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## $\pi$ -Deficient $\alpha$ -arylsulfonyl esters as soft nucleophiles in organic synthesis

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**Abstract**—Different  $\pi$ -deficient arylsulfonyl groups have been studied as candidates for the stabilization of  $\alpha$ -sulfonyl esters. The 3,5-bis(trifluoromethyl)phenylsulfonyl group has been shown to be the best substituent for the stereoselective synthesis of *E*-aconitates by a dialkylation–dehydrosulfinylation integrated process under PTC conditions using K<sub>2</sub>CO<sub>3</sub> as base. © 2001 Elsevier Science Ltd. All rights reserved.

The use of sulfones in organic synthesis has become a classic strategy in the preparation of complex molecules.<sup>1</sup> The sulfonyl group can be easily introduced in an intermediate molecule for the construction of carbon-carbon bonds, mainly as a carbanion-stabilizing group.<sup>2</sup> The desulfonylation is the last step to achieve the target compound, generally by a reductive process or via a base-promoted  $\beta$ -elimination.<sup>3</sup> The presence of electronwithdrawing substituents at the arylsulfonyl moiety should facilitate the deprotonation at the  $\alpha$ -position and the subsequent desulfonylation step. Some representative examples are the *p*-nitro, *p*-bromo and *p*-methylsulfonyl substituted (phenylsulfonyl)ethoxycarbonyl groups (Nsc, Bsc and Mpc) 1, which are base-labile amino-protective groups<sup>4</sup> for peptide synthesis as an alternative to the most popular 9-fluorenylmethoxycarbonyl (Fmoc).<sup>5</sup> More recently, the (2,4-dinitrophenylsulfonyl)ethoxycarbonyl group has also been described.<sup>6</sup> p-Fluorophenyl and 2-naphthyl sulfones increase the rate and the yield of the desulfonvlation reaction by sodium amalgam.<sup>7</sup> In addition, the radical-mediated cleavage of  $\alpha$ -fluoro- $\alpha$ -(arylsulfonyl)esters by means of tributyltin hydride takes place faster with  $\alpha$ -pyrimidin-2-yl sulfones 2.<sup>8</sup>  $\beta$ -Acetalic carbanions substituted with an electron-withdrawing group can be mainly dialkylated in the case of the (nitrophenyl)sulfonyl systems 3.9 In the total synthesis of Rhizoxin D, a natural macrolactone with potent antitumor and antifungal activity, the 3,4-(dichlorophenyl)sulfonyl group has been introduced to improve the yield in the alkylation of the LDA-generated carbanion derived from compound 4 and for the dehydrosulfinylation step (DBU, 105°C) in comparison with the phenylsulfonyl moiety.<sup>10</sup> Triflones can be used alternatively as electron-deficient sulfones for the stabilization of carbanions, as olefins in Michael additions and in cycloaddition reactions.<sup>11</sup> However, they have to be prepared from non-commercially available sodium triflinate<sup>12</sup> and have a great tendency to decompose by sulfur dioxide extrusion.<sup>3</sup> In this paper we report our studies on the double effect of different  $\pi$ -deficient arylsulfones on the stabilization of carbanions derived from  $\alpha$ -sulfonyl acetates and to assist the desulfonvlation by a successive β-elimination reaction in an integrated process.13



**3** (EWG =  $CO_2Me$ ,  $SO_2Ph$ ,  $SO_2-C_6H_4-p-NO_2$ ,  $SO_2-C_6H_4-p-NO_2$ )



Keywords: sulfones; PTC; aconitate; dialkylation.

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The  $\pi$ -deficient  $\alpha$ -(arylsulfonyl)acetates 5 were prepared by reaction of arylthiolates with alkyl  $\alpha$ -bromoacetates by using NaH or TEA as base in acetonitrile at rt, followed by oxidation with oxone<sup>®</sup> in methanol/water or with MCPBA in dichloromethane at room temperature (Scheme 1 and Table 1). The alkylation reaction was studied treating the different  $\alpha$ -arylsulfonyl esters 5 with benzyl bromide by using  $K_2CO_3$  as base and tetra-n-butylammonium bromide (TBAB) as phasetransfer catalyst in acetonitrile for 1 day at room temperature. (Scheme 1, Table 1). In all cases studied, the dialkylation process took place easily to afford quaternary compounds 6 in moderate yields except for 2-pyridine-1-oxide derivative 6ca, which decomposed. In the case of the pentafluorophenyl sulfone 6ha, secondary products resulting from aromatic nucleophilic substitution were also formed. When the dialkylation reaction was carried out with ethyl  $\alpha$ -bromoacetate as electrophile under the same PTC conditions as described above, only  $\alpha$ -sulfonyl esters **5a,d,e,f**, gave cleanly the dialkylation-elimination process to provide stereoselectively (*E*)-aconitate 7a (R = Bn) (Scheme 2, Table 2).<sup>14</sup> The 3,5-bis(trifluoromethyl)phenylsulfonyl group showed a strong electron-withdrawing effect and sulfone **5f** gave aconitate **7a** after 3 days reaction at rt with the higher yield. In order to accelerate this integrated process, the reaction was carried out with the isopropyl  $\alpha$ -(arylsulfonyl)acetate **5g** to avoid hydrolysis of the ester moiety. Aconitate **7b** was obtained in 71% yield after 3 days at rt and 60% when the reaction was warmed up to 60°C in 1 day reaction time (Table 2).

The dialkylation reaction was studied with the 3,5bis(trifluoromethyl)phenyl sulfonyl ester **5f** under PTC conditions with different alkyl halides and 1,4-dihalides to furnish products **6f** in good yields after 1 day at rt. Cyclopentenyl derivative **6ff** with a phenylsulfonyl group has been used as starting material for the generation of 3-(ethoxycarbonyl)cyclopentadienone, a very reactive dienophile.<sup>16</sup> In the case of ethyl acrylate, Michael diaddition took place by using substoichiometric amounts of DBU (0.2 equiv.) at 60°C in acetonitrile over 1 day (Scheme 3, Table 3).



Scheme 1.

**Table 1.** Synthesis and dibenzylation of  $\alpha$ -(arylsulfonyl)acetates

R	Ar	Base	Oxidant (time)	Product 5 <sup>a</sup>			Product 6 <sup>a</sup>		
				No.	Yield (%) <sup>b</sup>	$R_{\rm f}^{\ \rm c}$	No.	Yield (%) <sup>b</sup>	$R_{ m f}^{\  m c}$
Bn	$4-NO_2-C_6H_4$	NaH	Oxone (1 day)	5a	47	0.28	6aa	66	0.39
Bn	2-Pyridyl	TEA	MCPBA (3 h)	5b	56	0.33	6ba	64	0.26
Bn		TEA	Oxone (1 day)	5c	30	0.20	бса	Dec.	_
Bn	2-Pyrimidyl	TEA	MCPBA (1 day)	5d	62	0.24	6da	58	0.28
Bn	$3-CF_3-C_6H_4$	NaH	Oxone (1 day)	5e	83	0.38	6ea	30	0.33
Bn	$3,5-(CF_3)_2-C_6H_3$	NaH	Oxone (1 day)	<b>5</b> f	75	0.58	6fa	58	0.60
$\mathbf{Pr}^{i}$	$3,5-(CF_3)_2-C_6H_3$	NaH	Oxone (1 day)	5g	92	0.54	6ga	71	0.57
Bn	$C_6F_5$	NaH	Oxone (1 day)	5h	68	0.58	6ha	28	0.74

<sup>a</sup> All products gaved satisfactory IR, <sup>1</sup>H, <sup>13</sup>C NMR spectral data and elemental analysis.

<sup>b</sup> Isolated yield after flash chromatography.

<sup>c</sup> Hexane/AcOEt: 2/1.



Table	2.	Synthesis	of	aconitates	7
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Starting ester	R	Ar	<i>T</i> (°C)	Time (days)	No.	Yield (%) <sup>a</sup>	$R_{ m f}^{ m b}$
5a	Bn	$4-NO_2-C_6H_4$	Rt	3	7a	20	0.60
5d	Bn	2-Pyrimidyl	Rt	7	7a	30	0.59
5e	Bn	$3-CF_3-C_6H_4$	Rt	4	7a	50	0.60
5f	Bn	$3,5-(CF_3)_2-C_6H_3$	Rt	3	7a	64	0.60
5g	$\mathbf{Pr}^{i}$	$3,5-(CF_3)_2-C_6H_3$	Rt	3	7b	71	0.57
5g	$\mathbf{Pr}^{i}$	$3,5-(CF_3)_2-C_6H_3$	60	1	7b	60	0.57

<sup>a</sup> Based on  $\alpha$ -arylsulfonyl ester 5, after flash chromatography.

<sup>b</sup> Hexane/AcOEt: 2:1.



## Scheme 3.

## Table 3. Dialkylation of sulfonyl ester 5f

Electrophile	Base	Product					
		No.	R	Yield (%) <sup>a</sup>	$R_{ m f}^{ m b}$		
PhCH <sub>2</sub> Br	PTC	6fa	PhCH <sub>2</sub>	58	0.31		
MeI	PTC	6fb	Me	89	0.33		
CH <sub>2</sub> =CHCH <sub>2</sub> Br	PTC	6fc	CH <sub>2</sub> =CHCH <sub>2</sub>	74	0.33		
HC≡CCH <sub>2</sub> Br	PTC	6fd	$HC \equiv CCH_2$	67	0.38		
I(CH <sub>2</sub> ) <sub>4</sub> I	PTC	6fe	(CH <sub>2</sub> ) <sub>4</sub>	73	0.29		
(Z)-BrCH <sub>2</sub> CH=CHCH <sub>2</sub> Br	PTC	6ff	(Z)-CH <sub>2</sub> CH=CHCH <sub>2</sub>	92	0.38		
Br Br	РТС	6fg	Jose Andrewski and	57	0.35		
CH <sub>2</sub> =CHCO <sub>2</sub> Et	DBU	6fh	CH <sub>2</sub> CH <sub>2</sub> CO <sub>2</sub> Et	54	0.31		

<sup>a</sup> Based on sulfone 5f after flash chromatography.

<sup>b</sup> Hexane/AcOEt: 3/1.

Finally, the reduction of dibenzylated ester **6ga** was carried out with Zn in the presence of ammonium chloride under refluxing THF for 1 day, to give ester **8** in 70% yield (Scheme 4).<sup>17</sup>

In conclusion, the 3,5-bis(trifluorophenyl)sulfonyl group is an excellent substituent for the deprotonation of  $\alpha$ -arylsulfonyl esters which allows the quaternization of the corresponding enolates as well as the dehydro-



sulfinylation process under very mild reaction conditions.<sup>18</sup>

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