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Steric and Electronic Effects in the Synthesis of Biaryls and their Heterocyclic Congeners using Intramolecular Free Radical [1,5] *ipso* Substitution Reactions.

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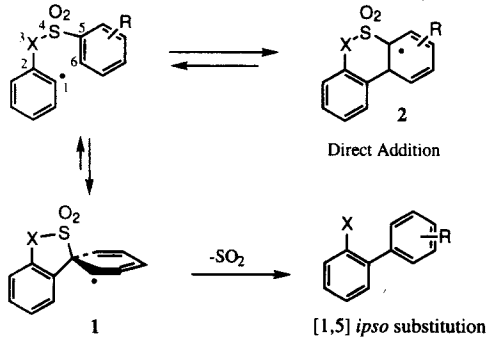
Abstract : Hindered biaryls and heterobiaryls are even easier to prepare by intramolecular free radical [1,5] ipso substition using sulfonamide and sulfonate tethering chains, since the introduction of either electron releasing or electron withdrawing groups ortho to the sulfonyl substituted acceptor ring facilitates the overall reaction. Copyright © 1996 Elsevier Science Ltd

The biaryl unit or a partially reduced form thereof, is a central feature of many natural product classes of differing structure, biosynthetic origin and biological activity[1]. In consequence, a wide variety of synthetic methods have been devloped for their construction[2], amongst which the palladium (0) catalysed Suzuki and Stille coupling reactions[3] are currently the most popular choice. Nevertheless, problems may still arise when the two rings are of incompatible electronic character and / or when more sterically congested products are required.

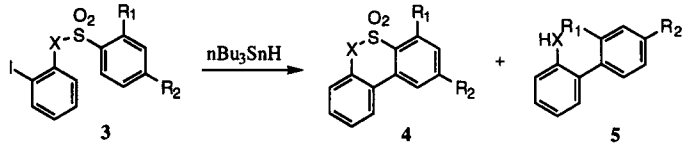
For these reasons we have recently demonstrated[4] that intramolecular free radical *ipso* substitution[5] of a suitably constituted sulfonyl substituted aromatic derivative by a second *ortho* substituted aryl radical represents a viable approach for biaryl coupling as shown in **Scheme 1.** The essential requirement for implementation of such a strategy lies in the ability to direct the reaction pathway *via* the spirocyclic intermediate **(1)** which is capable of rearomatisation through loss of sulphur dioxide and hence to avoid the alternative direct addition process. In this respect, both the nature and the number of atoms (X) in the tethering chain and the location and electronic character of substituents (R) on the sulfonyl substituted acceptor ring may well be expected to play pivotal roles.



Scheme 1

In the present communication, we now wish to report the preliminary results of a systematic study of substitutent effects (R) in terms of their ability to direct [1,5] *ipso* substitution reactions, both in the synthesis of biaryls and their heterocyclic congeners. The stannane induced reductive rearrangements were routinely carried out by slow addition of a benzene solution of tri-*n*-butylstannane and AIBN to a refluxing benzene solution of the iodoarene substrate.

In the first instance, we elected to examine the influence of locating a simple *ortho* tolyl substituent on the sulfonyl substituted acceptor ring. A comparison of the results with those we had previously obtained for the corresponding *para* tolyl derivatives in both the sulfonate and sulfonamide series is set out in **Scheme 2** and clearly reveals that the site specific location of even a single *ortho* methyl group favours *ipso* substitution in a dramatic fashion.



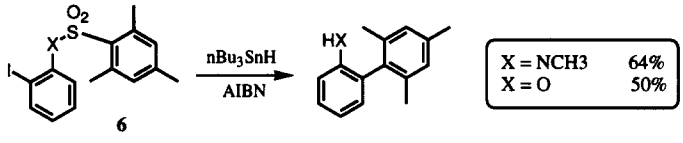
3 4 5

Substrate (3) X	R^1	R^2	Recovered starting material (Yield %)	Addition product (4) (Yield %)	*Ipso*-substitution product (5) (Yield %)
O	H	CH_3	37	63	0
O	CH_3	H	14	36	23
NCH_3	H	CH_3	25	39	34
NCH_3	CH_3	H	9	0	57

Scheme 2

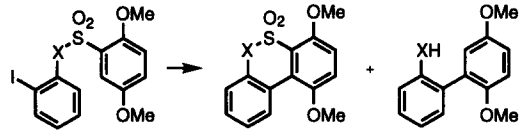
Since there are two possible sites for the alternative [1,6] addition process and only that bearing the *ortho* methyl group should be more kinetically disfavoured, a possible explaination for the above trend is that the buttressing effect of the *ortho* methyl group and the sulfonyl group in an intermediate of type **(2)** (R = *ortho* methyl group) **(Scheme 1)** leads to steric acceleration of the reverse reaction and hence channels a greater proportion of the reaction pathway *via* the corresponding spirocyclic intermediate **(1).**

As anticipated from the above observations, reaction of the corresponding mesityl derivatives **(6)** led to a cumulative enhancement of this tendency and no dihydroaromatic or rearranged products derived from the competing [1,6] addition process were isolated **(Scheme 3).**



6

Scheme 3



7 8 9

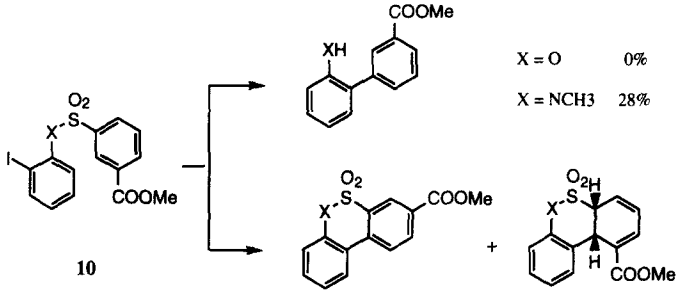
X = O (32% recovered starting material)	7%	43%
X = NCH_3	0%	63%

Scheme 4

As we had shown in our initial study that a *para* methoxy group was three times more efficient in promoting *ipso* substitution than a *para* methyl group, it was of particular interest to examine the case of the dimethoxy derivatives **(7)** shown in **Scheme 4,** wherein the internal competition between *ipso* substitution and addition both lead in the first instance to direct stabilisation of the intermediate radical by an ortho

methoxy group. The results obtained clearly indicate once again that the location of the methoxy group adjacent to the sulfonyl group is exerting a dominant directing effect which either minimises or totally eliminates [1,6] addition products **(8)**, even in the presence of the second methoxy group.

Since we have previously demonstrated[4] that the location of the carbomethoxy group adjacent to the sulfonyl moiety in the acceptor ring was a highly efficient "*ipso director*" it was appropriate to study the corresponding substrates **(10)** in the *meta* series. From the results shown in **Scheme 5**, it is apparent that the inherent tendency for the sulfonamide linkage to favour *ipso* substitution has been efficiently combatted by the *meta* location of the carbomethoxy group and a product distribution favouring [1,6] addition was obtained. The corresponding sulfonate provided two distinct groups of products both derived solely from [1,6] addition at the two possible sites of attack. It was of interest to note that, while the "normal" oxidation to aromatics[6] under tin hydride reduction occured for one set of regioisomers **(11)**, only the dihydroaromatic derivatives **(12)** were isolated from the second set; presumably as a consequence of the fact that aromatisation would have led to the introduction of a severe *peri* interaction from the carbomethoxy group.

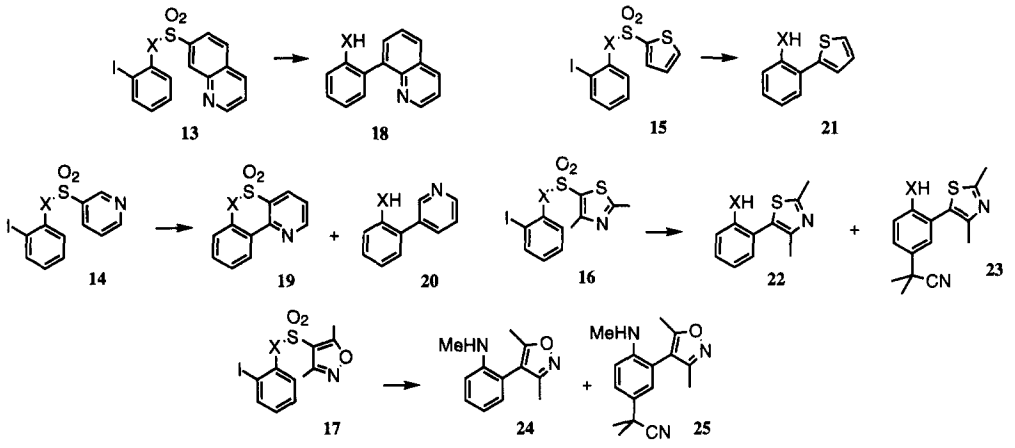


Scheme 5

X = O	52%	19%
X = NCH3	37%	11%

In view of the foregoing examples in the biaryl series, we reasoned that the location of an appropriately cited heteroatom could make such a strategy ideally suited for the synthesis of heterobiaryls. Some representative examples are shown in **Scheme 6** and serve to reinforce the previously established reactivity patterns. Thus, the reactions of the 8-quinoline derivatives **(13)** can be readily understood by analogy with the behaviour of the *ortho* substituted sulfonyl acceptor, whilst the case of the *meta* substituted pyridine **(14)** leads, as expected, to a preference for [1,6] addition. Comparison of the thiophene **(15)**, the thiazole **(16)** and the isoxazole derivative **(17)**, all of which gave only [1,5] *ipso* substitution products, further highlights the utility of this approach for the construction of sterically congested heterobiaryls. The isolation of significant amounts of compounds **(23)** and **(25)**, in which the cyanoisopropyl radical derived from the initiator is incorporated into the *para* position of the aniline ring, was also of interest and is presumably a reflection of the inefficiency of the chain propagation sequence and the relatively large quantity of AIBN used under these conditions.

In summary, these results have hopefully highlighted the fact that intramolecular free radical *ipso* substitution offers a useful strategy for the construction of biaryls and heterobiaryls. In constrast to many of the metal mediated coupling reactions which are most commonly employed, the formation of a sterically congested product is even advantageous and actively encouraged on mechanistic grounds; and both electron releasing and / or electron withdrawing groups sited either *ortho* and / or *para* to the sulfonyl substituted acceptor ring are beneficial and tolerated with equal impunity.



Substrate	Recovered Starting material (Yield %)	Products (Yields %)
(13) X = NCH_3	12	**(18)** 64
(13) X = O	56	**(18)** 27
(14) X = NCH_3	13	**(19)** 33; **(20)** 29
(14) X = O	5	**(19)** 43
(15) X = NCH_3	0	**(21)** 69
(15) X = O	0	**(21)** 50
(16) X = NCH_3	0	**(22)** 87; **(23)** 13
(16) X = O	0	**(22)** 51
(17) X = NCH_3	0	**(24)** 38; **(25)** 19

Scheme 6

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References:

1. (a) Torsell, K. G. B. *Natural Product Chemistry,* Wiley, Chichester,**1983**; (b) Manitto, P. *Biosynthesis of Natural Products*, Ellis Harwood,Chichester,**1981**; (c) Thomas, R. H.*The Chemistry of Natural Products*, Blackie and Sons, Glasgow, **1985**; (d) Cordell, G. A. *Introduction to Alkaloids, A Biogenetic Approach*, Wiley, New York, 1981.
2. For reviews see Sainsbury, M. *Tetrahedron,* **1980**, *36*, 3327; Bringmann, G.; Walter, R.; Weirich, R. Angew. *Chem., Int. Ed. Engl.* 1990, 9, 977.
3. Watanabe, T.; Miyaura, T.; Suzuki, A. *Synlett*, **1992**, 207 and references therein; Stille, J. K. *Angew. Chem., Int. Ed. Engl.*, **1986**, *25*, 508.
4. Motherwell, W. B.; Pennell, A. M. K. *J. Chem. Soc., Chem. Commun.*,**1991**, 877.
5. (a) Benati, L.; Spagnolo, P.; Tundo, A.;. Zanardi, G. *J. Chem. Soc., Chem. Commun.* **1979**, 141; (b) Huppatz, J. L.; Sasse, W. H. F. *Aust. J. Chem*, **1963**, *16*, 417; (c) Narsimhan, N. S.; Aidhen, I. S. *Tetrahedron Lett.*, **1988**, *29*, 2987; (d) For particular cases involving sulfonyl substituted aromatic derivatives see, *inter alia*: Kohler, J. J.; Speckamp, W. N. *Tetrahedron Lett.*, **1977**, *18*, 631; *ibid* **1977**, *18*, 635; Loven, R.; Speckamp, W. N. *Tetrahedron Lett.*, **1972**, *13*, 1567; Kohler, J. J.; Speckamp, W. N. *J. Chem. Soc., Chem. Commun.* **1978**, 166; *ibid* **1980**, 142 and references therein; Clive, D. L. J.; Boivin, T. L. J. Org. Chem. **1989**, *54*, 1997; Feigenbaum, A.; Pete, J. P.; Scholler, D. J. Org. Chem., **1984**, 49, 2355; Grimshaw, J.; Trocha, J. *J. Chem. Soc., Perkin Trans.* 1, **1979**, 799.
6. Bowman,W. R.; Heaney, H.; Jordan, B. M. *Tetrahedron,* **1991**, *47*, 10119.

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