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Tetrathiafulvalene as a Trigger for Sequential Radical Translocation and Functionalisation

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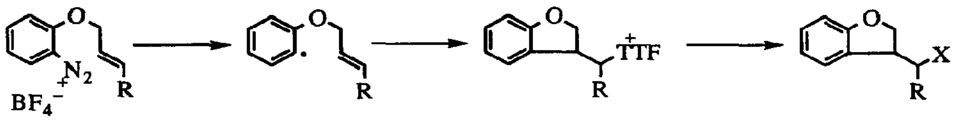
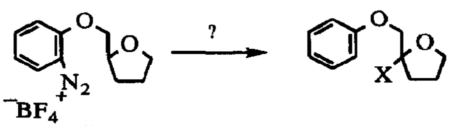
Abstract. Aryl diazonium salts react with tetrathiafulvalene to generate aryl radicals which undergo intramolecular hydrogen atom abstractions; the radicals which result lead to (a) oxidised product or (b) undergo an unprecedented carbon-carbon bond formation with the radical-cation of tetrathiafulvalene.

We have recently witnessed remarkable reactions using tetrathiafulvalene (TTF) as an electron donor. Diazonium salts were converted to aryl radicals which underwent cyclisation. The product alkyl radicals were then transformed into alcohols, ethers or amides[1].

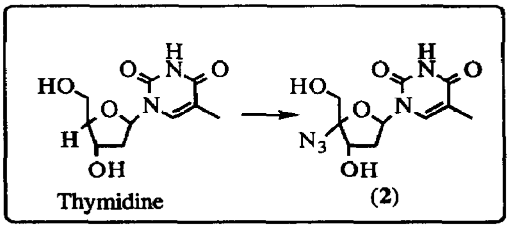


X= OH, OMe, NHAc

The mildness of the conversions led us to investigate whether this oxidative termination[2] of radical chemistry could be linked to other processes. This paper describes our initial results in combining this chemistry with radical translocation. Since the discovery of the Barton[3] and Hofmann-Loffler-Freytag reactions[4], radical translocation has been shown to be a remarkably powerful means of introducing functionality at unactivated sites. More recent studies[5,6] have extended the scope of this type of reaction, in particular by determining the ability of aryl and vinyl radicals to effect translocation. Our aim was to investigate whether aryl radicals, formed by electron transfer from tetrathiafulvalene to diazonium salts, would conduct a tandem translocation/functionalisation sequence.



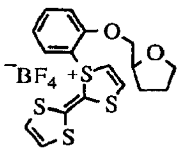
(1)



Thymidine (2)

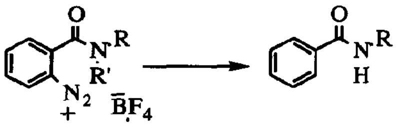
Studies started with the tetrahydrofuran diazonium salt (**1**). This molecule was of particular interest since it would provide guidance on the suitability of this approach for a very direct synthetic conversion of thymidine to ADRT (**2**)[7], a compound with anti-HIV properties, which features a 4'-azido-2'-deoxyribose. Treatment of (**1**) with TTF in acetone at room temperature led to isolation of two compounds. The product of radical translocation was best isolated by evaporating the crude reaction product and then reacting with sodium borohydride/ethanol giving the ethoxy derivative (**3**) (40%)[8]. The second compound (**4**), (23%) most likely formed by combination of the aryl radical with TTF+• shows that radical translocation and direct trapping of TTF+• compete. We are currently studying how to retard the direct aryl trapping reaction, but the directness of the functionalisation to (**3**) and the fact that ketals can be converted into azidoethers[8] thus make this a potentially attractive and direct approach for functionalising deoxyribose.

(**1**) (**3**)

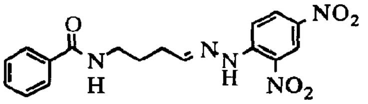


(**4**)

Curran and Snieckus have recently determined that aryl radicals cause efficient translocations in certain amides[5]. In our hands, N,N-disubstituted amides did indeed react rapidly and efficiently resulting in oxidative monodealkylation for primary (**5**) (39%), secondary (**6**) (85%), tertiary (**7**) (98%), benzylic (**8**) (61%) and cyclopropylmethyl (**9**) (87%) groups when the reactions were conducted in moist acetone. No aryl-TTF products analogous to (**4**) were observed.



(**5**) R=R'=Me
(**6**) R=R'= Et
(**7**) R=R'= ^{i}Pr
(**8**) R=R'=CH_2Ph
(**9**) R=^{t}Bu, R'=$C_3H_5CH_2$
(**10**) R, R'=$(CH_2)_4$

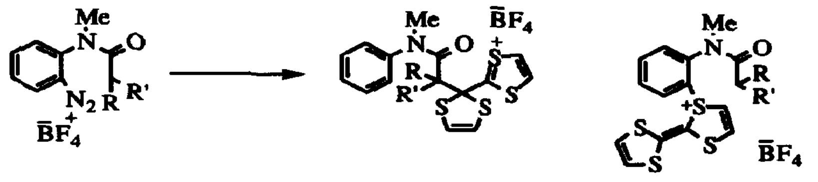


(**11**)

For these reactions, the low molecular weight oxidised by-products were not isolated. However, to demonstrate that oxidation was indeed occurring at the translocated site, addition of an ethanol solution of 2,4-dinitrophenylhydrazine to the crude product of the reaction of (**10**) [following evaporation of acetone] afforded the 2,4-dinitrophenylhydrazone (**11**). For all of these cases the site of the translocated radical must be converted to an aminol by (a) either direct electron transfer to another molecule of diazonium salt or by initial coupling with TTF+• followed by loss of TTF and (b) attack of water. These reactions were conducted successfully both with one equivalent and with catalytic quantities of TTF (10 mol %).

The amides (**12**) → (**14**), which would give rise to electrophilic translocated radicals were next studied. Here, all of the spectra of the crude products featured a prominent two-proton singlet at *ca.* δ9, due to dithiolium salts (**15**)(53%), (**16**)(47%), (**17**)(27%). This previously unobserved type of carbon-carbon bond formation indicates that electrophilic radicals prefer to react at the internal carbon[10] site of TTF+•, in contrast to nucleophilic radicals which couple to the sulfur[1]. Calculations indicate[11] that the unpaired spin density in TTF+• resides principally on sulfur, but with the internal carbon being the site of second highest density. The product of coupling of an α-carbonyl radical to sulfur, an α-carbonylsulfonium salt, would be destabilised by the adjacent dipoles. The transition state would be expected to mirror this, so slowing down the C-S coupling and permitting the observed coupling to the carbon of TTF.

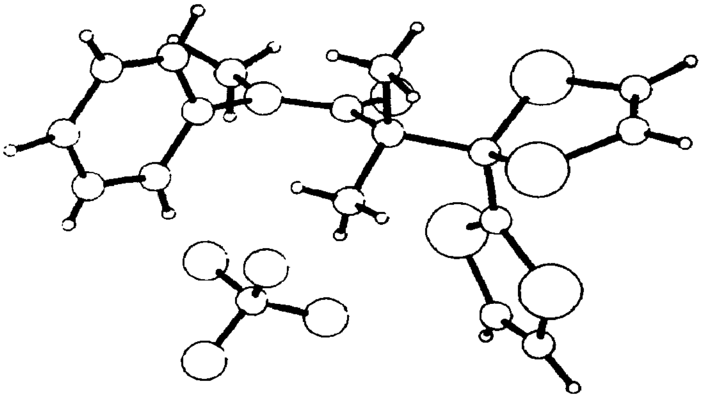
The structure of (15) was confirmed by single crystal X-ray analysis. Products (18) (14%), (19) (32%), and (20) (41%) resulting from trapping of TTF+• by the aryl radical were also observed from the above reactions; the relative yields show that the speed of hydrogen atom translocation was crucially dependent on the substitution pattern of the translocated radical (see Table II in reference 5a for precedent).



(12) R=R'=Me
(13) R=Me, R'=H
(14) R=R'=H

(15) R=R'=Me, 53%
(16) R=Me, R'=H, 47%
(17) R=R'=H, 27%

(18) R=R'=Me, 14%
(19) R=Me, R'=H, 32%
(20) R=R'=H, 41%



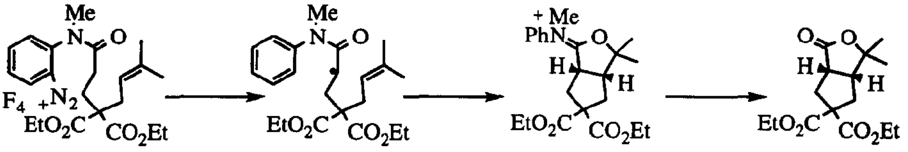
Crystal Structure of Compound (15)

Finally, we examined whether a translocation/cyclisation/oxidation sequence could be accomplished by treating diazonium salt (21) with TTF. From analogy with compound (16), we should expect 47% of product to result from translocated radical (22). If coupling to TTF+• by carbon-carbon bond formation is relatively slow, then cyclised product(s) will be observed. Examination of the crude reaction mixture indicated that the iminium salt (23) was the principal product. This was not isolated, but instead hydrolysed by base treatment and the products chromatographed to afford the lactone (24) in 45% yield. No product analogous to (15) was detected.

These studies show that in TTF/diazonium salt initiated translocation reactions, the ultimate fate of the translocated radical depends on its nature. Nucleophilic alkyl radicals proceed to oxidised products, whereas electrophilic radicals undergo a novel carbon-carbon bond formation to TTF+•. The observation of a tandem radical translocation, cyclisation and oxidative funtionalisation from (21) indicates that the diazonium salt/tetrathiafulvalene couple may have interesting applications to synthesis.

The studies reported here reflect an initial rather than an optimised system. Compounds (4) and (18)→(20) show that the major competing reaction is trapping of the aryl radical prior to hydrogen atom abstraction. Nevertheless the current studies provide a clue on how to prevent this competing reaction.

Electrophilic carbon radicals including both α-carbonyl radicals and aryl radicals derived from compounds (**5**)→(**10**) do not engage in C-S bond formation with TTF+•; the alternative C-C bond formation appears to be a much slower reaction. Hence diazonium salts related to (**1**) but with less electron-rich aromatic rings are predicted to undergo more efficient translocation reactions.



(**21**) (**22**) (**23**) (**24**)

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