

A catalyst-free, efficient and selective synthesis of asymmetric diarylsulfones

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Abstract

The synthetic potential of the catalyst-free reaction of arylstannanes and sulfonyl chlorides, for the generation of asymmetric diarylsulfones, is described. Moreover, the efficiency of the reaction is improved using diarylstannanes as starting substrates. All the reactions studied went, exclusively, through an *ipso*-substitution and give acceptable yields of sulfones from aryl sulfonyl chlorides supporting either electron-releasing or electron-attracting substituents. A special work up is carried out in order to recover the di- and trialkyltin chlorides generated as subproducts.

Keywords: Arylstannanes, Diarylsulfones, Catalyst-free

Introduction

Over the years, sulfones have emerged as interesting synthetic goals because they are valuable intermediates in organic synthesis¹ as well as important building blocks in biologically active compounds. Specially, aryl sulfones are found in several drugs, for example, in powerful inhibitors of enzymes² and for leprosy treatment.³ The usual procedures for their preparation are the oxidation of the corresponding sulfides⁴ and the sulfonylation of suitable arenes.⁵ Nevertheless, their scope of application is limited by the availability of sulfides and by the substituent-directing effects and the reactivity substrate requirements, respectively. On the other hand, the metal-mediated cross-coupling reactions between sulfinic acid salts and aryl derivatives (halides and triflates) are milder alternatives for the synthesis of arylsulfones.⁶ These reactions tolerate many functional groups but they imply the use of air or moisture sensitive reagents.

In recent years, we have been involved in searching new routes for the synthesis of arylstannanes⁷ and we have focused on these substrates as valuable and easily accessible reagents in C-C bond forming reactions through catalyst-free processes. Thus, we have performed new procedures for the regiospecific mono-, bi- and triarylation as well as hindered alkanoylation of aromatic rings⁸ based on the special reactivity of arylstannanes, a consequence of the exceptional leaving group ability of the trialkyltin group in electrophilic aromatic substitutions.⁹ On the basis of our previous

work and considering the importance of sulfones, we investigated the feasibility of the catalyst-free reaction of arylstannanes with sulfonyl chlorides as a synthetically useful route for the preparation of asymmetric diarylsulfones. Now, we are pleased to report the synthetic potential of this pair of reagents as well as the special work up carried out in order to recover the di- and trialkyltin chlorides generated (see experimental section).

Results and Discussion

We synthesized a series of electronically diverse starting trialkylarylstannanes (**1a-f**) and we studied their reactivity towards commercially available sulfonyl chlorides **2a** and **2b** (Fig. 1), under the optimized reaction conditions we have previously established, that is, in *ortho*-dichlorobenzene (ODCB) as solvent, at 180°C.^{8b} The reactions were followed by TLC until disappearance of starting stannane.

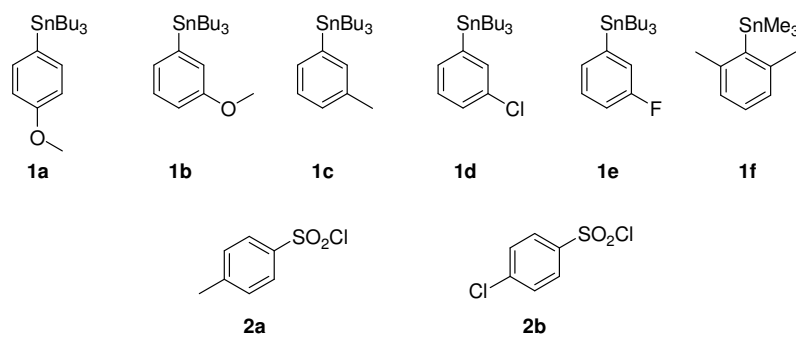
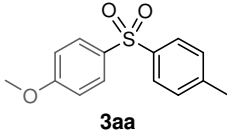
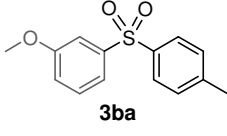
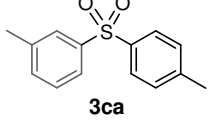
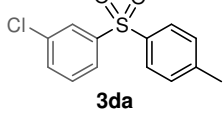
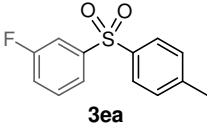
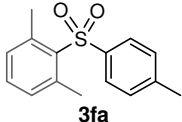
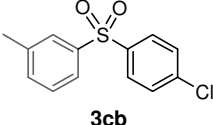
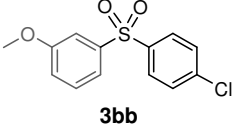


Figure 1

Table 1. Reaction of arylstannanes with sulfonyl chlorides

Entry ^a	ArSnR ₃	+	Ar'SO ₂ Cl	→	ArSO ₂ Ar'	Yield (%) ^b
	1		2	ODCB 180 °C	3	
	ArSnR ₃		Ar'SO ₂ Cl	Time (h)	ArSO ₂ Ar'	
1	1a		2a	2		65
2	1b		2a	5		60
3	1c		2a	5		58
4	1d		2a	5		52

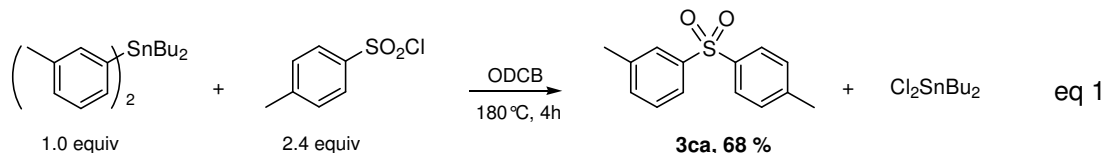
5	1e	2a	6		44
6	1f	2a	3		61
7	1c	2b	4		50
8	1b	2b	4,5		50

^a All reactions were conducted 1.0 M in ArSnR₃ with 1.2 equiv of **2**. ^b Isolated yield from 1.0 mmol scale experiments (CC)

The results obtained (Table 1) show that the arylstannanes reacted efficiently with both sulfonyl chlorides providing the corresponding diaryl sulfones in good isolated yields (44% to 65%) after relatively short times (2 to 6 h). The reactions proceeded with arylstannanes supporting either electron releasing or electron withdrawing groups; they were regioselective and went, exclusively, through an *ipso*-sulfonyldestannylation independently whether the directing influences of the aryl substituents and the trialkylstannyl group are either matched (compound **1a**) or mismatched (compounds **1b–f**). Even the known high *para*-directing force of OMe group could be completely overcompensated (compound **1b**). Also, experiment 1 shows that substrate **1a**, where the influence of the substituent and the trialkyltin group are matched, reacted in a shorter reaction time (2 h). The high *ipso*-directing force shown by trialkylstannyl groups is probably due to the β -effect of the tin atom which makes easier the cleavage of an aryl group from the tin *via* an electrophilic *ipso*-substitution.¹⁰ Experiment 6 shows that the more sterically hindered arylstannane **1f** gave sulfone **3f** in good yield (61%) after only 3 h, probable due to the fact that the electrophilic attack of arylstannanes is accelerated by the existence of neighboring groups on the arene system.¹¹ It should be mentioned that in all the experiments that we have carried out, it has been detected the presence of protodestannylation products, probably this being due to the presence of small amounts of HCl that could not be eliminated from the sulfonyl chloride. These protodestannylation products are irrelevant (3% to 9%) compared with the yields of the diarylsulfones obtained.

In order to improve the efficiency of these reactions we considered interesting to study the possibility of transferring more than one aryl group attached to tin. For this

purpose, we applied the protocol to the reaction of sulfonyl chloride **2** with dibutyldi(*m*-tolyl)stannane, as model system. After 4 h the starting stannane was consumed (TLC) and sulfone **3ca** was obtained in a good isolated yield (68%, referred to the stoichiometric equation).¹²



From a sustainable point of view this protocol implies the use of sub-stoichiometric amounts of organotin compounds and the by-product to be separated is Bu_2SnCl_2 which is less toxic than Bu_3SnCl and easily converted into insoluble $(\text{Bu}_2\text{SnO})_n$ (see experimental section). This preliminary result encourages us to continue studying the reactivity of diarylstannanes, supporting electronically different substituents, towards sulfonyl chlorides. This research is in progress.

Conclusions

In conclusion, the method provides a facile and specific access to a wide range of asymmetric diarylsulfones *via* arylstannanes. The method is attractive due to the availability, air- and moisture-stability of arylstannanes, as well as their compatibility with a variety of functional groups. Moreover, the transfer of two aryl groups from tin reduced the amount of non-benign organotin subproducts. The difficulties connected with organotin removal were largely solved in the workup and, in addition, these by-products were recovered and not rejected.

Experimental section

General experimental methods

The reactions were carried out under dry nitrogen in heavy walled Schlenk tubes fitted with a teflon plug valve. Sulfonyl chlorides were commercially available and fractionally distilled under nitrogen before use. Aryltributylstannanes **1a-e** and dibutyldi(*m*-tolyl)stannane were prepared by transmetalation of the appropriate Grignard reagents with tributyltin chloride in anhydrous THF. Aryltrimethylstannane **1f** was obtained from the corresponding commercial aryl chloride by photostimulated reaction with Me_3SnNa in liquid ammonia, according to the literature procedures.¹³ *o*-Dichlorobenzene was dried by standard methods, distilled under dry nitrogen atmosphere and stored over molecular sieves. Reactions were monitored by thin-layer chromatography on silica gel plates (60F-254) visualized under UV light and/or using

5% phosphomolybdic acid in ethanol. Column chromatography was performed over silica gel 60 (70-230 mesh) doped with 10% of potassium fluoride.¹⁴ Arylsulfones were characterized by comparing their ¹H NMR and ¹³C NMR spectra to the previously reported data.^{5e,g,i,15}

Representative procedure for sulfonyldestannylation

In a flame-dried 25 mL Schlenk tube, sulfonylchloride **2** (1.2 mmol)¹⁶ was added to a stirred solution of arylstannane **1** (1.00 mmol) in 1 mL of ODCB under a nitrogen atmosphere. The system was purged with nitrogen by means of three vac-refill cycles and the reaction mixture was heated at 180 °C (oil bath) monitoring the disappearance of **1** by TLC, for the time indicated in Table 1. After addition of 10% (m/v) solution of NaOH (2 mL) the mixture was stirred at room temperature for 15 min and then diluted with diethyl ether (5 mL). The organic phase was successively washed with water and brine, dried over Na₂SO₄, filtered, concentrated in vacuo and the residue purified by flash chromatography on silica gel-KF (10%).

Recovering method for organotin chlorides

Tributyltin chloride

After flash chromatographic procedure (10.0 g of 40-63 μm silica gel for 1.00-mmol scale reaction) the column was eluted with 100 mL of THF. The silica was dried using compressed air and poured into a 100-mL round-bottomed flask fitted with a condenser and a nitrogen T-joint. Sodium chloride (293 mg, 5.00 mmol) and 50 mL of dry THF were added and the mixture was heated at reflux with stirring for 4 days. It is then allowed to cool and poured into a chromatography column plugged with a small piece of cotton wool. All of the THF was drained with air pressure and then the column was eluted with ether (2 × 50 mL). The combined ethers were concentrated in vacuo giving tributyltin chloride in ca. 80 % with respect to the starting aryltributylstannane.

Dibutyltin dichloride

After workup of the reaction carried out with dibutyldi(*m*-tolyl)stannane, the resulting cloudy organic phase (~5 mL for 1.0 mmol scale) was centrifuged. The amorphous off-white sediment of (Bu₂SnO)_{*n*} was washed twice by centrifugation with DCM and reserved for its further conversion in Bu₂SnCl₂.¹⁷

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