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3,5-Bis(trifluoromethyl)phenyl sulfones in the modified Julia olefination: application to the synthesis of resveratrol

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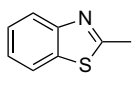
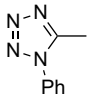
Abstract—The reaction between carbanions derived from alkyl 3,5-bis(trifluoromethyl)phenyl sulfones and aldehydes, affords with good yields and stereoselectivities the corresponding 1,2-disubstituted alkenes through the Julia–Kocienski olefination reaction. This one-pot protocol can be performed using KOH at room temperature or the phosphazene base P4-*t*-Bu at −78 °C, and has been successfully used in a high yielding and stereoselective synthesis of various stilbenes such as resveratrol.

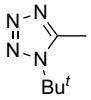
During several decades, a variety of fundamentally different approaches to the synthesis of olefins have been developed, which attempt to address the regio- and stereochemical demands that the synthesis of this moiety makes. The most generally applicable methods remain those involving direct olefination of carbonyl compounds such as Wittig,[1] Horner,[2] Wadsworth-Emmons,[3] Peterson,[4] Johnson,[5] and the classical Julia[6] reactions. The classical Julia olefination, also known as the Julia–Lythgoe olefination, was disclosed nearly 30 years ago and is based on a reductive elimination process of β-acyloxy phenyl sulfones.[7] Since its discovery, significant advances have been made in the reaction and it has become a crucial step in the synthesis of many natural products.[8] A new variant of the classical Julia reaction, the Julia–Kocienski olefination also known as the modified or one-pot Julia olefination,[9] has recently emerged as a powerful tool for olefin synthesis, and basically consists of the replacement of the phenyl sulfone moiety traditionally used in the classical reaction, with different heteroaryl sulfones, which allows the direct olefination process. Principally, four heterocyclic derivatives have been shown to give the highest yields and levels of stereoselectivity: benzothiazol-2-yl (BT, **1**),[9a] pyridin-2-yl (PYR, **2**),[10] 1-phenyl-1*H*-tetrazol-5-yl (PT, **3**),[11] and 1-*tert*-butyl-1*H*-tetrazol-5-yl (TBT, **4**).[12] The presence of an electrophilic imine-like moiety in the sulfone is responsible for the different reactivity and reaction pathway observed in the one-pot Julia olefination.

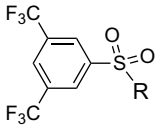
We have recently shown that the 3,5-bis(trifluoromethyl)phenylsulfonyl (BTFP-sulfonyl) group, is a strong electron-withdrawing group and an excellent nucleofuge in base-promoted β-elimination processes. Thus, α-arylsulfonyl acetates **5** are very soft nucleophiles, which can be easily dialkylated under very mild PTC conditions. The reaction with ethyl bromoacetate, allows the


1, BT


2, PYR


3, PT


4, TBT


5, R = CH_2CO_2R'
6, R = CH_2CH_2OH
7, R = CH_2R^1

Keywords: Julia olefination; Sulfones; (*Z*/*E*)-Selectivity; Resveratrol.
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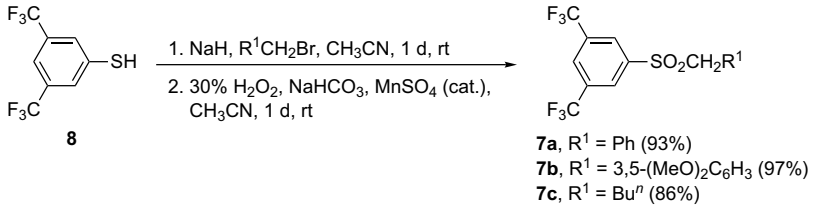


Scheme 1.

direct synthesis of *E*-aconitates via an alkylation–elimination integrated process.[13] On the other hand, β-arylsulphonyl ethanol **6**, is an efficient protecting group for carboxylic acids, easily removed with aqueous $NaHCO_3$.[14] We envisaged that the BTFP-sulfonyl group could undergo the Smiles rearrangement[15] necessary for the modified Julia olefination. As part of a program aimed at developing broadly useful applications of 3,5-bis(trifluoromethyl)phenyl sulfones in organic synthesis, herein we describe the use of alkyl BTFP-sulfones **7** in the Julia–Kocienski olefination reaction as well as their applications to the synthesis of stilbenes such as resveratrol.

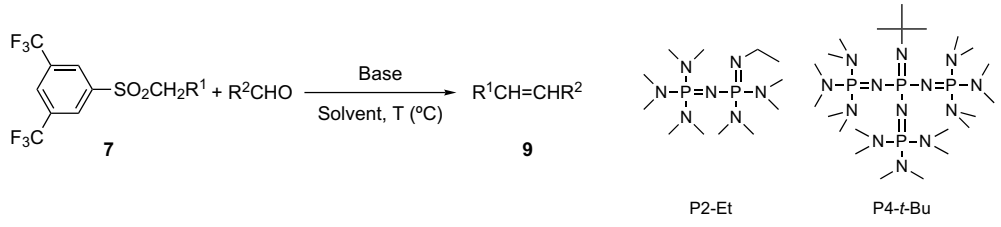
The π-deficient BTFP-sulfones **7** were prepared in high yields by reaction of the arylthiolate from **8** with the corresponding alkyl bromide using NaH as base in CH_3CN at room temperature, followed by oxidation with 30% H_2O_2 in the presence of catalytic amounts of $MnSO_4 \cdot H_2O$ (1 mol%) and a buffer solution of $NaHCO_3$[16] (Scheme 1).

In order to determine the stability of the sulfonyl carbanions derived from the BTFP compounds **7**, benzyl sulfone **7a**, and *n*-pentyl sulfone **7c** were treated with KOH in THF at rt, the phosphazene (triaminoiminophosphorane) base P4-*t*-Bu in THF at −78 °C and KHMDS in DME at −60 °C to rt for 24 h, and the reactions were then quenched with water. The sulfone recovery (Table 1), clearly showed the high stability of the BTFP-sulfonyl substituted carbanions even at rt. Only in the case of using the combination system KHMDS as base and DME as solvent, which has been previously shown to give very good results in terms of yield and stereoselectivity with other sulfones in the modified Julia olefination,[11,12] was the recovery unsatisfactory and some decomposition of the substrates observed. This problem, which has also been observed for phenyltetrazolyl sulfones (PT-sulfones) when KHMDS is used as base,[11] could be overcome in the case of BTFP-sulfones using either KOH or P4-*t*-Bu as base in THF (Table 1). Furthermore, the carbanions of the BTFP-sulfones did not exhibit any propensity to self-condense as is the case with BT-sulfones **1**[12] and in no case was self-condensation of the substrates detected even when the deprotonation reactions were carried out at rt. This allows the deprotonation step to be carried out in the absence of the aldehyde, which extends the scope of the olefination reaction to base-sensitive substrates.

Table 1. Stability of BTFP-sulfones **7**

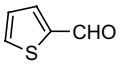
Reaction conditions	Sulfone recovery (%)	
	7a	**7c**
KHMDS, DME, −60 °C to rt, 24 h	50	28
KOH, THF, rt, 24 h	95	98
P4-*t*-Bu, THF, −78 °C, 24 h	88	77

The Julia–Kocienski olefination with BTFP-sulfones **7** was first evaluated through the coupling between benzyl derivative **7a** and PhCHO, employing different bases such as KHMDS, KOH, and the phosphazene bases[17] P2-Et and P4-*t*-Bu, either at rt (KOH) or at low temperatures (−78 °C for P2-Et and P4-*t*-Bu and −60 °C for KHMDS) in THF or DME as solvents (Scheme 2, Table 2). As shown in Table 2, entries 1–4, the yield of the olefination reaction was usually good except when KHMDS was used as base, as expected from the stability studies (see Table 1). With respect to the (*E*)-stereoselectivity of the reaction, this was not overly sensitive to changes of base and only in the presence of KOH (Table 2, entry 2), was it slightly decreased compared to the other bases, probably due to the rt conditions. Both P2-Et (2.2 equiv) and P4-*t*-Bu[18] (1.2 equiv) at −78 °C in THF gave satisfactory results in terms of yield and stereoselectivity (Table 2, entries 3 and 4). We also studied the effect of employing HMPA as an additive on



Scheme 2.

Table 2. Modified Julia olefination with BTFP-sulfones **7**

Entry	7	R^2CHO	Reaction conditions			Alkene				
			Base (equiv)	Solvent	T (°C)	No	R^1	R^2	Yield (%)[a]	Z/E[b]
1	**7a**	PhCHO	KHMDS (1.1)	DME	−60 to rt	**9a**	Ph	Ph	20[c]	1/99
2	**7a**	PhCHO	KOH (9)[d]	THF	rt	**9a**	Ph	Ph	78	16/84
3	**7a**	PhCHO	P2-Et (2.2)	THF	−78	**9a**	Ph	Ph	67[c]	3/97
4	**7a**	PhCHO	P4-*t*-Bu (1.2)	THF	−78	**9a**	Ph	Ph	65[c]	2/98
5	**7a**	PhCHO	P4-*t*-Bu (1.2)[e]	THF	−78	**9a**	Ph	Ph	78[c]	5/95
6	**7a**	4-$MeOC_6H_4CHO$	P4-*t*-Bu (1.2)	THF	−78	**9b**	Ph	4-$MeOC_6H_4$	67[f]	6/94
7	**7a**	4-$NO_2C_6H_4CHO$	P4-*t*-Bu (1.2)	THF	0	**9c**	Ph	4-$NO_2C_6H_4$	76[c]	70/30
8	**7a**	$C_6H_{11}CHO$	P2-Et (2.2)	THF	rt	**9d**	Ph	C_6H_{11}	75	75/25
9	**7a**	$C_6H_{11}CHO$	P4-*t*-Bu (1.2)	THF	rt	**9d**	Ph	C_6H_{11}	86	50/50
10	**7b**	4-$MeOC_6H_4CHO$	KOH (9)[d]	THF	rt	**9e**	3,5-$(MeO)_2C_6H_3$	4-$MeOC_6H_4$	81	25/75
11	**7b**	4-$MeOC_6H_4CHO$	P4-*t*-Bu (1.2)	THF[g]	−78	**9e**	3,5-$(MeO)_2C_6H_3$	4-$MeOC_6H_4$	15[c]	1/99
12	**7b**	4-$MeOC_6H_4CHO$	P4-*t*-Bu (1.2)[e]	THF[g]	−78	**9e**	3,5-$(MeO)_2C_6H_3$	4-$MeOC_6H_4$	74[c]	2/98
13	**7b**		KOH (9)[d]	THF	rt	**9f**	3,5-$(MeO)_2C_6H_3$		81	15/85
14	**7b**		P4-*t*-Bu (1.2)[e]	THF[g]	−78	**9f**	3,5-$(MeO)_2C_6H_3$		73	10/90
15	**7c**	PhCHO	KOH (9)[d]	THF	rt	**9g**	Bu^n	Ph	70	33/67
16	**7c**	PhCHO	P4-*t*-Bu (1.2)	THF	rt	**9g**	Bu^n	Ph	45	25/75
17	**7c**	$C_6H_{11}CHO$	KOH (9)[d]	THF	rt	**9h**	Bu^n	C_6H_{11}	40	25/75
18	**7c**	$C_6H_{11}CHO$	P2-Et (2.2)	THF	rt	**9h**	Bu^n	C_6H_{11}	70	10/90
19	**7c**	$C_6H_{11}CHO$	P4-*t*-Bu (2.2)	THF	rt	**9h**	Bu^n	C_6H_{11}	60	15/85

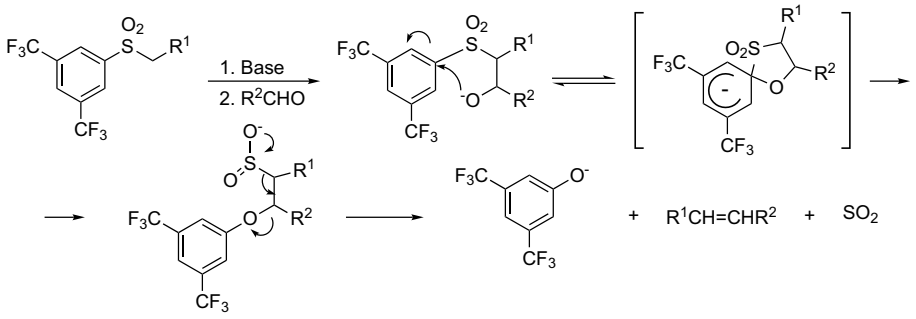
[a] Isolated yield after flash chromatography (hexane).
[b] Determined by GC over the crude reaction mixture.
[c] Isolated yield of (*E*)-isomer.
[d] 0.01 Equiv of TBAB were added to the reaction mixture.
[e] 1.2 Equiv of HMPA were added to the reaction mixture.
[f] Isolated yield of (*Z*)-isomer.
[g] The reaction was stirred for 48 h.

the scope of the reaction. The presence of this additive (1.2 equiv) in the reaction medium when using P4-*t*-Bu (1.2 equiv) as base involved a notable increase in the reaction yield, still with a high (*E*)-selectivity (Table 2, entry 5). The olefination reaction was also successful when coupling the sulfone **7a**, in the presence of the system P4-*t*-Bu/THF, with *para*-substituted electron-rich and electron-deficient benzaldehydes (Table 2, entries 6 and 7). It is noteworthy that the olefination reaction with *p*-nitrobenzaldehyde afforded the corresponding alkene **9c** with an opposite sense of stereoselectivity ($Z/E = 70/30$). This behavior can be attributed to a diastereomeric equilibration between the *syn* and *anti*-β-alkoxysulfone intermediates via a retroaddition/addition process. The lower energy barrier to Smiles rearrangement for the *syn* isomer[19] could then explain the aforementioned (*Z*)-selectivity observed when an electron-poor aldehyde is used in the one-pot Julia olefination reaction. This result is also consistent with the stereochemical trend observed by Julia in the reaction of BT sulfones with different substituted benzaldehydes, which led him to postulate a plausible mechanism for the reaction involving zwitterionic species.[9b]

With respect to aliphatic aldehydes, the BTFP-sulfone **7a** condensed with cyclohexanecarbaldehyde in the presence of the phosphazene bases at rt (Table 2, entries 8 and 9), to give alkene **9d** with no or moderate (*Z*)-stereoselectivity. In this particular case, P2-Et gave the best result (75% yield, $Z/E = 75/25$).

With the aim of studying the applicability of BTFP-sulfones to the synthesis of resveratrol,[20] the benzylic sulfone **7b** was tested in the modified Julia olefination (Table 2, entries 10–12). After an extensive study of different bases, solvents, and temperatures, the reaction between sulfone **7b** and *p*-methoxybenzaldehyde with KOH in the presence of TBAB yielded the corresponding trimethoxyresveratrol **9e** in an 81% yield with a moderate (*E*)-selectivity[21] ($Z/E = 25/75$). In this case, P4-*t*-Bu in THF, gave a very poor 15% yield in the reaction, although with an excellent selectivity. However, when this reaction was carried out in the presence of HMPA, trimethoxyresveratrol **9e** was obtained with an excellent yield and selectivity (Table 2, entry 12). This strong positive effect of HMPA on the reaction[22] is probably due to interactions between the additive and the P4-*t*-Bu-derived carbanion, which could modify its structure and hence, the reactivity of the system.[23] This is, to the best of our knowledge, the first stereoselective synthesis of resveratrol through a Julia–Kocienski olefination protocol. Sulfone **7b** also showed good reactivity with other aromatic aldehydes such as thiophenecarbaldehyde, again when the reaction was carried out in THF at −78 °C in the presence of P4-*t*-Bu as base and HMPA as additive (Table 2, entry 14).[24]

Finally, we also studied the reactivity of alkyl BTFP-sulfone **7c** towards benzaldehyde and cylohexanecarbaldehyde (Table 2, entries 15–19). The study was carried out employing KOH, P2-Et, and P4-*t*-Bu as bases, due



Scheme 3.

to the low stability of this sulfone towards KHMDS (see Table 1). The (*E*)-selectivity of the olefination reaction with sulfone **7c** was in general lower than observed for benzylic sulfones **7a** and **7b**, and the best result was observed when the coupling with cyclohexanecarbaldehyde was carried out at rt in the presence of 2.2 equiv of P2-Et (Table 2, entry 18).

With respect to the reaction mechanism, we have observed, after completion of the reaction, the formation of 3,5-bis(trifluoromethyl)phenol as a side product, which supports the postulated pathway for the modified Julia olefination (Scheme 3): addition of the sulfonyl carbanion to the aldehyde, Smiles rearrangement, and spontaneous sulfur dioxide and 3,5-bis(trifluoromethyl)phenolate eliminations.[9c]

In conclusion, the 3,5-bis(trifluoromethyl)phenyl sulfonyl (BTFP-sulfonyl) group, is a very stable and excellent activator for the synthesis of olefins through the Julia–Kocienski olefination reaction using P4-*t*-Bu as base. The reaction works with aromatic and aliphatic aldehydes, to give, especially in the case of the synthesis of stilbenes, good yields and (*E*)-selectivities. Additionally, the high stability of the BTFP-sulfone anions allows the deprotonation step to take place prior to the addition of the aldehyde, which is a very important aspect in the case of base-sensitive substrates. This one-pot protocol has been used in a high yield and stereoselective synthesis of stilbenes such as the biologically active resveratrol. Additional applications of BTPF-sulfones in olefination reactions are currently under investigation.

Typical experimental procedure: To a stirred solution, under nitrogen (except for the reaction with KOH), of the corresponding sulfone **7** (0.1 mmol) in 2 mL of the corresponding anhydrous solvent was added dropwise the base (see Table 2). The mixture was then stirred for 30 min before addition of the corresponding aldehyde (1.2 mmol). After stirring for 18–48 h, the reaction mixture was quenched with a saturated solution of NH_4Cl (5 mL), extracted with EtOAc (10 mL), and the organic phase was washed first with a saturated solution of $NaHCO_3$ (15 mL) and then with a saturated solution of NaCl (15 mL). The organic phase was then dried (Na_2SO_4), filtered and the solvent evaporated to afford the corresponding crude olefin, which was purified by flash chromatography (hexane) to afford pure compounds **9**.

Acknowledgements

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