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N-Alkylations of *N*H-Sulfoximines and *N*H-Sulfondiimines with Alkyl Halides Mediated by Potassium Hydroxide in Dimethyl Sulfoxide

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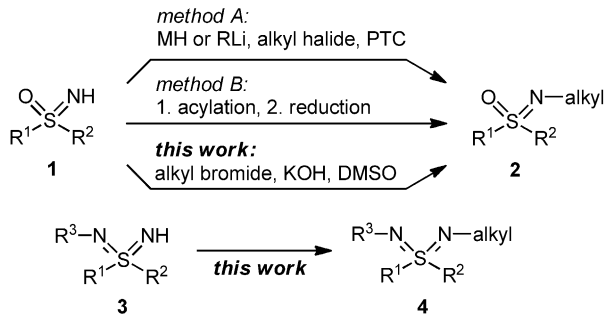
Abstract: A general method for the *N*-alkylation of *N*H-sulfoximines and *N*H-sulfondiimines has been developed, employing alkyl bromides with KOH in DMSO at room temperature. A variety of previously inaccessible *N*-alkylated sulfoximines and sulfondiimines was prepared in good to excellent yields (up to 97%). As an application, the conditions were used to access the biologically active Suloxifen.

Keywords: *N*-alkylation; metal-free reactions; sulfondiimines; sulfoximines; superbase; synthetic methods

Sulfoximines have been applied with great success in asymmetric synthesis,[1] and more recently, much attention has been focused on the bioactive profiles of such compounds.[2,3] In drug development, *N*-methyl- and *N*-alkylamino-substituted sulfoximines have proved to be attractive.[4,5] For the synthesis of the former, several methods have been introduced including methylations of *N*H-sulfoximines **1** under Eschweiler–Clark conditions[6] and alkylations of such compounds with strong methyl-transfer agents such as trimethyloxonium salts[7] and "magic methyl" (methyl fluorosulfate).[8] For the introduction of longer alkyl chains, however, these simple *N*-functionalization strategies have remained largely unsuccessful[9] presumably due to the low nucleophilicity of the sulfoximine nitrogen atom. Thus, nucleophilic substitution reactions of sulfoximines with alkyl halides commonly involve the use of strong bases such as alkali metal hydrides (MH) or butyllithium in combination with phase-transfer catalysts (PTC) under strictly anhydrous conditions (Scheme 1, method A).[10] Furthermore, long reaction times are required for reasonable conversions which often depend on the steric and electronic properties of the individual substrate, resulting in a limitation of the product scope. In several cases, a two-step protocol involving an acylation/reduction sequence proved advantageous (Scheme 1, method B).[11]

While sulfoximines are monoaza analogues of sulfones, sulfondiimines can be regarded as diaza analogues of the latter. Although already discovered in 1964,[12] sulfondiimines are still difficult to prepare. Only few approaches towards these interesting molecules have been reported,[13] and this lack of general accessibility has limited the number of their synthetic applications.[14] With the goal to facilitate the synthesis of sulfondiimines and to broaden the substrate scope, we have recently focused attention on these attractive high-valent sulfur compounds.[15] *N*-Monosubstituted sulfondiimines **3** appear to be particularly interesting because *N*-functionalization of **3** is a high-potential strategy for introducing molecular diversity.



Scheme 1. Representative procedures for the *N*-alkylation of sulfoximines **1** and sulfondiimines **3**.

Along those lines, we have already developed *N*-arylation[16] and *N*-alkenylation reactions of *N*H-sulfondiimines[16b] leading to a broad product portfolio. As in the chemistry of sulfoximines, *N*-alkylations of *N*H-sulfondiimines are difficult, and to date only few examples have been reported. Those include the preparation of *N*-alkylamino sulfondiimines by deprotonation of *N*H-sulfondiimines with sodium hydride followed by alkylations of the resulting anions with alkyl halides at elevated temperature.[17] A general, mild method for the preparation of *N*-alkylated sulfondiimines is still lacking.

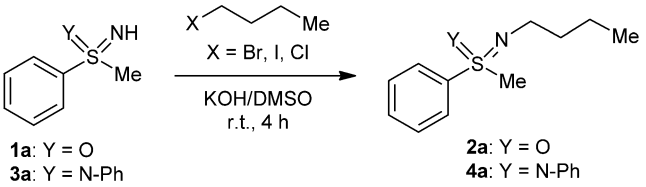
Realizing the synthetic demand and feeling challenged by the preparative difficulties, we decided to search for an alkylation strategy allowing specific conversions of *N*H-derivatives of sulfoximines and sulfondiimines. The success of this investigation is reported here.

Initially, an early experimental observation reported by Heaney and Ley in 1973 caught our attention.[18] They found KOH in DMSO to be a superb reagent combination for *N*-alkylations of indoles and pyrroles with alkyl halides, providing the desired *N*-alkylated products in high yields. Apparently, the reactions proceeded through *N*-metallated intermediates which required strongly ionizing solvents to be reactive enough for the subsequent nucleophilic substitution reactions with the alkyl halides.[19–21] We anticipated an analogous reactivity profile in *N*-alkylations of sulfoximines and sulfondiimines. To our delight, this hypothesis was confirmed. Starting from *N*H-sulfoximine **1a** and *N*H-sulfondiimine **3a** alkylations with *n*-butyl bromide (1.5 equiv.) in combination with KOH (2 equiv.) in DMSO afforded the corresponding *N*-butylated products **2a** and **4a** in yields of 83% and 84%, respectively (Table 1, entry 1).[22] The transformations occurred at room temperature, and the common reaction time was 4 h.

Employing *n*-butyl iodide as alkylating agent raised the yield of **2a** (from 83% to 95%), but lowered it slightly for **4a** (from 84% to 79%; Table 1, entry 2). Also *n*-butyl chloride could be used for the *N*-alkylations, but in these cases the yields were lower even after an extended reaction time (6 h instead of 4 h; Table 1, entry 3). Performing the reactions at ambient temperature proved optimal for conversions of both **1a** and **3a**. Raising the temperature to 60 °C or 90 °C had almost no effect in alkylations of sulfoximine **1a** with *n*-butyl bromide to give **2a**. In contrast, the yields of **4a** were lower under those modified conditions, presumably due to an accelerated partial decomposition of the starting material (Table 1, entries 4 and 5).

Commonly, the sulfur reagents were employed as racemates. In order to ensure the stereochemical integrity of the transformation, an *N*-butylation of enantiopure (*R*)-**1a** with *n*-butyl bromide and KOH in DMSO was performed. The exclusive formation of (*R*)-**2a** confirmed the expected stereospecificity of the *N*-alkylation. Although not explicitly confirmed experimentally, we assume an identical reaction course for the analogous *N*-functionalizations of sulfondiimines.

Table 1. Conditions for the *N*-alkylation reaction of sulfoximine **1a** and sulfondiimine **3a** with *n*-butyl halides.[a]



1a: Y = O
3a: Y = N-Ph

2a: Y = O
4a: Y = N-Ph

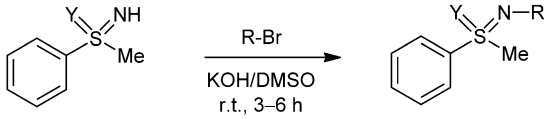
Entry	X	*T* [°C]	Yield of **2a**[b] [%]	Yield of **4a**[b] [%]
1	Br	r.t.	83	84
2	I	r.t.	95	79
3	Cl	r.t.	62	73[c]
4	Br	60	83	59
5	Br	90	80	56

[a] *Reaction conditions:* alkyl halide (1.5 equiv.), KOH (2.0 equiv.), DMSO, 4 h, argon atmosphere.
[b] After flash column chromatography.
[c] Reaction performed for 6 h.

With optimal conditions in hand, the substrate scope with respect to the alkyl halides was investigated. Considering the results summarized in Table 1 and taking into account factors such as cost, accessibility and environmental impact, alkyl bromides were chosen as electrophiles for the intended *N*-alkylation reactions. Again, *N*H-sulfoximine **1a** and *N*H-sulfondiimine **3a** served as representative substrates. As the data in Table 2 reveal, the established *N*-alkylation protocol proved general, and in most cases the *N*-alkylated products were obtained in good to excellent yields. Commonly, the *N*-alkylated sulfoximines **2** were obtained in slightly higher yields than the corresponding sulfondiimines **4**. We attribute this fact, as discussed before, to the lower stability of the sulfondiimine derivatives under the strongly basic reaction conditions.

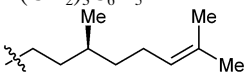
All *N*-alkylations with linear alkyl bromides proceeded well irrespective of the chain length affording the corresponding sulfoximines **2** and sulfondiimines **4** in yields ranging from 80% to 89% and 64% to 80%, respectively (Table 2, entries 1–4). For the introduction of the *N*-octadecyl group the alkyl iodide was used and **2f** and **4f** were obtained in 92% and 70%, respectively (Table 2, entry 5). A decrease in yield was observed when certain branched alkyl bromides were applied (Table 2, entries 6–9). In such transformations the position of the methyl substituent was important as, for example, reflected by the yields of sulfoximines **2g–i**. Whereas *N*-isopropyl derivative **2g**

Table 2. Conditions for the *N*-alkylation reaction of sulfoximine **1a** and sulfondiimine **3a** with various alkyl bromides.[a]



1a: Y = O
3a: Y = N-Ph

2a–r: Y = O
4a–r: Y = N-Ph

Entry	R	2/4	Yield of 2[b] [%]	Yield of 4[b] [%]
1	$-CH_2CH_3$	**b**	87	72
2	$-(CH_2)_6CH_3$	**c**	89	80
3	$-(CH_2)_{11}CH_3$	**d**	80	76
4	$-(CH_2)_{13}CH_3$	**e**	82	64
5[c]	$-(CH_2)_{17}CH_3$	**f**	92	70
6	$-CH(CH_3)_2$	**g**	14	0
7	$-CH_2CH(CH_3)_2$	**h**	34	38[d]
8	$-(CH_2)_2CH(CH_3)_2$	**i**	95	79
9	$-(CH_2)_2C_6H_{11}$	**j**	83	73
10	$-CH_2CH=CH_2$	**k**	79	72
11	$-(CH_2)_3CH=CH_2$	**l**	81	72
12	$-(CH_2)_9CH=CH_2$	**m**	83	78
13	$-CH_2C\equiv CH$	**n**	83	88
14	$-CH_2C\equiv CCH_2CH_3$	**o**	93	69
15	$-CH_2C_6H_5$	**p**	75	70
16	$-(CH_2)_3C_6H_5$	**q**	88	80
17		**r**	97[e]	65[e]

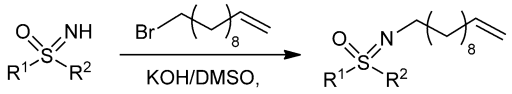
[a] *Reaction conditions:* alkyl bromide (1.5 equiv.), KOH (2.0 equiv.), argon atmosphere.
[b] After flash column chromatography.
[c] Reaction performed with iodide.
[d] Reaction performed for 9 h.
[e] The product was isolated as a mixture of diastereomers.

was only formed in 14% yield, the respective data for isobutyl- and isoamyl-containing products **2h** and **2i** were better (34% and 95% yield, respectively). Analogous observations were made in *N*-alkylations of sulfondiimine **3a** with branched alkyl bromides, targeting products **4g–i** (Table 2, entries 6–8). A variety of unsaturated substituents could be introduced, and in these cases no structural limitations were apparent (Table 2, entries 10–14). Both *N*-alkenylated and *N*-alkynylated products were formed in good to high yields starting from sulfoximine **1a** as well as sulfondiimine **3a**. In all cases, the unsaturated moieties remained intact. The high yield (88%) in the preparation of *N*-propargylic sulfondiimine **4n** (Table 2, entry 13) is particularly noteworthy because it demonstrates the superiority of the new protocol over the existing technology applying a combination of KH and propargylic bromide in THF which provided **4n** in only 68% yield.[15] The use of two aryl-substituted alkyl bromides (benzyl bromide and 3-phenylpropyl bromide) afforded the expected products (**2p**, **2q** and **4p**, **4q**) in yields between 70% and 88% (Table 2, entries 15 and 16). In this context, the formation of *N*-benzyl sulfondiimine **4p** (Table 2, entry 15) is of particular interest because this compound had proven to be difficult to prepare by other means.[16] Finally, citronellyl bromide was applied leading to sulfoximine **2r** and sulfondiimine **4r** in 97% and 65% yield, respectively (Table 2, entry 17). As the sulfur-containing starting materials were used as racemates, diastereomeric products (in *ca.* 1:1 ratios) were obtained in these cases.[23]

To further investigate the newly devised method, conversions of diversely substituted sulfoximines **1** and sulfondiimines **3** were studied. As alkylating agents, 11-bromo-1-undecene and *n*-butyl bromide were selected. The results are summarized in Table 3 and Table 4. To our delight, all substituent combinations on sulfur (alkyl/aryl, dialkyl, and diaryl) were tolerated well, and from both **1** and **3** the corresponding *N*-alkylated products **5–9** and **10–16** were obtained in high yields. Although different alkylating agents were used, the reactions of the sulfoximines appeared to lead to slightly higher yields than those performed with the analogous sulfondiimine derivatives (for example, Table 3, entry 3 *versus* Table 4, entry 1). Methoxy and bromo substituents on the *S*-aryl groups remained intact (Table 3, entries 1 and 2 as well as Table 4 entries 4 and 5), which might prove useful for subsequent functionalizations.

A variety of *S*-aryl-*S*-alkyl sulfondiimines with a phenyl, a 4-methoxyphenyl (PMP), or a tosyl group on the second imine nitrogen reacted well with *n*-butyl bromide as alkylating agent affording the corresponding *N*-butylated products **10–15** in good to high yields (Table 4, entries 1–6). The *N*′-substituent did not have a major effect on the alkylation behaviour as illustrated by the comparison between the yields of phenyl-substituted **4a** (84%, Table 1, entry 1) and tosyl-containing **12** (79%, Table 4, entry 3). Alkylating the *S*,*S*-diimine of tetrahydrothiophene as a represen-

Table 3. *N*-Alkylation reactions of sulfoximines **1b–j**.[a]

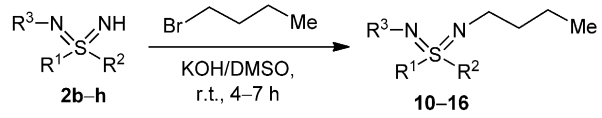


1b–j **5–9**

Entry	Starting Material	R^1	R^2	Product, Yield [%][b]
1	**1b**	4-Br-C_6H_4	Me	**5**, 83
2	**1c**	4-MeO-C_6H_4	Me	**6**, 87
3	**1d**	Ph	cyclopropyl	**7**, 91
4	**1e**	Ph	Ph	**8**, 88
5	**1f**	Me	Me	**9**, 88

[a] *Reaction conditions:* 11-bromo-1-undecene (1.5 equiv.), KOH (2.0 equiv.), argon atmosphere.
[b] After column chromatography.

Table 4. *N*-Alkylation reactions of sulfondiimines **2b–h**.[a]



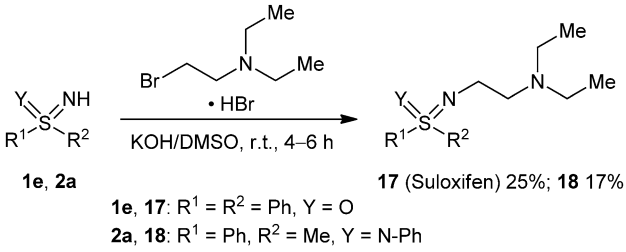
Entry	R^1	R^2	R^3	Product, Yield [%][b]
1	Ph	cyclopropyl	Ph	**10**, 75
2[c]	Ph	Me	4-$MeOC_6H_4$	**11**, 78
3	Ph	Me	tosyl	**12**, 79
4	4-$MeOC_6H_4$	Me	Ph	**13**, 85
5	4-BrC_6H_4	Me	Ph	**14**, 79
6	4-MeC_6H_4	Me	Ph	**15**, 83
7	tetrahydrothiophene		Ph	**16**, 94

[a] *Reaction conditions: n*-butyl bromide (1.5 equiv.), KOH (2.0 equiv.), argon atmosphere.
[b] After flash column chromatography.
[c] Reaction performed with 12-bromo-1-dodecene.

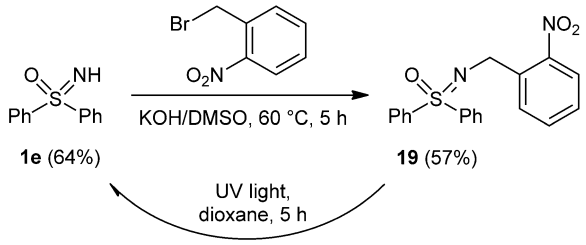
tative *S*,*S*-dialkyl sulfondiimine provided **16** in 94% yield (Table 4, entry 7).

Finally, two applications of the newly devised *N*-alkylation method with KOH in DMSO were investigated. The first focused on the preparation of *N*-aminoalkylated *S*,*S*-diphenyl sulfoximines[3,5a–c] and sulfondiimines,[17] which have been reported to exhibit significant spasmolytic activity. In this context, Suloxifen (**17**) proved particularl< interesting as it exhibited both oral and parental spasmolytic and antiasthmatic effects.[5a–c] To our delight, the KOH/DMSO method was also applicable here providing Suloxifen (**17**), albeit in low yield (25%), in a single step by reacting sulfoximine **1e** with 1-bromo-2-(diethylamine)-ethane hydrobromide (Scheme 2). An analogous reaction of sulfondiimine **2a** gave **18** in 17% yield.

The second application was followed with the wider vision to introduce a light-cleavable *N*-protecting group into sulfoximine chemistry. Following this idea and applying the KOH/DMSO protocol developed before, sulfoximine **1e** was reacted with *ortho*-nitrobenzyl bromide (for 5 h at 60 °C) to give **19** in 57% yield (Scheme 3).[24] Confirming the original idea, it



Scheme 2. Synthesis of Suloxifen (**17**) and a related sulfondiimine **18**.



Scheme 3. Protection of sulfoximine **1e** with a photo-cleavable protecting group and regeneration of the starting material.

was then shown that the photolabile nitrobenzyl protecting group could be cleaved under irradiation with UV light in dioxane regenerating sulfoximine **1e** in 64% yield after 5 h.

In summary, we have developed a general protocol for the *N*-alkylation of both *N*H-sulfoximines and *N*H-sulfondiimines, employing alkyl bromides with KOH in DMSO at room temperature. This cost-effective and operationally simple method proved suitable for the synthesis of a variety of *N*-alkylated sulfoximines and sulfondiimines in good to excellent yields (up to 97%). In terms of application, the protocol has been used for the preparation of the biologically active Suloxifen and a related sulfondiimine. In addition, using the same method, a light-cleavable *N*-protecting group was introduced into a sulfoximine, and subsequently cleaved with UV-light.

Experimental Section

General Procedure for the Synthesis of *N*-Alkylated Sulfoximines and Sulfondiimines

Into an argon-flushed Schlenk tube were added *N*H-sulfoximine **1** (1 equiv.) or *N*H-sulfondiimine **3** (1 equiv.) and potassium hydroxide (2 equiv.). The mixture was dissolved in DMSO (1.5 mL mmol^{-1}) and stirred for 5 min. Then, the alkyl bromide (1.5 equiv.) was added, and the reaction mixture was stirred for 3 to 6 h at room temperature. Water (6 mL) was added and the mixture was extracted with DCM (3×8 mL). The combined organic layers were dried over anhydrous magnesium sulfate, and the solvents were removed under reduced pressure. Finally, the product was purified by flash column chromatography.

Acknowledgements

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