Kinetics and mechanism of the C-S coupling reactions of aryl Grignard reagents with aryl arenesulfonates

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Abstract: The kinetics of the C–S coupling of arylmagnesium bromides with phenyl tosylate has been studied in THF: toluene at 90°C. The reaction is first order in Grignard reagent and first order in phenyl tosylate. Kinetic data, Hammett relationship and activation parameters are consistent with a nucleophilic addition mechanism involving rate determining attack of carbanion to sulfonyl group followed by a fast phenoxide group leaving.

Keywords: Grignard reagents • Aryl carbanions • C-S coupling • Hammett plot • Activation parameters

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1. Introduction

Sulfones [1] are of great use in organic synthesis as useful intermediates, in medicine as important drugs, [2,3] and also in industry [4]. The use of sulfones in organic synthesis has increased significantly in the past twenty years and they have been employed for the synthesis of many functionalized compounds and naturally occurring products [5,6].

Sulfones can be synthesized by a variety of methods [1,7]. However, the use of organometallic methods are quite limited and they generally depend on the sulfonylation of carbanions with sulfonyl chlorides [8-10]. The use of sulfonates as partners in C-S coupling of organometallic reagents are rare (Scheme 1, path a). Organolithiums [11] and Grignard reagents [12,13] have been reported to react with arenesulfonates by S-O bond cleavage leading to the formation of sulfones.

However, sulfonates are well known as partners like halides in C-C coupling reactions of organometallic reagents, which are conceptionally among the most straightforward processes for forming C-C bonds [14]. Uncatalyzed or transition metal catalyzed reactions of organolithium, Grignard and organozinc reagents with sulfonates have been extensively studied. Copper catalyzed organolithiums [15], organocuprates [16-18]; or copper, nickel or palladium catalyzed Grignard reagents [16,19-22] and nickel or palladium catalyzed organozinc reagents [23,24] react with alkyl esters of alkane- and arenesulfonates by C–O bond cleavage leading to C-C coupling products (path b).

Recently, Grignard reagents have been reported to react with neopentyl arenesulfonates under nickel catalysis to yield C-C coupling products by C-S bond cleavage (path c) [25-27]. These findings show that in the reactions of sulfonates, either sulfonate groups (path b) or under nickel catalysis, neopentoxyxsulfonyl groups (path c) can act as chemoselective leaving groups for C-C coupling. For C-S coupling, organoxy groups are leaving groups (path a).

Sulfonyl chlorides also have ambident character. Grignard reagents and organozincs are known to give sulfones in their reactions with sulfonyl chlorides while organozincs generate C-C coupling products under Pd catalyzed conditions [28].

We have already investigated the reaction of aryllithium, -magnesium and -zinc reagents with arenesulfonates to develop a new route for the preparation of arylsulfones. We observed selective
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**Scheme 1.** Reactions of organometallic reagents with sulfonates. (a) C-S coupling reaction. (b) and (c) C-C coupling reactions.

formation of C-C and C-S coupling products in the reaction of phenyllithium with 2-chloroethyl tosylate depending on the type of Cu(I) catalyst [29]. In uncatalyzed and Cu (I) catalyzed reactions of aryl Grignard reagents with phenyl tosylate, we found [30] that, aryl Grignard reagents 1 attack tosylate 2 only by S-O bond cleavage to give sulfones 3 (Scheme 2).

Our interest in the thiophilic reactivity of aryl magnesium bromides in their reaction with aryl arenesulfonates prompted us to find kinetic support for the sulfonyl transfer to Grignard reagents and to obtain information concerning the reaction mechanism. To the best of our knowledge, there is no reported work on the kinetics and mechanism of the reaction of Grignard reagents with sulfonates at sulfur center, although numerous studies have been reported on the kinetics and mechanism of the reactions of nitrogen and oxygen nucleophiles with sulfonates [31-36].

In this paper, we report our results in the kinetics and mechanism of the C-S coupling of Grignard reagent derived aryl carbanions with phenyl tosylate.

**2. Experimental Procedures**

All reactions were carried out under a nitrogen atmosphere in oven-dried glassware using standard syringe-rubber septum techniques [37]. THF was distilled from sodium benzophenone and toluene was distilled over sodium. The magnesium generally used was more than 99.9% pure. Commercially available bromobenzene and substituted bromobenzenes were purified using literature procedures. Phenyl tosylate was prepared according to the published procedure and authentic sample of phenyl p-tolyl sulfone was prepared by our reported sulfone synthesis procedure [30] using phenyl magnesium bromide-phenyl tosylate coupling. Grignard reagent was prepared in THF by standard method and their concentrations were found by titration prior to use [38]. Thermo-Focus gas chromatograph equipped with a ZB-1 capillary column (immobilized with phenyl polydimethylsiloxane) and a flame ionization detector was used for GLC analysis.

The kinetics were followed by measuring the concentration of remaining phenyl tosylate and also concentrations of formed sulfone and phenol by GLC analysis using internal standard technique. In a jacketed two necked reaction vessel of approximately 25 ml capacity equipped with a reflux condenser and a magnetic stirrer, phenyl tosylate, toluene and internal standard was thermostatted at 90°C. THF solution of Grignard reagent was added rapidly to initiate the reaction. Aliquots (7-11) were withdrawn from the homogeneous solution at 15 minute intervals by syringe and were added to a vial containing a quenching solution of aqueous NH₄Cl solution for hydrolysis and ether. The vial was capped and shaken. Extraction of the remaining phenyl tosylate and products sulfone and phenol to the ethereal phase was found to be essentially quantitative. The ethereal phase was analyzed by GLC. Generally, self consistent data could be obtained for 2 or 3 half lives. Reproducibility of the rate constants was generally ±4%.

**3. Results**

For the kinetic study, the model reaction of phenylmagnesium bromide (X=Y:H, 1a) with phenyl tosylate (2) was carried out in THF: toluene (7:10) at 90°C (Scheme 2). The rate data were collected by taking at least 7-11 samples at 10-15 minutes intervals and measuring the concentrations of phenyl tosylate (2), sulfone (3a) and phenol (4) in each sample by GLC analysis.

Since phenyl tosylate 2 reacts with phenylmagnesium bromide (1a) to give only C-S coupling we expected to find the same rate for the disappearance of sulfonate (2) and appearance of sulfone (3a). In addition, the observed amounts of sulfone (3a) and phenol (4) versus time are expected to be equal. So, in the evaluation of rate data, we used directly measured and also calculated values for $c = [\text{PhOTos}]$, i.e. the concentration of phenyl tosylate (2) at time t. As tosylate (2) reacts by giving only sulfone (3a) and phenol (4), then $c$ can also be calculated as $c = [\text{PhOTos}]_i - [\text{PhTos}]$, and $c = [\text{PhOTos}]_i - [\text{PhOH}]$. 

![Scheme 2. Reaction of aryl Grignard reagents with phenyl tosylate to give sulfones.](image-url)