Pergamon

Tetrahedron Letters 39 (1998) 723–726

TETRAHEDRON LETTERS

A Novel Route to Unsymmetrical Stilbene Derivatives *via* Intramolecular Free Radical *ipso* Substitution Reactions

Christopher R. A. Godfrey[a], Philip Hegarty[b], William B. Motherwell[b*] and Muhammed K. Uddin[b]

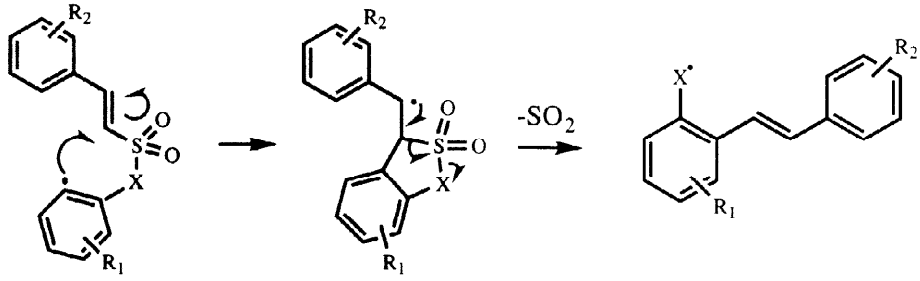
(a) Zeneca Agrochemicals, Jealott's Hill Research Station, Bracknell, Berkshire, RG42 6ET, UK; (b) Department of Chemistry, Christopher Ingold Laboratories, University College London, 20 Gordon Street, London, WC1H 0AJ, UK

Received 20 October 1997; revised 10 November 1997; accepted 14 November 1997

Abstract: Unsymmetrical stilbene derivatives can be prepared *via* intramolecular free radical *ipso* substitution reactions using suitably constituted vinyl sulfonate and sulfonamide tethering chains.

The importance of molecules possessing the stilbene unit as a central feature has been widely recognised, as highlighted by their use in such diverse areas as non linear optical materials and medicinal chemistry. In consequence, a wide variety of methods have been developed for their preparation, including, for example, those based on palladium catalysed coupling reactions,[1] the Horner reaction,[2] the Ramberg-Bäcklund rearrangement[3] and the Knoevenagel condensation.[4]

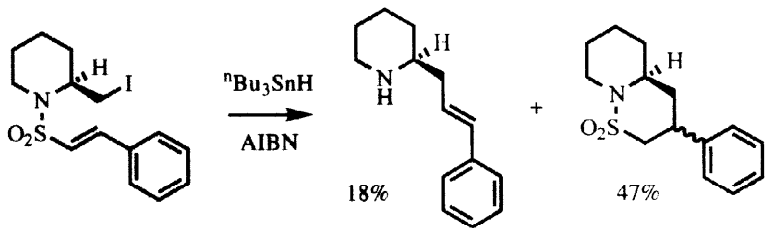
For this reason, and as part of our interest in the development of intramolecular free radical *ipso* substitution reactions[5] for organic synthesis it was of interest to examine the viability of the sequence outlined in **Scheme 1** which involves the *exo* addition of an aryl radical to a β-substituted sulfonyl styrene derivative as the key step. As in our studies in the biaryl series,[6] we anticipated that the nature and number of atoms (**X**) in the linking chain would be a critical variable in determining the successful outcome of such a reaction.



Scheme 1

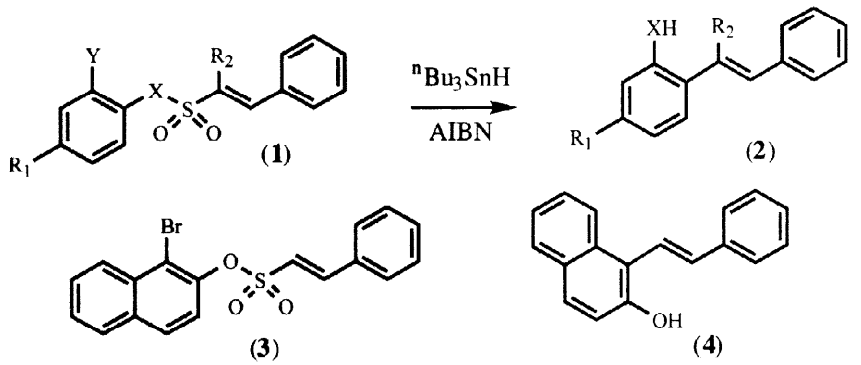
To our initial surprise however, examination of the literature[7] revealed a very unfavourable precedent in the form of the single example shown in **Scheme 2**. In this case, the electronically favoured [1,6] *endo* addition of the nucleophilic alkyl radical to the unsaturated sulfonyl acceptor has clearly dominated over the normally anticipated kinetic preference for [1,5] *exo* addition. On the basis of our studies in the preparation of unsymmetrical biaryls however, we reasoned that the selection of the more electrophilic aryl radical could not only moderate the inherently unfavourable electronic situation, but also alter the crucial geometry of the tethering chain for the case of stilbene formation.

0040-4039/98/$19.00
PII: S0040-4039(97)10645-1



Scheme 2

In the first instance, we elected to study the possibilities of the [1,5] *ipso* substitution reaction. A simple series of vinyl sulfonates and sulfonamides were accordingly prepared from the corresponding *ortho* halo phenol or aniline derivative *via* reaction with *trans ß*-styrenesulfonyl chloride, and the stannane induced reductive rearrangement was routinely carried out by slow addition of a benzene solution of tri-n-butyltin hydride containing AIBN to a refluxing solution of the substrate in the same solvent. The results of this preliminary study are collected in **Table 1** and indicate that unsymmetrical stilbene derivatives can be prepared in moderate to good yield *via* the [1,5] *ipso* substitution route. It should be noted that the relatively reactive N-methyl aniline products (entries **5** and **6**) were most conveniently isolated by acetylation prior to work up. The stereochemistry in the products was rigorously assigned by NMR measurements and comparison with reported literature data.

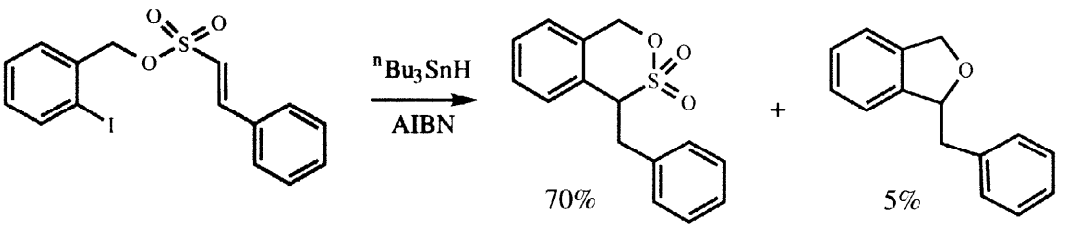


Entry	Substrate	Recovered Starting Material (yield %)	Product (yield %)
1	(1)X=O,Y=I, R_1=H, R_2=H	25	(2) 42
2	(1)X=O,Y=Br, R_1=Me, R_2=H	35	(2) 43
3	(1)X=O, Y=I, R_1=H, R_2=Me	41	(2) 30
4	(3)	30	(4) 50
5	(1)X=NMe, Y=I, R_1=H, R_2=H	24	(2) 67
6	(1)X=NMe, Y=I, R_1=H, R_2=Me	35	(2) 41
7	(1)X=NCOMe, Y=I, R_1=H, R_2=H	30	(2) 38
8	(1)X=NCO_2Me, Y=I, R_1=H, R_2=H	26	(2) 21
9	(1)X=N-allyl, Y=I, R_1=H, R_2=H	8	(2) 38

Table 1

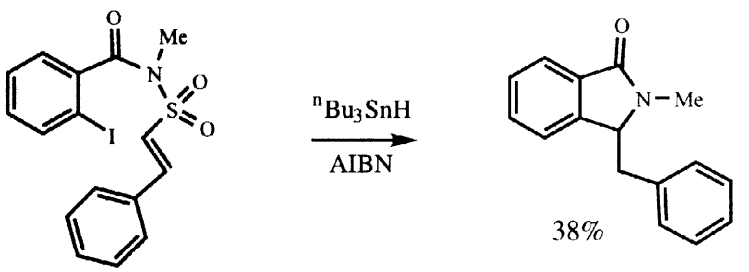
Several additional features of interest are also apparent from these results. Thus, as in the case of biaryl and heterobiaryl synthesis[5] the selection of a simple N-methyl sulfonamide tethering chain gives consistently higher yields of isolated *ipso* substitution product than the corresponding vinyl sulfonate (entries **1** and **5**). This trend is also mirrored in those substrates where the incorporation of the additional methyl group (R_2) at the vinylic carbon atom bearing the sulfonyl residue leads to a trisubstituted alkene (entries **3** and **6**). The lower yields of isolated products in these latter two cases are presumably a reflection of a slower and less efficient initial 5-*exo* cyclisation, as is well documented in all carbon systems.[8] Within the sulfonamide series, we have also studied a series of N-protected derivatives (entries **7**, **8** and **9**), all of which gave the corresponding stilbene product, albeit in lower yield. The compatibility of the N-allyl group (entry **9**) which can also undergo a competitive [1,5] *exo* cyclisation is, at first sight, somewhat surprising, but has previously been noted in the isolated case of stannane reduction of an N-allyl *ortho* bromo benzanilide derivative.[9]

Finally, we have also studied two examples of potential [1,6] *ipso* substitution reactions. In the first of these (**Scheme 3**) attempted reductive rearrangement of the vinylic sulfonate derived from *ortho* iodobenzyl alcohol afforded the cyclic sultone as the major product, clearly indicating that the extrusion of sulfur dioxide was much less favourable than in those cases involving generation of a more stable phenoxyl radical as an intermediate. We have previously noted, in a preparation of cyclic sultones from homopropargylic sulfonates, that the loss of sulfur dioxide from an alkyloxysulfonyloxy radical is sufficiently slow to allow competitive intramolecular cyclisation.[10]



Scheme 3

By way of contrast, as shown in **Scheme 4**, the N-acyl sulfonamide derived from *ortho* iodo benzoic acid furnished the lactam derivative shown, presumably as a result of [1,6] *ipso* substitution followed by loss of sulfur dioxide and final 5-*exo* cyclisation of the resultant amidyl radical to the stilbene.



Scheme 4

In summary, the above results indicate that a variety of functionalised stilbene derivatives can be prepared *via* [1,5] and [1,6] intramolecular free radical *ipso* substitution reaction, and, as in the use of this method for biaryl synthesis, sulfonamide tethering chains are preferred over phenolic sulfonates in [1,5] *ipso* substitutions.

Acknowledgements: We wish to thank Zeneca plc for the award of a Fellowship (to P. H.) and EPSRC for a studentship (to M. K. U.). We also wish to acknowledge the facilities provided by the ULIRS Mass Spectral Group.

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