Unexpected products from the formylation of *N*,*N*-dimethylanilines with 2-formamidopyridine in $POCl_3$

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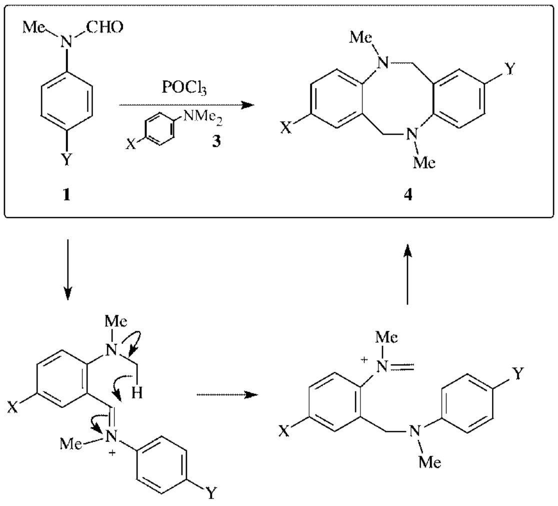
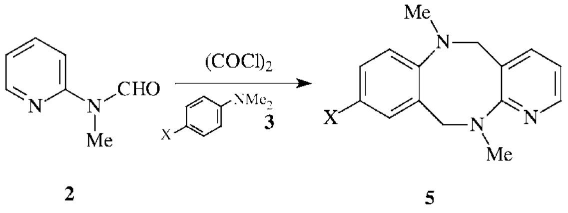
2-Formamidopyridine in $POCl_3$ solution reacts with *N*,*N*-dimethylaniline to give tris(4-dimethylaminophenyl)methane in 80% yield but with 4-X-*N*,*N*-dimethylanilines it gives 2-dimethylamino-5-X-phenyl[2-(*N*-methyl)formamido-5-X-phenyl](2-pyridylamino)methanes.

Introduction

Formanilide in the presence of $POCl_3$ was first used as a formylating agent by Dimroth and Zoeppritz in 1902[1] who employed it to formylate resorcinol. However it failed to formylate *N*,*N*-dimethylaniline. Similar results were reported by Johnson and Lane,[2] Pratt and Robinson,[3] Froeschl and Bomberg,[4] Nenitzescu and Isacescu[5] and Oesterlin[6] who were able to formylate related highly activated systems with this combination. The limitations of formanilide as the formylating amide led to the discovery by Vilsmeier and Haack of the excellent reagent, *N*-methylformanilide.[7] From then on, the Vilsmeier's reaction has been extensively studied and more recently, widely used in the preparation of heterocyclic compounds.[8] In earlier work, we demonstrated that the Vilsmeier reagents derived from *N*-methylformanilides **1** and $POCl_3$,[9] or from 2-(*N*-methyl)formamidopyridine **2** and $(COCl)_2$[10] reacted with 4-substituted dimethylanilines **3** to afford *N*,*N'*-dimethyl-5,6,11,12-tetrahydrodibenzo[*b*,*f*][1,5]diazocines **4** or *N*,*N'*-dimethyl-5,6,11,12-tetrahydrobenzo[*f*]pyrido[2,3-*b*][1,5]diazocines **5** respectively, by way of the '*t*-amino effect'[11] (Scheme 1). We considered that the *N*-unsubstituted [1,5]diazocines, which could be useful intermediates for the preparation of unsymmetrical Tröger's bases (Tröger's base is 5,11-methano-5,6,11,12-tetrahydrodibenzo[*b*,*f*][1,5]diazocine), might be accessible by the use of a formanilide as the Vilsmeier amide. Furthermore, 2-formamidopyridine should be a stronger formylator than formanilide itself, especially if *N*-protonated or acylated.

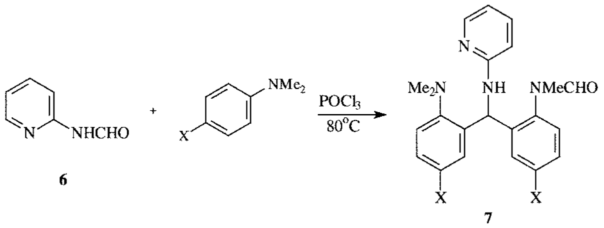




Scheme 1

Results and discussion

In fact, formanilides proved ineffective agents as indicated above. We therefore reacted 2-formamidopyridine with various *para*-substituted *N*,*N*-dimethylanilines in $POCl_3$ solution. Surprisingly, the reaction took a totally different course leading to a product derived from two units of the *t*-aniline and one of the pyridine, less four protons, as indicated by mass spectral and CHN analytical data. The infrared and NMR spectra were insufficient to put the structure beyond doubt and the structure **7** (X = Cl) was established by X-ray crystallography for the product from 4-chloro-*N*,*N*-dimethylaniline, as shown in Fig. 1 Further examples are tabulated in Scheme 2, the yields being based upon the optimal use of 1 : 2 mol of aniline to pyridine reactant respectively. Full details of conditions, yields and



7	a	b	c	d	e
X (%)	Me (57)	OMe (42)	F (71)	Cl (31)	Br (68)

Scheme 2

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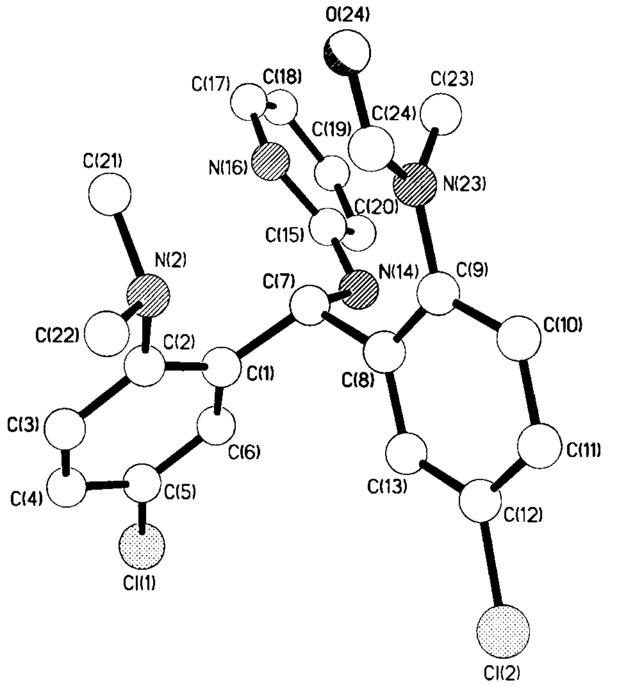


Fig. 1 the X-ray structure of **7** (X = Cl).[12] The principal intermolecular interaction is an N–H · · · O hydrogen bond between N(14) in one molecule and O(24) in the next [N · · · O, H · · · O distances 2.97, 2.27 Å, N–H · · · O angle 134°]. This interaction is supplemented by a weaker C–H · · · π interaction between C(10)–H in one molecule and the C(15) pyridyl ring of another [H · · · π distance 2.82 Å, C–H · · · π angle 151°].

Table 1 Reaction conditions and results

3 X =	Ratio of **3**:**6**	Time/h	Temp./°C	Yields (%) **7**	Yields (%) **8**
Me	2:1	8	80	—	
Me	2:1	20	75	—	
Me	2:1	17	94	25	
Me	1:1	18	96	47[a]	
Me	1:2	18	96	57	
OMe	2:1	17	94	35	
OMe	2:1	8	100	32	
OMe	1:2	18	94	42	
F	1:1	36	90	44	
F	1:2	18	90	71	
Cl	2:1	18	90	34	
Cl	1:2	18	96	31	
Br	2:1	19	90	17	
Br	1:1	18	90	29	
Br	1:2	18	94	48	
Br	1:2	15	96	68	
H	2:1	18	90		80

[a] Under N_2.

spectral data are recorded in Tables 1–3. Clearly, the 2-formamidopyridine is indeed a more powerful formylator than formanilide.

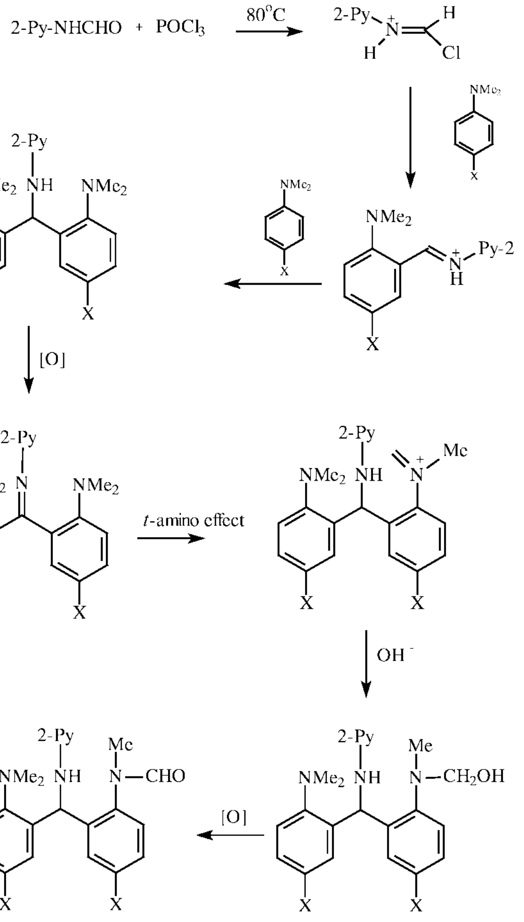
The formation of these surprising products involves an oxidation of one of the methyl groups of an *N*,*N*-dimethylaniline moiety, a process that we propose is initiated by a '*t*-amino effect' interaction. A possible pathway is illustrated in Scheme 3. In fact, the reaction appears to require aerial oxidation for optimal yields. Nevertheless it does proceed under nitrogen. As noted in earlier work[10] it is probable that iminium intermediates behave as dehydrogenating agents and hence the need for an excess of the pyridine amide. Addition of an oxidant, *e.g.* copper(II) acetate, does not improve yields.

When *N*,*N*-dimethylaniline itself was treated with 2-formamidopyridine in $POCl_3$ solution the reaction took a different course yielding tris(4-dimethylaminophenyl)methane **8** in high yield (80%). This well known compound, the precursor to 'Crystal Violet' (the tritylium salt thereof), has in fact been formed by, for example, the interaction of 4-dimethylaminobenzaldehyde with *N*,*N*-dimethylaniline and an acid[13] or by treatment of a 4,4′-bis(dimethylamino)benzhydryl† derivative with *N*,*N*-dimethylaniline under acid catalysis.[14] Similar benzaldehyde (*i.e.* an iminium salt derivative) and benzhydryl analogues can be easily formed in our case to account for this efficient reaction. It is of interest that while classical Vilsmeier reagents with *N*,*N*-dimethylaniline yield solely 4-formyldimethylaniline, this reagent proceeds further, due to the greater formylating ability of the derived iminium ion (*cf.* Scheme 3). When the iminium intermediate of the formylation of *N*,*N*-

Table 2 Melting points and elemental analysis of compounds **7** and **8**

Compound	Mp/°C	CHN%
7a	152–153	C, 74.51; H, 7.33; N, 14.29. $C_{24}H_{28}N_4O$ requires C, 74.20; H 7.26; N, 14.42
7b	153–154	C, 68.63; H, 6.96; N, 13.16. $C_{24}H_{28}N_4O_3$ requires C, 68.55; H, 6.71; N, 13.32
7c	169–171	C, 66.59; H, 5.46; N, 14.02. $C_{22}H_{22}F_2N_4O$ requires C, 66.48; H, 5.83; N, 14.10
7d	195–197	C, 61.52; H, 5.14; N, 12.82. $C_{22}H_{22}Cl_2N_4O$ requires C, 61.40; H, 5.38; N, 13.02
7e	182–184	C, 51.27; H, 4.41; N, 10.55. $C_{22}H_{22}Br_2N_4O$ requires C, 50.99; H, 4.28; N, 10.81
8	177–179[a]	

[a] Lit.[15] mp 177–178 °C.



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Scheme 3

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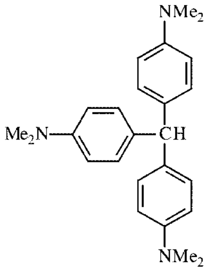
† The IUPAC name for benzhydryl is diphenylmethyl.

Table 3 Spectroscopic data of compounds **7** and **8**

Cmpd.	IR (KBr) ν/cm^{-1}	^{1}H NMR (CDCl$_3$) δ	^{13}C NMR (CDCl$_3$) δ	MS *m*/*z* (%)
7a	3280, 1660, 1600, 1480	8.05 (1H, d, *J* 4.2, CHO), 6.87–7.41 (7H, m), 6.57(1H, dd, *J* 5.4 and 2.7), 6.38 (1H, d, *J* 8.1), 6.22 (1H, d, *J* 8.1), 5.04 (1H, d, *J* 8.1, NH), 3.02 (3H, br s, NCH$_3$), 2.67 (1H, s, NCH), 2.54 (6H, s, 2NCH$_3$), 2.33 (3H, s, ArCH$_3$), 2.21 (3H, s, ArCH$_3$)	161.8, 157.7, 149.9, 147.5, 142.0, 137.7, 137.2, 136.4, 132.1, 128.7, 128.4, 128.2, 128.1, 128.0, 120.1, 111.9, 108.7, 48.3, 44.7, 32.3, 20.9, 20.6	134 (62), 222 (56), 235 (62), 294 (100), 388 (85, M$^+$), 389 (24)
7b	3380, 3260, 1680, 1600, 1500, 1480	8.0 (1H, d, *J* 4.8 CHO), 7.47 (1H, t, *J* 8.4), 7.17 (1H, d, *J* 8.7), 6.70–7.08 (5H, m), 6.63 (1H, t, *J* 5.7), 6.41 (1H, t, *J* 6.8), 6.34 (1H, d, *J* 8.5), 5.90 (1H, br s, NH), 3.76 (3H, s, OCH$_3$), 3.71 (3H, s, OCH$_3$), 3.06 (3H, br s, NCH$_3$), 2.64 (1H, s, NCH), 2.50 (6H, s, 2NCH$_3$)	163.2, 162.6, 159.7, 156.5, 145.8, 142.1, 139.2, 137.7, 137.1, 133.1, 130.3, 122.5, 113.9, 113.3, 113.2, 112.8, 112.7, 107.2, 55.7, 51.1, 45.8, 33.4, 30.8	254 (58), 267 (70), 268 (54), 326 (100), 420 (51, M$^+$), 421 (17)
7c	3300, 1680, 1620, 1500, 1480	8.01 (1H, d, *J* 4.7, CHO), 7.42 (1H, t, *J* 7.2), 6.94–7.27 (5H, m), 6.79 (1H, dd, *J* 9.3 and 2.9), 6.64 (1H, t, *J* 5.5), 6.50 (1H, d, *J* 6.4), 6.31 (1H, d, *J* 8.3), 5.27 (1H, d, *J* 6.3, NH), 3.07 (3H, s, NCH$_3$), 2.65 (1H, s, NCH), 2.54 (6H, s, 2NCH$_3$)	164.2, 157.8, 156.8, 148.7, 147.9, 138.4/138.3, 138.0, 131.0/130.9, 122.8/122.7, 115.6, 115.4, 115.3, 115.1, 114.8, 114.5, 113.9, 113.5, 107.0, 50.5, 45.5, 33.1	124 (56), 136 (54), 138 (56), 230 (100), 243 (58), 302 (68), 396 (50, M$^+$), 397 (13)
7d	3280, 1660, 1600, 1480	8.05 (1H, d, *J* 5.4, CHO), 7.52 (1H, d, *J* 2.7), 6.98–7.44 (6H, m), 6.62 (1H, dd, *J* 8.1 and 5.4), 6.52 (1H, d, *J* 8.1), 6.32 (1H, d, *J* 8.1), 4.92 (1H, d, *J* 5.4, NH), 3.03 (3H, s, NCH$_3$), 2.67 (1H, s, NCH), 2.58 (6H, s, 2NCH$_3$)	162.1, 157.4, 151.6, 147.9, 144.3, 139.4, 138.9, 137.2, 133.1, 131.0, 128.4, 128.3, 128.2, 127.7, 127.5, 122.7, 113.0, 109.3, 48.7, 44.6, 32.7	154 (61), 246 (100), 334 (64), 428 (53)/430 (34)/432 (6) (M$^+$)
7e	3300, 1680, 1610, 1490	8.03 (1H, d, *J* 4.8, CHO), 6.95–7.67 (7H, m), 6.65 (1H, t, *J* 5.6), 6.49 (1H, d, *J* 6.5), 6.25 (1H, d, *J* 6.0), 5.35 (1H, br s, NH), 3.03 (3H, s, NCH$_3$), 2.67 (1H, s, NCH), 2.57 (6H, s, 2NCH$_3$)		117 (99), 290 (100), 292 (88), 405 (54), 407 (46), 424 (77), 516 (27)/518 (52)/520 (25) (M$^+$)
8	1620, 1530	7.03 (6H, d, *J* 8.4), 6.91 (6H, d, *J* 7.7), 5.37 (1H, s, CH), 2.98 (18H, s, 6NCH$_3$)		252 (65), 253 (100), 254 (20), 372 (44), 373 (96, M$^+$), 374 (26)



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dimethylaniline with DMF–POCl$_3$ is reacted with further *N*,*N*-dimethylaniline, the same triarylmethane is formed.[15]

Experimental

Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra in CDCl$_3$ were obtained on Varian Unity 200 and 300 spectrometers. IR spectra were recorded using a Perkin-Elmer 782 spectrometer and mass spectra were recorded on a KYKY-ZHT-5 instrument. Elemental analyses were performed on a GMBH Vario EL instrument. Light petroleum refers to bp 60–80 °C.

2-Dimethylamino-5-X-phenyl[2-*N*-(methyl)formamido-5-X-phenyl](2-pyridylamino)methane 7

General procedure for the formylation of *N*,*N*-dimethylanilines. 2-Formamidopyridine (0.02 mol) in POCl$_3$ (10 ml) was warmed at 80 °C for 2 h with stirring to form a green mixture. To this solution, cooled in an ice-bath, was slowly added a dimethylaniline **3** (0.01 mol). The mixture was heated at 90–100 °C for a period of time (see Table 1), and then poured into ice (100 g). The aqueous solution was basified to pH ~ 8 with 10% NaOH and extracted with CHCl$_3$ (3 × 100 ml). The extract was dried with MgSO$_4$ and after removal of solvent, the products were isolated by silica gel column chromatography followed by recrystallisation from ethyl acetate–light petroleum.

Acknowledgements

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12 *Crystal data for* **7** (X = Cl): C$_{22}$H$_{22}$N$_4$OCl$_2$, M = 429.3, monoclinic, space group $P2_1/c$ (no. 14), a = 9.667(3), b = 14.060(2), c = 17.366(3) Å, β = 105.90(2)°, V = 2270.0(8) Å^3, Z = 4, D_c = 1.256 g cm^{-3}, μ(Cu-Kα) = 27.3 cm^{-1}, F(000) = 896, T = 293 K; colourless blocks, 0.33 × 0.30 × 0.17 mm, Siemens P4/PC diffractometer, ω-scans, 3555 independent reflections. The structure was solved by direct methods and the non-hydrogen atoms were refined anisotropically using full matrix least-squares based on F^2 to give R_1 = 0.058, wR_2 = 0.151 for 2771 independent observed absorption corrected reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta \leq 124°$] and 270 parameters. CCDC reference number 207/497. See http://www.rsc.org/suppdata/p1/b0/b006148o/ for crystallographic files in .cif format.
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