Pergamon

Tetrahedron Letters, Vol. 35, No. 46, pp. 8675-8678, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01838-3

Novel Synthetic Applications of Arenediazonium Salts

Christopher Lampard, John A. Murphy* and Faiza Rasheed,
Department of Chemistry, University of Nottingham, University Park, Nottingham NG7 2RD

Norman Lewis,
SmithKline Beecham Pharamaceuticals, Old Powder Mills, Leigh,
Tonbridge, Kent TN11 9AN

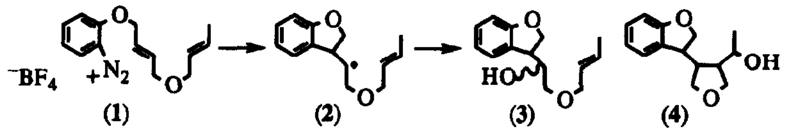
Michael B. Hursthouse and D. E. Hibbs,
EPSRC X-Ray Crystallography Service, School of Chemistry and Applied Chemistry,
P.O. Box 912, Cardiff, CF1 3TB

Abstract: Tetrathiafulvalene reacts with diazonium salts to afford functionalised nitrogen and oxygen heterocycles.

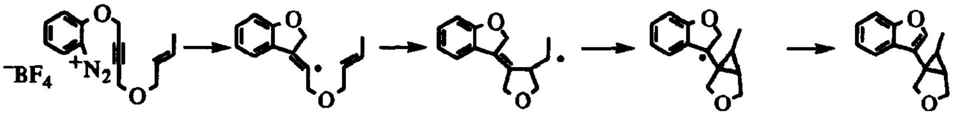
We have recently reported the use of tetrathiafulvalene in electron transfer to diazonium salts which caused radical cyclisation followed by oxidative termination[1,2]. In this paper, we report on the scope of this reaction in producing more complex oxygen heteropolycycles, and in producing nitrogen heterocycles.

Initially, the diene (1) and enyne (5) were prepared to test the possibility of tandem radical cyclisations prior to oxidative termination. Treatment of the diene with 1 equivalent of TTF in moist acetone afforded a mixture of two products, the alkene (3)(41%) and the bicyclised compound (4)(15%) each as a mixture of diastereomers. This suggested that the rate of oxidative interception of the radical (2) was competitive with the second cyclisation. It follows either that the second cyclisation is considerably slower than the cyclisation of the aryl radical[3] or that oxidative interception[4] is much slower for the aryl radical than for (2).

In view of this, we tested substrate (5). This compound should feature an aryl radical cyclisation followed by a vinyl radical cyclisation. Although rate data for vinyl radical cyclisations are sparse, we suspected that the aryl and vinyl cyclisation rates might be very similar and therefore that this substrate might deliver the product of two sequential cyclisations. In fact, the sole product of this reaction was the tetracycle (7)(64%) [isolated as a separable pair of diastereomers], indicating that not only had both cyclisations occurred but that a further cyclopropane formation had also been accomplished. This reaction adds to a growing number of recently observed radical cyclopropane syntheses[5]. Analysis of the position of equilibrium between phenyl-substituted cyclopropylcarbinyl radicals and the corresponding ring-opened butenyl radicals has shown that the ring closed form predominates under standard reaction temperatures[6]. Although in this case the fused cyclopropane will have added ring strain, the benzylic nature of radical (6) must assist formation of the observed product. In the formation of (7), the intermediate benzylic radical (6) may couple to TTF+• and then yield the product by loss of TTF and a proton, or, alternatively, (6) may be directly oxidised to a cation by electron transfer to another molecule of diazonium salt and then suffer proton loss. These studies define the scope of radical cyclisations to occur in the presence of TTF+•.

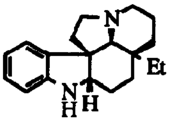


(1) (2) (3) (4)

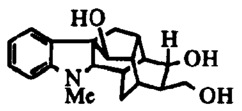


(5) (6) (7)

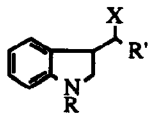
Attention was next directed towards forming nitrogen heterocycles. Aspidospermidine and ajmaline (shown below) are two of many indoline alkaloids which pose interesting synthetic challenges. Both molecules feature a heteroatom β to the 3-position of the indoline as in (8). To investigate initially whether simple indolines like (8) could be prepared, the N-benzoyl, N-allyl diazonium salt (9) was synthesised.



Aspidospermidine

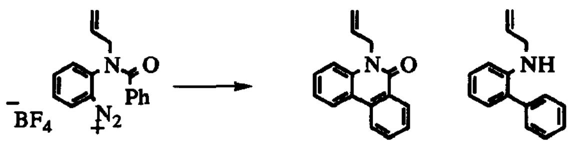


Ajmaline

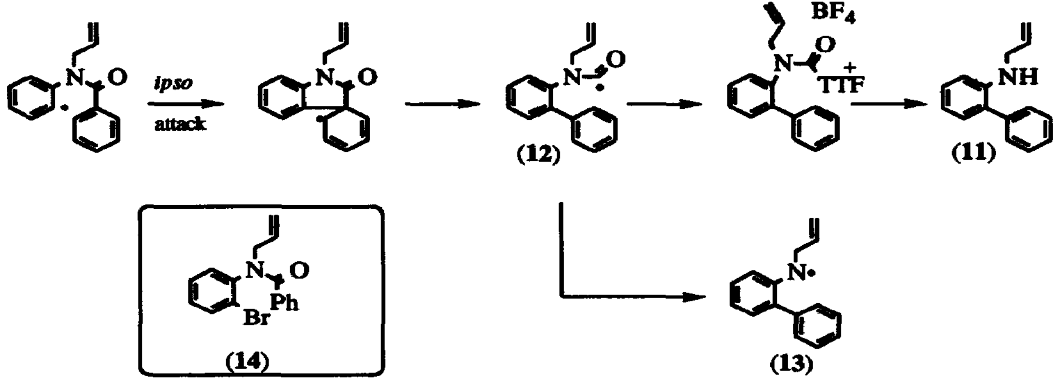


(8)
X = Heteroatom

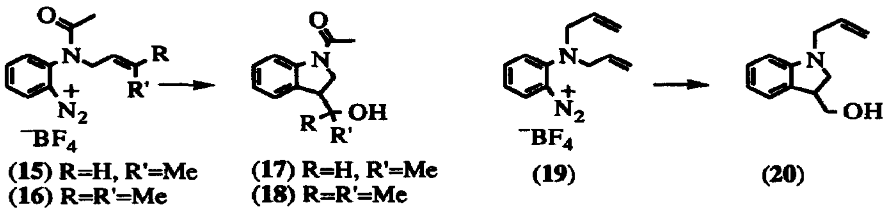
Disappointingly, reaction with TTF gave rise to two products in low yield : the lactam (10)(8%) and the biphenyl (11)(6%). These products arise from attack of the aryl radical on the aromatic ring of the benzoyl group. We speculate that *ipso* attack led to radical (12) and that subsequent quenching by TTF+• afforded an intermediate which on hydrolytic work-up afforded TTF, carbon dioxide and the observed biphenyl (11).

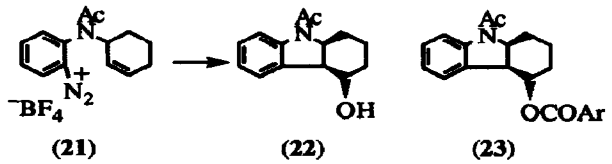


(9) (10) (11)



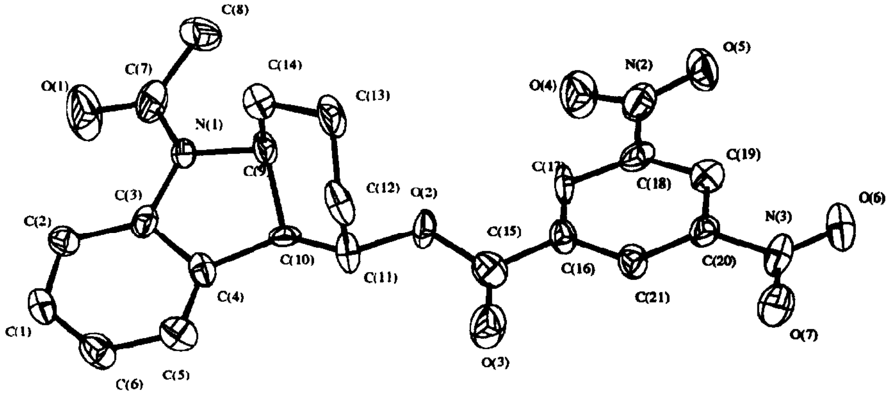
It is unlikely that radical (13) is an intermediate in this reaction, because of the dearth of examples[7] of decarbonylation of radicals like (12) and also because radical (13) should react with TTF$^{+\bullet}$ rather than undergo reductive work-up. It is interesting to compare the results of this experiment with those of Togo[8], who reacted the aryl bromide (14) with tributyltin hydride and AIBN to form (10) with no trace of products derived from intermediate radical (12). Although the reaction of (9) was not encouraging, inspection of the literature showed that the N-benzoyl group[9] causes unusual chemistry. To avoid this and achieve an indoline synthesis[9], the acetyl substrates (15) and (16) were examined. Reaction with TTF in moist acetone afforded the indolines (17)(59%) and (18)(59%) respectively. Diallyl diazonium salt (19) also afforded indoline (20) in 40% yield.





Finally, as a prelude to the synthesis of more complex heteropolycycles, the diazonium salt (21) was prepared. Cyclisation in moist acetone gratifyingly afforded the tricyclic alcohol (22) as a single diastereomer (65%). The stereochemistry of this product was defined by an X-ray crystal structure determination of the corresponding 3,5-dinitrobenzoate ester (23).

The yields of these reactions reported in this paper have not been optimised, and so this chemistry holds considerable synthetic promise. The scope and synthetic utility of these reactions are currently under investigation.



X-Ray Crystal Structure of Compound (23)

Acknowledgements. We thank the EPSRC and SmithKline Beecham for CASE awards to C.L. and F.R. We also thank the EPSRC Mass Spectrometry Unit, Swansea for high resolution FAB mass spectra.

References.

1. Lampard, C.; Lewis, N.; Murphy, J. A., *J.Chem. Soc., Chem. Commun.*, **1993**, 295-297;
2. For alternative radical functionalisation reactions using diazonium salts, see: Meijs, G. F.; Beckwith, A. L. J., *J. Am. Chem. Soc.*, **1986**, *108*, 5890; Meijs, G. F.; Beckwith, A. L. J., *J. Org. Chem.*, **1987**, *52*, 1922. Cohen, T.; Dietz, A. G. Jr.; Miser, J. R., *J. Org. Chem.*, **1977**, *42*, 2053;
3. Beckwith, A. L. J.; Gara, W. B., *J.Chem. Soc., Perkin Trans. II*, **1975**, 795;
4. Begley, M. J.; Murphy, J.A. ; Roome, S. J. accompanying manuscript.
5. Bowry, V. W.; Lusztyk, J.; Ingold, K. U., *J. Chem. Soc., Chem. Commun.*, **1990**, 923; Zhang, W.; Dowd, P., *Tetrahedron Lett.*, **1992**, *33*, 7307; Weng, W.-W.; Luh, T.-Y.,*J. Org. Chem.*, **1993**, *58*, 5574; Journet, M.; Malacria, M., *J. Org. Chem.*, **1994**, *59*, 718; Begley, M. J.; Pattenden, G.; Smithies, A. J.; Walter, D. S., *Tetrahedron Lett.***1994**, *35*, 2413; Cekovic, Z.; Saicic, R., *Tetrahedron Lett.***1990**, *31*, 6085 *Tetrahedron Lett.*, **1989**, *30*, 3229; Denis, R. C.; Gravel, D. *Tetrahedron Lett.***1994**, *35*, 4531.
6. Beckwith, A. L. J.; Bowry, V. W. *J. Am. Chem. Soc.*, 1994, **116**, 2710.
7. Gill, G. B.; Pattenden, G.; Reynolds, S. I.*J.Chem. Soc., Perkin Trans. I*, **1994**, 369.. Friedman, L.; Schechter, H., *Tetrahedron Lett.*, **1961**, *2*, 238.
8. Togo, H.; Kikuchi, O., *Tetrahedron Lett.*, **1988**, *29*, 4133.
9. Jones, K.; Storey, J. M. D., *J. Chem. Soc., Chem. Commun.*, **1992**, 1766.

(*Received in UK* 10 *August* 1994; *revised* 14 *September* 1994; *accepted* 16 *September* 1994)