Pergamon

Tetrahedron Letters, Vol. 38, No. 35, pp. 6249-6250, 1997

PII: S0040-4039(97)01378-6
0040-4039/97 $17.00 + 0.00

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

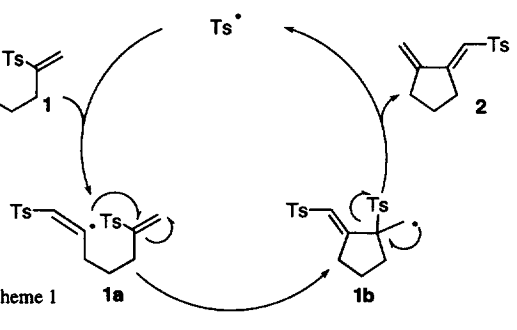
Stephen Caddick*[a], Craig L. Shering[a] and Sjoerd N. Wadman[b]

[a]The Chemistry Laboratory, University of Sussex, Falmer, Brighton BN1 9QJ
[b]GlaxoWellcome, Medicines Research Centre, Gunnels Wood Road, Stevenage, Herts SG1 2NY

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).

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.

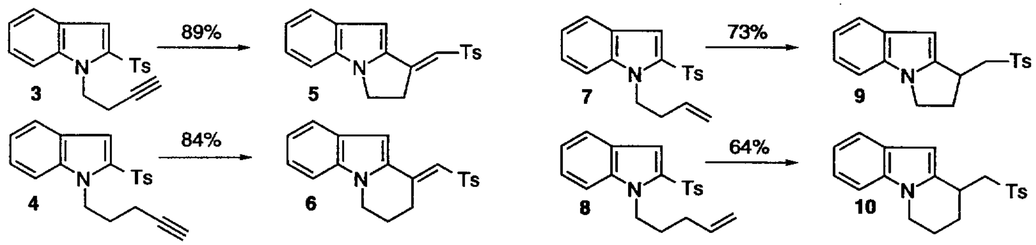


Scheme 1

Our primary objective has been to demonstrate the principle of *scheme 1*. We initiated feasibility studies in the context of indole synthesis[7] as we had previously shown that radical *ipso*-substitution of 2-tosyl-indoles could be used to prepare fused indole systems.[8]

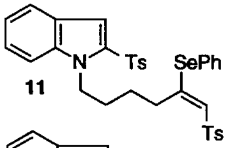
Herein, we present results which show that a tosyl radical *catalysed* isomerisation can provide an effective route to the biologically valuable fused [1,2-a]indole ring system.

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 TsSePh[10] 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.

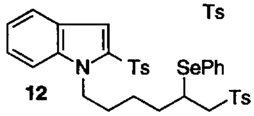


Scheme 2[11]*:Reaction conditions, TsSePh (0.25), AIBN*,[12] *benzene, 80 °C.*

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.



11



12

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*.

Acknowledgements: We are grateful to the EPSRC and GlaxoWellcome for a CASE award (CLS). We are also grateful to BBSRC, Rhone-Poulenc Rorer, Parke-Davis and Zeneca for additional financial support. We thank the EPSRC Mass Spectrometry Service at Swansea and A. Abdul-Sada, A. G. Avent and P. B. Hitchcock for their help with this work.

References and Notes

[1] For a lead reference see Jasperse, C. P.; Curran, D. P.; Fervig, T. L. *Chem. Rev.* **1991**, *91*, 1237

[2] For reviews of the area: Chatgilialoglu, 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

[3] Simpkins, N. S. *Sulfones in Organic Synthesis* **1993**, Pergamon Press, Oxford.

[4] 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.

[5] For related work: Harvey, I. W.; Whitham, G. H. *J. Chem. Soc., Perkin Trans. 1* **1993**, 185 and references therein.

[6] Caddick, S.; Shering, C. L.; Wadman, S. N. *J. Chem. Soc., Chem. Commun.* **1997**, 171.

[7] Radical based methods for indole synthesis: Ziegler, F. E.; Belema, 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.

[8] 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.

[9] Bhawgwat, S. S.; Gude, C. *Tetrahedron Lett.* **1994**, *35*, 1847

[10] Back, T. G.; Collins, S. *Tetrahedron Lett.* **1980**, *21*, 2213

[11] All compounds exhibited data consistent with their formulae (IR, ^{1}H & ^{13}C NMR, HRMS)

[12] Optimal yields obtained with AIBN (1 eq.); the use of 10% gave only slightly diminished yields e.g. for **5** (72%) and **6** (76%).

(*Received in UK* 6 *June* 1997; *revised* 3 *July* 1997; *accepted* 4 *July* 1997)