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

Fatma Eroğlu [a], Didem Kâhya [b], Ender Erdik [a,*]

[a] Ankara University, Science Faculty, Beşevler, Ankara 06100, Turkey
[b] Ankara University, Biotechnology Institute, Beşevler, Ankara 06100, Turkey

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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:

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

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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* Corresponding author. Address: Ankara Üniversitesi Fen Fakültesi, Kimya Bölümü, Beşevler, Ankara 06100, Turkey. Tel.: +90 312 212 67 20x1031; fax: +90 312 223 23 95.

E-mail address: erdik@science.ankara.edu.tr (E. Erdik).

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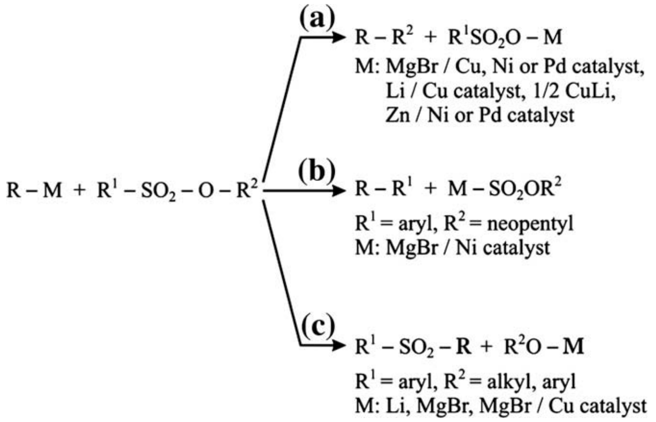
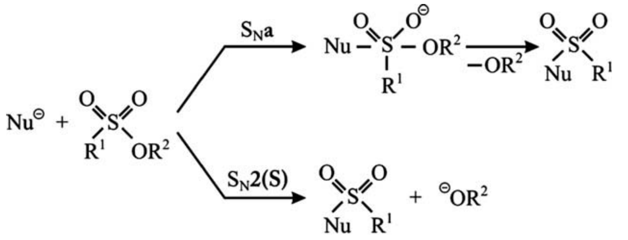


Scheme 1. Sulfonates as C–C and C–S coupling partners in reactions with organometallic reagents.

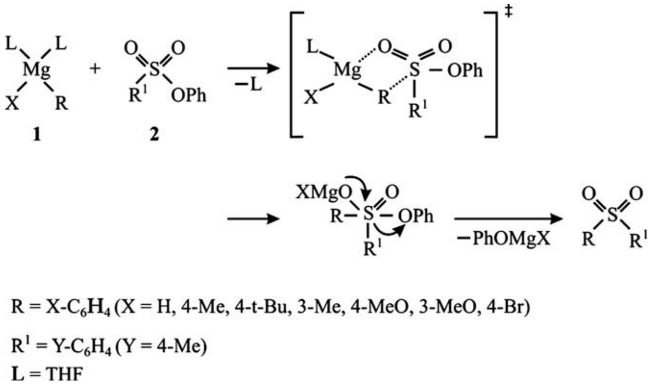
Reactions of nucleophiles with aryl arenesulfonates at S atom are known to take place generally by stepwise S_Na mechanism or concerted $S_N2(S)$ mechanism (Scheme 3) [28–33]. S_Na mechanism involves a pentacoordinate intermediate [29,33] and $S_N2(S)$ mechanism proceeds via a transition state in which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

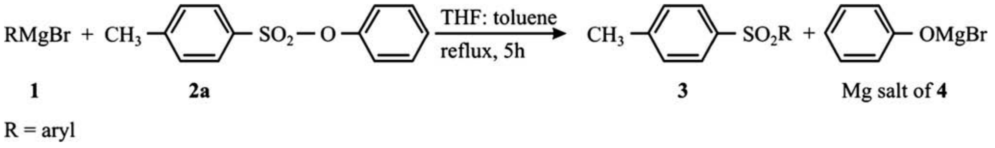
In order to find another support for the proposed mechanism, we tried Hammett treatment of substituent effects on the arenesulfonyl groups of the sulfonate esters. We expect that the reactivity of arenesulfonates **2** changes depending on the substituents on the arenesulfonyl group, R^1 and the transition 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–$C_6H_4SO_2$OPh **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–$C_6H_4SO_2$OPh **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 $[\mathrm{PhOTos}]_t$ 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.