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On The Mechanism of the Tetrathiafulvalene-Mediated Radical-Polar Crossover Reactions

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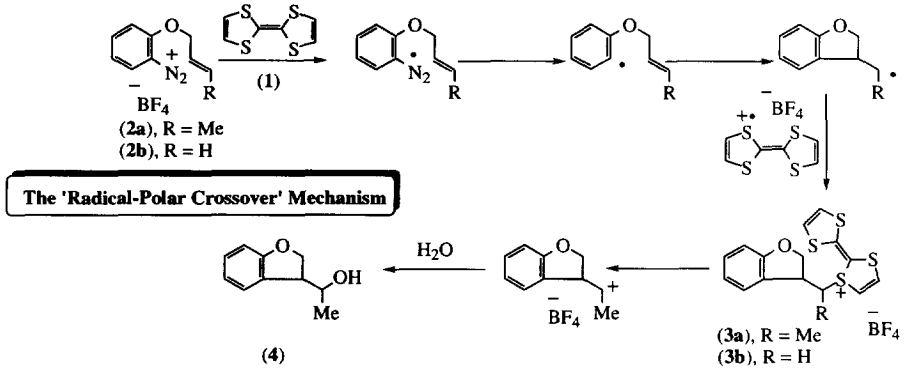
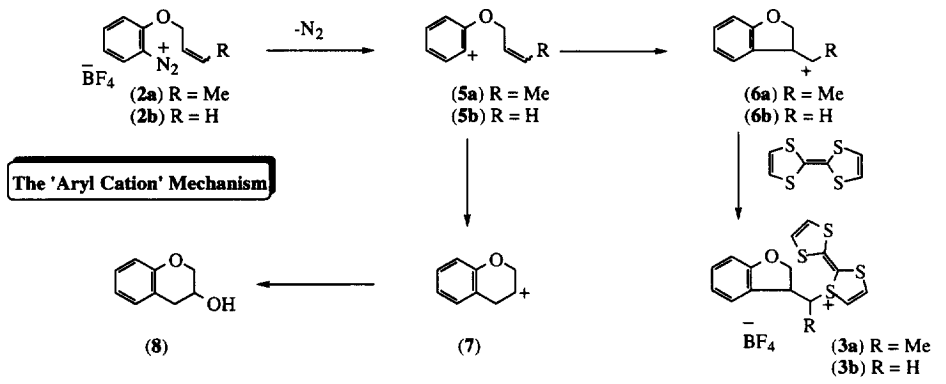
Abstract. Strong evidence supports the previously proposed mechanism of the radical-polar crossover reactions, and discounts a totally ionic mechanism. © 1997 Elsevier Science Ltd.

The utility of tetrathiafulvalene (TTF, **1**) as a catalyst in the preparation of functionalised heterocycles has recently been described[1-8] and reviewed[9]. A typical transformation is shown below [(**2a**) → (**4**)], together with the proposed intermediates. As part of earlier studies[1], we reported the isolation of salts (**3**), and the clean conversion of (**3a**) into (**4**). By contrast, compound (**3b**) in which the TTF moiety is attached to a primary carbon was resistant to substitution by water. Hence, an S_N1 mechanism was proposed for the transformation of (**3a**).

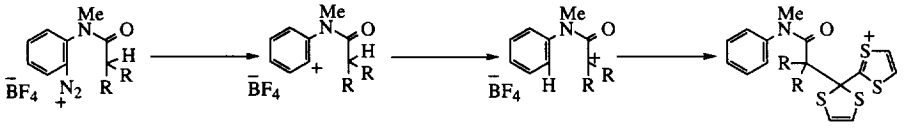


Since the initial publication, many have questioned whether an alternative mechanism might operate to produce the sulfonium salts (**3**), featuring not the aryl radical but the aryl cation (**5**). In principle, this could lead to the same product, but without the need to invoke radical intermediates; in these circumstances, TTF would function simply as a nucleophile rather than as an electron transfer agent[10].

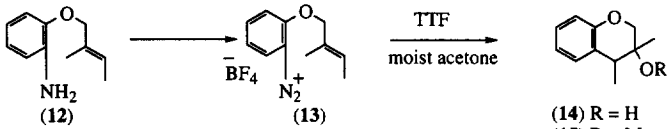
One of the factors which argued against such a mechanism was the regiochemistry of cyclisation for certain substrates. For example, cyclisation of allyloxybenzenediazonium tetrafluoroborate (**2b**) led to formation of the dihydrobenzofuran (**3b**). If this had occurred *via* cyclisation of the aryl cation (**5b**), a primary carbocation (**6b**) would have been an intermediate. The exceptional instability of such a cation should prevent its formation and, instead, drive the reaction towards formation of the corresponding tetrahydrobenzopyran (**8**) *via* a more stable secondary carbocation (**7**). No tetrahydropyran had ever been observed in our reactions.



The second factor which weighed against the aryl cation mechanism related to the reactions which had been observed with the amide substrates (**9**). To explain the observed products (**11**) by the aryl cation mechanism would imply intramolecular hydride ion delivery to the aryl cation. The resulting cation (**10**) resides α- to a carbonyl group, and while this is not too serious for the tertiary carbocation[11,12] (**10a**), a primary carbocation (**10b**) adjacent to a carbonyl group is untenable.

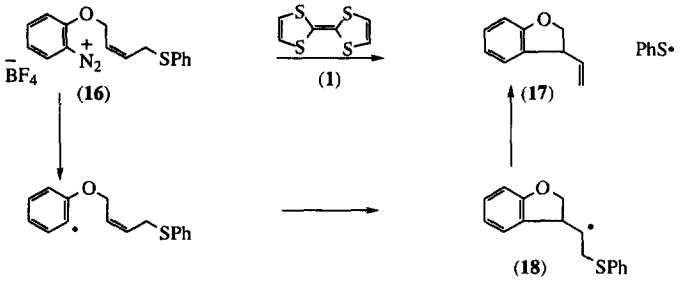


These facts gave support to our 'radical-polar' view of the mechanism. However, when the diazonium salt (**13**) was reacted with TTF, a tetrahydropyran (**14**) was now observed as the major product. This product was contaminated by a small amount of an inseparable second product. This mixture was methylated (KOH, DMSO, MeI) to afford pure methyl ether (**15**) [65% from amine (**12**)], which was fully characterised. The most notable feature of the ^{1}H NMR spectrum of (**15**) was the benzylic proton (δ 2.95). Although there could be many explanations for the formation of tetrahydropyran, its appearance caused us to undertake a more rigorous scrutiny of the mechanism of 'radical-polar' chemistry.

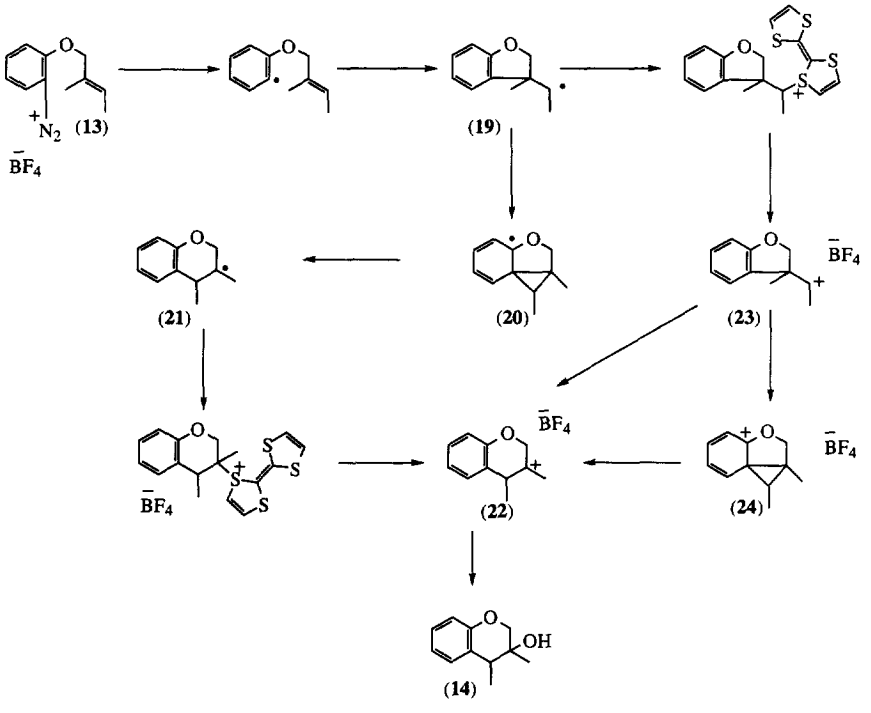


Substrate (**2a**) was used in the first part of this study. The aryl cation mechanism would imply that TTF intercepted alkyl cation (**6a**). If TTF were able to perform such a reaction, so also should other sulfides. To test this, dimethyl sulfide was selected. It was necessary firstly to establish that this compound was at least as good a nucleophile as TTF. Accordingly, TTF and dimethyl sulfide were separately treated with dimethyl sulfate in dichloromethane at room temperature. After 12h, the dimethyl sulfide had been completely transformed into the corresponding trimethyl sulfonium salt, whereas even after 72h, TTF was completely unchanged. This demonstrated that dimethyl sulfide is a considerably better nucleophile than TTF and hence would be competent at trapping intermediate cations such as (**6a**). When two parallel experiments were now conducted in which the diazonium salt (**2a**) was treated in moist acetone with (a) TTF and (b) dimethyl sulfide, immediate effervescence

was observed in the TTF experiment, but not in the other. ^{1}H NMR indicated that after 30 min. in the TTF experiment, the diazonium salt (**2a**) had been transformed into the alcohol (**4**), but was left completely unchanged even after stirring for three days with dimethyl sulfide. Hence, TTF specifically triggers the reaction. We conclude that it must be the facile electron transfer from TTF which is responsible.

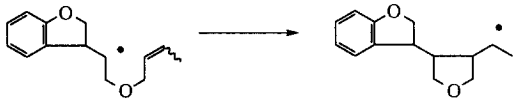


A further line of evidence was sought to support the radical-polar crossover mechanism. This emerged from the substrate (**16**). The radical-polar crossover mechanism predicts the formation of the intermediate radical (**18**), which should lead to facile loss of the phenylthiyl radical[13]. When the experiment was conducted, clean tranformation to the alkene (**17**) (isolated yield 60%) was observed and diphenyl disulfide was isolated from the reaction (41%). Such a reaction is completely inconsistent with the aryl cation mechanism, but is clearly consistent with the radical-polar crossover mechanism.



Returning to diazonium salt (**13**), its transformation to tetrahydropyran (**14**) can be explained in one of two ways. Both require initial radical cyclisation[14-17] to dihydrobenzofuran (**19**); this radical can then undergo a

neophyl rearrangement *via* radical (**20**) to radical (**21**) which then couples with TTF+• giving cation (**22**) prior to substitution by water to afford the observed alcohol (**14**). Alternatively, dihydrobenzofuran (**19**) couples with TTF+•; loss of TTF affords the secondary cation (**23**) which undergoes either a direct Wagner-Meerwein ring expansion to the tertiary cation (**22**) or arrives there *via* the Meisenheimer complex (**24**). Attack by water upon (**22**) affords the product alcohol (**14**). Of these two rearrangement mechanisms, the cationic rearrangement *via* (**23**) must be favoured, since the rate constant for neophyl rearrangement of (**19**) has been estimated[14] as 3.1 x 10^4 sec^{-1}. We have previously demonstrated that, under similar concentrations of substrate and of TTF, the trapping of secondary carbon radical (**25**) by TTF+• can compete with its cyclisation to (**26**). The rate constant in this case[18] is likely to be > $10^6 sec^{-1}$. Hence, the neophyl rearrangement of (**19**) is likely to be very much too slow to be observed.



(**25**) (**26**)

In conclusion, these studies clearly support the previously proposed radical-polar crossover mechanism for the reactions of TTF with arenediazonium salts. The observation of tetrahydrobenzopyran (**14**) as the principal reaction product from (**13**) once again illustrates how radical-polar chemistry extends what is possible beyond that seen in the purely radical world.

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