JOC The Journal of Organic Chemistry

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Practical Synthesis of β-Acyl and β-Alkoxycarbonyl Heterocyclic Sulfones

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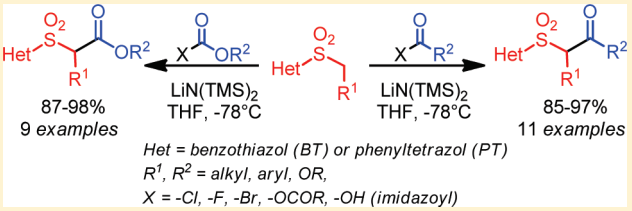
Supporting Information

ABSTRACT: A short and efficient synthesis for β-acyl and β-alkoxycarbonyl heterocyclic sulfones containing benzothiazol (BT) and phenyltetrazol (PT) heterocyclic core is presented here. The method seems to be general and provides the desired C-nucleophiles in very good to excellent yields from readily available starting materials.



Over the past two decades, asymmetric organocatalysis has developed into a field permitting the elegant introduction of chiral information into a plethora of various substrates.[1] During this period, several efficient organocatalytic protocols that create a novel C−C bond have been developed. The asymmetric organocatalytic conjugate addition of carbon nucleophiles to α,β-unsaturated carbonyl substrates is one typical example.[2] It is therefore surprising that efficient protocols allowing the addition of alkynylic[3] and alkenylic[3,4] functionalities have only been recently developed by MacMillan[4] and Jørgensen.[3] Even though both of these protocols provide the desired alkenylic derivatives in excellent yields and enantioselectivities, they are conceptually different. MacMillan's approach is based on the use of vinyl-type borate complexes[5] that acts as nucleophiles during the organocatalytic asymmetric conjugate addition process. The Jørgensen approach, on the other hand, is based on a two-step tandem process (see Scheme 1). First, an organocatalyst-promoted conjugate addition of β-keto heterocyclic sulfone **2** nucleophile to α,β-unsaturated carbonyl compound generates adduct **3**, which is then transformed to olefin **4** (via reduction/Smile rearrangement[6] protocol) or alkyne **5** (via enolization/Smile rearrangement protocol[6]).

Later on, Jørgensen et al. used the same β-keto heterocyclic sulfones **2** to perform a formal transition-metal-free Sonogashira coupling and α-carbonyl arylation reaction[7] (Scheme 1).

Finally, if β-acyl-heterocyclic sulfones **9** are used as reagents in the Julia−Kocienski olefination reaction, α,β-unsaturated esters **10** can be prepared (Scheme 2).[8]

In our laboratory we recently started several synthetic ventures that use and/or are based on the compounds that contains β-keto and/or β-alkoxycarbonyl motifs, and to our great surprise, we found out that in the literature there is only one synthetic approach that yields sulfones **2** or **9**. In this method, sulfones **2** and **9** are prepared in two steps starting from α-bromo (halo) ketones or esters as the key intermediates toward **2** or **9** (Scheme 3). Unfortunately, in our case the synthesis of the desired α-halo carbonyl compounds proved to be long and tedious, and therefore we decided to evaluate a new synthetic approach to β-carbonyl heterocyclic sulfones that would better fit our purposes.

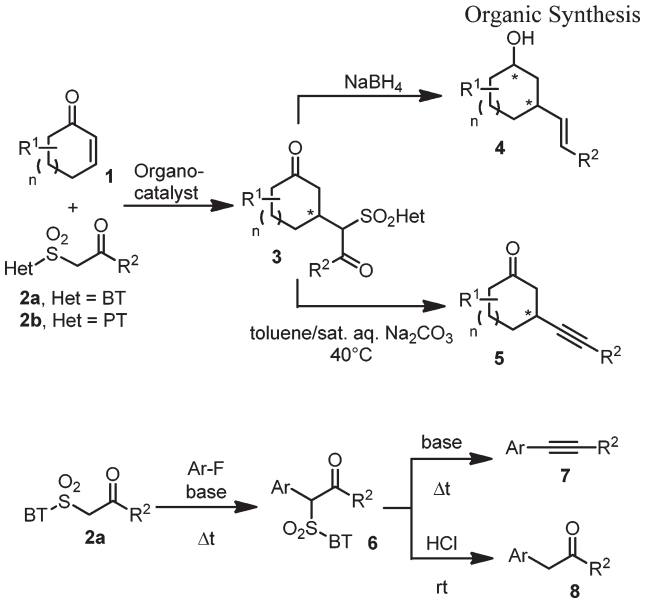
To achieve the most versatile approach to sulfones of general structure **11**, we decided to base the synthesis on the pairing of sulfone **13** with electrophile **14** (Scheme 4). Even though this type of disconnection seems to be obvious and is easily applicable to β-keto phenyl sulfone synthesis,[9] this approach is not easily applicable if β-keto BT- and PT-sulfones are wanted. The reason is that both BT- and PT-sulfones contain one electrophilic center within their heterocyclic core. As a consequence, if BT- or PT-sulfones **13** are treated with a non-nucleophilic base,[10] self-condensation occurs (Scheme 5).[11]

Thus if we want to prepare the desired β-carbonyl sulfones **11** starting from sulfone **13** and carbonyl electrophile **14**, conditions under which nucleophiles present in the reaction mixture are unreactive toward the nucleophilic center have to be found.

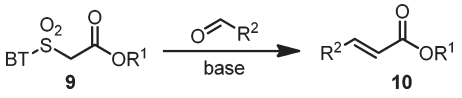
To find suitable coupling conditions, we decided to study a pairing between sulfone **13a** and benzoyl chloride **14a** (Table 1). Initially, the Li anion generated from **13a** was prepared with the use of the non-nucleophilic base ($LiN(TMS)_2$) at low temperature, and BzCl, an electrophile, was added after 30 min (Table 1, entry 1). In this case, the desired product **11a** was obtained only in very low yield. Since the control experiment showed that the low yield is not caused by instability or self-condensation of the intermediate[16,12] it remains that the low yield is caused by self-condensation of **13a**. To avoid this side reaction, the mixing time of **13a** with the base was progressively diminished (Table 1, entries 2 and 3). Gratifyingly, it was observed that the desired product **11a** was isolated in excellent yield (96%) if generated sulfone anion **13a** was quenched rapidly (BzCl was added immediately after the base).[13]

Received: November 23, 2010
Published: March 02, 2011

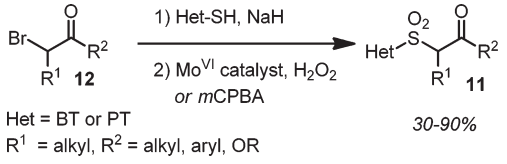
Scheme 1. Application of β-Keto-heterocyclic Sulfone 2 in Organic Synthesis



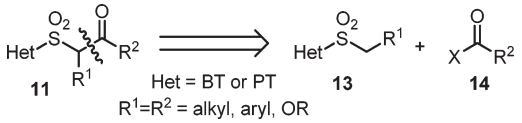
Scheme 2. β-Acyl-heterocyclic Sulfone 9 in the Context of a Julia−Kocienski Reaction



Scheme 3. Standard Approach to β-Carbonyl Heterocyclic Sulfones 11



Scheme 4. Retrosynthetic Approach to β-Carbonyl Heterocyclic Sulfones 11



At this stage we decided to test the coupling reaction with other types of benzoyl electrophiles to evaluate its scope and limitations. Unsurprisingly benzoylating agents with reactivity similar to that of benzoyl chloride, such as BzF, BzBr, Bz_2O, or benzoyl imidazole[14] (Table 1, entries 7, 9−11), yielded the desired β-keto sulfone **11a** in essentially the same yield. On the other hand, methyl benzoyl ester proved to be unreactive under our reaction

Scheme 5. Alkyl BT-Sulfone Base-Mediated Self-Condensation

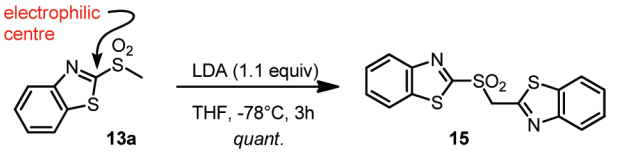
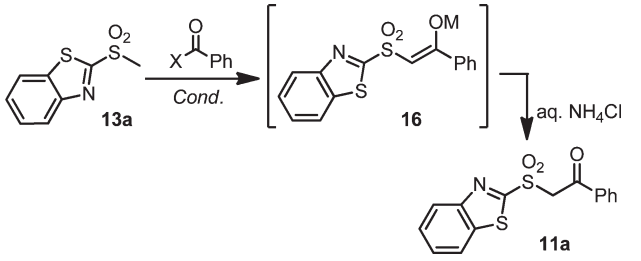


Table 1. Optimization of the Reaction Conditions



entry	X	Conditions	yield[a] (%)
1	Cl	$LiN(TMS)_2$ (2.2 equiv), -78°C, THF, 30 min *then* BzCl (1.2 equiv)	7
2	Cl	$LiN(TMS)_2$ (2.2 equiv), -78°C, THF, 15 min *then* BzCl (1.2 equiv)	15
3	Cl	$LiN(TMS)_2$ (2.2 equiv), -78°C, THF, 1 min *then* BzCl (1.2 equiv)	65
4	Cl	$LiN(TMS)_2$ (2.2 equiv), -78°C, THF *then* BzCl (1.2 equiv)	96
5	Cl	$NaN(TMS)_2$ (2.2 equiv), -78°C, THF *then* BzCl (1.2 equiv)	67
6	Cl	$KN(TMS)_2$ (2.2 equiv), -78°C, THF *then* BzCl (1.2 equiv)	42
7	OCOPh	$LiN(TMS)_2$ (2.2 equiv), -78°C, THF *then* Bz_2O (1.2 equiv)	92
8	OMe	$LiN(TMS)_2$ (2.2 equiv), -78°C, THF *then* BzOMe (1.2 equiv)	traces
9	F	$LiN(TMS)_2$ (2.2 equiv), -78°C, THF *then* BzF (1.2 equiv)	93
10	Br	$LiN(TMS)_2$ (2.2 equiv), -78°C, THF *then* BzBr (1.2 equiv)	97
11		$LiN(TMS)_2$ (2.2 equiv), -78°C, THF *then* Bz-Im (1.2 equiv)	92

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

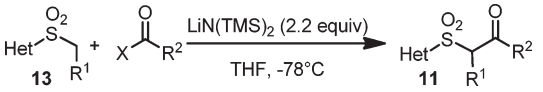
conditions (Table 1, entry 8). In this case, only the self-condensation product of **13a** (compound **15**) was observed.[15]

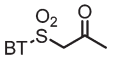
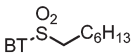
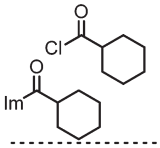
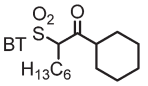
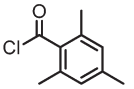
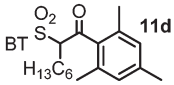
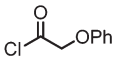
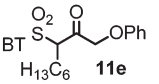
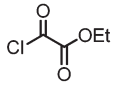
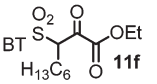
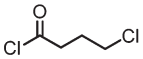
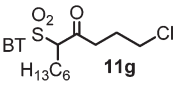
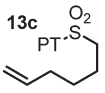
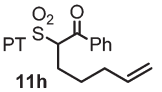
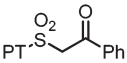
Having devised suitable reaction conditions to prepare this β-acyl sulfone, its scope and limitations were explored. A selection of pertinent results is shown in Table 2.

Both alkyl and aryl acyl derivatives react smoothly with lithiated sulfones **13** (Table 2). In all cases the reaction yields were more than 80% except when sulfone **13b** was reacted with monoethyl oxalyl chloride (Table 2, entry 8). In this case the desired product **11f** was obtained in 78% yield. Even acyl chlorides, bearing enolizable hydrogen atoms in the α position, reacted under the given reaction conditions to yield the desired α-acyl sulfones in very good yields.

dx.doi.org/10.1021/jo102326p |J. Org. Chem. 2011, 76, 2269–2272

Table 2. Preparation of Acyl Heterocyclic Sulfones 11 Starting from Sulfones 13 and Acyl-Containing Electrophiles



entry	sulfone	electrophile	product	yield[a] (%)
1	 **13a**	AcCl	 **11b**	90
2		Ac_2O		92
3		Im-Ac		89
4	 **13b**		 **11c**	83
5				92
6			 **11d**	89
7			 **11e**	86
8			 **11f**	78
9			 **11g**	81
10	 **13c**	PhCOCl	 **11h**	88
11		Bz_2O		89
12		PhCO-Im		93
13	 **13d**	PhCOCl	 **11i**	97
14		$(PhCO)_2O$		85
15		PhCO-Im		92

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

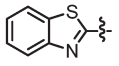
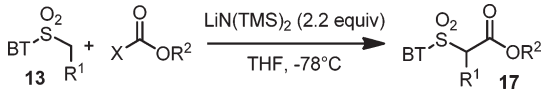
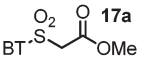
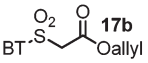
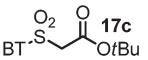
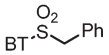
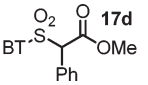
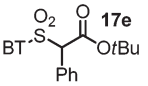
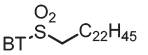
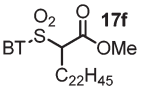
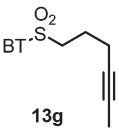
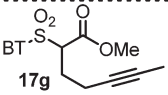
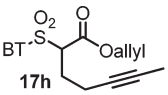
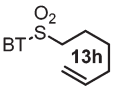
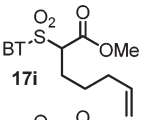
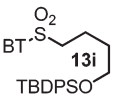
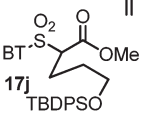
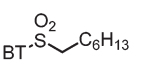
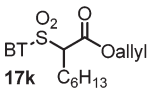
Het = BT 
Het = PT 
Im = 

Table 3. Preparation of Alkoxycarbonyl Heterocyclic Sulfones 11 Starting from Sulfones 13 and Alkoxy Carbonyl-Containing Electrophiles



entry	sulfone	electrophile	product	yield[a] (%)
1	 **13a**	Cl-COOMe	 **17a**	94
2		Im-COOMe		89
3		ClCOOallyl	 **17b**	95
4		Boc_2O	 **17c**	94
5		ImCOO*t*Bu		98
6	 **13e**	Cl-COOMe	 **17d**	88
7		Im-COOMe		94
8		Boc_2O	 **17e**	91
9		ImCOO*t*Bu		98
10	 **13f**	Cl-COOMe	 **17f**	88
11		Im-COOMe		94
12	 **13g**	Cl-COOMe	 **17g**	88
13		Im-COOMe		93
14		ClCOOallyl	 **17h**	89
15	 **13h**	Cl-COOMe	 **17i**	87
16		Im-COOMe		95
17	 **13i** TBDPSO	Cl-COOMe	 **17j** TBDPSO	89
18		Im-COOMe		93
19	 **13j**	ClCOOallyl	 **17k** C_6H_{13}	92

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

BT =
Im =

At this stage this protocol was extended to the synthesis of *β*-alkoxy carbonyl sulfones **17** (Table 3). For this purpose, three different types of alkoxy carbonylating reagents (bearing Cl, imidazole,[16] or OCOR as a leaving group) were tested. The nature of the leaving group was shown to have little effect on the reaction yields, and all three electrophiles might be used as coupling partners.

Additionally, the reaction conditions tolerate various functionalities, e.g., TBDPS ethers, phenyl ethers, and halogenated or unsaturated alkanes (Table 2, entries 7−10 and Table 3, entries 12−18).

In summary, we have uncovered a short and efficient approach to α-acyl and α-alkoxy carbonyl heterocyclic sulfones **11** and **17**, respectively, starting from heterocyclic sulfones and acyl or alkoxy carbonyl derivatives. We believe that this general approach to making this class of C-nucleophiles, which can be easily transformed into olefins or alkynes, will extend their use beyond the field of asymmetric organocatalysis. Further development and use of *β*-carbonyl heterocyclic sulfones of general structure **11** and **17** is now in progress in our laboratory.

EXPERIMENTAL SECTION

Representative Procedure for the Preparation of 2-(Benzo[*d*]thiazol-2-ylsulfonyl)-1-phenylethanone (11a). A solution of

dx.doi.org/10.1021/jo102326p |*J. Org. Chem.* 2011, 76, 2269–2272

sulfone **13a** (100 mg, 0.47 mmol, 1.0 equiv) in THF (2.4 mL, 0.20M) was cooled to −78 °C, and $LiN(TMS)_2$ (1.0 M solution in THF) (1.03 mL, 1.03 mmol, 2.2 equiv) was added dropwise. The color of the reaction mixture turned from colorless or slightly yellow to orange within approximately 10−20 s. Immediately after, a solution of benzoyl chloride (60 μL, 0.52 mmol, 1.1 equiv) in THF (0.25 mL) was added. The color of the reaction mixture faded within 1 to 5 min after the benzoyl chloride addition. 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 a saturated aqueous solution of NH_4Cl (7.5 mL) was added. The whole mixture was extracted with EtOAc (3 × 40 mL); the combined organic layers were washed with brine (25 mL), dried over $MgSO_4$, and filtered; and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography on SiO_2 (petroleum ether/EtOAc = 4:1 → 2:1 → 1:1), and the reaction yielded 143 mg (96%) of **11a** as slightly yellow solid: mp 123−124 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 5.22 (s, 2H), 7.43−7.53 (m, 2H), 7.55−7.69 (m, 3H), 7.94 (dd, J = 8.4 Hz, J = 1.2 Hz, 2H), 8.01 (dd, J = 7.0 Hz, J = 2.2 Hz, 1H), 8.20 (dd, J = 7.2 Hz, J = 2.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 61.4, 122.6, 125.7, 127.9, 128.4, 129.17, 129.19, 134.9, 135.6, 137.3, 152.6, 165.5, 187.3; IR (neat) ν^{-1} 1683 (s); MS (APCI) (relative intensity) m/z 318 ($M^+ + 1$, 100), 319 (20), 236 (9), 105 (11). Anal. Calcd for $C_{15}H_{11}NO_3S_2$: C, 56.76; H, 3.49; N, 4.41. Found: C, 56.78; H, 3.11; N, 4.67.

■ ASSOCIATED CONTENT

Supporting Information. Spectroscopic and analytical data for all new compounds, as well as experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

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.S.R.-FNRS to J.P.), Socrates-Erasmus exchange program (H.S.), and Tohoku University G-COE program (IREMC) (H.S.) for financial support.

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