



Pergamon

Tetrahedron Letters 41 (2000) 421–424

TETRAHEDRON
LETTERS

Radical-polar crossover reactions with a water-soluble tetrathiafulvalene derivative

Balaram Patro,^a Martin C. Merrett,^a Scott D. Makin,^a John A. Murphy^{a,*} and Kevin E. B. Parkes^b

^a*Department of Pure and Applied Chemistry, University of Strathclyde, 295 Cathedral St, Glasgow G1 1XL, UK*

^b*Roche Discovery Welwyn, 40 Broadwater Road, Welwyn Garden City, Hertfordshire AL7 3AY, UK*

Received 5 October 1999; accepted 2 November 1999

Abstract

The water-soluble TTF reagent **7** undergoes the radical-polar crossover reaction in 1:1 acetone:water with a range of arenediazonium tetrafluoroborates and in water with diazonium chlorides. Purification of the reaction products is greatly facilitated by using **7** compared with TTF. © 2000 Elsevier Science Ltd. All rights reserved.

The chemistry of free radicals has undergone a massive renaissance over the past thirty years. The real burst in synthetic applications arose from the use of trialkyltin and triaryltin hydrides as radical-chain carriers. However, the toxicity of the tin reagents, coupled with the difficulty in separation of their by-products from the desired reaction products, meant that they were never acceptable to the pharmaceutical industry. Although improved methods¹ of separation and operation have been developed, there is still a reluctance to use toxic tin reagents. This is unfortunate, since the properties of free radicals — e.g. lack of solvation (useful in assembling congested quaternary carbons) and predictable kinetics regardless of the reaction solvent (useful for predicting the relative speed of desired vs side-reactions) — give them a unique advantage in certain synthetic manoeuvres.

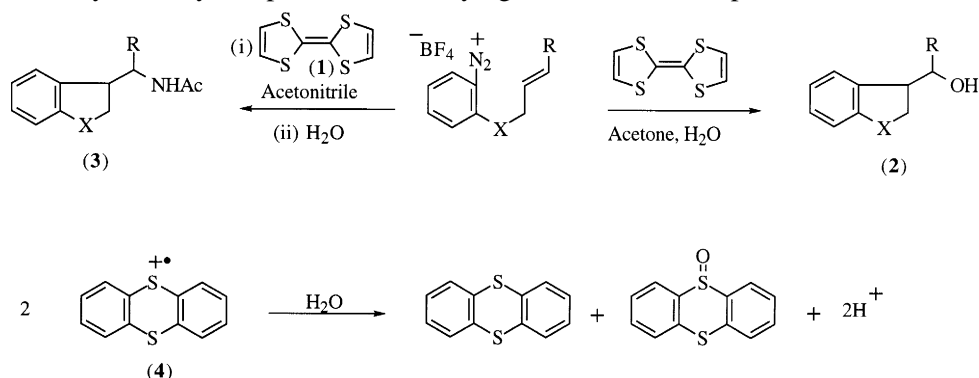
The radical-polar crossover reaction² shown below affords a means of conducting radical-based carbon–carbon bond formation avoiding the use of toxic organotin derivatives. Here, tetrathiafulvalene (TTF, **1**) donates an electron to the diazonium group. Loss of dinitrogen affords an aryl radical which cyclises, and the resulting radical couples with TTF⁺ to form a sulfonium salt, solvolysis of which affords either an alcohol **2** or an amide **3**. Hence this reaction affords a unique polar termination to the radical chemistry, allowing novel functionalisation of the site of the ultimate radical. The applicability of this chemistry to the synthesis of complex molecules is demonstrated in our recent synthesis of (±)-aspidospermidine.³

The reaction has some key features making it worthy of attention. The tetrathiafulvalene reagent can be used catalytically. Moreover, since diazonium salts are, in principle, water-soluble, and since the products

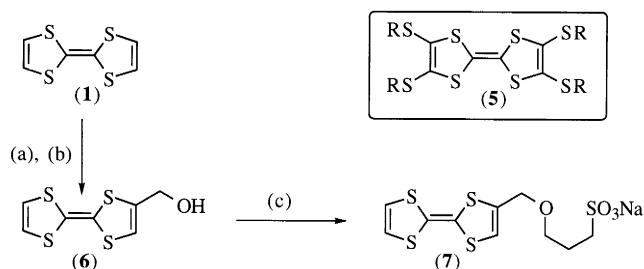
* Corresponding author.

of the reaction with water, alcohols, in general are not, use of a water-soluble version of tetrathiafulvalene should permit isolation of the reaction product simply by extraction. This paper reports our initial results with a water-soluble derivative of TTF.

At the start, the feasibility of the whole project was in doubt following the extensive and elegant work⁴⁻⁶ performed over many years by the groups of Shine^{4,5} and Parker⁶ who had shown that sulfur radical-cations derived from thianthrene **4** are readily trapped by water in a complex reaction which affords thianthrene as well as its sulfoxide. If this process occurred rapidly with TTF⁺, it could completely inhibit the radical-polar crossover reaction. Whereas we had previously been successful in carrying out such reactions in undried acetone, the concentrations of water involved under those conditions are very small by comparison with carrying out the reaction in pure water or 1:1 acetone:water.



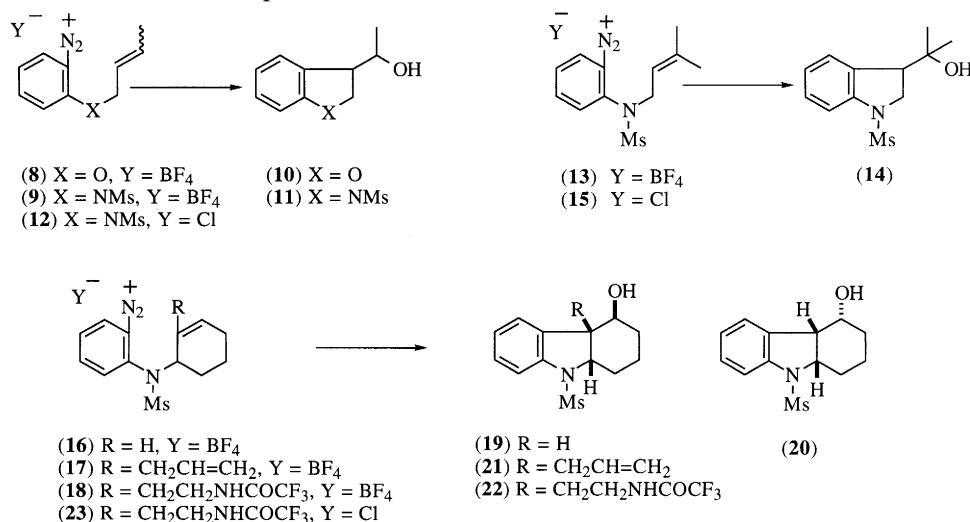
To carry out these studies, the sulfonate **7** was prepared (Scheme 1). It is important to note that although alkylthio derivatives of TTF **5** abound in the literature, we could not use such a derivative, since they are less powerful electron-donors than TTF and alkyl TTFs, and we have shown in unpublished preliminary studies that alkylthio derivatives cannot trigger the radical-polar crossover reaction. Tetrathiafulvalene **1** was converted into the hydroxymethyl derivative **6** by the literature procedure.⁷ Reaction of the sodium salt of this alcohol with 1,3-propanesultone afforded the sulfonate salt **7**.



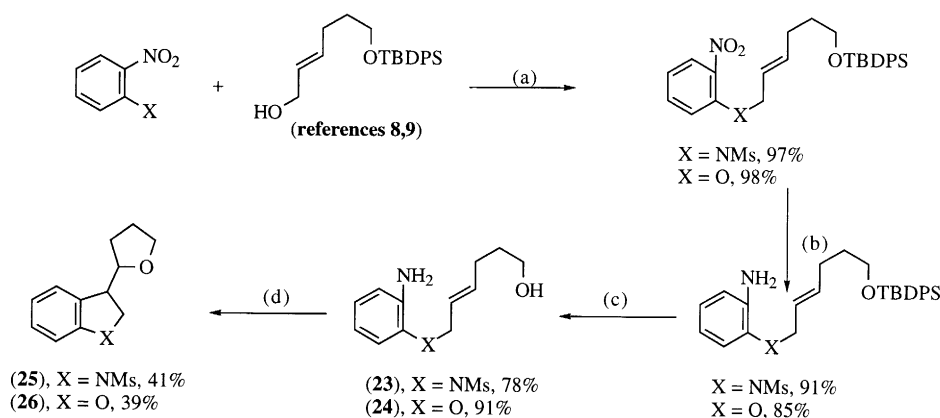
Scheme 1. Reagents and conditions. (a) LDA, PhNMeCHO; (b) NaBH₄, EtOH; (c) NaH, 1,3-propane sultone

This was reacted firstly with diazonium tetrafluoroborate salt **8** in water as solvent. The reaction was initially not very successful, since the tetrafluoroborate salt was sparingly soluble in water. However, we were pleased to find that a change of reaction medium to 1:1 water:acetone afforded 57% of alcohol **10**. At the end of the reaction, simple extraction into organic solvent and evaporation afforded 95% pure products, which were further purified by column chromatography. The residual water-layer was evaporated to leave a dark-coloured solid. Extraction with acetone afforded a solution containing no significant organic compound. The residue consisted of the water-soluble reagent **7** in its radical-cation form. (The NMR spectrum showed the signals of the side-chain, while the signals of the TTF nucleus are too broad to observe).

A series of aromatic amines was then prepared and converted into the corresponding diazonium tetrafluoroborates **9**, **13**, **16**, **17** and **18** by reaction with nitrosonium tetrafluoroborate. The diazonium salts were reacted directly with sulfonate **7** in 1:1 water:acetone to afford the alcohols **11** (37%), **14** (23%), **19** (21%) plus **20** (5%), **21** (35%) and **22** (20%). The quoted yields represent the conversions to isolated product from the amine precursors.



Diazonium chlorides are much cheaper to prepare than diazonium tetrafluoroborates. They also have the advantage of being more water-soluble, and so it should be possible both to prepare and react them with **7** in water. The potential complication is that chloride could now compete as a nucleophile in the final stage of the radical-polar crossover reaction. Salts **12**, **15** and **23** were prepared and reacted in situ in water with **7** and afforded **11** (32%), **14** (37%) and **22** (20%), respectively. No trace of the proposed chloride products was detected.



Scheme 2. Reagents and conditions. (a) DEAD, PPh₃, THF, rt; (b) NaBH₄/Cu(acac)₂/EtOH; (c) TBAF, THF, 12 h, rt; (d) (i) NOBF₄, CH₂Cl₂; (ii) **7**, degassed acetone:water 1:1

Finally, the more complex amines **23** and **24** were prepared as shown in Scheme 2.^{8,9} These compounds were converted into the corresponding diazonium tetrafluoroborates which successfully underwent radical cyclisation, radical-polar crossover and intramolecular termination in 1:1 acetone:water, demon-

strating that the water-soluble reagents can effect reaction with more complex substrates, providing that solubility is not a problem.

In conclusion, the radical-polar crossover reaction has been effected for the first time with a water-soluble derivative of tetrathiafulvalene, allowing very easy isolation of the organic products.

Acknowledgements

We thank the EPSRC for funding and EPSRC Mass Spectrometry Service, Swansea, for high resolution mass spectra and Roche Discovery Welwyn for a CASE award to S.D.M. We thank Professor Jan Becher for samples of water-soluble alkylthio-TTF derivatives used in preliminary experiments.

References

1. Among the many methods and strategies are the following: Renaud, P.; Lacote, E.; Quaranta, L. *Tetrahedron Lett.* **1998**, *39*, 2123. Crich, D.; Sun, S. *J. Org. Chem.* **1996**, *61*, 7200. Curran, D. P.; Chang, C. T. *J. Org. Chem.* **1989**, *54*, 3140. Barton, D. H. R.; Motherwell, W. B.; Stange, A. *Synthesis* **1981**, 743. Berge, J. M.; Roberts, S. M. *Synthesis* **1979**, 471. Leibner, J. E.; Jacobus, J. *J. Org. Chem.* **1979**, *44*, 449. Corey, E. J.; Suggs, J. W. *J. Org. Chem.* **1975**, *40*, 2554.
2. Lampard, C.; Murphy, J. A.; Lewis, N. *J. Chem. Soc., Chem. Commun.* **1993**, 295.
3. Callaghan, O.; Lampard, C.; Kennedy, A. R.; Murphy, J. A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 995.
4. Bard, A. J.; Ledwith, A.; Shine, H. J. *Adv. Phys. Org. Chem.* **1976**, *13*, 229.
5. Shine, H. J. In *The Chemistry of the Sulfonium Group*; Stirling, C. J. M.; Patai, S., Eds.; Wiley: New York, 1981; pp. 523–570.
6. Hammerich, O.; Parker, V. D. *Adv. Phys. Org. Chem.* **1984**, *20*, 55.
7. Garin, J.; Orduna, J.; Uriel, S.; Moore, A. J.; Bryce, M. R.; Wegener, S.; Yufit, D. S.; Howard, J. A. K. *Synthesis* **1994**, 489.
8. Murphy, J. A.; Rasheed, F.; Roome, S. J.; Scott, K. A.; Lewis, N. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2331.
9. Kim, D.; Yang, Y. M.; Kim, I. O.; Park, S. W. *J. Chem. Soc., Chem. Commun.* **1988**, 760.