C-Sulfinylation of Grignard Reagents and Enamines with Sulfinic Acid

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Synopsis. Direct *C*-sulfinylation of Grignard reagents with sulfinic acid (**4**) in the presence of activating reagents, such as phenyl phosphorodichloridate (**1**), diphenyl phosphorochloridate (**2**), and 3-phthalimidooxy-1,2-benzisothiazole 1,1-dioxide, were investigated. β-Keto sulfoxides were also formed by the reaction of enamines with **4** using **1** and **2** under similar conditions.

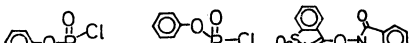
We have recently developed a series of new one-pot *O*- and *N*-sulfinylations with sulfinic acid in the presence of an activating reagent,[1] and more recently found that some reagents were sufficiently effective for *S*-sulfinylation of thiols, giving thiosulfinates in comparatively good yields.[2]

We newly tried to extend these methods to *C*-sulfinylations of Grignard reagents and enamines. The employed activating reagents are as follows: Phenyl phosphorodichloridate (**1**), diphenyl phosphorochloridate (**2**), and 3-phthalimidooxy-1,2-benzisothiazole 1,1-dioxide (**3**). The methods differ from each other only in the reagents employed for activation of sulfinic acid. In one case, **1** or **2** and pyridine (or triethylamine) are used, and in the other, **3** and 1,8-diazabicyclo-[5,4,0]undec-7-ene (DBU).

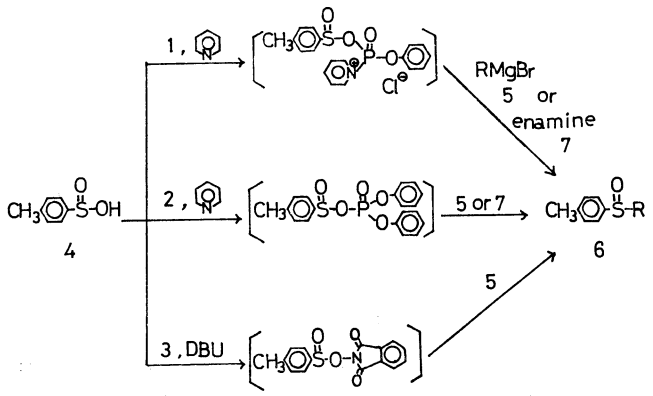
The reagent **1** has been reported to be sufficiently effective as an activating reagent for transformation of carboxylic acids to the esters[3] under virtually neutral and mild conditions. In the present study, p-toluenesulfinic acid (**4**) was treated with an equivalent of **1** and an excess pyridine in THF at −15—0 °C; when this mixture was then allowed to react with Grignard reagents (**5**) at room temperature, the corresponding sulfoxides (**6**) were obtained in low yields.

A comparable activating effect was observed by using **2**, which possesses a similar structural moiety; this gave somewhat lower yields of **6**. The reaction probably proceeds *via* a mixed anhydride intermediate, as well as by *O*-sulfinylation.[2]

Better results for sulfinylation of **5** were obtained by using **3** and DBU in some cases. The reaction was achieved by adding a solution of two equivalents of **5** in ether to a mixture of equivalents of **4**, **3**, and DBU in THF below −5 °C under a nitrogen stream and by stirring the reaction mixture at room temperature. Purification was carried out by silica gel column chromatography. The yields of sulfoxides obtained by these methods are shown in Table 1.



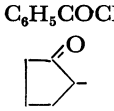
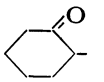
1 2 3



Scheme 1.

We also tried to extend these methods to sulfinylation of enamines (**7**). An example of β-sulfinylation of **7** has not been reported in the literature. The reaction was carried out by treating **7** with an equivalent of **4** in dichloromethane in the presence of equivalent of **1** and an excess of triethylamine to afford the corresponding β-keto sulfoxides (**6**, R=α-keto alkyl) in 10—43% yields, along with small amounts of several

Table 1. Yields of sulfoxides and β-keto sulfoxides $CH_3C_6H_4$-S(=O)-R

R	Yield/%			Mp θ_m/°C	IR $\tilde{\nu}_{max}$/cm^{-1}		Calcd (Found) (%)	
	Method A	Method B	Method C		S=O	C=O	C	H
C_2H_5	40	26	18	Oil	1045			
i-C_3H_7	25	16	19	Oil	1045			
C_6H_5	31	14	53	64—15	1050			
$C_6H_5CH_2$	35	15	37	141—142	1038			
$C_6H_5COCH_2$	10	34		75—78	1048	1680	69.77(69.77)	5.43(5.39)
$C_6H_5COCHCH_3$	12	36		98—99	1045	1660	70.56(70.22)	5.92(5.90)
	11	41		92—93	1040	1738	64.84(64.72)	6.35(6.38)
	43	50		99—101	1042	1710	66.10(66.05)	6.78(6.84)

by-products such as disulfide and thiosulfonate.

Better results were obtained by using **2** instead of **1** to give **6** (R=α-keto alkyl) in 34—50% yields. In this case, a small amount of diphenyl *N,N*-pentamethylenephosphoramidate was isolated as the by-product, no formation of disulfide and thiosulfonate being observed. In both cases, purification was carried out by column chromatography on silica gel. The results are summarized in Table 1. Unfortunately, **3** was inaffective as the activating reagent.

β-Keto sulfoxides are known to be useful starting materials and versatile synthetic intermediates in organic synthesis.[4] These vicinally difunctionalized compounds have previously been prepared by oxidation of α-substituted thioketone,[5] acylation of sulfinyl stabilized carbanions with esters,[6] or sulfinylation of ketone enolate anions with sulfinates.[7] An especially notable feature of our methods is the application of mild and nearly neutral conditions throughout the reactions; therefore the acid or base sensitive functional groups will be expected to remain unaffected.

Experimental

All the melting points are uncorrected. IR and NMR spectra were measured on a JASCO IRA-1 grating infrared spectrometer and JEOL high resolution NMR instrument C-60 at 60 MHz, respectively. Mass spectra were determined at 75 eV on a JEOL-01SG mass spectrometer.

*Preparation of Sulfoxides (**6**).* *Method A*: A solution of **1** (2.11 g, 10 mmol) in anhyd THF (5 ml) was added dropwise with stirring into a solution of **4** (1.56 g, 10 mmol) and pyridine (2.37 g, 30 mmol) in anhyd THF (30 ml) at −15 °C under a nitrogen atmosphere; then the mixture was stirred for 1 h. A Grignard reagent (**5**) (20 mmol) prepared in the usual way in ether was added slowly to the mixture below −5 °C under a nitrogen atmosphere. The mixture was stirred for 3 h from 0 °C up to room temperature. After the solvents were evaporated under reduced pressure, the residue was dissolved in $CHCl_3$ (60 ml), and the solution was washed with 1 M HCl (1 M=1 mol dm^{-3}), 5% aq $NaHCO_3$, and finally with H_2O, dried over anhyd Na_2SO_4 and evaporated. The residue was chromatographed on silica gel by using benzene–ethyl acetate (4:1) as an eluent to give **6** and by-products, di-*p*-tolyl disulfide and *S*-*p*-tolyl *p*-toluenethiosulfonate.

Method B: A solution of pyridine (0.9 g, 12 mmol) in anhyd THF (5 ml) was added dropwise with stirring into a solution of **4** (1.56 g, 10 mmol) and **2** (2.7 g, 10 mmol) in anhyd THF (30 ml) at −10 °C under a nitrogen atmosphere, and the mixture was stirred for 1 h. A solution of **5** (20 mmol) prepared in the usual way in ether was added slowly to the mixture below −5 °C. After stirring for 3 h, the mixture was quenched with H_2O and extracted with ether (50 ml×3), and the extracts were worked up and chromatographed as in Method A to give **6**, along with di-*p*-tolyl disulfide and *S*-*p*-tolyl *p*-toluenethiosulfonate.

Method C: To a solution of **4** (0.78 g, 5 mmol) and **3** (1.64 g, 5 mmol) in anhyd THF (30 ml) was added dropwise with stirring a solution of DBU (0.76 g, 5 mmol) in anhyd THF (5 ml) at room temperature under a nitrogen atmosphere. Grignard reagent **5** (15 mmol) prepared in the usual way in ether was added slowly to the mixture below −5 °C under a nitrogen stream. After stirring at −15 °C for 30 min, the mixture was stirred at room temperature for 1.5 h and evaporated. The residue was dissolved in $CHCl_3$ (60 ml), and the solution was treated and chromatographed as in Method A to give **6** along with di-*p*-tolyl disulfide and *S*-*p*-tolyl *p*-toluenethiosulfonate as by-products.

*Preparation of β-Keto Sulfoxides (**6**, R=α-Keto Alkyl).* *Method A*: A solution of triethylamine (1.1 g, 11 mmol) in anhyd CH_2Cl_2 (10 ml) was added dropwise with stirring into a solution of **4** (1.56 g, 10 mmol) and **1** (2.3 g, 11 mmol) in anhyd CH_2Cl_2 (30 ml) at −10 °C under a nitrogen atmosphere, and the mixture was stirred for 1 h below −10 °C. A solution of **7** (12 mmol) and triethylamine (2.2 g, 22 mmol) in anhyd CH_2Cl_2 (10 ml) was added gradually to the mixture. After stirring for 3 h, the mixture was washed with 0.1 M HCl, 1% aq $NaHCO_3$, and H_2O, dried over anhyd Na_2SO_4, and evaporated. The residue was purified by silica gel column chromatography using benzene–ethyl acetate (4:1 100 ml, 2:1 50 ml, 1:1 150 ml) to give β-keto sulfoxide along with di-*p*-tolyl disulfide and *S*-*p*-tolyl *p*-toluenethiosulfonate as by-products.

Method B: A solution of triethylamine (1.2 g, 12 mmol) in anhyd CH_2Cl_2 (10 ml) was added dropwise with stirring into a solution of **4** (1.56 g, 10 mmol) and **2** (2.7 g, 10 mmol) in anhyd CH_2Cl_2 (40 ml) at −10 °C under a nitrogen atmosphere. After the mixture was stirred for 1 h, a solution of **7** (12 mmol) and triethylamine (1.2 g, 12 mmol) in anhyd CH_2Cl_2 (15 ml) was gradually added. The mixture was stirred for 2 h at room temperature, and washed with 0.1 M HCl, 1% aq $NaHCO_3$, and with H_2O, dried over anhyd Na_2SO_4, and evaporated. The residue was purified by silica-gel column chromatography using benzene–ethyl acetate (4:1 100 ml, 2:1 50 ml, 1:1 100 ml) to give β-keto sulfoxide along with diphenyl *N,N*-pentamethylenephosphoramidate.

*Preparation of 3-Phthalimidooxy-1,2-benzisothiazole 1,1-Dioxide (**3**).* A solution of triethylamine (3.8 g, 28 mmol) in acetonitrile (10 ml) was added dropwise into a suspension of 3-chloro-1,2-benzisothiazole 1,1-dioxide (5.6 g, 28 mmol) and *N*-hydroxyphthalimide (4.8 g, 30 mmol) in acetonitrile (60 ml) with stirring at 0—5 °C, and the mixture was stirred overnight. After removal of the precipitates, the filtrate was concentrated. The residue was recrystallized from $CHCl_3$–CH_2Cl_2. Yield 66%. Mp 238—241 °C. Found: C, 54.85; H, 2.25; N, 8.53%. Calcd for $C_{15}H_8N_2O_5S$: C, 54.87; H, 2.45; N, 8.53%. IR (KBr): 1760, 1625, 1570, 1470, 1350, 1190, and 800 cm^{-1}. MS *m/e*: 328 (M^+), 166, 162, 104, 76.

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