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Synthesis of biaryls via intramolecular free radical *ipso*-substitution reactions

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ABSTRACT

A variety of functionalised biaryls and heterobiaryls are prepared by intramolecular free radical [1,5]-*ipso*-substitution using sulfonamide and sulfonate derived tethering chains. The overall efficiency of the process is determined by appropriately positioned substituents on the aromatic acceptor ring. The extension of the process to benzylic sulfonates and their corresponding *N*-methylsulfonamide alternatives as substrates in potential [1,6]-*ipso*-substitution reactions leads mainly to the alternative [1,7] addition products.

1. Introduction

The biaryl moiety is a common feature in natural products, functioning as an integral part of a diverse range of compounds, with vastly different structures, chemical properties, biological functions and biosynthetic origin, including, for example, polyketides, terpenes, lignans, coumarins, flavonoids, tannins and alkaloids.[1] The properties of this important class of compounds and their derivatives have been extensively studied over the years. Their importance is exemplified in their numerous applications, for example, as biologically active natural products, as chiral reagents,[2] as crown ethers,[3] as polymers,[4] as organic materials for non-linear optics[5] and also as the foundation of chiral liquid crystals.[6]

As a consequence of their enormous importance and widespread use, a wide variety of methods have been developed for biaryl construction.[7,8] Nowadays, the most frequently adopted strategy for preparing both symmetrical and unsymmetrical functionalised biaryls revolves around the use of transition metal mediated coupling reactions.[9] Nevertheless, problems may still arise when the two rings are of incompatible electronic character and/or especially when severely hindered products are required.[10]

Over the last four decades, the importance of free radicals in new carbon–carbon bond formation for synthetic organic chemistry has been well documented.[11] The rise of interest in this area has almost certainly resulted as a direct consequence of the availability of a range of mild methods for the generation of carbon centred free radicals.[12] Moreover, it is now well established that these reactive intermediates possess a number of important advantages for the organic chemist. We reasoned that the ability of free radicals to operate with impunity in hindered environments of widely differing polarity could overcome some of the disadvantages encountered when applying transition metals mediated coupling reactions to the synthesis of biaryls.

Our interest in this area was aroused by the early observation from Speckamp that an apparently straightforward free radical chain reduction of a primary iodide by Bu_3SnH also afforded significant quantities of the products **2** and **3** via 1,5-*ipso*-substitution and 1,6-addition processes (Scheme 1).[13]

We therefore envisaged that modification of this reaction could lead to a general biaryl synthesis, using an intramolecular free radical *ipso*-substitution[14] approach for the formation of the aryl–aryl bond and featuring the selection of a sulfonyl substituted

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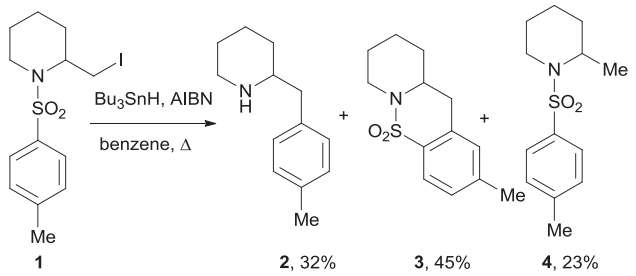
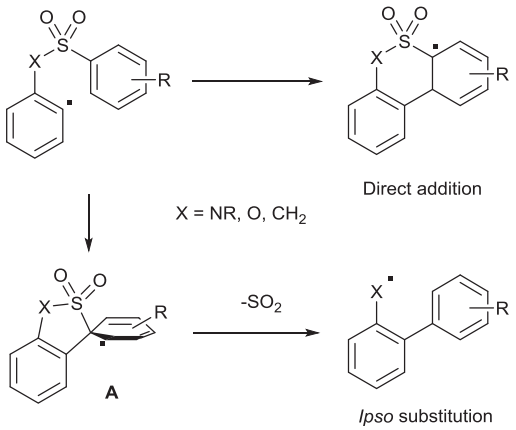


Scheme 1. Speckamp's study.

aromatic acceptor for the *ortho* substituted aryl radical, with subsequent extrusion of sulfur dioxide from the resultant spirocyclic intermediate **A** (Scheme 2).[14h,15] The study of such a system had the added attraction that the factors affecting the regiochemical outcome of the reaction could be probed. For example, it seemed plausible that variation of the length and nature of bridging group intermediate **A** could affect the distribution of products resulting from processes such as 1,5-*ipso*-substitution or 1,6-addition and thus, if this were the case, the reasons for such control might be ascertained.[16]



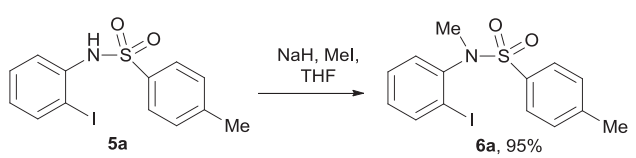
Scheme 2. This work.

2. Results and discussion

2.1. 1,5-*ipso*-Substitution versus 1,6-addition

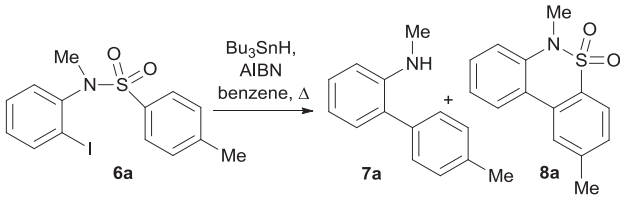
Initially, we decided to synthesise the rearrangement precursor **5a**, easily prepared in 79% yield by stirring 2-iodoaniline and tosyl chloride in pyridine. The addition over 15 h of Bu_3SnH (2.5 equiv, 0.2 M) and AIBN (0.7 equiv) in benzene to a solution of **5a** in refluxing benzene (0.05 M) led to extensive decomposition. Therefore, we methylated the nitrogen atom in **5a** (Scheme 3), the supposition being that the tertiary nitrogen atom in **6a** would have a closer electronic disposition to that of compound **1**. On this occasion the outcome of the radical reaction proved to be of greater interest as outlined in Table 1, entry a.

In an attempt to increase the yield of the 1,5-*ipso*-substitution product, **7a**, relative to that produced via 1,6-addition, **8a**, we



Scheme 3. Synthesis of **6a**.

Table 1
Attempts to increase the ratio 1,5-*ipso* (**7a**) versus 1,6-addition (**8a**) product



Entry	Concentration[a]	Time[b]	Stannane[c]	AIBN[d]	**7a**	**8a**	**6a**
1	0.2	15	2.5	0.7	34	39	25
2	0.2	15	2.5	0.1	—	—	90
3	0.2	15	1.2	0.7	27	30	30
4	0.8	19	1.2	0.7	46	25	13
5	0.2	0.5	1.2	0.7	39	22	18
6[e]	0.2	15	1.2	0.7	44	30	15
7[f]	0.25	15	1.2	0.7	11	38	44

[a] Concentration of stannane solution.
[b] Addition time (hours).
[c] Equivalents of stannane.
[d] Equivalents of AIBN.
[e] Refluxing anisole was used.
[f] TTMSH was used as reductor.

altered the rate of addition of the solution of stannane reagent, the concentration of this solution, with respect to the stannane and to AIBN, and the temperature and solvent used during the radical reaction (Table 1). The implications of these results were:

1. The conversion of starting sulfonamide **6a** into products is heavily dependent upon the quantity of radical initiator used, implying that the chain processes involved are extremely inefficient (compare entries 1 and 2 in Table 1).
2. Whether one or more equivalents of Bu_3SnH are used appears to be irrelevant in terms of product distribution (compare entries 1 and 3 in Table 1).
3. The fact that raising the concentration of the stannane solution (either reducing the solvent or increasing the addition rate, entries 4 and 5) increases the ratio of products derived from 1,5-*ipso*-substitution/1,6-addition suggests that one or more of the steps outlined in Scheme 4 are reversible. It is known that trichloromethylsulfonyl radical abstracts hydrogen atoms from hydrocarbons.[17] Therefore, it is possible to envisage intermediate **13** being trapped by Bu_3SnH and, as the concentration of the stannane solution is raised, the probability of this occurrence would also be expected to increase. The sulfinic acid **16** would then lose SO_2 on work up to yield the amine **7a**. For this explanation to be valid, the rate constant for the reaction depicted in Scheme 4 must be of approximately the same order of magnitude as those for steps K_A and K_B. A further requirement is that a mechanism must exist by which the spirocyclic intermediate **11** can convert into the sultam intermediate **10**.[18] The conversion of the spirocyclic intermediate **11** into the sultam intermediate **10** might occur via two different mechanisms, either via collapse of **11** back to the initial aryl radical followed by 1,6-ring closure, or via the cyclopropyl intermediate **12**.[19]
4. In his studies, Speckamp noticed a temperature dependence on the ratio of products.[13b] Thus, the increase of temperature led to an important increase in the 1,5-*ipso*-substitution product, the best result being obtained in refluxing diphenylether (190 °C). Entropy should become more important at higher temperatures, and so SO_2 would be released more easily from the postulated intermediate **13** hence denying it the opportunity to recyclise to the intermediate **11**. Even though we did notice the same trend in our system using refluxing anisole