Pergamon

Tetrahedron Letters, Vol. 37, No. 14, pp. 2511-2514, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00306-1

Studies of the Tetrathiafulvalene Mediated Radical-Polar Crossover Reaction Directed Toward the Total Synthesis of Alkaloid Natural Products

Murat Kizil,[a] Christopher Lampard [a,b] and John A. Murphy [a,b]*

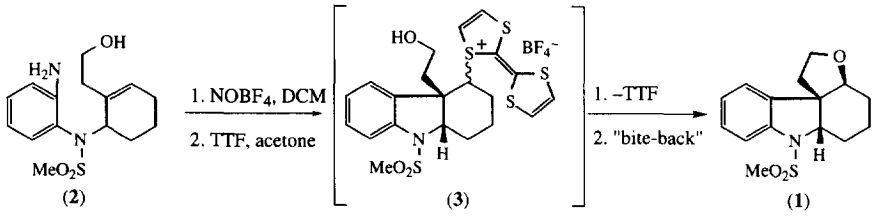
[a] Department of Chemistry, The University of Nottingham, University Park, Nottingham, NG7 2RD,

[b] Department of Pure and Applied Chemistry, The University of Strathclyde,

295 Cathedral Street, Glasgow G1 1XL.

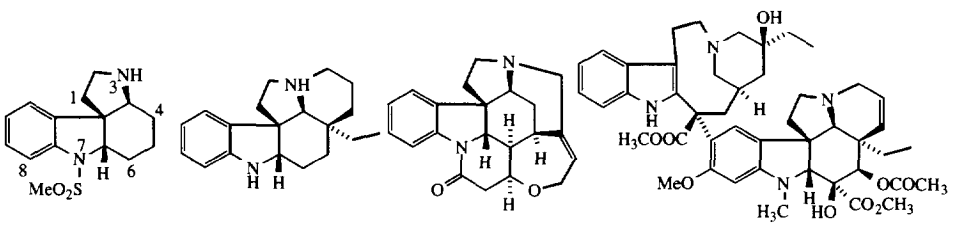
Abstract: The carbon skeleton of octahydro-1*H*-pyrrolo[2,3-*d*]carbazole (**4**), a tetracylic sub-unit which is common to a wide range of alkaloid natural products has been prepared by two approaches which exploit the one-pot radical-polar crossover chemistry mediated by tetrathiafulvalene. Both approaches proceed with complete stereoselectivity. Copyright © 1996 Elsevier Science Ltd

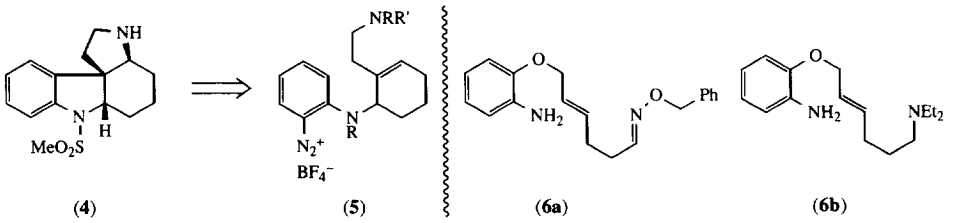
The stereocontrolled construction of complex polycyclic systems is a challenging goal in synthetic organic chemistry. We have previously shown that our tetrathiafulvalene radical/polar crossover chemistry[1] can be used to construct tetracyclic molecules, such as (**1**), in a "one-pot" procedure from aniline (**2**).



Hence, diazotisation of (**2**) followed by removal of solvent and *in situ* reaction with tetrathiafulvalene results in the generation of alkylsulfonium intermediate (**3**). Loss of TTF gives an intermediate carbocation[2] which is trapped by an internal nucleophile, a process we have termed "bite-back". The conversion of (**2**) into (**1**) is achieved in a highly stereoselective manner; complete control of the stereochemistry of the three new contiguous chiral centres of (**1**) is observed.

This paper reports the extension of this chemistry to the formation of the 2,3,3a,4,5,6,6a,7-octahydro-1*H*-pyrrolo[2,3-*d*]carbazole (**4**), a tetracylic subunit the carbon skeleton of which is common to a wide range of alkaloid natural products (representative examples being aspidospermidine, strychnine and vinblastine).

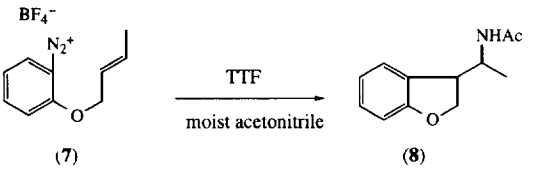




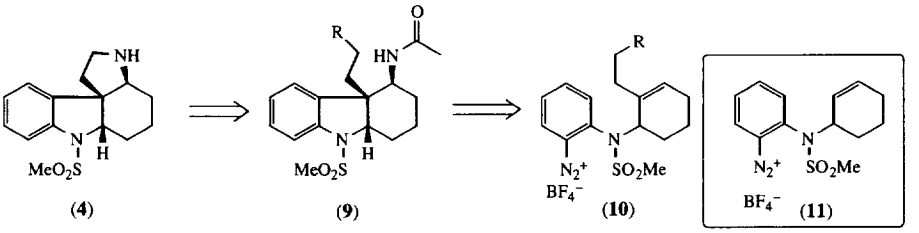
(4) (5) (6a) (6b)

Initially it was thought that an arenediazonium salt such as (**5**), in which a suitably substituted nitrogen atom would be disposed to act as an internal nucleophile, might make a good choice as precursor to (**4**). We had not previously demonstrated intramolecular carbon-nitrogen bond formation using radical-polar crossover chemistry, and hence model compounds (**6a**) and (**6b**) were prepared. However, when they were exposed to diazotisation and then to reaction with TTF under our standard reaction conditions, complicated mixtures of products were produced, and no evidence of carbon-nitrogen bond formation to the oxime ether of (**6a**) or to the tertiary amine of (**6b**) was seen. Consequently two alternative approaches to the skeleton of (**4**) were examined.

The substituted 1,2,3,4,4a,9a-hexahydrocarbazole (**9**) was proposed as a precursor for (**4**). We had previously shown that using acetonitrile as solvent (rather than acetone), the reaction between TTF and arenediazonium salt (**7**) gave the amide (**8**) in moderate yields[2b]. This amide was formed by hydrolysis of a nitrilium cation, itself formed by trapping of the intermediate carbocation with acetonitrile. Accordingly, it was apparent that (**9**) ought to be available from diazonium salt (**10**), by reaction with TTF in acetonitrile. To examine the feasibility of preparing (**9**) *via* our methodology, the reaction of the arenediazonium salt (**11**) was initially examined. Here, all the elements of (**10**) were present, except for the carbon side chain that would ultimately lead to the formation of the fourth ring.

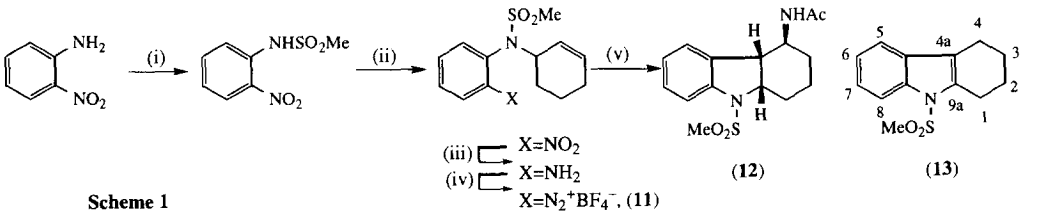


(7) (8)



(4) (9) (10) (11)

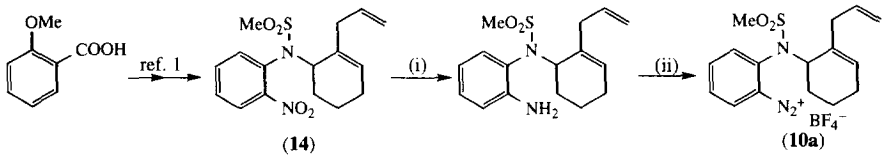
(**11**) was conveniently prepared as outlined in scheme 1 and reacted smoothly with TTF in acetonitrile to give the desired 1,2,3,4,4a,9a-hexahydrocarbazole (**12**). A second product, 9-methanesulphonyl-1,2,3,4-tetrahydrocarbazole (**13**) was also formed. [This presumably arises when the intermediate carbocation formed in the reaction eliminates a proton from position 4a, to give the 9-methanesulphonyl-1,2,3,9a-tetrahydrocarbazole, which tautomerises to (**13**) *in situ*. The formation of indole (**13**) did not cause concern, since in our approach to target molecule (**4**), using diazonium salt (**10**), no proton is available at position 4a and so the reaction should be funnelled exclusively towards an indoline analogous to (**12**).



Scheme 1

(i) $MeSO_2Cl$, DMAP, pyridine, reflux, 12h, 56%; (ii) 2-cyclohexen-1-ol, DEAD, PPh_3, THF, 24h, 67%; (iii) $Cu(acac)_2$, $NaBH_4$, EtOH, 12h, 80%; (iv) isoamylnitrite, HBF_4(aq), EtOH, 0°C, 30 min., 70%; (v) TTF, CH_3CN, 48h, **12**, 51%, **13**, 20%.

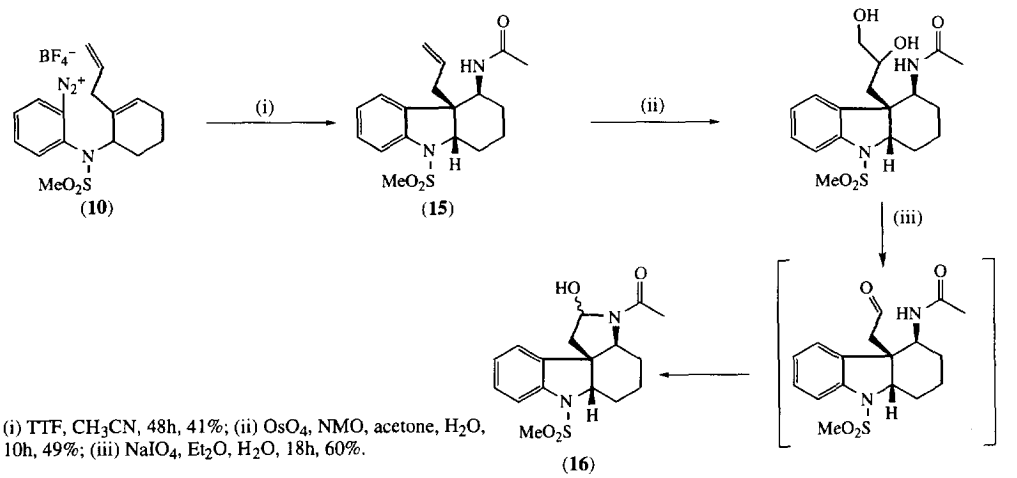
Hence, having shown that carbon-nitrogen bond formation was feasible in these systems, the more complex case of (**10a**) was then studied. This arenediazonium salt was readily prepared from known compound (**14**)[1] using the procedures outlined in scheme 2.



(i) $Cu(acac)_2$, $NaBH_4$, EtOH, 12h, 81%; (ii) $NOBF_4$, CCl_4, 0°C, 30 min., 73%.

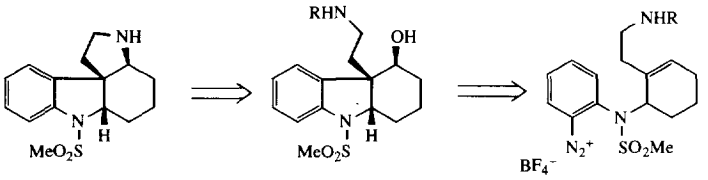
Scheme 2

Reaction of (**10a**) with TTF in acetonitrile led to the desired hexahydrocarbazole (**15**) as a single diastereoisomer. (Previous studies made with a similar compound[3] infer that the stereochemistry of this single isomer is as shown, *i.e.* with the three carbon side chain and the amide group disposed *cis* to each other.) Dihydroxylation of the alkene of (**15**) and sodium periodate cleavage gave (**16**) directly, in which the desired octahydro-1*H*-pyrrolo[2,3-*d*]carbazole skeleton has been assembled with complete control of stereochemistry.



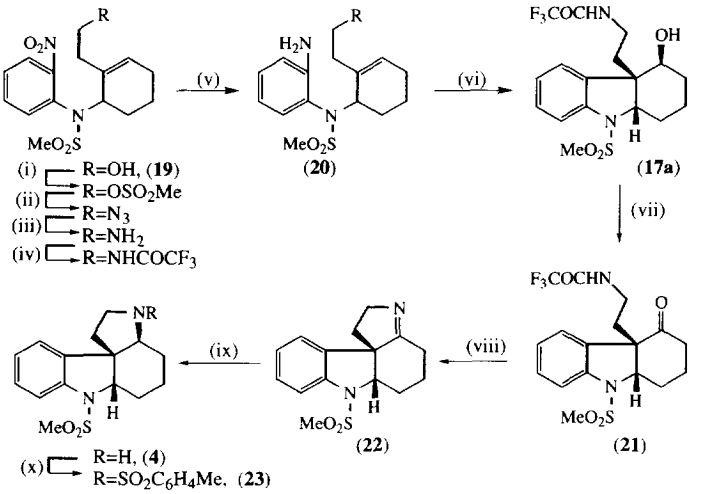
(i) TTF, CH_3CN, 48h, 41%; (ii) OsO_4, NMO, acetone, H_2O, 10h, 49%; (iii) $NaIO_4$, Et_2O, H_2O, 18h, 60%.

Our second approach to the octahydro-1*H*-pyrrolo[2,3-*d*]carbazole skeleton (**4**) used the alcohol (**17**). Previous studies have shown that the preparation of alcohols using our TTF methodology generally proceeds in higher yield than the formation of the corrresponding amides[4]. Hence, preparation of (**17**) from arenediazonium salt (**18**) was expected to occur efficiently.



(4) (17) (18)

The salt (**18**, R = $COCF_3$) was prepared from the known alcohol (**19**)[1] as outlined in scheme 3. Aniline (**20**) reacted smoothly to give the desired product (**17a**), again formed as a single diastereoisomer. Oxidation with pyridinium chlorochromate gave the ketone (**21**), deprotection of which led directly to imine (**22**). Reduction of the imine with sodium boranuide occurred with excellent stereoselectivity to give the desired tetracycle (**4**), which was isolated and characterised as its toluenesulfonamide (**23**).The toluenesulfonamide (**23**) was found to be identical[4] to a previous sample prepared by an alternative route[5], for which an X-ray crystal structure had been obtained that confirmed the *cis-cis* fused stereochemistry shown.



Scheme 3

(i) $MeSO_2Cl$, Et_3N, DMAP, DCM, 19h, 70%; (ii) NaN_3, DMF, 70°C, 3h, 96%; (iii) $HS(CH_2)_3SH$, Et_3N, iPrOH, $NaBH_4$, 48h followed by (iv) $(CF_3CO)_2O$, Et_3N, DMAP, THF, 0°C to r.t., 4 days, 87% over 2 steps; (v) $NaBH_4$, $Cu(acac)_2$,EtOH, 1h, 70%; (vi) $NOBF_4$, DCM, 0°C, 1h then TTF, acetone, H_2O, 2 days, 51%; (vii) PCC, DCM, 18h, 83%; (viii) K_2CO_3, H_2O, MeOH, 24h, 79%; (ix) $NaBH_4$, MeOH, 2h and then (x) TsCl, DMAP, pyridine, reflux, 20h, 65%.

In conclusion, we have developed a new synthesis of the complex polycyclic octahydro-1*H*-pyrrolo[2,3-*d*]carbazole skeleton **4**, in which the stereochemistry of all three new chiral centres is controlled. This molecular sub-unit is common to a wide range of alkaloid natural products. We are currently examining the use of this methodology in total synthesis.

REFERENCES

1. Fletcher, R. J.; Lampard, C.; Murphy, J. A. *J. Chem. Soc. Chem. Commun.*, **1996**, in press.
2. (a) Lampard, C.; Murphy, J. A., Lewis, N. *J. Chem. Soc. Chem. Commun.*, **1993**, 295; (b) Fletcher, R. J.; Lampard, C.; Murphy, J. A., Lewis, N. *J. Chem. Soc. Perkin Trans I*, **1995**, 623.
3. Lampard, C.; Murphy, J. A.; Rasheed, F.; Lewis, N.; Hursthouse, M. B.; Hibbs, D. E. *Tetrahedron Lett.*, **1994**, 35, 8675.
4. The ^1H and ^{13}C nmr spectra of the two samples, **23**, were identical; a mixed melting point determination reinforced this conclusion.
5. Kizil, M., Murphy, J. A. *J. Chem Soc., Chem, Commun.*, **1995**, 1409.

(*Received in UK* 5 *February* 1996; *accepted* 16 *February* 1996)