Pergamon

Tetrahedron Letters, Vol. 37, No. 15, pp. 2679-2682, 1996
Copyright © 1996 Elsevier Science Ltd
Printed in Great Britain. All rights reserved
0040-4039/96 $15.00 + 0.00

S0040-4039(96)00359-0

The Vilsmeier Formylation of *N*-(4-Tolyl)pyrrolidine, -piperidine and -perhydroazepine: Further Examples of the 't-Amino Effect'.

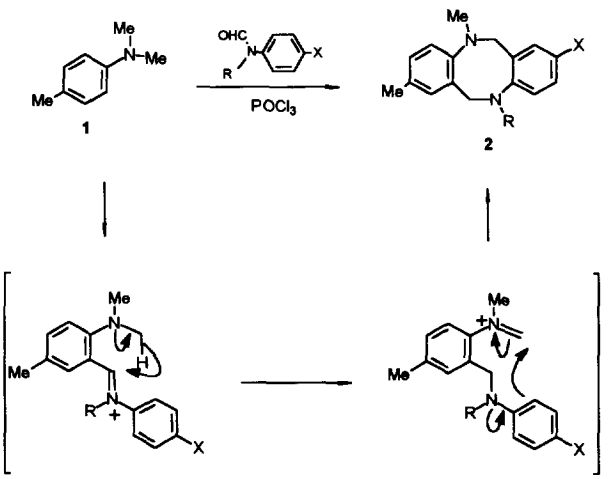
Otto Meth-Cohn* and Ying Cheng

Chemistry Department, University of Sunderland, Sunderland SR1 3SD, UK

(Email: otto.meth-cohn@sunderland.ac.uk)

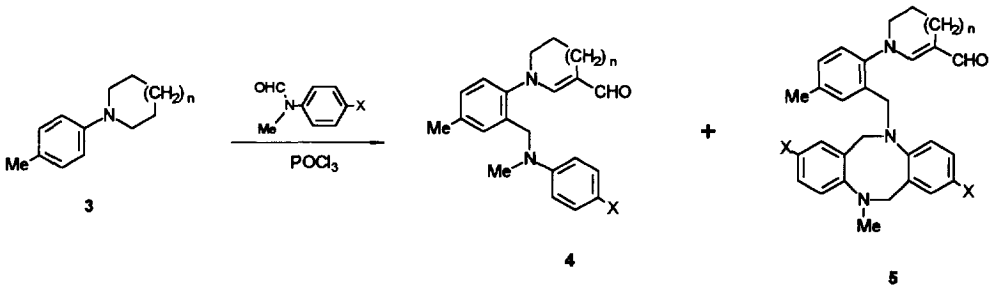
Abstract: Formylation of *N*-4-tolylpiperidine with various *N*-formylated sec-anilines in phosphoryl chloride results in 1,4,5,6-tetrahydro-1-(2-[*N*-aryl-*N*-alkylaminomethyl]-4-methyl-phenyl) -pyridine-3-carbaldehydes (**4b**) or their iminium salts depending upon workup, together with 5,6,11,12-tetrahydro-*N*-alkyl-*N'*-(5-methyl-2-[1,2,3,4-tetrahydro-3-formylpyrid-1-yl]benzyl)dibenzo-[*b,f*][1,5]diazocines (**5b**); Related products are formed from the analogous pyrrolidines and perhydroazepines. Copyright © 1996 Elsevier Science Ltd

We recently disclosed[1] a remarkable reaction whereby the interaction of a *p*-substituted *NN*-dimethylaniline **1** with *N*-formyl-*N*-substituted arylamides in $POCl_3$ gave a dibenzo[1,5]diazocine **2** in good yield (Scheme 1). The reaction is an example of the 't-amino effect'[2] and proceeds by Vilsmeier formylation *ortho* to the dimethylamino-group, followed by hydride migration (1,5-sigmatropic shift). The resulting new



Scheme 1

iminium ion is positioned ideally to attack the adjacent aromatic ring or nitrogen atom (Scheme 1). Although dibenzo-1,5-diazocines are known[3] routes to unsymmetrical derivatives are very limited. Our simple approach makes these interesting systems readily available with unsymmetrical substitution patterns. We therefore extended the reaction to other t-anilines including 4-tolyl -pyrrolidines, -piperidines and -perhydroazepines (3a-c). However these cyclic amines underwent quite different chemistry giving the products of diformylation 4[4] and triformylation 5[5], the latter being formed from the former (Scheme 2). Yields of the salts 4 were generally fair (34-60%) (X = Cl or F) increasing as the heterocyclic ring increased in size. Those of the diazocines 5 were 15-20%.

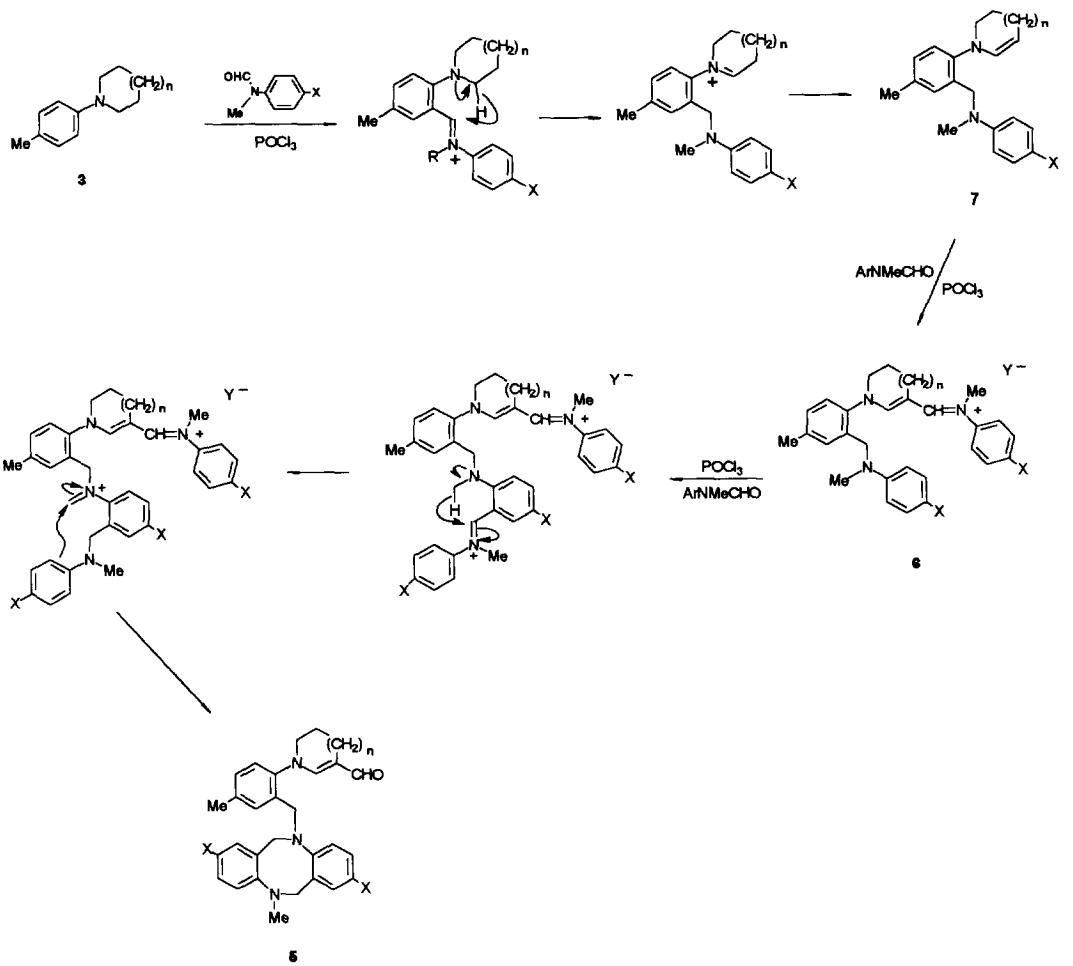


a, n=0; b, n=1; c, n=2

Scheme 2

Surprisingly the iminium salt precursors 6 (Y = OH or PF_6) of the salts 4 were easily extracted with dichloromethane and chromatographable on silica, the latter salt with ethyl acetate/petroleum! They proved remarkably resistant to hydrolysis but gave the corresponding aldehydes 4 in high yield after 1-2 hours in refluxing sodium hydroxide. The diazocine structure **5b** was corroborated by X-ray crystallography[6].

The key feature in the formation of both products is the hydride transfer form the α–position of a tertiary amine to an unsaturated *ortho*-substituent, in this case $CH{=}NR_2^+$, the 't-amino effect' (Scheme 3). However in the case of the cyclic aliphatic amines, proton loss from the ring's β-position is more rapid than the diazocine cyclisation, giving the enamine 7 which can then undergo ready formylation. The newly generated t-aniline is also capable of subsequent *ortho*-formylation leading by way of the mechanism illustrated in Scheme 1 to the formation of the diazocine ring of 5. The chemistry illustrates further the powerful synthetic potential of the 't-amino effect'.



Scheme 3

Acknowledgements We thank SmithKline Beecham for their financial support that made this work possible and Dr Brian Warrington of SB for his interest and help.

References and notes

1. O. Meth-Cohn and D. L. Taylor, *J. Chem. Soc., Chem. Commun.*, **1995**, 1463-1464

2. O. Meth-Cohn and H. Suschitzky, *Adv. Het. Chem.*, **1972**, *14*, 211-278; W. Verboom and D. N. Reinhoudt, *Recl. Trav. Chim. Pays-Bas*, **1990**, *109*, 311-324; O. Meth-Cohn, *Adv. Het. Chem., in press.*

3. H. D. Perlmutter, *Adv. Het. Chem.*, **1989**, *46*, 1-72.

4. Data for compounds **4**: **4a** (X = Cl); m.p. 123-5°C, M^+ 340 ($C_{20}H_{21}ClN_2O$ requires 340), 172 (100%); IR (KBr) 2856, 2790, 1621, 1598, 1573; ^1H NMR ($CDCl_3$): 2.30(3H,s), 2.97(3H,s), 2.97(2H,t, J=10), 3.95(2H,t,J=10), 4.41(2H,s), 6.60-7.2(8H, m, aromatic H's), 9.37(1H,s,CHO); ^{13}C NMR ($CDCl_3$):21.1, 25.3, 38.6, 55.3, 113.8, 120.2, 122.2, 124.5, 128.9, 129.0, 129.2, 133.0, 137.2, 138.0, 148.2, 156.4,182.9.

4b (X=Cl); oil, M^+ 354 ($C_{21}H_{23}ClN_2O$ requires 354), 214 (100%); IR (KBr) 2850, 2711, 1648, 1596, 1500; ^1H NMR ($CDCl_3$): 1.98(2H,quint,J=6.2), 2.31(3H,s), 2.40(2H,t, J=6.2), 2.98(3H,s), 3.52(2H,t, J=6.2), 4.39(2H,s), 6.60-7.2(8H, m, aromatic H's), 8.99(1H,s,CHO).

4b (X=F); oil, M^+ 338 ($C_{21}H_{23}FN_2O$ requires 338), 214 (100%); IR (KBr) 2850, 2715, 1675, 1648, 1598 1511; ^1H NMR ($CDCl_3$): 1.99(2H,quint, J=6.2), 2.32(3H,s), 2.39(2H,t, J=6.2), 2.93(3H,s), 3.50(2H,t, J=6.2), 4.34(2H,s), 6.60-7.2(8H, m, aromatic H's), 8.97(1H,s,CHO).

4c(X=Cl): oil, M^+ 368 ($C_{22}H_{25}ClN_2O$ requires 368), 228 (100%); IR (KBr) 2857, 2707, 1652, 1598 1498; ^1H NMR ($CDCl_3$): 1.65(2H,m), 1.95(2H,m), 2.30(3H,s), 2.56(2H,t, J=6.5), 2.98(3H,s), 3.64(2H,t,J=5.7), 4.42(2H,s), 6.60-7.2(8H, m, aromatic H's), 8.95(1H,s,CHO).

5. Data for compounds **5**: **5a** (X = Cl); M.p.217-9°C, M^+ 491 ($C_{28}H_{24}Cl_2N_3O$ requires 491), 291, 201 (100%); IR (KBr) 2859, 2763, 1623, 1567, 1498; ^1H NMR ($CDCl_3$): 2.36(3H,s), 2.79(2H,t, J=9.7), 2.83(3H,s), 3.76(2H,t, J=9.7), 4.20(2H,s), 4.22(2H,s), 4.27(2H,s) 6.5-7.2(10H, m, aromatic H's), 9.16(1H,s,CHO); ^{13}C NMR ($CDCl_3$): 183.0, 156.5, 148.8, 148.7, 138.6, 136.4, 131.4, 131.2, 131.0, 129.5, 128.3, 127.9, 124.4, 123.6, 122.8, 119.9, 118.7, 115.5, 58.3, 55.0, 52.6, 39.2, 25.0, 21.2.

5b (X = Cl); M.p.137-9°C, M^+ 505 ($C_{29}H_{26}Cl_2N_3O$ requires 505), 291(100%), 215 ; IR (KBr) 2867, 1614, 1590, 1502; ^1H NMR ($CDCl_3$): 1.78(2H, quint, J=5.7), 2.28(2H,t, J=6.2), 2.34(3H,s), 2.84(3H,s), 3.30(2H,t, J=5.7), 4.28(2H,s), 4.34(2H,s), 4.40(2H,s) 6.5-7.2(10H, m, aromatic H's), 8.86(1H,s,CHO); ^{13}C NMR ($CDCl_3$): 187.8, 153.5, 149.1, 148.8, 142.8, 137.6, 133.6, 131.3, 131.0, 130.0, 129.8, 129.2, 128.2, 128.1, 126.9, 126.2, 124.4, 122.9, 119.4, 115.9, 113.7, 58.0, 55.1, 51.9, 50.6, 38.9, 21.2, 20.8, 17.8.

5b (X = F); M.p.212-4°C, M^+ 473 ($C_{29}H_{26}F_2N_3O$ requires 505), 259(100%), 215 ; IR (KBr) 2854, 2807, 1646, 1598, 1577, 1500; ^1H NMR ($CDCl_3$): 1.74(2H, quint, J=5.7), 2.27(2H,t, J=6.5), 2.34(3H,s), 2.83(3H,s), 3.23(2H,t, J=5.7), 4.12(2H,s), 4.16(2H,s), 4.21(2H,s) 6.3-7.25(10H, m, aromatic H's), 8.85(1H,s,CHO); ^{13}C NMR ($CDCl_3$): 187.8, 153.8, 142.6, 137.6, 133.8, 130.3, 129.0, 126.2, 120.6, 120.5, 117.9, 117.6, 117.4, 117.1, 115.9, 115.8, 114.6, 114.5, 114.3, 114.2, 113.1, 58.4, 55.0, 52.5, 50.3, 39.3, 21.2, 20.7, 17.7.

5c(X = F); M.p.245-7°C, M^+ 519 ($C_{30}H_{28}F_2N_3O$ requires 519), 219(100%); IR (KBr) 2863, 2790, 1673, 1614, 1592, 1500; ^1H NMR ($CDCl_3$): 1.75(2H, quint), 2.47(2H,t, J=5.9), 2.30(3H,s), 2.85(3H,s), 3.46(2H,t, J=5.1), 4.17(2H,s), 4.20(2H,s), 4.29(2H,s), 6.51(1H,s), 6.7-7.1(9H, m, aromatic H's), 8.87(1H,s,CHO).

6. We are grateful to Drs Drake Eggleston and Curt Haltiwanger of SmithKline Beecham, Pennsylvania for the X-ray crystallographic results which will be fully reported in the full paper of this work.

(*Received in UK* 9 *February* 1996; *revised* 22 *February* 1996; *accepted* 23 *February* 1996)