *para* position was tolerated, enabling the preparation of sulfilimines **2ba-bc** in 77-87% yield (Scheme 2). On the other hand, the presence of a nitro-substituent as for ethyl *p*-nitrophenyl sulfinimidate **1c** affected the reactivity, and only PhMgBr and CH_2=CHMgBr furnished the corresponding sulfilimine **2ca** and **2cb** in 71% and 54% yield respectively. The addition of MeMgBr and *i*PrMgCl to **1c** gave only complex mixtures. Electron-donating substituents, such as the methoxy group in *meta* or *ortho* positions, were tolerated giving access to sulfilimines **2da-de** and **2ea-ee** in moderate to excellent yields (Scheme 2). The scope was further explored using

diverse aromatic sulfinimidate esters. Addition to naphtyl sulfinimidate ester **1f** furnished adducts **2fa-fe** in very good yields. Moreover, the use of 2-pyridinyl and 2-benzothiazolyl derived sulfinimidate esters allowed the preparation of sulfilimines **2ga-gc** and **2ha-hc** in moderate yields (39%-59%). It is worth pointing out that such heterosubstituted sulfilimines are hardly accessible using other reported methods. Moreover, the reactivity of *S*-alkyl sulfinimidate esters was also evaluated. It was disclosed that the transformation of *S*-alkyl sulfinimidate was slightly less efficient with respect to the corresponding S-aryl counterpart. Nevertheless, *S*-aryl, *S*-alkyl and *S*,*S*-dialkyl sulfilimines could be obtained from *S*-cyclohexyl and *S*-4'-chlorobenzyl sulfinimidate esters with variable yields (Scheme 2, **2ia-ic** and **2ja**). Remarkably, the yield for **2ja** was improved from 20% to 55% by using 3.0 equivalents of phenyl magnesium bromide (Scheme 2). The scope was further expanded by using freshly prepared 2-thienyl, 4-fluorophenyl, and 3-pyridinyl Grignards, and sulfilimines **2ag**, **2bd-e** and **2hd** were prepared in good yields (Scheme 2). Interestingly, this method allows to accessing challenging heterosubstituted sulfilimines such as **2hd** (43%).

Scheme 2. Substrate scope



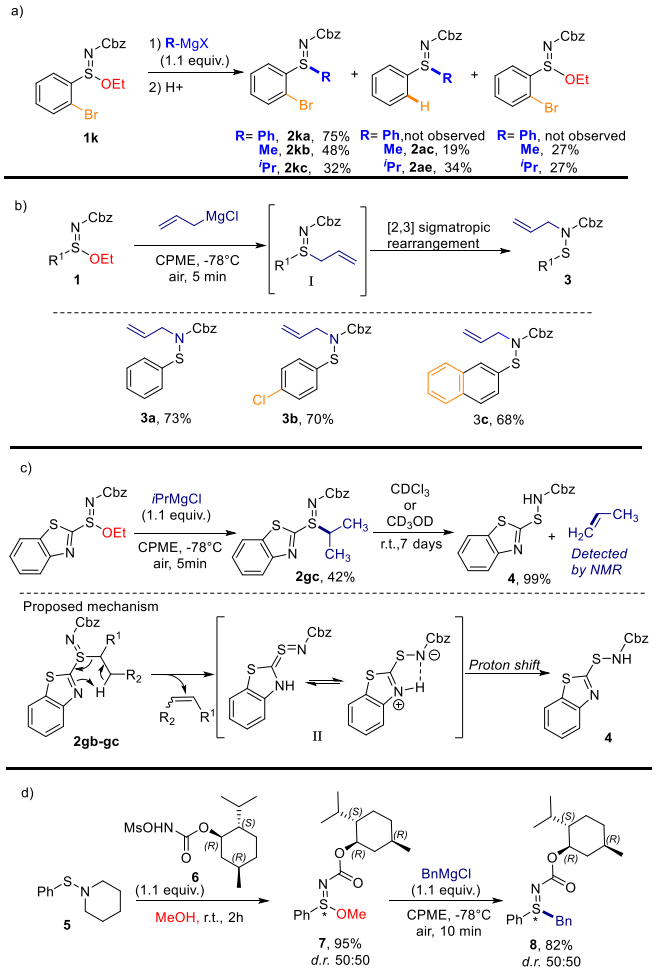
(a) 2.1 equivalents of vinylmagnesium bromide used, reaction time: 2h; b) the product rapidly underwent an intramolecular elimination reaction and could not be fully characterized (see Scheme 3, c); c) 3.0 equivalents of phenylmagnesium bromide used.

The outcome of the reactions of Grignard reagents with *ortho*-bromophenyl sulfinimidate ester **1k** need a separate discussion. In fact, this substrate may undergo competition between the formal nucleophilic substitution at the sulfur atom and the Br/Mg exchange reaction on the aromatic ring (Scheme 3, a). Our results suggest that the nucleophilic attack to the sulfur might be the first event. Subsequently, the resulting brominated sulfilimines might be highly activated towards the Br/Mg exchange reaction by a second equivalent of Grignard reagent, affording the protonated products after acidic quenching (Scheme 3, a). In particular, the halogen-metal exchange could be kinetically competitive with prior nucleophilic attack to sulfur, leading to a mixture of brominated sulfilimine, protonated sulfilimines, and unreacted sulfinimidate. Reasonably, Br/Mg exchange reaction is slower with PhMgBr with respect to alkyl Grignards (i. e. MeMgBr or *i*PrMgCl), producing selectively brominated sulfilimine **2ka** (Scheme 3, a). Accordingly, the more reactive MeMgBr or *i*PrMgCl produced lower yields of **2kb** and **2kc** because of a faster (and competitive) Br/Mg exchange furnishing discrete amounts of protonated sulfilimine **2ac** and **2ae** (Scheme 3, a). These results showcase that judicious choice of the Grignard reagent is required with this kind of substrates.

A deviation from standard reactivity was observed in the reaction of sulfinimidate esters with allylMgCl. Recently, the [2,3]-sigmatropic rearrangement of *S*-propargylic and allylic sulfilimines was reported.[4,5c] Consequently, *N*-allyl-*N*-(thio)amides and carbamates could be easily prepared from

thioethers through sulfur imidation.[5c,17] We therefore explored the reaction of sulfinimidate esters with allylmagnesium chloride, which indeed afforded the corresponding *N*-allyl-*N*-(thio)carbamates **3a-c** in good yields (Scheme 3, b). According to previous reports, the [2,3]-sigmatropic rearrangement might occur instantaneously after the generation of the expected sulfilimine **I**, that could not be detected (Scheme 3, b).

Scheme 3. Further reactivity of Sulfinamidate esters.



A different rearrangement was observed instead with *S*-alkyl-*S*-2-benzothiazolyl sulfilimines **2gb** and **2gc**. Most surprisingly, we observed a spontaneous intramolecular elimination of alkenes (i.e. propene), leading to sulfenamide **4** (Scheme 3, c). The reaction proceeded spontaneously when the *S*-isopropyl derivative **2gc** was dissolved in CD_3OD or $CDCl_3$ in an NMR tube, reaching full conversion to **4** within 7 days. However, we were able to detect the signals of propene by ^1H NMR analysis (see Supporting Information). A reasonable reaction mechanism involves an intramolecular β-elimination reaction affording intermediate **II**, that releases sulfenamide **4** after proton shift (Scheme 3, c).

With the aim to introduce a stereocontrol in the reaction of sulfinimidate esters with Grignard reagents, the preparation of sulfinimidate esters from a chiral enantioenriched nitrogen source **6** was attempted (Scheme 3, d). Nevertheless, the reaction of sulfenamide **5** and the *N*-source **6** was not stereoselective producing an inseparable mixture of diastereoisomers **7** (*d.r.* 50:50). Disappointingly, addition of BnMgCl to **7** afforded the expected sulfilimine **8** in 82% yield, albeit as an inseparable mixture of diastereoisomers.

In summary, we reported an efficient method for the synthesis of protected sulfilimines from sulfinimidate esters and organomagnesium reagents. The reactivity of a wide range of sulfinimidate esters as unprecedented electrophilic sulfinimidoyl source was explored, and the transformations were performed upon environmentally responsible conditions using CPME as a green solvent, and under air. Moreover, the addition of allylmagnesium chloride enabled the preparation of *N*-allyl-*N*-(thio)carbamates via [2,3]-sigmatropic rearrangement. Finally, first attempts to obtain optically active sulfilimines were reported. Further investigation on the reactivity of these neglected sulfur(IV) functional group are ongoing in our lab and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

Characterization data for the prepared molecules, general procedures are available as Supplementary material. The Supporting Information is available free of charge on the ACS Publications website.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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