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Sulfonyl transfer mechanism in C–S coupling of phenylmagnesium bromide with phenyl arenesulfonates

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ABSTRACT

The kinetics of C–S coupling of phenylmagnesium bromide with phenyl arenesulfonates has been studied in THF:toluene (7:10) at 90 °C. Kinetic data and Hammett relationship are consistent with an asynchronous S_Na mechanism in which rate determining thiophilic attack of carbanion takes place much ahead of phenoxy group departure.

1. Introduction

Sulfones are useful intermediates in organic synthesis [1,2] and also in medicine as drugs [3,4]. They can be synthesized by a variety of methods [5,6]. However, the use of organometallic methods are quite limited and a few papers have been published on sulfonylation of carbanions with sulfonyl chlorides [7–9] and sulfonates [10–12]. Sulfonates are useful partners in C–C coupling reactions [13] of organolithium [8], -copper [14–16] and -zinc reagents [17–19] (Scheme 1, pathway a). Grignard reagents can react either by C–O bond cleavage [7,20–22] or C–S bond cleavage [23–25] (Scheme 1, pathway a and pathway b, respectively) to give C–C coupling products. Organolithiums [10] and Grignard reagents [11,12] are also known to react with arenesulfonates to give C–S coupling leading to the formation of sulfones by S–O bond cleavage (Scheme 1, pathway c).

Although synthetic and mechanistic aspects of C–C coupling of sulfonates are well known, C–S coupling of sulfonates have not been investigated in detail. In our long term investigation on the C-heteroatom coupling of organometallic reagents, we already found that aryl Grignard reagents **1** attack phenyl tosylate **2a** to give only sulfones **3**, i.e. S–O bond cleavage takes place (Scheme 2) [26,27].

There are various mechanistic possibilities for S–O bond cleavage in aryl arenesulfonates and there has been considerable interest in the kinetics and mechanism of the sulfonyl transfer reactions of oxygen, sulfur and nitrogen anionic nucleophiles [28–33]. However, no work has been published on the mechanism of the reactions of organolithiums and Grignard reagents with sulfonates at sulfur center.

In order to gain some insight into the mechanism of thiophilic attack of carbon nucleophiles at S on the sulfonates, we have undertaken a detailed kinetic and mechanistic study [34]. We proposed a mechanism for C–S coupling of aryl Grignard reagents with aryl arenesulfonates, which is consistent with kinetic data, activation parameters and Hammett relationship for the substituent effects of aryl nucleophile. In order to provide another support for the mechanism, herein we wish to report the results of a Hammett study for the substituent effects of the electrophile, i.e. arenesulfonyl groups in the aryl arenesulfonates.

2. Results and discussion

We have already discussed the kinetics of phenylmagnesium bromide **1a** with phenyl tosylate **2a** in THF:toluene (7:10) at 60 °C [34]. The reaction obeys clean second order kinetics:

$$-\frac{d[PhOTos]}{dt} = k\,[PhMgBr]\,[PhOTos] \quad (1)$$

The first order kinetics in aryl Grignard reagent and in phenyl tosylate seems consistent with thiophilic attack of aryl carbonions at sulfonate sulfur to give C–S coupling products.

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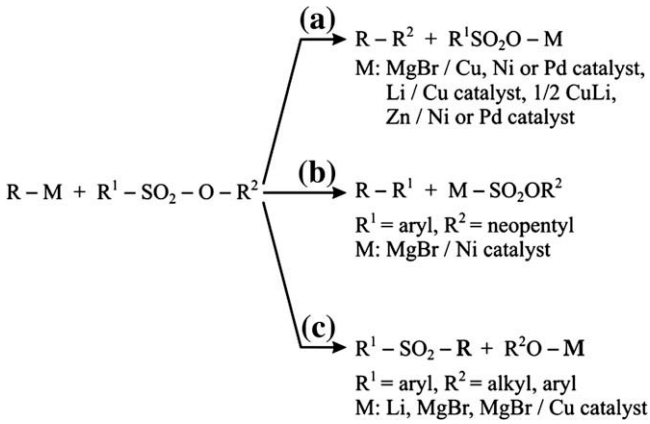
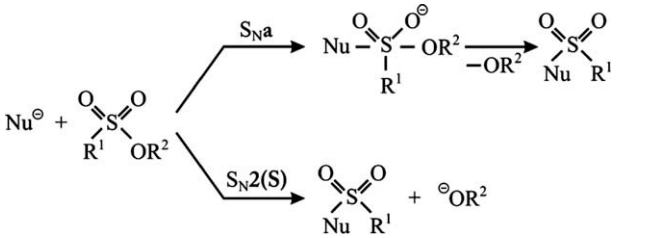


Scheme 1. Sulfonates as C–C and C–S coupling partners in reactions with organometallic reagents.

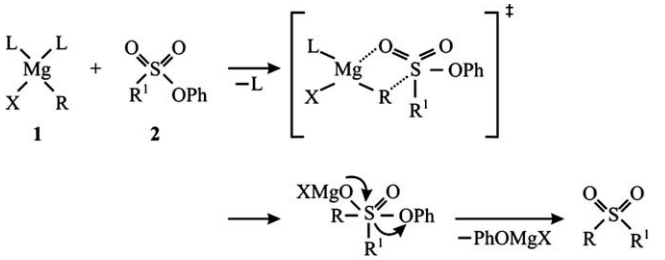
Reactions of nucleophiles with aryl arenesulfonates at S atom are known to take place generally by stepwise S_Na mechanism or concerted $S_N2(S)$ mechanism (Scheme 3) [28–33]. S_Na mechanism involves a pentacoordinate intermediate [29,33] and $S_N2(S)$ mechanism proceeds via a transition state in which bond formation and bond breaking occur synchronously.

In order to propose a mechanism for the C–S coupling of Grignard reagents with aryl arenesulfonates, we applied Hammett methodology for the substituent effects of the nucleophile, i.e. aryl Grignard reagents X–C_6H_4MgBr in the sulfonation with phenyl tosylate **2b** and also calculated activation parameters for the sulfonation of phenylmagnesium bromide [34]. Kinetic data, solvent effect, Hammett relationship and activation parameters suggest that the C–S bond formation at the transition state is significantly advanced than S–O bond cleavage or at least the reaction process involves thiophilic attack of carbanion on the sulfonate. However, this results did not seem to help us to make a clear distinction between a concerted $S_N2(S)$ mechanism and S_Na mechanism in which addition is the rate determining step. Nevertheless, it seemed us conceivable to propose a nucleophilic addition mechanism involving a rate determining attack of solvated Grignard reagent to sulfonyl group followed by a fast phenoxide group leaving (Scheme 4). The coordination of ester with Mg occurs by replacement of donor THF coordinated to Grignard reagent and replacement of THF with toluene results in a more favorable complex formation leading to observed reactivity of Grignard reagent in S–O bond cleavage.

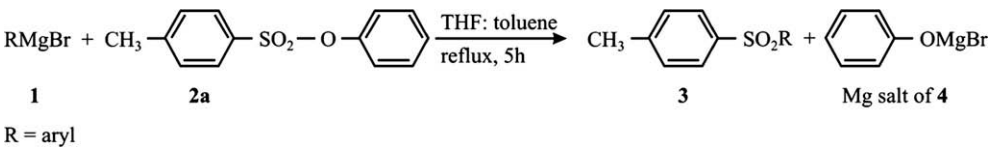
In order to find another support for the proposed mechanism, we tried Hammett treatment of substituent effects on the arenesulfonyl groups of the sulfonate esters. We expect that the reactivity of arenesulfonates **2** changes depending on the substituents on the arenesulfonyl group, R^1 and the transition state of the reaction will be more stabilized by the presence of electron withdrawing substituents. In this work, we found the rate constants of the reactions of phenylmagnesium bromide **1a** with phenyl substituted benzenesulfonates Y–$C_6H_4SO_2OPh$ **2** in the THF:toluene (7:10) at 90 °C and calculated the reaction constant ρ of Hammett ρ–σ correlation. However, before evaluating the Hammett relationship, we first carried out kinetic studies to check that the kinetics of the reaction between **1a** and Y–$C_6H_4SO_2OPh$ **2a,c–e** (Y = H **a**, 3-Me **c**, 4-t-Bu **d**, 4-MeO **e**) obey the second order as the reaction between **1a** and phenyl tosylate **2b** (Y = 4-Me **b**) [34]. For this purpose, we carried out reactions under pseudo-first order conditions by using variable concentration of phenylmagnesium bromide **1a** in excess and varied to find the reaction order in phenyl arenesulfonates **2a,c–e** and phenylmagnesium bromide **1a**. As we already found that the use of directly measured $[PhOTos]_t$ values, i.e. the concentration of phenyl tosylate **2b** at time t give minimum error in the evaluation of rate data, we followed the kinetics by measuring the concentration of remaining arenesulfonates **2a,c–e**. By keeping the initial concentration of arenesulfonate **2** constant and changing the concentration of phenylmagnesium bromide **1a** between 5 and 15 times than that of **2a,c–e**, we obtained pseudo-first order plots which are linear up to 60–80% completion of the reaction. Pseudo-first order plot for the sulfonation of phenylmagnesium bromide **1a** with phenyl 3-toluenesulfonate **2c** is given in Fig. 1. Pseudo-first order rate constants k_1 were calculated by linear regression analysis ($r \geqslant 0.99$). The linearity of k_1 values with excess concentration of phenylmagnesium bromide **1a** for the sulfonation with phenyl 4-methoxybenzenesulfonate **2e** is illustrated in Fig. 2. Plots of log k_1 versus log[PhMgBr] for sulfonation with **2a,c–e** yielded a slope between 0.94 and 1.19 ($r \geqslant 0.97$) confirming the first order reaction in phenylmagnesium bromide **1a**. We calculated the second order rate constants k as $k = k_1/[C_6H_5MgBr]$



Scheme 3. Reactions of nucleophiles with aryl arenesulfonates by S–O bond cleavage. S_Na: Addition-elimination reaction, $S_N2(S)$: Concerted mechanism.



Scheme 4. Proposed mechanism for C–S coupling of aryl Grignard reagents with aryl arenesulfonates.



Scheme 2. Reaction of aryl Grignard reagents with phenyl tosylate to give sulfones.

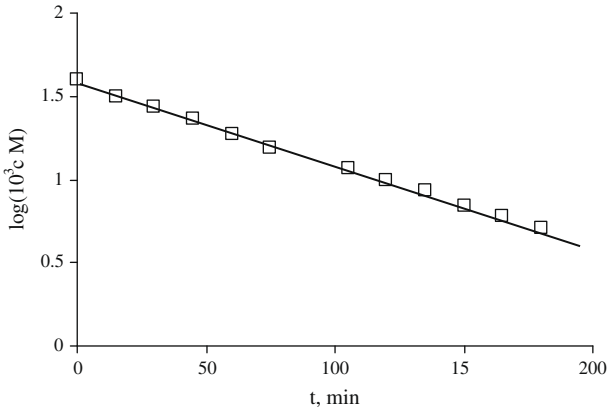


Fig. 1. Typical first order plots for the reaction of phenylmagnesium bromide **1** with phenyl 3-toluenesulfonate **2c** in THF:toluene (7:10) at 90 °C, $c = [3\text{-}MeC_6H_4SO_2OPh]_t$ $[PhMgBr]_0 = 0.040$ M, $[3\text{-}MeC_6H_4SO_2OPh]_0 = 0.520$ M.

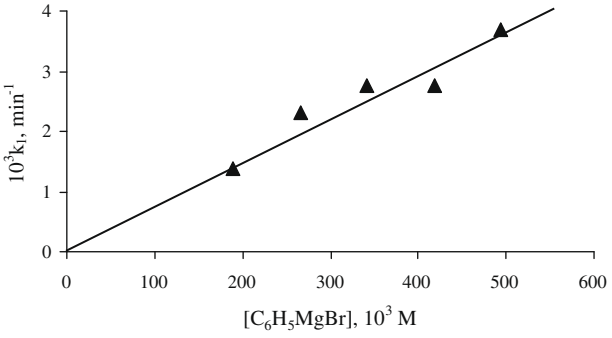
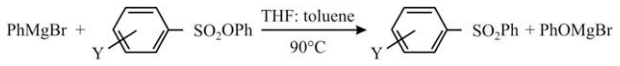


Fig. 2. Effect of phenylmagnesium bromide **1a** concentration on the pseudo-first order rate constants in the reaction of phenylmagnesium bromide **1a** with phenyl 4-methoxybenzenesulfonate **2e** in toluene.

Table 1
Rate constants for the sulfonation of phenylmagnesium bromide **1** with phenyl esters of substituted benzenesulfonates **2a–e** in THF:toluene (7:10) at 90 °C



1a **2a-e** **3a-e**

Compound	Y	σ[a]	10^3 k, M^{-1} min^{-1}[b]
2d	4-$(CH_3)_3C$	−0.15	10.8
2b	4-CH_3	−0.14	13.0[c]
2e	4-CH_3O	−0.12	7.9
2c	3-CH_3	−0.06	21.3
2a	H	0.00	22.3

[a] Substituent constants are taken from Ref. [35].
[b] Second order rate constants were calculated under pseudo-first order conditions.
[c] Rate constant is taken from Ref. [34].

and taking the average of k values with the uncertainty of 5–10%, which is in the error limit of GC analysis.

The kinetic reactions of phenylmagnesium bromide **1a** with all substituted benzenesulfonates **2a–e** obeyed second order kinetics.

The second order rate constants are given in Table 1 and the plot of the rate constants against Hammett σ constants is shown in Fig. 3. As seen, a reasonably good ρ–σ correlation with a value of $\rho = 2.13$ ($r = 0.954$) was obtained. For the correlation, the point for the 4-CH_3O substituent lying significantly of the linear plot

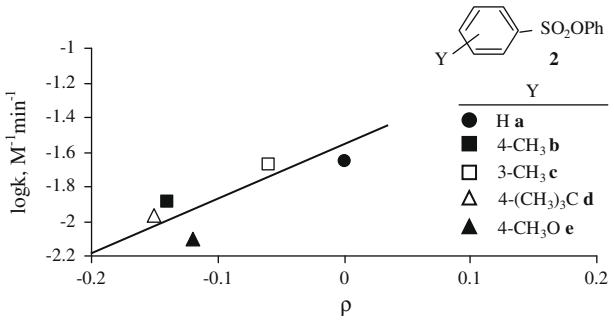


Fig. 3. Variation of rate constants with Hammett substituent constants for the sulfonation of phenylmagnesium bromide **1** with phenyl esters of substituted benzenesulfonates **2a–e** in THF:toluene (7:10) at 90 °C.

was not used. However, a number of deviations have been already reported with 4-CH_3O containing reactants in the Hammett plots for Grignard reactions [36–38]. The high ρ value indicates that the reactivity of the arenesulfonates is significantly increased by the electron withdrawing effect of the substituents, as expected.

As the electron withdrawing substituent on the arenesulfonyl group can decrease the electron density of the reaction center, the attack of the nucleophilic carbanion will be easier and the rate of C–S bond formation will increase resulting in a large positive value for reaction constant ρ. However, we may think that the electron withdrawing substituent on the arenesulfonyl group can also decrease the leaving ability of the phenoxide group. Then, the opposing effect of substituent Y of Y–$C_6H_4SO_2OPh$ **2** on the C–S bond formation and on the S–O bond cleavage might cause a low positive value or even a negative value of reaction constant ρ if the leaving group departure is involved in the rate determining step [39]. In our study, the large positive value of reaction constant ρ indicates the absence of the contribution of leaving group ability in the transition state and excludes a single step concerted mechanism. This result supports that C–S formation between Grignard reagents and aryl arenesulfonates proceeds by a stepwise mechanism in which the rate determining step is the thiophilic attack of carbanion on the arenesulfonate or at least carbanion attack possibly takes place much ahead of phenoxy group departure in the transition state. The present study of substituent effects on the C–S coupling of Grignard reagents with aryl arenesulfonates provides another support for asynchronous S_Na mechanism.

In our continuing work, we will study to provide another support for the mechanism of the sulfonyl transfer reactions of aryl Grignard reagents.

3. Experimental

3.1. General methods

All reactions were carried out under a nitrogen atmosphere in oven-dried glassware reagents and solvents were handled using standard syringe-rubber septum techniques [40]. Quantitative GC analysis were performed on a Thermo-Focus gas chromatograph equipped with a ZB-1 capillary column (immobilized with polydimethylsiloxane) and a flame ionization detector using internal standard techniques.

3.2. Reagents

Magnesium 99.9% pure and purified bromobenzene were used. THF was distilled over sodium benzophenone dianion and toluene was distilled over sodium. Phenylmagnesium bromide **1a** was prepared in THF by standard method and its concentration was found

by titration prior to use [41]. Phenyl arenesulfonates **2a–e** were prepared by the published procedures using arenesulfonyl chlorides and phenol and were confirmed by melting points, IR and ^{1}H NMR spectroscopy [25,33,42–44] as follows:

3.3. $C_6H_5SO_2OC_6H_5$ **2a**

Mp 34–35 °C (lit. [44] mp 34–35 °C); IR (KBr) $\overline{V}$ cm^{-1}: 1618, 1489, 1384 (SO_2), 1170 (SO_2), 619 (S–O); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.82 (2H, d, J = 7.2 Hz), 7.66 (1H, t, J = 7.6 Hz), 7.52 (2H, t, J = 7.6 Hz), 7.23–7.31 (3H, m), 6.97 (2H, d, J = 7.2 Hz).

3.4. 4-$CH_3C_6H_4SO_2OC_6H_5$ **2b**

Mp 50–53 °C (lit. [33] mp 76 °C, lit. [25] 93–94 °C, lit. [44] 96–97 °C); IR (KBr) $\overline{V}$ cm^{-1}: 1597, 1510, 1355 (SO_2), 1182 (SO_2), 810 (S–O); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.70 (2H, d, J = 8.4 Hz), 7.24–7.31 (5H, m), 7.03 (2H, d, J = 7.2 Hz), 2.44 (3H, s).

3.5. 3-$CH_3C_6H_4SO_2OC_6H_5$. **2c**

Oil form, IR (KBr) $\overline{V}$ cm^{-1}: 1618, 1489, 1384 (SO_2), 1170 (SO_2), 619 (S–O); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.65 (1H, s), 7.60 (1H, d, J = 6.8 Hz), 7.43 (1H, d, J = 7.4 Hz), 7.37 (1H, t, J = 7.3 Hz), 7.22–7.29 (3H, m), 6.97 (2H, d, J = 7.2 Hz), 2.37 (3H, s).

3.6. 4-$(CH_3)_3CC_6H_4SO_2OC_6H_5$ **2d**

Mp 50–55 °C, IR (KBr) $\overline{V}$ cm^{-1}: 1618, 1488, 1384 (SO_2), 1170 (SO_2), 619 (S–O); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.76 (2H, d, J = 8.4 Hz), 7.53 (2H, d, J = 8.4 Hz), 7.24–7.31 (3H, m), 7.01 (2H, d, J = 7.2 Hz), 1.34 (9H, s).

3.7. 4-$CH_3OSO_2OC_6H_5$ **2e**

Mp 60–63 °C (lit. [44] 62–63 °C), IR (KBr) $\overline{V}$ cm^{-1}: 1592, 1495, 1369 (SO_2), 1158 (SO_2), 670 (S–O); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.73 (2H, d, J = 8.4 Hz), 7.23–7.31 (3H, m), 6.98 (2H, d, J = 7.2 Hz), 6.96 (2H, d, J = 8.0 Hz), 3.88 (3H, s).

Kinetic procedure for the reaction of phenylmagnesium bromide **1a** with phenyl arenesulfonates **2a–e**: The kinetics were followed by measuring concentration of remaining phenyl arenesulfonate by GC analysis. Phenyl arenesulfonate, toluene and internal standard were thermostated at 90 °C in a jacketed two necked reaction vessel of approximately 25 ml capacity equipped with a reflux condenser and a magnetic stirrer. THF solution of phenylmagnesium bromide was added rapidly to initiate the reaction. Aliquots (7–13) were withdrawn from the homogeneous solution at 15 min intervals by syringe and were added to a vial containing a quenching solution of aqueous NH_4Cl for hydrolysis and diethyl ether. The vial was capped and shaken. Extraction of the remaining phenyl arenesulfonate and products sulfone and phenol was found to be essentially quantitative. The ethereal phase was analyzed by GC analysis. Generally self consistent data could be obtained for 2 or 3 half lives. Reproducibility of the rate constants was generally ±5%.

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