



Application of a Radical Catalysed Isomerisation Reaction to the Synthesis of Fused [1,2-a]indoles

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Abstract: A new radical triggered isomerisation approach to fused indoles is presented; the proposed mechanism involves the radical cyclization of a β -toluenesulfonyl-vinyl radical or β -toluenesulfonyl-alkyl radical onto a sulfone substituted indole and is catalysed with *Se*-phenyl-*p*-toluene-selenosulfonate (TsSePh).

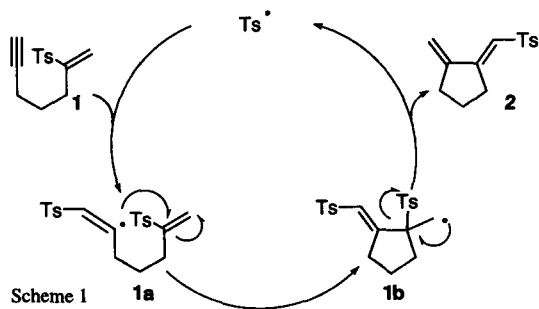
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Radical cyclizations have gained widespread and popular appeal in organic synthesis and are proven methods for the preparation of numerous classes of ring containing compounds.¹ Recently, many research teams have directed their effort toward the development of non-tin based methodologies. As such, sulfonyl radicals are gaining popularity,² particularly in view of the synthetic versatility of the sulfone moiety.³ We have been interested in radical transformations in which aromatic sulfones are transformed into carbon-carbon and carbon-tin bonds.⁴

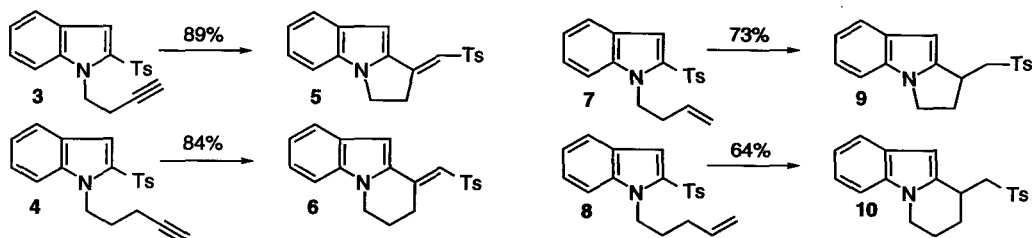
We decided to examine the prospect of developing a novel isomerisation reaction generalised in the transformation of **1** to **2**.⁵ The use of the electrophilic sulfonyl radical should hinder further undesirable reactions of the product diene **2**; a tactic we have recently employed in a radical based synthesis of sulfonyl dienes.⁶ One of the most attractive features of this proposed isomerisation approach is the potential for using a sub-stoichiometric quantity of tosyl radical to promote the reaction *via* the proposed mechanistic pathway shown in *scheme 1*. Addition of the tosyl radical to the terminal alkyne should result in the formation of the β -tosylvinyl radical **1a**. Intramolecular addition would lead to **1b**; β -scission of the tosyl radical should lead to the desired product **2** and regeneration of the catalyst.

Our primary objective has been to demonstrate the principle of *scheme 1*. We initiated feasibility studies in the context of indole synthesis⁷ as we had previously shown that radical *ipso*-substitution of 2-tosyl-indoles could be used to prepare fused indole systems.⁸

Herein, we present results which show that a tosyl radical *catalysed* isomerisation can provide an effective route to the biologically valuable fused [1,2-a]indole ring system.



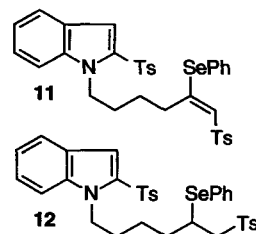
We were able to prepare the desired precursors from 2-tosyl-indole using Mitsunobu reaction conditions.⁹ Of note, the mildness of this method allowed the synthesis of precursor **3** in good yield (63%) from the commercially available alcohol without modification of the alkyne functionality. The results of the isomerisation reactions promoted using catalytic TsSePh¹⁰ are presented in *scheme 2*. Alkynes **3** and **4** undergo high yielding cyclisation to give **5** and **6**; which is noteworthy as we had previously found that *ipso* substitutions involving vinyl radicals had proceeded in poor yields. In a closely related transformation alkenes **7** and **8** have been shown to undergo smooth isomerisation to give sulfones **9** and **10** in good yields.



*Scheme 2*¹¹: Reaction conditions, TsSePh (0.25), AIBN, ¹² benzene, 80 °C.

We have been unable to isolate the desired cyclised materials from the appropriate *N*-hexynyl and *N*-hexenyl substrates. However, the isolation of **11** (91%) and **12** (88%) from treatment of TsSePh (1 eq.) demonstrates the relatively slow rate of 7-membered ring formation.

Overall we have shown that the isomerisation of aromatic sulfones can be promoted using a novel radical cascade catalysed by TsSePh. The key ring forming reaction can involve a vinyl or alkyl radical cyclisation and has been applied to fused [1,2-*a*]indoles synthesis. The work we have presented is consistent with the proposed catalytic cycle proposed in *scheme 1*.



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References and Notes

- For a lead reference see Jasperse, C. P.; Curran, D. P.; Fervig, T. L. *Chem. Rev.* **1991**, *91*, 1237
- For reviews of the area: Chatgililoglu, C. *The Chemistry of Sulfones and Sulfoxides: Sulfonyl Radicals* **1988**, Wiley, New York.
- Bertrand, M.-P. *Org. Prep. Proceed. Int.* **1994**, *26*, 257. See also Gung, J.; Fuchs, P. L. *Tetrahedron Lett.* **1997**, *38*, 787. Phillips, E. D.; Warren, E. S.; Whitham, G. H. *Tetrahedron* **1997**, *53*, 307. Quiclet-Sire, B.; Zard, S. Z. *J. Am. Chem. Soc.* **1996**, *118*, 1205
- Simpkins, N. S. *Sulfones in Organic Synthesis* **1993**, Pergamon Press, Oxford.
- Caddick, S.; Aboutayab, K.; Jenkins, K.; West, R. I. *J. Chem. Soc., Perkin Trans. 1* **1996**, 675. Aboutayab, K.; Caddick, S.; Jenkins, K.; Oshi, S.; Khan, S. *Tetrahedron*, **1996**, *52*, 11329.
- For related work: Harvey, I. W.; Whitham, G. H. *J. Chem. Soc., Perkin Trans. 1* **1993**, 185 and references therein.
- Caddick, S.; Shering, C. L.; Wadman, S. N. *J. Chem. Soc., Chem. Commun.* **1997**, 171.
- Radical based methods for indole synthesis: Ziegler, F. E.; Belesma, M. *J. Org. Chem.* **1997**, *62*, 1083. Jones, K.; Wilkinson, J.; Ewin, R. *Tetrahedron Lett.* **1994**, *35*, 7673. Moody, C. J.; Norton, C. L. *Tetrahedron Lett.* **1995**, *36*, 9051.
- Caddick, S.; Aboutayab, K.; West, R. I. *Synlett* **1993**, 231. For other radical additions to aromatic sulfones: Ziegler, Y.; Antonia, M. A.; De la Cruz, E.; Galeazzi, E.; Guzman, A.; Bray, B. L.; Greenhouse, R.; Kurz, L. J.; Lustig, D. A.; Maddox, M. L.; Muchowski, J. M. *Can. J. Chem.* **1994**, *72*, 15.
- Bhawgwat, S. S.; Gude, C. *Tetrahedron Lett.* **1994**, *35*, 1847
- Back, T. G.; Collins, S. *Tetrahedron Lett.* **1980**, *21*, 2213
- All compounds exhibited data consistent with their formulae (IR, ¹H & ¹³C NMR, HRMS)
- Optimal yields obtained with AIBN (1 eq.); the use of 10% gave only slightly diminished yields e.g. for **5** (72%) and **6** (76%).

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