The role of neighbouring group participation in TTF-mediated 'radical-polar crossover' reactions: trapping of aliphatic radicals by TTF+•

Nadeem Bashir and John A. Murphy*

Department of Pure and Applied Chemistry, University of Strathclyde, 295 Cathedral Street, Glasgow, UK G1 1XL. E-mail: John.Murphy@strath.ac.uk
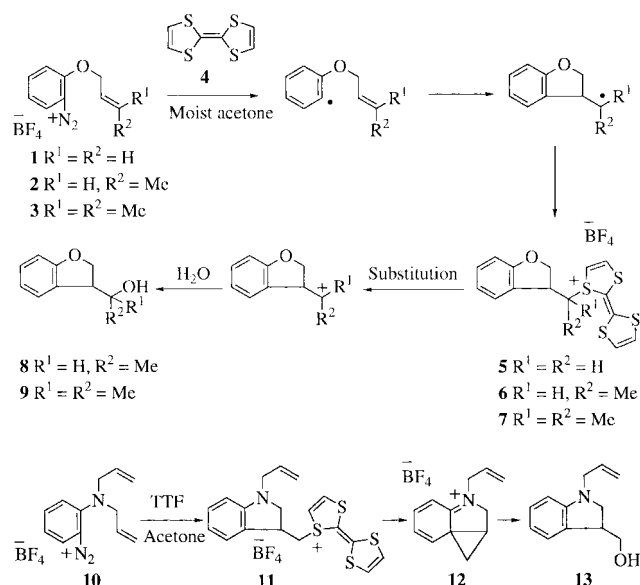
Trapping of secondary alkyl radicals with tetrathiafulvalenium tetrafluoroborate (TTF+•BF4−) leads to S-alkyltetrathiafulvalenium tetrafluoroborate salts; the solvolysis of such salts is critically dependent on the presence of appropriately sited neighbouring groups.

The radical-polar crossover reaction[1] (Scheme 1) features a unique sequence of radical and polar steps in one pot. Tetrathiafulvalene (TTF) transfers an electron to an arenediazonium salt, dinitrogen is lost and the resulting radical can then cyclise before being trapped by the radical-cation of TTF to afford a sulfonium salt and terminate the radical chemistry. In the polar crossover step, solvolysis of the sulfonium salt occurs affording a useful functionalisation at the site of the ultimate radical. The reaction has recently been used as the key step in a novel route to (±)-aspidospermidine.[2]

The substitution (solvolysis) step is of particular interest. Whereas alcohols **8** and **9** were formed on treatment of diazonium salts **2** and **3** with tetrathiafulvalene **4** in undried acetone at room temperature, diazonium salt **1** proceeded only up to the tetrathiafulvalenium salt stage **5**. This strongly suggested that the solvolysis step involved an S_N1 substitution; solvolysis of the salt **5** would not be possible since it would require the intermediacy of a primary carbocation, while sulfonium salts **6** and **7** undergo solvolysis without difficulty. More recently, attempts to force the substitution of the sulfonium group of **5** uncovered a range of novel fragmentation reactions.[3]

Although **5** is resistant to solvolysis, the conversion[4] of the diallylamino diazonium salt **10** to the alcohol **13** suggested that matters could be more complex. Here, the powerful electron donating effect of the *ortho*-amino group must act through the aromatic ring to assist the departure of the TTF molecule from **11** *via* a cyclopropane intermediate **12**. However, the inability of the *ortho*-alkoxy group to trigger the solvolysis of **5** shows that there are strict demands for solvolysis at a primary carbon.[5] However, almost all examples of the radical-polar crossover reaction have involved substitution at secondary carbon. This paper provides experimental evidence that neighbouring group participation is mandatory for solvolysis at secondary carbon under our usual conditions and reveals the requirements for substrate structure in order for solvolysis to be observed.

To investigate whether solvolysis could occur at a secondary carbon in the absence of neighbouring groups, an alkyl radical free of other functionalities was required to be generated under radical-polar crossover conditions. This was achieved using intramolecular radical displacement at sulfur. This reaction has been investigated by the groups of Kampmeier,[6] Beckwith[7] and Schiesser.[8] More recently, Crich *et al.* have used this method to generate acyl radicals both from iodide[9] and diazonium salt[10] precursors. Accordingly, the cyclohexyl substrate **14** was prepared (all amines were prepared by reduction of the corresponding nitro compounds), diazotised and subjected to the radical-polar crossover conditions (Scheme 2). This afforded benzothiophene **16** (48%), (arising from facile elimination of methanol from methoxydihydrobenzothiophene **17** together with the salt **18** (32%) as major products. The S-coupled salt **18** was completely resistant to solvolysis under our conditions (room temperature, 2% water in acetone, 48 h), showing that a tetrathiafulvalenium salt linked *via* a secondary carbon could not of itself undergo solvolysis under these conditions.

Because the outcome of the experiment on the cyclohexyl radical differed from results found with all previously studied secondary radicals, there was some concern that the sulfur substitution reaction conditions might in some way have prevented the normal radical-polar crossover process from occurring. To test this, the intramolecular sulfur displacement reaction was used to generate a radical which had been previously studied under radical-polar conditions, namely **19**, the intermediate in the reaction of **2**. The required substrate, **20**, was prepared, diazotised and subjected to the radical-polar crossover reaction and afforded both dihydrobenzothiophene **21**
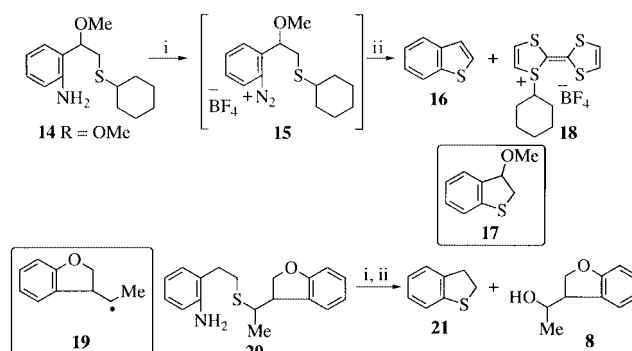
Scheme 1

Scheme 2 *Reagents*: i, NOBF4, CH2Cl2; ii, TTF, acetone, H2O.
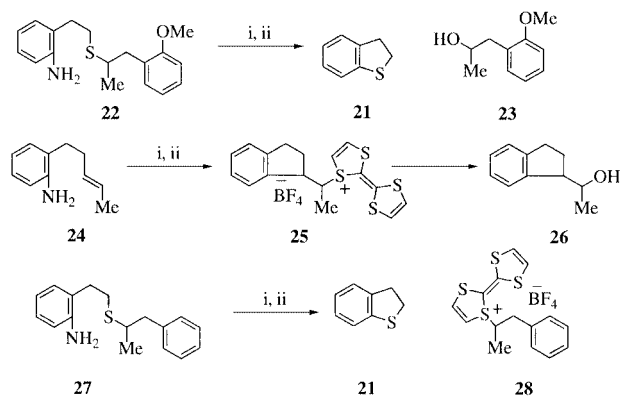
Scheme 3 *Reagents*: i, NOBF$_4$, CH$_2$Cl$_2$; ii, TTF, acetone, H$_2$O.

Scheme 4 *Reagents*: i, NOBF$_4$, CH$_2$Cl$_2$; ii, TTF, acetone, H$_2$O.

(52%) and the alcohol **8** (58%), showing that the radical **19** generated under these conditions was behaving exactly as it had in the reaction of **2**.

The contrast between cyclohexyl TTF salt **18** and salt **6** indicated that a solvolysis of a secondary TTF salt could not occur without some assistance from neighbouring groups. The nature and extent of the assistance were now probed directly. First, to investigate whether some special effect resulted from the dihydrobenzofuran ring system, amine **22** was prepared and diazotised to afford a diazonium salt analogue of **2** (Scheme 3). This duly cyclised to form dihydrobenzothiophene **21** (52%) and the alcohol **23** (53%). No TTF salts were detected after the solvolysis.
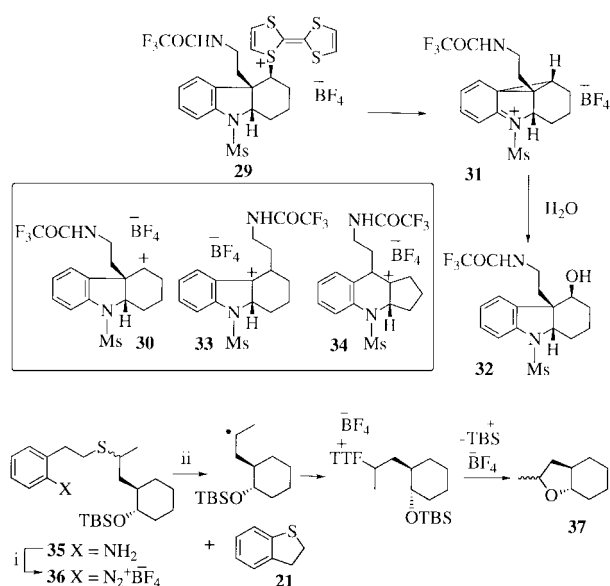
Next, amine **24**, lacking the electron-donating oxygen atom, was prepared and diazotised affording **25**. Surprisingly, the compound also afforded an alcohol product, *i.e.* **26** (24%), indicating that the oxygen atom is not essential for solvolysis.

In contrast, when the diazonium salt derived from **27** was subjected to the radical-polar crossover reaction, **21** was produced (45%) as well as the sulfur-coupled TTF salt **28** (21%). Intriguingly, this sulfur-coupled salt was stable to solvolysis. We deduce that there is a sharp demarcation between substrates that undergo solvolysis in acetone and those that do not. Salt **25** features an *ortho*-dialkylarene and so should be more electron-rich than the monosubstituted arene in **28**; hence it should more effectively promote neighbouring group participation.

The observation of neighbouring group assistance suggests an answer to one of the key questions on the mechanism of these reactions. Until now, solvolysis of TTF salts such as **29** (Scheme 4) was thought to involve intermediates such as the open secondary cation **30**. This cation should easily undergo rearrangement and/or fragmentation (*e.g.* to products **33** and **34**), but this was not observed. With neighbouring group participation, the delocalised cation **31** can be proposed as the true intermediate, and this involvement by the aryl ring can decelerate rearrangements by stabilising the cation and altering the orbital alignment from that required for rearrangement. (The delocalised cation could also control the stereochemistry of attack by the nucleophile water.)

The question now arose about whether groups other than an aromatic ring could assist the solvolysis step. An immediate answer was obtained from diazotisation of the silyl ether **35** and subjection of the product diazonium salt to reaction with TTF (Scheme 4). This afforded the perhydrobenzofuran **37** (23% from amine **35**) indicating that a side-chain oxygen can participate. Dihydrobenzothiophene **21** (56% from amine **35**) was also isolated from this reaction.

Summarising the findings: (i) for the first time, radicals have been produced under TTF-induced radical-polar crossover conditions which are totally aliphatic. Although we do not advocate the intramolecular sulfur displacement reaction as a synthetic route to aliphatic radicals, it allows us to determine the properties of such systems. The development of more powerful radical-polar crossover catalysts than TTF should lead to such products starting from *e.g.* alkyl and aryl halides, thus extending the scope of the reaction.

(ii) A TTF salt linked to a *secondary* carbon will undergo solvolysis with a little assistance from the arene—the arene needs to bear at least two alkyl functions to be sufficiently electron-rich to trigger the solvolysis in acetone under our conditions. This contrasts with the situation for *primary* carbon, where more powerful assistance is required. (The requirement for neighbouring group participation at a secondary carbon has important implications for stereochemical control.)

(iii) Groups other than arenes can participate in the solvolysis. This extends the scope of the radical-polar crossover reaction.

Notes and references

1 J. A. Murphy, C. Lampard and N. Lewis, *J. Chem. Soc., Chem. Commun.*, 1993, 295.
2 O. Callaghan, C. Lampard, A. R. Kennedy and J. A. Murphy, *J. Chem. Soc., Perkin Trans 1*, 1999, 995.
3 O. Callaghan, X. Franck and J. A. Murphy, *Chem. Commun.*, 1997, 1923.
4 C. Lampard, J. A. Murphy, F. Rasheed, N. Lewis, M. B. Hursthouse and D. E. Hibbs, *Tetrahedron Lett.*, 1994, **35**, 8675.
5 For a review of the extensive area of solvolysis of β-arylalkyl substrates, see: J. C. Lancelot, D. J. Cram and P. von R. Schleyer, *Carbonium Ions*, ed. G. A. Olah and P. v. R. Schleyer, Wiley-Interscience, 1972, vol. 3, pp. 1347–1483.
6 J. A. Kampmeier and T. R. Evans, *J. Am. Chem. Soc.*, 1966, **88**, 4096.
7 A. L. J. Beckwith and S. A. M. Duggan, *J. Chem. Soc., Perkin Trans. 2*, 1994, 1509.
8 B. A. Smart and C. H. Schiesser, *J. Chem. Soc., Perkin Trans 2*, 1994, 2269; C. H. Schiesser, M. L. Styles and L. M. Wild, *J. Chem. Soc., Perkin Trans. 2*, 1996, 2257.
9 D. Crich and Q. Yao, *J. Org. Chem.*, 1996, **61**, 3566.
10 D. Crich and X. L. Hao, *J. Org. Chem.*, 1997, **62**, 5982.

Communication b000786m