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Organic &
Biomolecular
Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 1225

www.rsc.org/obc

PAPER

Practical synthesis of β-oxo benzo[*d*]thiazolyl sulfones: Scope and limitations†

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Received 2nd September 2011, Accepted 2nd November 2011
DOI: 10.1039/c1ob06510f

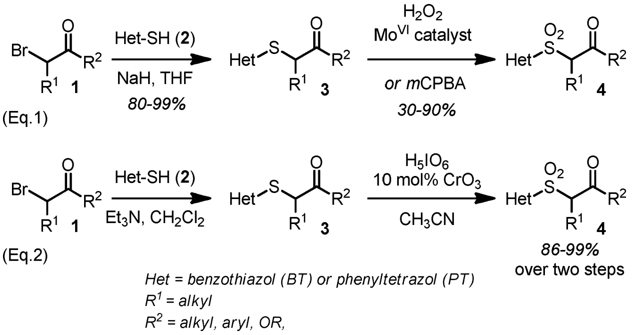
In this paper, we discuss our new synthetic approach towards functionalized benzo[*d*]thiazolyl (BT) sulfones, based on the reunion of alkyl BT sulfones and various electrophiles (*e.g.* R–CO–X, RO–CO–X, RS–CO–X, Ts–X . . .). All important aspects of this coupling reaction, including relevant and undesirable side reactions, are evaluated by means of calculations and competitive experiments. The scope and limitations of this method are established.

Introduction

Over the past 5 years, the use of β-carbonyl heteroaryl sulfones in organic synthesis, particularly in the domain of organocatalysis, has dramatically increased.[1] Especially, the use of these type of compounds as nucleophiles in the context of organocatalysis led to the synthesis of new classes of previously inaccessible compounds and structural motives. For example, the use of β-oxo benzo[*d*]thiazolyl sulfones or β-oxo phenyltetrazolyl sulfones in combination with α,β-unsaturated aldehydes and ketones has led, in the presence of a prolinol-based catalyst, to the stereoselective formation of both β-alkynylated and β-alkenylated carbonyl derivatives.[1i] The drawback of this method was the long and expensive synthesis of the starting material, β-oxo heteroaryl sulfones.[2] Additionally, only a small library, from a structural diversity point of view, of β-oxo heteroaryl sulfones could be prepared using the standard synthetic protocols.

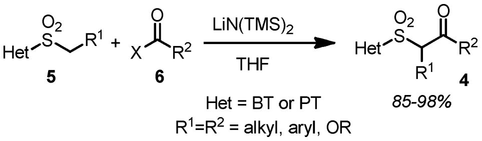
In general, this class of compounds is prepared in two steps, starting from α-bromo carbonyl compounds and corresponding heteroaryl sulfides (Scheme 1, eq. 1). To achieve a reasonable conversion of starting material to product **4**, prolonged reaction times are required (days). Unfortunately, sulfones **4** often slowly degrade under the given reaction conditions. This drawback was recently solved by Jørgensen *et al.*,[3] by introducing a new oxidation protocol of β-oxo hetoroaryl sulfides **3** to sulfones **4**. This procedure allows the isolation of the desired products, not only in excellent yields but also in very short reaction times (10–45 min) (Scheme 1, eq. 2).

Recently, we started several synthetic ventures based on the use of β-oxo benzo[*d*]thiazolyl sulfones **4** and we were searching for a more versatile access to this class of compounds. The standard approach to sulfones **4** was not only inefficient but also not general enough for our purposes.



Scheme 1 Previous approaches to β-oxo heteroaryl sulfones.

In this context, we have recently reported a practical synthesis of β-acyl and β-alkoxycarbonyl heterocyclic sulfones **4** based on the pairing of sulfone **5** with electrophile **6** (Scheme 2).[4]



Scheme 2 An alternative approach to β-oxo heteroaryl sulfones **4**.

Herein, we wish to present a full report of our experimental and computational studies, which focused on the evaluation of the reaction between benzo[*d*]thiazolyl (BT) sulfone α-anions and various electrophiles. Firstly, the behaviour of BT sulfones and targeted β-oxo BT sulfones under non-nucleophilic basic conditions is discussed. Based on these results, the reactivity of α BT sulfonyl anions with various electrophiles is evaluated, with a special mention to carbonyl electrophiles.[5] The scope and limitations of these coupling reactions are also discussed.

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† Electronic supplementary information (ESI) available: detailed experimental and computational procedures and data. See DOI: 10.1039/c1ob06510f

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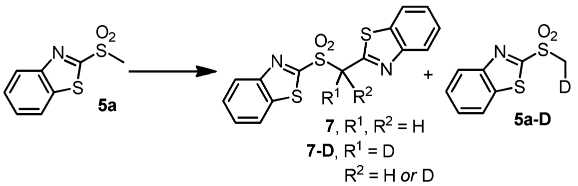
Table 1 Dimerization of sulfone **5a** under basic conditions[a]



Entry	Base (equiv)	Time at −78 °C (min)	Conv. of **5a**[b] (%)	Yield (%)[c] **5a–D**	**7**	**7–D**
1[d]	LDA (1.1)	120	>99	n.a.	52	n.a.
2[g]	LDA (1.1)	120	>99	n.a.	61	n.a.
3	$LiN(TMS)_2$ (1.1)	120	>99	<5[e]	53[f]	
4	$LiN(TMS)_2$ (4.0)	120	>99	<5[e]	<5[e]	49
5	$KN(TMS)_2$ (1.1)	120	>99	<5[e]	82[f]	
6	$KN(TMS)_2$ (4.0)	120	>99	<5[e]	<5[e]	91
7	$LiN(TMS)_2$ (5.0)	0.5	>99	97	<5[e]	<5[e]
8	$LiN(TMS)_2$ (5.0)	2	>99	91	<5[e]	<5[e]
9	$LiN(TMS)_2$ (5.0)	5	>99	85	<5[e]	7
10	$LiN(TMS)_2$ (5.0)	15	>99	61	<5[e]	16
11	$LiN(TMS)_2$ (5.0)	30	>99	48	<5[e]	24
12	$LiN(TMS)_2$ (5.0)	60	>99	21	<5[e]	31
13	$KN(TMS)_2$ (5.0)	0.5	>99	90	<5[e]	2
14	$KN(TMS)_2$ (5.0)	2	>99	76	<5[e]	20
15	$KN(TMS)_2$ (5.0)	5	>99	53	<5[e]	31
16	$KN(TMS)_2$ (5.0)	15	>99	26	<5[e]	63
17	$KN(TMS)_2$ (5.0)	30	>99	<5[e]	<5[e]	81
18	$KN(TMS)_2$ (5.0)	60	>99	<5[e]	<5[e]	80

[a] Conditions: (i) base, THF, −78 °C, (ii) stirred at −78 °C for given time, (iii) DCl in MeOD added. [b] Based on ^1H NMR spectra of crude reaction mixure. [c] Isolated yield. [d] Taken from lit[9] [e] No traces of product observed (^1H NMR) in crude reaction mixture. [f] Mixture of mono- and di-deuterated and non-deuterated products **7-D** and **7**, respectively. [g] The reaction was quenched using HCl in MeOH.

Results and discussion

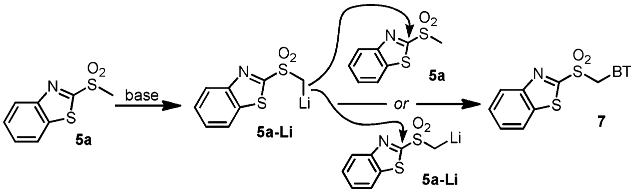
Preliminary studies

First, we evaluated the reliability of our synthetic approach to β-oxo BT sulfones, **4**, based on the addition of the sulfone **5** α anion onto the electrophile, **6**. From the literature it is known that sulfone **5** undergoes rapid self-condensation under basic conditions (Table 1, entry 1).[6] Of course, if this self-condensation reaction was too fast it would compete with the addition to electrophile **6** and our newly designed approach to the synthesis of **4** would be compromised.

To evaluate this risk, we first reproduced the literature results and reacted sulfone **5a** with a slight excess of LDA (Table 1, entry 2). Similar to the literature, we obtained the product of self-condensation **7** in 61% yield.[7] Next, we decided to use the less nucleophilic $[M]N(TMS)_2$ bases that are successfully used in the Sylvestre Julia olefination reaction to deprotonate BT sulfone **5a**,[7] even though the pK_a values of **5a** and $HN(TMS)_2$ (conjugate acid) are presumably very close.[8] These pK_a values, of course, raised the question whether the deprotonation of sulfone **5a** by $[M]N(TMS)_2$ base is quantitative. To answer the question, we decided to perform series of experiments in which sulfone **5a** would react with either a slight (1.1 equiv) or a large excess (4.0 equiv) of $LiN(TMS)_2$ and $KN(TMS)_2$ (Table 1, entries 3–6).

In all cases, complete conversion of sulfone **5a** was observed after 2 h. Interestingly, neither unreacted sulfone **5a** nor, after the reaction work-up with DCl/MeOD, its deuterated equivalent **5a-D** could be detected by ^1H NMR in the crude mixture. Only the dimers of **5a**, compounds **7** and/or **7-D** were observed.

To our great surprise, the self-condensation of **5a** to **7** occurred even if a large excess of base was used (Table 1, entries 4 and 6). This observation suggested that either (a) deprotonation of **5a** is not quantitative and the dimerization proceeds *via* the addition of anion **5a-Li** to non-deprotonated sulfone **5a**, or (b) the anion **5a-Li** reacts with itself (Scheme 3).

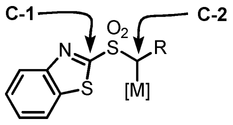


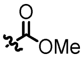
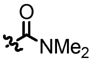
Scheme 3 Self-condensation reaction of sulfone **5a**.

To determine which of these hypotheses is correct, sulfone **5a** was reacted with a large excess (5.0 equiv) of $LiN(TMS)_2$ and the conversion of **5a** and the formation of its dimer **7** was monitored (Table 1, entries 4 and 7 – 12).

These experiments showed that, in the presence of an excess of the base, the deprotonation of the acidic hydrogen α to a sulfone group is very fast (less than 30 s, Table 1, entry 7)[9] and the concentration of anion **5a-Li** is slowly decreasing with time. Correspondingly, the formation of dimer **7-D** is increasing.

Table 2 Computed charges (NBO) at C-1 and C-2 carbons in sulfone **5a** and its derivatives[a]



Entry	R	[M]	C-1	C-2
1	H	H	−0.211	n.d.
2	H	Li	−0.191	−1.061
3		Li	−0.184	−0.802
4		Li	−0.185	−0.844
5		Li	−0.180	−0.856
6	$-SO_2Ph$	Li	−0.194	−1.140

[a] For details, see ESI.†

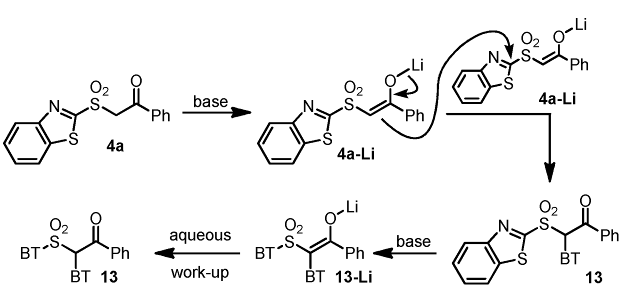
These results indicate that deprotonation of sulfone **5a** is rapid (presumably due to high kinetic acidity of the hydrogens α to sulfone group) and that dimerization of sulfone **5a** proceeds, even if this latter is fully transformed into its anion **5a-Li**. This suggests thus that anion **5a-Li** reacts with itself.

Similar behaviour was observed if an excess of $KN(TMS)_2$ was used (Table 1, entries 6 and 13–18). However, in this case we observed that newly generated anion **5a-K** is dimerizing even faster than **5a-Li**, substantially diminishing the concentration of anion **5a-K** in the reaction mixture. We believe that faster dimerization process of anion **5a-K**, as compared to anion **5a-Li**, is caused by the higher nucleophilicity of the potassium anion **5a-K**.

To shed more light into the reactivity of anion **5a-Li** and to evaluate the possibility that anion **5a-Li** might also behave as an electrophile under the reaction conditions, we decided to evaluate and compare the electrophilicity of the BT group in **5a** and **5a-Li** by computational means.[10] Relative electrophilicity of the BT group has been estimated by computing the charge on the C-1 carbon atom (Table 2).[11] The obtained partial charges on C-1 for **5a** (–0.211) and **5a-Li** (–0.191) were very similar suggesting that both species should have essentially the same electrophilic properties.[12] These results thus support our hypothesis that dimer **7** is formed by the self-reaction of **5a-Li**.

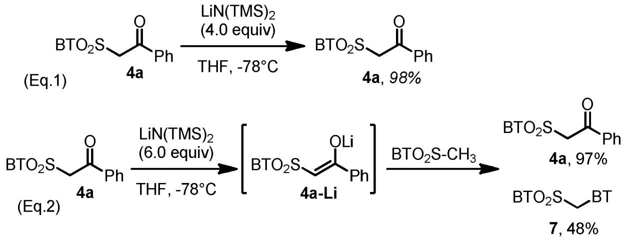
Having described the behaviour of sulfone **5a** in the presence of the base, we focused on the evaluation of the stability of the β-oxo BT sulfone **4**. As a model substrate, we used keto sulfone **4a**.[13] We feared that compound **4a** might undergo a self-condensation reaction similarly to sulfone **5a** (Scheme 4). Indeed, according to the corresponding computed charges, the C-1 carbon atom of the enolate of **4b** should be (at least) as electrophilic as the one in **5a** and **5a-Li** (Table 2, entry 3).

On the other hand, lithiated keto sulfone **4a-Li** should be less nucleophilic than sulfone anion **5a-Li** due to additional negative charge stabilization by the carbonyl group (enolate). This expectation is supported by our computational results (see charges on C-2, Table 2).



Scheme 4 Possible self-condensation of keto sulfone **4a**.

To experimentally evaluate this information, keto sulfone **4a** was first stirred with an excess of $LiN(TMS)_2$ (Scheme 5, eq. 1). No degradation of **4a** was observed. Once the stability of **4a** under basic conditions was determined, the resistance of enolate **4a-Li** against the attack of anion **5a-Li** was tested (Scheme 5, eq. 2). Again, no reaction of **4a-Li** was observed.



Scheme 5 Determination of keto sulfone **4a** stability in the presence of base and α sulfonyl anion.

These experiments did show us that self-condensation of sulfone **5a** is rather rapid (full conversion within 2 h), whereas keto sulfones **4** (the desired class of compounds) are stable under basic conditions and do not react with external nucleophiles, such as anion **5a-Li**.

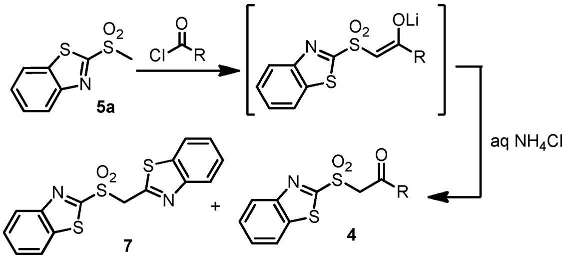
Synthesis of β-keto sulfones 4

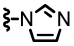
Having collected these results, we were able to investigate the coupling between sulfone **5a** and benzoyl chloride **6a** (Table 3).

Our primary goal was to find suitable reaction conditions for this coupling (Scheme 6). We thus had to design a system in which the addition of α sulfonyl anion of **5a-Li**[14] to electrophile (**6a**) would be faster than its self-condensation to adduct **7** ($k_1 \gg k_2$). Additionally, the transformation of the adduct, **4a**, into its enolate, **4a-Li**, should be more rapid than the eventual Sylvestre Julia reaction that could occur between the ketone presented in **4a** and sulfone anion **5a-Li** ($k_5 \gg k_6$). Once all of adduct **4a** is transformed into its enolate, **4a-Li**, it should be safe, since we demonstrated that enolate **4a-Li** is stable in the presence of a base or nucleophile (Scheme 5).

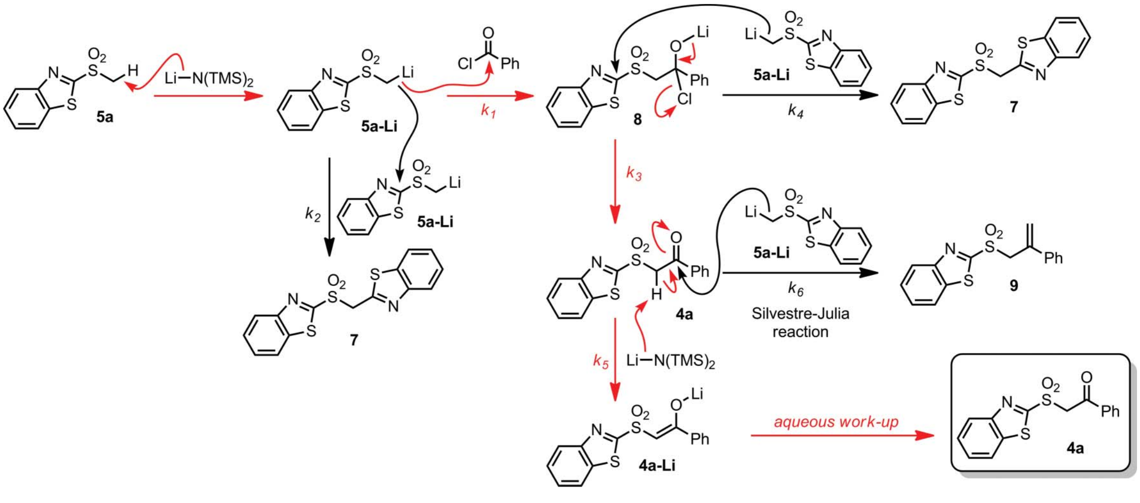
Taking into account these considerations, we started to investigate the coupling between sulfone **5a** and benzoyl chloride **6a**. Initially, generated anion **5a-Li** was stirred at −78 °C for 15 min prior to the benzoyl chloride **6a** addition (Table 3, entry 1). The desired product **4a** was isolated in 15% yield along with 32% of the dimerization product **7**. As expected, if the pre-metallation period was longer (Table 3, entry 2), the self-condensation was the predominant reaction and only trace amounts of products were formed. On the other hand, the progressive decrease of

Table 3 Optimization of reaction conditions



Entry	X	Conditions	Yield (%)[a,b]	
			4a	**7**[c]
1	Cl	LiN(TMS)$_2$ (2.2 equiv), −78 °C, THF, 15 min then BzCl (1.2 equiv)	15	32
2	Cl	LiN(TMS)$_2$ (2.2 equiv), −78 °C, THF, 30 min then BzCl (1.2 equiv)	7	48
3	Cl	LiN(TMS)$_2$ (2.2 equiv), −78 °C, THF, 1 min then BzCl (1.2 equiv)	65	7
4	Cl	LiN(TMS)$_2$ (2.2 equiv), −78 °C, THF, then BzCl (1.2 equiv)	96	<5
5	Cl	BzCl (1.2 equiv), −78 °C, THF, then LiN(TMS)$_2$ (2.2 equiv)	97	<5
6	Cl	NaN(TMS)$_2$ (2.2 equiv), −78 °C, THF, then BzCl (1.2 equiv)	82	11
7	Cl	KN(TMS)$_2$ (2.2 equiv), −78 °C, THF, then BzCl (1.2 equiv)	72	17
8	Cl	LiN(TMS)$_2$ (2.2 equiv), 12-crown-4 (4.5 equiv), −78 °C, THF, then BzCl (1.2 equiv)	74	11
9	Cl	LiN(TMS)$_2$ (2.2 equiv), −78 °C, THF/HMPA = 6 : 1 (v/v), then BzCl (1.2 equiv)	78	9
10	Cl	KN(TMS)$_2$ (2.2 equiv), 18-crown-6 (4.5 equiv), −78 °C, THF, then BzCl (1.2 equiv)	64	12
11	Cl	KN(TMS)$_2$ (2.2 equiv), −78 °C, THF/TDA-1 = 6 : 1 (v/v), then BzCl (1.2 equiv)	52	13
12	Cl	LiN(TMS)$_2$ (2.2 equiv), −78 °C, Et$_2$O, then BzCl (1.2 equiv)	95	<5
13	Cl	LiN(TMS)$_2$ (2.2 equiv), −78 °C, DME, then BzCl (1.2 equiv)	88	5
14	F	LiN(TMS)$_2$ (2.2 equiv), −78 °C, THF, then BzF (1.2 equiv)	93	<5
15	Br	LiN(TMS)$_2$ (2.2 equiv), −78 °C, THF, then BzBr (1.2 equiv)	97	<5
16	OCOPh	LiN(TMS)$_2$ (2.2 equiv), −78 °C, THF, then Bz$_2$O (1.2 equiv)	92	<5
17		LiN(TMS)$_2$ (2.2 equiv), −78 °C, THF, then Bz-Im (1.2 equiv)	92	<5
18	CN	LiN(TMS)$_2$ (2.2 equiv), −78 °C, THF, then BzCN (1.2 equiv)	91	<5
19	OMe	LiN(TMS)$_2$ (2.2 equiv), −78 °C, THF, then BzOMe (1.2 equiv)	<5	63
20	OMe	BzOMe (1.2 equiv), −78 °C, THF, then LiN(TMS)$_2$ (2.2 equiv)	<5	71

[a] Overall yields refer to pure, isolated products. [b] Average of two runs. [c] Yield recalculated to 100%.

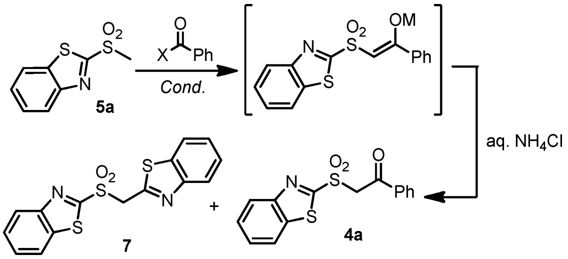


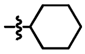
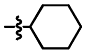
Scheme 6 Considered undesired side reactions that could compete with the β-keto sulfone **4** synthetic pathway (red).

the metallation period led to an increased yield of adduct **4a**. Finally, the highest yield of **4a** was obtained when electrophile **6a** was added immediately after the base (Table 3, entry 4).[15] We thus tested also the coupling step under the Barbier-type reaction conditions.[16] Not surprisingly, the desired product **4a** was isolated in excellent 95% yield (Table 3, entry 5).

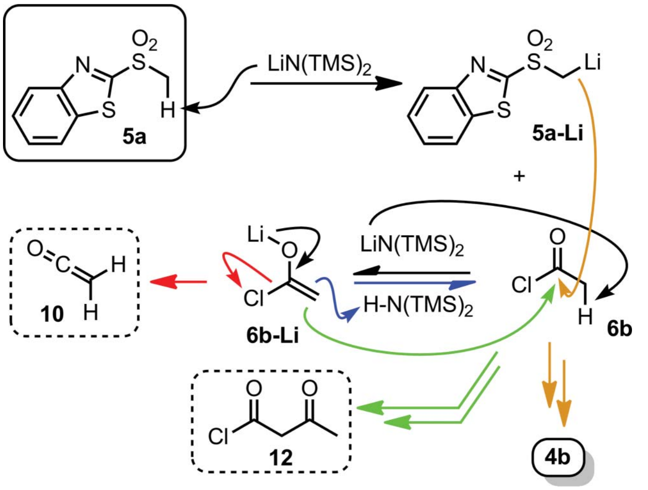
At this stage, we decided not to use the Barbier-type reaction conditions as our standard reaction protocol since we thought that they might be applicable only in the case of acylating agents that possess no α hydrogen atoms. Indeed, we expected that if, for example, acetyl chloride **6b** was used as electrophile, several side reactions might occur. Some of them are depicted in Scheme 7.

Table 4 Barbier-type reaction conditions evaluation

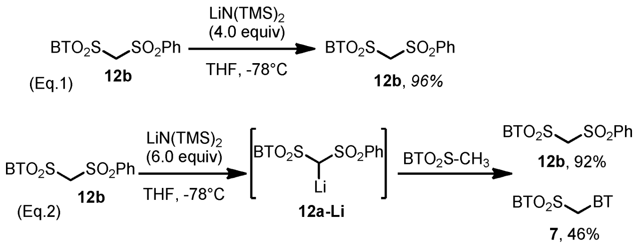


Entry	R	Conditions	Yield (%)[a]	
			4	7[b]
1	CH_3	$LiN(TMS)_2$ (2.2 equiv), −78 °C, THF, then RCOCl (1.2 equiv)	**4b**, 90	<5
2	CH_3	RCOCl (1.2 equiv), −78 °C, THF, then $LiN(TMS)_2$ (2.2 equiv)	**4b**, 67	14
3		$LiN(TMS)_2$ (2.2 equiv), −78 °C, THF, then RCOCl (1.2 equiv)	**4h**, 83	<5
4		RCOCl (1.2 equiv), −78 °C, THF, then $LiN(TMS)_2$ (2.2 equiv)	**4h**, 54	21

[a] Overall yields refers to pure, isolated products. [b] Yield recalculated to 100%.



Scheme 7 Possible side reactions that could be observed if Barbier-type reaction conditions are used for the β-keto sulfone **4** synthesis.



Scheme 8 Determination of bis-sulfone **12b** stability in the presence of base and α sulfonyl anion.

As a consequence, a lower yield of the desired adducts would be isolated. To verify this hypothesis, the mixing of sulfone **5a** with acetyl chloride (**6b**) and cyclohexyl acyl chloride (**6c**) was investigated (Table 4). As suspected, the desired products **4b** and **4c** were formed in lower yield than if Barbier-type conditions were used (Table 4, entries 1 vs. 2, and 3 vs. 4).

Next, $NaN(TMS)_2$ and $KN(TMS)_2$ were tested as bases but, in both cases, lower reaction yields of **4a** were observed (Table 3, entries 6 and 7). This observation is in agreement with anion **5a-K** stability experiments we made previously (Table 1).

To gain indirect evidence that would provide a link between the anion **5a-[M]** reactivity and the rate of dimerization, we decided to evaluate the coupling reaction of anions **5a-Li** and **5a-K** in the presence of selective Li^+ and K^+ chelating agents (12-crown-6, 18-crown-6, TDA-1 and HMPA). By this method, we expected to generate, *in situ*, a more reactive "naked" anion of **5a** (Table 3, entries 8–11). As a consequence, the introduction of chelating agents increased the speed of sulfone **5a** self-condensation.

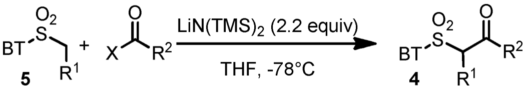
We reasoned that the nature of the solvents could have a similarly large influence. We therefore attempted the coupling reaction in THF, Et_2O and DME (Table 3, entries 4, 12 and 13, respectively).[17] As expected, reactions carried out in Et_2O and THF gave comparable yields, whereas the use of DME increased the yield of the self-condensation product **7**.

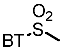
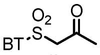
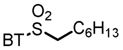
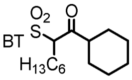
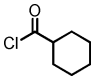
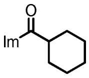
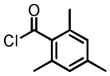
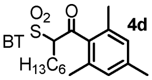
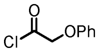
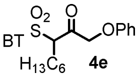
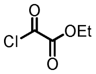
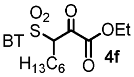
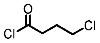
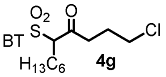
Next, we focused our attention on the nature of the leaving group in the electrophile (Table 3, entries 14–20). Benzoylating agents with reactivity similar to that of benzoyl chloride, such as BzF, BzBr, Bz_2O, benzoyl imidazole[18] or BzCN, produced the adduct **4a** in essentially same yields. On the other hand, methyl benzoyl ester was found to be unreactive under our reaction conditions as well as under Barbier-type reaction conditions (Table 3, entry 19 and 20). In both cases, only the product of dimerization **7** was isolated.

Having devised suitable reaction conditions for β-acyl sulfone synthesis, the scopes and limitations of this method were explored. A selection of pertinent results is shown in Table 5.

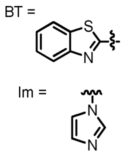
It was demonstrated that both alkyl and aryl acyl electrophiles react smoothly with lithiated sulfones **5**. In all cases the reaction yields were greater than 80%, except for when sulfone **5b** was

Table 5 Preparation of acyl benzo[*d*]thiazol sulfones **4**, starting from sulfones **5** and acyl-containing electrophiles



Entry	Sulfone	Acylating agent	Product	Yield (%)[a]
1	 **5a**	AcCl	 **4b**	90
2	 **5b**	Ac_2O	 **4c**	92
3		Ac–Im		89
4				83
5				92
6			 **4d**	89
7			 **4e**	86
8			 **4f**	78
9			 **4g**	81

[a] Overall yields refer to pure, isolated products.



reacted with monoethyl oxalyl chloride (Table 5, entry 8). In this case the desired product **4f** was obtained in 78% yield. Additionally, even acyl chlorides with enolizable hydrogen atoms reacted under the given reaction conditions to yield the desired α-acyl sulfones **4** in very good yields.

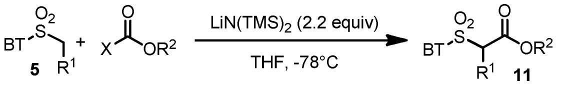
Synthesis of α-sulfonyl carboxylic acid derivatives

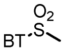
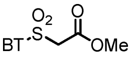
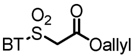
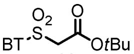
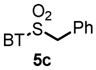
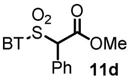
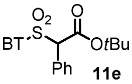
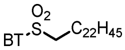
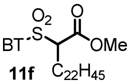
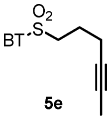
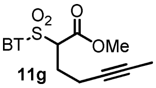
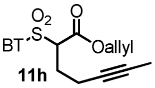
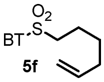
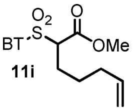
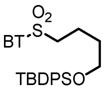
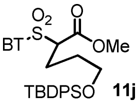
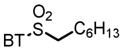
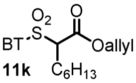
Our new protocol was also applied to the synthesis of α-sulfonyl carboxylic acid derivatives **11** (Table 6). For this purpose, four different types of alkoxy carbonylating reagents (bearing Cl, imidazole,[19] OCOR or CN as a leaving group) were tested. The nature of the leaving group was shown to have little effect on the reaction yield and all four electrophiles could be used as coupling partners. Additionally, standard functional groups are tolerated under the reaction conditions. In all cases, the desired products, **11**, were prepared in good to excellent yields.

After establishing the access to sulfonyl esters, we decided to extend this methodology to other carboxylic acid derivatives (Table 7). Interestingly, at this moment the abilities the of activating/leaving groups presented on electrophile were fully revealed.

As shown in Table 7, when a Cl^- group was used as an activating/leaving group, ester, thioester and amide BT sulfonyl derivatives **11** could be easily prepared (Table 7, entries 1–3). However, in the case of amides, the product of sulfone **5a** self-condensation, compound **7**, was also formed, along with the desired adduct, **11m**, in 11% yield (Table 7, entry 3). This observation suggests that in the case of *N*,*N*-dialkylamino chlorocarbamates, the addition of anion **5a-Li** to the carbonyl is much slower than in the case of alkyl chloroformates and thioformates. The difference in the reactivity between chloroformates and chlorocarbamates became even more evident when CN^- group was used as Cl^- equivalent (Table 7, entries 4–6). In this case, the ester and thioester derivatives were formed in very good yields (Table 7, entries 4

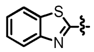
Table 6 Preparation of alkoxycarbonyl benzo[*d*]thiazol sulfones, **11**, starting from sulfone **5** and alkoxy carbonyl-containing electrophiles



Entry	Sulfone	Electrophile	Product	Yield (%)[a]
1	 **5a**	Cl–COOMe	 **11a**	94
2		Im–COOMe		89
3		NC–COOMe		91
4		Cl–COOallyl	 **11b**	95
5		Boc_2O	 **11c**	94
6		Im–COO*t*Bu		98
7	 **5c**	Cl–COOMe	 **11d**	88
8		Im–COOMe		94
9		NC–COOMe		92
10		Boc_2O	 **11e**	91
11	 **5d**	Im–COO*t*Bu	 **11f**	98
12		Cl–COOMe		88
13	 **5e**	Im–COOMe	 **11g**	94
14		NC–COOMe		93
15		Cl–COOMe		88
16		Im–COOMe		93
17		NC–COOMe		94
18		Cl–COOallyl	 **11h**	89
19	 **5f**	Cl–COOMe	 **11i**	87
20	 **5g**	Im–COOMe	 **11j**	95
21		NC–COOMe		94
22		Cl–COOMe		89
23	 **5h**	Im–COOMe		93
24		NC–COOMe		91
25		Cl–COOallyl	 **11k**	92

[a] Overall yields refer to pure, isolated products.

BT =



Im =

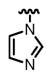
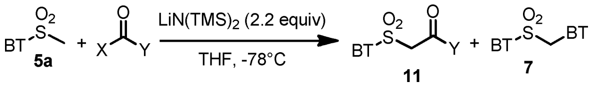
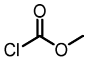
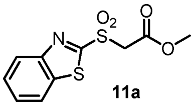
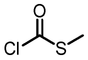
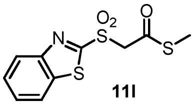
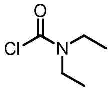
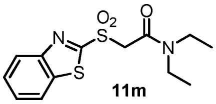
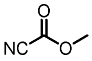
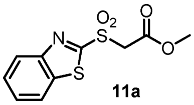
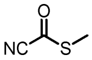
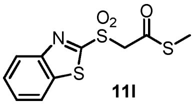
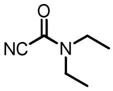
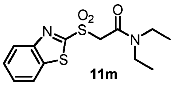
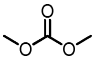
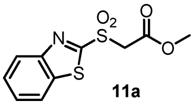


Table 7 Extending of the methodology to other carboxylic acid derivatives



Entry	Electrophile	Product	Yield (%)[a] 11	Yield (%)[a] 7
1			94	<5
2			94	<5
3			63	11
4			91	<5
5			95	<5
6			<5	77
7			<5	49

[a] Overall yields refers to pure, isolated products.

and 5), but no amide derivative was formed (Table 7, entry 6). If dimethyl carbonate was used as electrophile, no adduct **11a** of the addition was observed (Table 7, entry 7).

These results suggest that only sufficiently reactive electrophiles are capable to react with BT sulfone anions under the coupling conditions. If the electrophile is not reactive enough (Table 7, entries 3, 6 and 7), the competitive dimerization reaction starts to play an important role.

Non-carbonyl-containing electrophiles

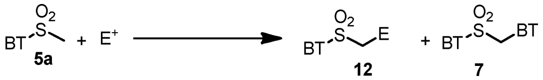
At this stage, we decided to extend our methodology to other non-carbonyl-containing electrophiles such as TMSCl, TsCl and MsCl (Table 8). Unfortunately, in all cases only the product of sulfone **5a** self-condensation, compound **7**, was isolated. Interestingly, no traces of any self-condensation or degradation products that could arise from potentially formed adducts **12a–c** were identified.

This observation suggests that the self-condensation is the fastest step under our reaction conditions. To verify this hypothesis, we decided to evaluate the bis-sulfone **12b**[20] stability under the basic conditions (Scheme 8). No degradation of bis-sulfone **12b** was observed when it was placed under the reaction conditions. This observation suggests that, at any time, desired bis-sulfone **12b** was not formed under the given reaction conditions. At this stage we believe that our unsuccessful synthesis of BT sulfonyl derivatives **12a–c** is caused by the lack of reactivity of the corresponding electrophiles (TMSCl, TsCl and MsCl) towards nucleophile **5a-Li**.

Conclusions

In summary, we have disclosed a short and efficient approach to α-acyl and α-carboxylic acid-derivative sulfones, **11**, starting from heterocyclic sulfones and appropriate electrophile. Reaction conditions tolerate various functionalities, such as TBDPS ethers, phenyl ethers and halogenated or unsaturated alkanes. We believe that this is a general approach towards this class of C-nucleophiles, which can be easily used in the context of the formation of olefins

Table 8 Coupling reaction using other non-carbonyl-containing electrophiles



Entry	E+	Conditions	Yield (%)[a] 12	7
1	TMSCl	LiN(TMS)$_2$ (1.2 equiv), −78 °C, THF, then TMSCl (1.2 equiv)	**12a**, <5	62
2	TMSCl	TMSCl (1.2 equiv), −78 °C, THF, then LiN(TMS)$_2$ (1.2 equiv)	**12a**, <5	54
3	TsCl	LiN(TMS)$_2$ (2.2 equiv), −78 °C, THF, then TsCl (1.2 equiv)	**12b**, <5	55
4	TsCl	MsCl (1.2 equiv), −78 °C, THF, then LiN(TMS)$_2$ (2.2 equiv)	**12b**, <5	57
5	MsCl	LiN(TMS)$_2$ (2.2 equiv), −78 °C, THF, then TsCl (1.2 equiv)	**12c**, <5	48
6	MsCl	MsCl (1.2 equiv), −78 °C, THF, then LiN(TMS)$_2$ (2.2 equiv)	**12c**, <5	60

[a] Overall yields refer to pure, isolated products.

or alkynes. Unfortunately, the extension of this methodology to other, non-carbonyl containing electrophiles proved to be unsuccessful. We believe that it is due to a low reactivity of these electrophiles. Additionally, the dimerization of BT sulfone **5a** under the basic conditions was evaluated using both, experimental approach and theoretical calculations.

Finally, we believe that our simple newly developed approach to β-carbonyl BT sulfones will extend their use beyond the field of asymmetric organocatalysis. Further development and use of β-carbonyl heterocyclic sulfones of general structure **4** and **11** is now under progress in our laboratory and will be reported shortly.

Experimental section

General experimental

^{1}H and ^{13}C NMR spectra were recorded on a Brucker AC-300 Avance II (working frequency 300 MHz and 75 MHz, respectively) at ambient temperature in CDCl$_3$ (Aldrich). Coupling constants (*J* value) are reported in hertz. The chemical shifts are shown in ppm downfield from tetramethylsilane, using residual chloroform (δ = 7.27 in ^{1}H NMR) or the middle peak of CDCl$_3$ carbon triplet (δ = 77.23 in ^{13}C NMR) as an internal standard. Low resolution mass spectroscopic data were recorded on a Finigan TSQ 7000. High resolution mass spectra were acquired at the University College London Mass spectroscopy facility using the Thermo Finnigan MAT900xp spectrometer.

Melting points were determined using a Büchi Flawil apparatus and are uncorrected.

Chemicals were purchased from Acros, Sigma-Aldrich and Fluka and were used as received. THF was distilled under argon from sodium benzophenone ketyl. Flash chromatography was performed on silica gel 60 (40–63 µm) (ROCC). All reactions were carried out under an atmosphere of argon in flame-dried apparatus with magnetic stirring, unless otherwise indicated. Brine refers to a saturated aqueous solution of sodium chloride.

The identity of known products was confirmed by comparison with literature spectroscopic data. The structure determination of new compounds was made with a help of 2D-COSY, HSQC, HMBC, 2D-NOESY and NOEdiff experiments.

Preparation of imizadole-containing acylating and alkoxycarbonylating reagents: Ac–Im and Bz–Im,[18] and Im–CO$_2$Me and Im–CO$_2$*t*Bu.[19]

The sulfones **5a–g**[4] and bis-sulfone **12b**[20] were prepared according to published procedures.

General procedure for the synthesis of β-oxo sulfonyl derivatives

A solution of sulfone (1.0 mmol, 1.0 equiv) in THF (5 mL, 0.20 M) was cooled to −78 °C and LiHMDS (1.0 M sol. in THF) (2.2 mL, 2.2 mmol, 2.2 equiv) was added dropwise. The colour of the reaction mixture turned from colourless or slightly yellow to orange/red within approx. 20 to 30 s. Immediately afterwards, a solution of acylating agent (acyl halide, carboxylic acid anhydride, acyl nitrile or acyl imidazole) or alkoxy carbonylating agent (alkoxy chloroformate, alkoxy imidazoylformate, alkoxy cyanoformate or Boc$_2$O) (1.1 mmol, 1.1 equiv) in THF (0.5 mL) was added. The colour of the reaction mixture faded within few minutes. The resulting mixture was stirred at −78 °C for 30 min, allowed to warm to 0 °C within 1 h and stirred at 0 °C for a further 30 min before sat. aq. sol. of NH$_4$Cl (15 mL) was added. The whole mixture was extracted with EtOAc (3 × 75 mL) and the combined organic layers were washed with brine (50 mL), dried over MgSO$_4$, filtered and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography on SiO$_2$. See ESI file for characterization data.†

Acknowledgements

J. P. is grateful to Prof. István E. Markó (U.C.L.) for his continuous support. We gratefully acknowledge the Université catholique de Louvain, the Fond de la Recherche Scientific (Chargé de Recherche F. R.S.-FNRS to J. P., Chercheur Qualifié F.R.S.-FNRS to R. R. and FRFC Project N° 2.4502.05), Socrates-Erasmus exchange program (H. S.) and Tohoku University G-COE program (IREMC) (H. S.) for financial support.

Notes and references

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5 Sylvestre Julia reaction (reaction of BT sulfones **5** with aldehydes or ketones) was not the object of this research and therefore simple carbonyl-containing electrophiles (aldehydes and ketones) were not used. For more details about Sylvestre Julia reaction see: (*a*) P. R. Blakemore, *J. Chem. Soc., Perkin Trans. 1*, 2002, 2563; (*b*) C. Aïssa, *Eur. J. Org. Chem.*, 2009, **2009**, 1831; (*c*) J. Pospíšil, *Tetrahedron Lett.*, 2011, **52**, 2348.

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7 Of course, the maximal yield of sulfone **5a** self-condensation reaction is 50% but for comparison purposes the yield was recalculated to 100% value. Valid for all the yields of self-condensation reaction presented in this paper.

8 (*a*) The pK_a values known in the litterature (http://www.chem.wisc.edu/areas/reich/pkatable/): for $(TMS)_2N–\underline{H}$, pK_a = 30 (in DMSO); (*b*) for BT $SO_2–CH_2–\underline{H}$, pK_a value is not known, but pK_a for $PhSO_2CH_2–\underline{H}$ is 29 (in DMSO). The value for **5a** is expected to be approximately the same or lower.

9 Originally we thought that the self-condensation of **5a** in basic media is a consequence of the reaction between already deprotonated sulfone **5a** with its parent molecule.

10 Geometry optimisation has been carried out using the Jaguar 7.5 program package (Jaguar 7.5, Schrödinger, LLC, New York, NY, 2008) at the B3LYP/6-31+G*(THF) level. NBO analysis has been performed at the B3LYP/cc-pVTZ level of theory. See Electronic Supplementary Information† for full details.

11 Interestingly, optimization of **5a-Li** reveals that in the most stable isomer lithium cation is not linked to the carbon atom but instead complexed to both the nitrogen atom and one oxygen of the sulfone function. Since the charge on C-1 carbon atom was found not to depend highly on the nature of the isomer, results given in Table 2 refer only to the lowest energy isomer (see ESI† for full results).

12 In fact calculations suggest that the deprotonated sulfone **5a-Li** is even a slightly better electrophile than its protonated form **5a**.

13 Prepared for this purpose *via* standard literature protocol: C. B. Jacobsen, L. Lykke, D. Monge, M. Nielsen, L. K. Ransborg and K. A. Jørgensen, *Chem. Commun.*, 2009, (43), 6554.

14 The competitive reaction that might occur with sulfone **5** are not considered, because we showed that the transformation of sulfone **5a** to its anion **5a-Li**, in the presence of the excess of the base, is very fast (Table 1, entry 7).

15 The solution of BzCl in THF was precooled (−78 °C) before addition.

16 A precooled (−78 °C) solution of $LiN(TMS)_2$ in THF was added to a cold (−78 °C) solution of sulfone **5a** and BzCl in THF.

17 Other solvents such as toluene or DMF (reaction performed at −50 °C) were also tested, but the desired adduct **4a** was isolated in significantly lower yields.

18 Prepared *in situ* from the corresponding carboxylic acid: (*a*) C. A. Ibarra, R. C. Rodriguez, M. C. Fernandez Monreal, F. J. Garcia Navarro and J. J. Martin Tesorero, *J. Org. Chem.*, 1989, **54**, 5620.

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20 Prepared for this purpose *via* standard literature protocol: M. He, A. K. Ghosh and B. Zajc, *Synlett*, 2008, **2008**, 999.