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Controlled α-Mono- and α,α-Di-Halogenation of Alkyl Sulfones using Reagent-Solvent Halogen Bonding[†]

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The direct and selective α -mono-bromination of alkyl sulfones was achieved through base-mediated electrophilic halogenation. The appropriate combination of solvent and electrophilic bromine source was found to be critical to control the nature of the products formed, where reagent-solvent halogen bonding is proposed to control the selectivity via alteration of the effective size of the electrophilic bromine source. Conversely, the α, α -di-brominated sulfones were selectively obtained in good yields following polyhalogenation followed by selective de-halogenation during workup. Both procedures can be applied on gram scale, and the mono-halogenation was successfully extended to the fully selective α -chlorination, α -iodination and α -fluorination of alkyl sulfones.

 α -Halogenated sulfone derivatives constitute key intermediates in organic synthesis for the formation of biologically relevant molecules.¹ Aside from simple substitution chemistry,² α halosulfones are used in the Ramberg-Bäcklund rearrangement for the regioselective formation of alkenes through cheletropic extrusion of sulfur dioxide.³ Moreover, they can be employed as stabilised nucleophiles in presence of carbonyl compounds or imines, leading to haloalkenes via Julia olefination⁴ or to chiral epoxides/aziridines via Darzens-like reactions.⁵ A typical route to these intermediates involves the formation of a β ketosulfone by α -acylation of an alkylsulfone, followed by electrophilic halogenation and deacylation, a process which suffers from poor step- and atom-economy. (Scheme 1a).⁶ Another approach involves the nucleophilic substitution of sulfinate salts with dihalomethanes (Scheme 1b),⁷ which relies on the accessibility of sulfinic acid derivatives from the corresponding organometallic reagent and is essentially limited to Br and I. While the direct base-mediated halogenation of alkyl sulfones constitutes the most straightforward process to these compounds, it is rarely used as it typically suffers from

Although the difference in acidity between the sulfone substrate and the α -halosulfone product cannot be avoided, one can envision that sterically hindered electrophilic halogen sources should lead to higher selectivity towards the α-monohalogenated product. In this work, we report a simple and general procedure for the fully selective base-mediated electrophilic α -mono-bromination of alkyl sulfones (Scheme 1d). The combination of Br₂ as electrophilic halogen source and 1,4-dioxane as solvent was found to be key to the selectivity, which is attributed to the formation of a Br₂•dioxane halogenbonded polymeric complex as sterically hindered, effective halogen source. The concept was extended to the selective α iodination, α -chlorination and α -fluorination of sulfones when using the appropriate reagents. Strong Base 1. KBr/H₂O₂ (a) PhC(O)X 2. aq. NaOH DABSO CH₂Br₂ (b) DMSO

poor selectivity due to the increased acidity of the α -mono-

halogenated product as compared with the starting sulfone,

leading to unseparable mixtures of halogenated sulfones (Scheme 1c).^{4b,8,9} In the case of carbonyl compounds, this lack

of control can usually be circumvented through the use of acidic

conditions, effectively leading to halogenation via an enol

intermediate (see Scheme 1a).¹⁰ Sulfones, however, do not tautomerise in this way and require strongly basic conditions for

the formation of an α -carbanion prior to halogenation.¹



Scheme 1 Comparison of different synthetic strategies to α-bromosulfones

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In addition, it was found that a different reagent-solvent combination (CBr₄/OEt₂) afforded complete selectivity towards the α, α -di-brominated products instead via an unselective polybromination followed by reductive workup, leading to the development of the first direct and selective α, α -di-halogenation of sulfone derivatives. Both procedures are fully selective in all cases, can be applied on gram scale with similar efficiency and are run at room temperature. Considering the importance of α -halosulfones as synthetic intermediates, these methods constitute effective tools to streamline their formation and are broadly applicable to the synthesis of complex molecules.

Our initial investigations began with methyl phenyl sulfone (1a) as model substrate (Table 1). A survey of various strong bases with Br₂ as electrophilic bromine source in Et₂O identified lithium bases as ideal both in terms of yield and selectivity for the α -monobrominated product **2a**, with *n*-BuLi affording the highest yield (entries 1-7). Although other Br⁺ sources such as succinimide (NBS) and N-bromo 1.3-dibromo-5.5dimethylhydantoin (DBDMH) afforded improved selectivity (entries 9-10), the significantly lower yield of 2a obtained convinced us to continue with Br₂ as inexpensive reagent. Variation of the order of addition, reaction time, temperature and equivalents of base and Br⁺ source used did not permit to further increase the yield or selectivity.¹¹

Table 1 Optimisation of the selective α -bromination of sulfones ^a .					
0 0 Ph∕ S Me 1a		Base (1.1 equiv); Br' source (1.5 equiv); Solvent, rt, 3.5 h Ph ⁻ S ⁻ Br ⁺ Ph ⁻ S ⁻ Br Br 2a 3a		Br 3a	
Entry	Base	Br⁺	Solvent	Yield 2a	Yield 3a
		Source		(%) ^b	(%) ^b
1	KO <i>t</i> -Bu	Br ₂	Et ₂ O	4	20
2	KHMDS	Br ₂	Et ₂ O	23	20
3	NaHMDS	Br ₂	Et ₂ O	37	18
4	Lihmds	Br ₂	Et ₂ O	51	18
5	Litmp	Br ₂	Et ₂ O	36	9
6	LDA	Br ₂	Et ₂ O	37	7
7	<i>n</i> -BuLi	Br ₂	Et ₂ O	59	22
8	<i>n</i> -BuLi	CBr ₄	Et ₂ O	5	45
9	<i>n</i> -BuLi	NBS	Et ₂ O	21	5
10	<i>n</i> -BuLi	DBDMH	Et ₂ O	34	0
11	<i>n</i> -BuLi	Br ₂	THF	12	15
12	<i>n</i> -BuLi	Br ₂	<i>i</i> -Pr₂O	42	14
13	<i>n</i> -BuLi	Br ₂	<i>t</i> -BuOMe	48	21
14	<i>n</i> -BuLi	Br ₂	DME	56	3
15	<i>n</i> -BuLi	Br ₂	1,4-dioxane	68	0
16 ^c	<i>n</i> -BuLi	Br ₂	1,4-dioxane	67	8
17 ^c	Lihmds	Br ₂	1,4-dioxane	64 (57) ^d	0
18 ^e	LDA	CBr ₄	1,4-dioxane	54	2
19 ^e	Lihmds	CBr ₄	Et ₂ O	0	36
20 ^e	<i>n</i> -BuLi	CBr_4	Et ₂ O	0	52
21 ^e	LDA	CBr₄	Et ₂ O	0	67 (64) ^{<i>d,f</i>}

^aReactions performed with 0.32 mmol of **1a** unless otherwise stated. ^bYield determined by NMR using 1,3,5-trimethoxybenzene as internal standard. ^c1 mmol of **1a** was used. ^dIsolated yield. ^e2.2 equiv base and 3.0 equiv Br⁺ source were used. ^f0.5 equiv H₂O was added.

While most conditions evaluated initially led to the formation of a significant amount of unseparable α , α di brominated side product 3a, adjusting the reagent-solvent combination was found to have a crucial impact and could allow control of the selectivity, with 1,4-dioxane as solvent in presence of Br₂ affording complete selectivity and optimal yield for the formation of 2a (entries 11-15).¹¹ Since n-BuLi was found to lead to variation in selectivity on larger scale, LiHMDS was selected as ideal base for this transformation (entries 16-17). Conversely, the combination of CBr₄ as bromine source with Et₂O as solvent provided complete selectivity for the α, α -di-bromination of **1a**, with the use of LDA as base affording the highest yield of 3a (entries 8, 19-21). With these conditions in hand, the scope of the selective α -mono-bromination reaction was evaluated with different sulfones 1 (Table 2). In the case of methyl aryl sulfones, both electron-donating and withdrawing substituents were tolerated without much effect on the yield (2a-2e), and the phenyl group could be replaced by a naphthyl or thiophene ring (2f-2g). α -Substituted alkyl sulfones were also found to be compatible and afford complete selectivity for the secondary α mono-brominated product (**2h**-**2i**), and α , α -diphenylmethyl phenyl sulfone afforded the fully substituted α -halosulfone **2***j* in good yield. Di-alkyl sulfones were also shown to be tolerated, with an unsymmetrical substrate affording complete regiocontrol for the most acidic position (2k-2l). Importantly, the procedure could be applied on gram-scale in comparable yield (see 2a), and complete selectivity for the α -monobrominated product was observed in all cases.

The significant effect of the reagent-solvent combination on the selectivity observed can be attributed to modification of the effective size of the electrophilic bromine source through halogen bonding. Indeed, 1,4-dioxane is known to rapidly react with bromine at room temperature to form the halogenbonded polymeric complex bromine 1.4-dioxanate (Br2•dioxane) as an orange solid, which constitutes one of the first examples reported of halogen bonding observed by X-ray crystallography (Scheme 2a).^{12,13} This drastically increases the size of the electrophilic bromine reagent and allows for only a single bromination to occur, regardless of the fact that product 2 can be deprotonated in the reaction conditions due to its increased acidity compared to the starting sulfone 1.



^aIsolated yield of reaction performed on gram scale (7.7 mmol). ^bn-BuLi was used as base instead of LiHMDS.

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Scheme 2 Halogen-bonded structure of $\mathsf{Br}_2{}^{\bullet}\mathsf{dioxane}^{12}$ and evaluation as effective sterically hindered mono-brominating agent with sulfone 1a

To evaluate if this complex is in fact the effective bromine source in the reaction, we performed the bromination of sulfone **1a** with the Br₂•dioxane complex instead of Br₂ (Scheme 2b). While the NMR yield of **2a** obtained was slightly lower, the selectivity was complete, suggesting that this is the active reagent in the mono-halogenation reaction. The α -monohalogenation reaction could be extended to the selective α iodination (**4**), α -chlorination (**5**) and α -fluorination (**6**) of sulfones by simple modification of the electrophilic halogen source, as exemplified here starting from sulfone **1a** (Scheme 3).¹⁴ While all four reactions afforded complete selectivity for the α -mono-halogenated product, the α -fluorination reaction produced the product **6** in only poor yield, even after extensive optimisation.¹¹



Notably, CBr4 is also known to be an excellent halogen bond donor and is calculated to form strong dimeric complexes with ethers such as Et₂O.^{12,15} It is thus reasonable to think that a complex such as CBr₄•OEt₂ could be the active reagent in the selective α, α -di-bromination reaction developed. A closer look at this transformation revealed that the selectivity for the α, α di-brominated product 3a did not come from the halogenation step itself, but rather from the reductive workup using a saturated solution of sodium sulfite (Scheme 4). Indeed, analysis of the crude mixture using a non-reductive aqueous workup showed a mixture of α, α -di-brominated product **3a** and α, α, α -tri-brominated product 7, in a 1:3 ratio favoring 7. When this mixture was treated under reductive workup with saturated aqueous Na2SO3, only 3a was observed as halogenated product, which suggests that these reductive conditions lead to the selective mono-debromination of trihalogenated 7 (Scheme 4a). To confirm this effect, the pure tribrominated sulfone 7 was treated in the same reductive workup, which led to the formation of α, α -di-brominated product 3a in quantitative yield.



It should be noted that this type of α, α -di-halogenation strategy involving an unselective polybromination followed by controlled de-halogenation is unprecedented and was also found to be efficient for a variety of electronically different sulfones (Table 3). Interestingly, in some cases, the addition of 0.5 equiv H₂O led to a significant improvement in isolated yield (see **3a**, **3d**, **3k**).¹¹ The reaction is amenable to gram-scale as exemplified with **3a**, and constitutes the first selective and direct α, α -di-bromination of sulfone derivatives.¹⁶



 o 0.5 equiv H₂O was added. b Isolated yield of reaction performed on gram scale (9.6 mmol).

In addition to transformations referred to earlier,²⁻⁵ the α -halogenated sulfones obtained from these two methods are shown to be useful intermediates for various synthetic applications (Scheme 5).



Scheme 5 Various synthetic applications of the α -halosulfones synthesised

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Darzens-type epoxidation by reaction of **2a** with benzaldehyde afforded *trans*-epoxide **8** in excellent yield and diastereoselectivity,⁵ and nickel-catalysed cross-coupling conditions adapted from Fu and co-workers led the formation α -arylsulfone **9** (Scheme 5a).²ⁱ Additionally, treatment of α , α -dibrominated sulfone **3a** with neat household bleach led to the formation of hetero-polyhalogenated product **10**, known to have moderate anti-fungal activity, in good yield (Scheme 5b).¹⁷

In summary, a general, direct and selective base-mediated α -mono- and α, α -di-bromination of alkylsulfones is reported, where reagent-solvent halogen bonding is proposed to control the selectivity via alteration of the effective size of the electrophilic reagent. The use of Br₂ in 1,4-dioxane provided complete selectivity for the α -mono-brominated products, presumably through the *in situ* formation of a Br₂•dioxane complex as sterically congested electrophilic bromine source. The reaction could be extended to the selective α -chlorination,

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Conflicts of interest

There are no conflicts to declare.

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