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Observations on the Nature of the Tethering Chain in the Synthesis of Biaryls and Heterobiaryls via Intramolecular Free Radical *ipso* Substitution Reactions.

Maria Lucília E. N. da Mata[a], William B. Motherwell[a]* and Feroze Ujjainwalla[b]

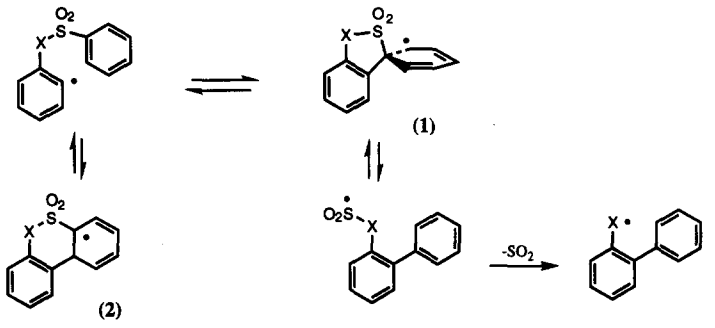
Departments of Chemistry, (a) Christopher Ingold Laboratories, University College London, 20 Gordon Street, London WC1H 0AJ, UK. (b) Imperial College of Science, Technology and Medicine, South Kensington, London SW7 2AY, UK.

Abstract: *A study of benzylic sulfonates and their corresponding N-methylsulphonamide derivatives as substrates in potential free radical [1,6] ipso substitution reactions reveals a preference for the alternative [1,7] addition mode. Empirical guidelines for biaryl and heterobiaryl synthesis using this approach can then be made.* Copyright © 1996 Elsevier Science Ltd

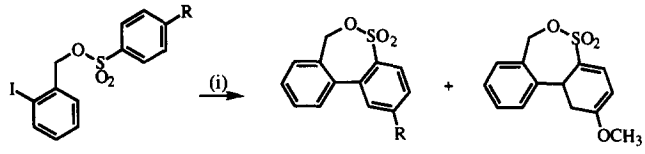
In the preceding communication, we have shown that steric and electronic effects around the sulphonyl substituted aromatic acceptor can play a significant role in the synthesis of biaryls and their heterocyclic congeners via intramolecular free radical [1,5] *ipso* substitution[1] and that *ortho* substituents are particularly effective in terms of encouraging this reaction pathway. The observant reader will also have noticed however,that in every single case, the selection of the sulfonamide tethering chain (X=NMe) led to higher isolated yields of [1,5] *ipso* substitution products and improved substitution versus addition ratios than the corresponding phenolic sulfonates (X=O). In the first instance, as implied in **Scheme 1**, it is tempting to speculate that this inherent preference is kinetically driven. Thus, a significant number of studies[2] have provided evidence that the rate of decarboxylation of alkoxycarbonyloxyl radicals ($ROCO_2\cdot$) is a very slow process ($k \leq 10^5 sec^{-1}$) relative to their nitrogen counterparts ($R_2NCO_2\cdot$). Given the probability of interconversion between the spirocyclic intermediate (**1**) and the radical (**2**) produced by [1,6] addition, and a similar rate difference for the loss of sulfur dioxide, the trend noted above would then follow. Some strong presumptive evidence for the relatively slow loss of sulfur dioxide from aryloxysulfonyloxyl radicals comes from our own study on the formation of cyclic sulfones from homopropargylic sulfonates[3].

In view of the above observations, and since the geometry, nature and number of atoms in the tethering chain can play a profound role, *per se*, in controlling the outcome of any intramolecular reaction, it was therefore of interest to probe the reactivity pattern of systems in which intramolecular [1,6] *ipso* substitution competes with [1,7] addition. Although a wide variety of tethering chains fulfilling this criterion may be envisaged, the simple incorporation of an additional methylene group was initially selected for a comparitive study.

The first reactions to be examined involved reduction of the two ortho iodo benzylic sulfonates (**3**) and (**4**), both of which contain sterically remote *para* functionality on the sulfonyl substituted acceptor ring. (**Scheme2**). In sharp contrast to the clean behaviour of the analogous phenolic derivatives, relatively complex reaction mixtures were produced and the only biaryl derived products to be isolated were the cyclic sulfones (**5**), (**6**) and (**7**), all of which are derived *via* the direct [1,7] addition process. The structure of (**7**) is based on NMR evidence, which shows that one of the protons of the methylene group of dihydroaromatic ring is coupled with the neighbouring proton. It was also of interest to compare these results with the phenolic sulfonate series wherein selection of the *para* tolyl derivative gave only cyclic sulfone by direct addition, whereas the electronic effect on replacement of the methyl group by a *para* methoxy group had led to a significant increase in the relative proportion of *ipso* substitution product,(addition:substitution; 6:4)[4].



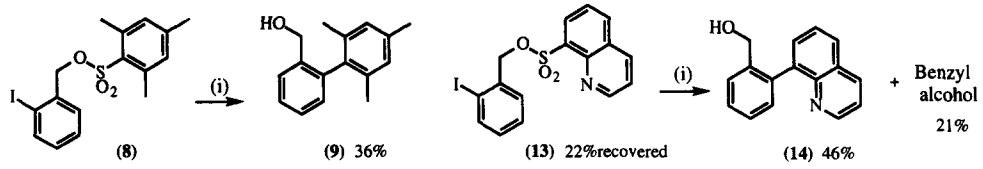
Scheme 1

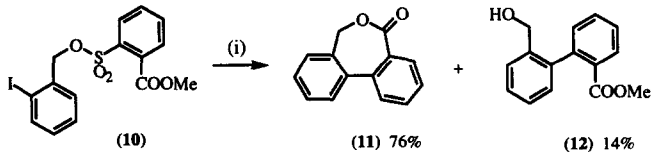


(3) R = CH3 ⟶ (5) R = CH3 (10%)
(4) R = OCH3 ⟶ (6) R = OCH3 (19%) + (7) 14%

Scheme 2

For all reactions in Schemes 2-6.
Reagents (i) = nBu_3SnH, AIBN, slow addition, benzene reflux.

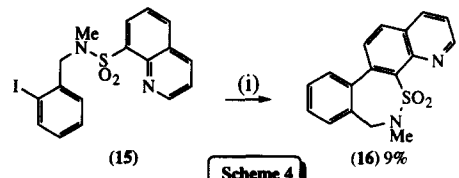




Scheme 3

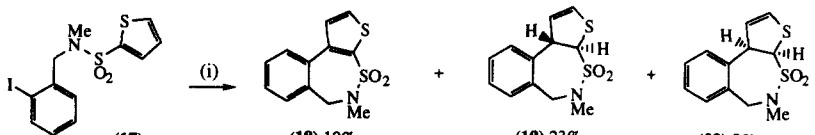
Gratifyingly however, as shown by the representative examples in **Scheme 3**, this tendency for addition could be effectively counteracted once again by the introduction of dominant *ortho* substitutents, thereby reinforcing our earlier observations in the study of [1,5] *ipso* substitution reactions and providing further evidence that this strategy is especially suited for the preparation of more hindered biaryls and heterobiaryls. The powerful directing effect exerted by the *ortho* carbomethoxy substituent in the high yielding conversion of the sulfonate (**10**) is particularly noteworthy in this series. It was also of interest to observe that the lactone (**11**) was formed directly in the crude reaction mixture, possibly as a result of a tri-n-butyltin iodide mediated transesterification. It is appropriate to note however, that although the formation of the quinoline derivative (**14**) from the labile sulfonate (**13**) was an encouraging result, the isolation of benzylalcohol from this reaction may be indicative of competitive stannyl radical induced cleavage of the heterocyclic sulfonate linkage[5].

Our attention was then directed towards the reactions of the analogous series of N-methyl sulfonamide derivatives. On the basis of our earlier studies involving [1,5] *ipso* substitution and the resultant kinetic analysis presented in **Scheme 1**, we anticipated that these sulfonamides would also exhibit an increased preference for [1,6] *ipso* substitution, when compared with the corresponding sulfonates. In the event however, all efforts to study the behaviour of simple aromatic N-methyl sulfonamides ($ArSO_2$=*para* toluenesulfonyl, 2,5 dimethoxphenylysulfonyl) led to extremely complex reaction mixtures, possibly as a consequence of the introduction of the additional methylene group now providing a kinetically competitive pathway initiated by intramolecular hydrogen atom abstraction from the N-methyl group of the sulfonamide by the aryl radical trigger.



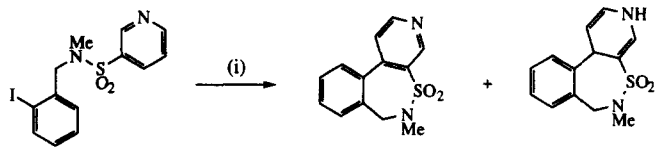
(15) (16) 9%

Scheme 4



(17) (18) 10% (19) 23% (20) 8%

Scheme 5



(21) (22) 55% (23) 24%

Scheme 6

In an effort to increase the rate of aryl radical addition to the sulfonyl substituted acceptor ring, we therefore elected to study the use of heteroaromatic derivatives. The results for the three examples in this series are shown in **Schemes 4, 5 and 6** and are uniformly consistent, inasmuch as we failed to isolate any

quantitative amount of a product derived from the [1,6] *ipso* substitution pathway. Interestingly, an isolated example of an intramolecular Pschorr reaction using an N-phenylbenzylamine derived arenesulfonamide has also been reoprted to favour [1,7] addition[6].

In particular, the complex behaviour of the quinoline derivative **(15)** **(Scheme 4)** provides a direct and remarkable contrast both with the analogous benzylic sulfonate **(13)** and with the entire series of [1,5] *ipso* substitution examples in which the sulfonamide linkage had performed so well[1,4]. An additional feature of interest in both the thiophene **(17)** **(Scheme 5)** and pyridine **(21)** **(Scheme 6)** substrates was the isolation of the dihydroheteroaromatic products **(19)**, **(20)** and **(23)** whose structures were all rigorously proven by single crystal X-ray structure determination. In view of the therapeutic utility of 4-aryl-1,4 dihydropyridines as cardiovascular agents[7],we were especially intrigued to isolate the conformationally restricted derivative **(23)**. The lack of regioselectivity observed with pyridine as a radicophile in an intramolecular addition reaction has also been noted by Abramovitch[8].

From the forgoing results, it is clear that simplistic ideas relating to a kinetically driven pathway and a preference for six membered ring formation over seven are invalid, and in all probability much more subtle stereoelectronic and conformational factors in the tethering chain hold sway in determining the final outcome of the reaction.

Nevertheless, on the basis of the present work and that described in the preceeding communication, a relatively simple set of of empirical guidelines for the use of this intramolecular *ipso* substitution protocol for biaryls can be advanced, viz.

• *Ipso* substitution is particularly favoured by the location of either electron withdrawing or electron releasing *ortho* substituents around the sulfonyl substituted acceptor ring, thereby leading to hindered products.

• In [1,5] *ipso* substitution reactions the sulfonamide linkage is preferred over the phenolic sulfonate, while [1,7] addition is the inherently favoured pathway for both benzylic sulfonates and sulfonamides, although oxygen displays a slight preference over nitrogen in terms of [1,6] *ipso* substitution.

Current work is directed towards the use of different radical triggers and the study of additional tethering chains in order to understand the constraints involved in harnessing this mild and neutral method for carbon carbon bond formation.

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