Vilsmeier formylation of *tert*-anilines: dibenzo[*b*,*f*][1,5]diazocines and quinazolinium salts *via* the '*t*-amino effect'[1]

Ying Cheng, Otto Meth-Cohn* and David Taylor

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

The attempted Vilsmeier *ortho*-formylation of *p*-substituted *N*,*N*-dimethylanilines 1 with *N*-formyl-*N*-alkylarylamides 2 unexpectedly gives dibenzo[*b*,*f*][1,5]diazocines 5 in 26–74% yield. This reaction proceeds by Vilsmeier formylation *ortho* to the dimethylamino group of 1 followed by hydride migration from the *N*-methyl group to the newly formed iminium =CH group, followed by intramolecular cyclisation, a new example of the '*t*-amino effect'. Similar formylation of cyclic *tert*-anilines such as 4-tolyl-pyrrolidines 6a,e,g, -piperidines 6b,f,h, -perhydroazepines 6c,i and -morpholine 6d, however, shows a different chemistry giving diformylated enamines 7 as the major products (12–60%). A small amount of diazocines 8 (1–13%) with a substituted benzyl at the nitrogen and *N*-formylated diazocines 9 are also isolated in some cases. When *N*-formyl-1,2,3,4-tetrahydroquinoline is used as the Vilsmeier reagent, normal formylation is observed, while use of aliphatic Vilsmeier reagents such as DMF and *N*-formylmorpholine give quinazolinium salts 16 and 17, also by way of the '*t*-amino effect'. The key feature in these formylations is the hydride transfer from the α-position of a tertiary amine to an unsaturated *ortho*-substituent CH=NR_2^+, the '*t*-amino effect'.

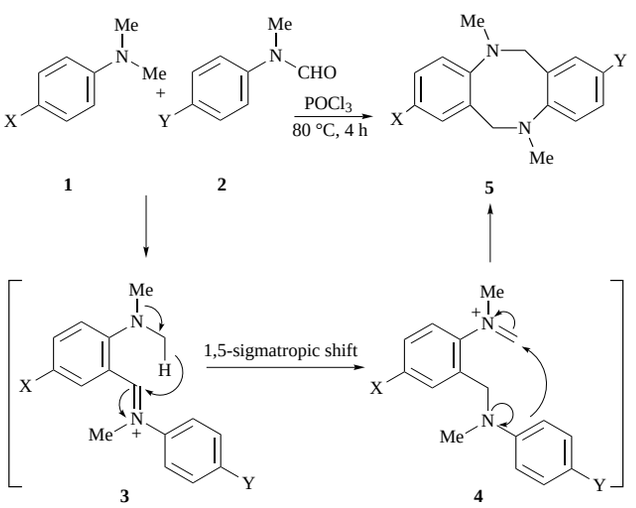
Introduction

Although the first example of the Vilsmeier formylation involved the *para*-formylation of dimethylaniline,[2] very little work has been reported on the corresponding *ortho*-formylation of 4-substituted *tert*-anilines. Thus while 4-acetyl-[3] and 4-(β-styryl)-dimethylanilines[4] give low yields of the 2-aldehyde, 4-tolylbis(2-cyanoethyl)amine is reported to give a high yield of the expected aldehyde.[5] Similarly, while 4-tolyl-*N*,*N*-dibenzylamines *ortho*-formylate effectively, *N*-(4-tolyl)-*N*-(2-cyanoethyl)-benzylamines undergo a novel 2-formylation and consequent debenzylation reaction under similar conditions.[6] 3-Dialkylaminothiophenes and 2-morpholinobenzo[*b*]thiophenes are reported to formylate efficiently in the 2- and 3-position respectively.[7] We have undertaken a study of the 2-formylation of 4-substituted *tert*-anilines. The results were surprisingly diverse, depending upon the nature of the Vilsmeier reagent (dialkylformamides, alkylformanilides and some heterocyclic formamides gave different results) and of the *tert*-aniline (dimethylanilines behaved differently to other *tert*-anilines).

Results and discussion

Formylation of 4-substituted dimethylanilines with *N*-methylformanilides

The interaction of 4-substituted *N*,*N*-dimethylanilines **1** with *N*-methylformanilides **2** in $POCl_3$ did not give the expected *ortho*-formylated products but resulted in the formation of dibenzo[*b*,*f*][1,5]diazocines **5** generally in fair yield (Scheme 1). We explain this remarkable transformation as follows: the Vilsmeier reagent derived from **2** and $POCl_3$ attacks at the position *ortho* to the dimethylamino group of the anilines **1** forming iminium ion **3**. A 1,5-sigmatropic shift of hydride from the α-position of a tertiary amine to the unsaturated iminium group gives a new iminium intermediate **4** (this step is an example of the now well established '*t*-amino effect'[8]) which undergoes an electrophilic cyclisation by attacking the adjacent activated aromatic ring to yield diazocines **5** (Scheme 1). *N*,*N*-Dimethylanisidine **1f** gave a lower yield (26%) of diazocine **5f** probably due to the inductive deactivation of the site of formylation. With the parent *N*-methylformanilide **2c**, a further formylated diazocine **5c** (Y = CHO) was obtained, due to formylation of the initially formed diazocine **5c** (Y = H). This simple one-pot method for the construction of pharmaceutically attractive diazocines is a major improvement on existing methodology, particularly in that unsymmetrically substituted derivatives are easily accessible.[9] Furthermore this reaction extends the scope of the *t*-amino effect which until now has been used only for the generation of five- and six-membered rings.



Scheme 1

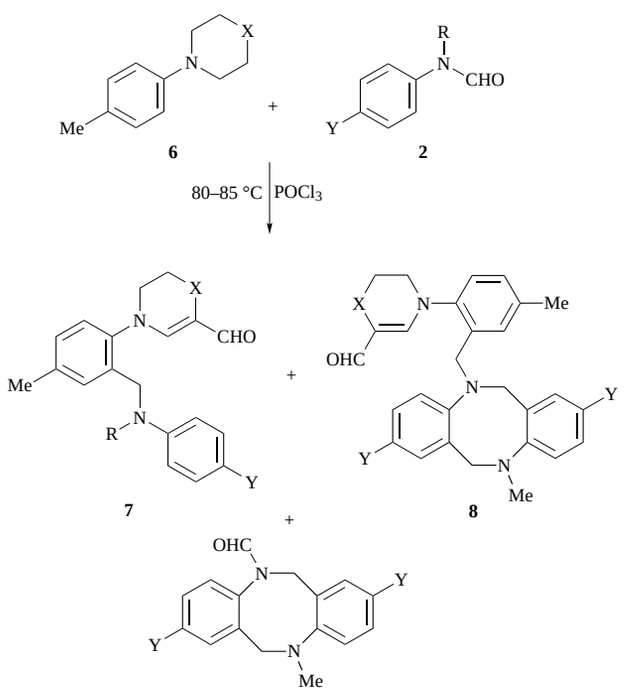
1–5	X	Y	Yield of **5** (%)[a]
a	Me	MeO	44
b	Me	Me	74
c	Me	H	52[b]
d	Me	Cl	57
e	Cl	Cl	49
f	MeO	Cl	26

[a] Isolated yield. [b] Y = CHO.

The very broad, almost invisible methylene signals in the ^1H NMR spectrum of the diazocines **5** at probe temperature at 4.0 and 4.7 ppm indicate a slow conformational flexion of the eight-membered ring. These peaks sharpen on heating to 80 °C

Table 1 Reaction of cyclic *tert*-anilines **6** with formanilides **2** in $POCl_3$

					Yield (%)		
Entry	X	Y	R	*t*/h	**7**	**8**	**9**
1	—	Cl	Me	7	36	10	3
2	—	Cl	Me	24	49	6	9
3	CH_2	Cl	Me	7	12	9	5
4	CH_2	Cl	Me	24	34	1	4
5	$(CH_2)_2$	Cl	Me	7	54	6	4
6	$(CH_2)_2$	Cl	Me	24	58	2	3
7	O	Cl	Me	15	31	11	—
8	—	F	Me	24	60	—	—
9	CH_2	F	Me	7	15	13	—
10	—	F	Et	6	40	—	—
11	CH_2	Cl	Et	6	35	—	—
12	$(CH_2)_2$	H	Et	4	60 (Y = CHO)	—	—



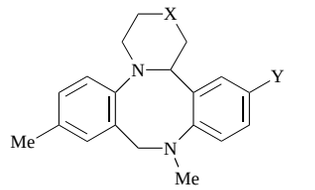
Scheme 2

2,**6**–**9**	X	Y	R
a	—	Cl	Me
b	CH_2	Cl	Me
c	$(CH_2)_2$	Cl	Me
d	O	Cl	Me
e	—	F	Me
f	CH_2	F	Me
g	—	F	Et
h	CH_2	Cl	Et
i	$(CH_2)_2$	H(CHO)	Me

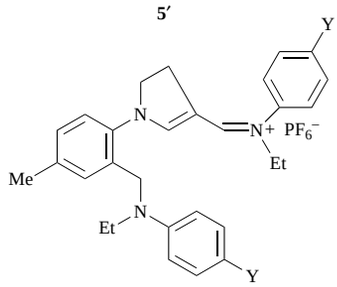
to give one singlet and resolve into two AB pairs of doublets with ~16 Hz coupling on cooling the solution to −40 °C. Ollis and co-workers[10] have examined the temperature NMR of simple dibenzodiazocines thoroughly and showed that the boat-like conformation was preferred at low temperatures while at 60 °C flipping between boat and chair conformations was observed.

Formylation of other 4-substituted *tert*-anilines with *N*-methylformanilides

A quite different chemistry was encountered when the reaction was extended to the cyclic *tert*-anilines. Thus when 4-tolyl-pyrrolidines **6a**,**e**,**g**, -piperidines **6b**,**f**,**h**, -perhydroazepines **6c**,**i** and -morpholine **6d** were formylated under the same conditions the enamino aldehydes **7** were obtained as the major products instead of the expected diazocines **5′** (Scheme 2). More interestingly, a diazocine **8** bearing a substituted benzyl group was



5′



10a, Y = F; **10b**, Y = Cl

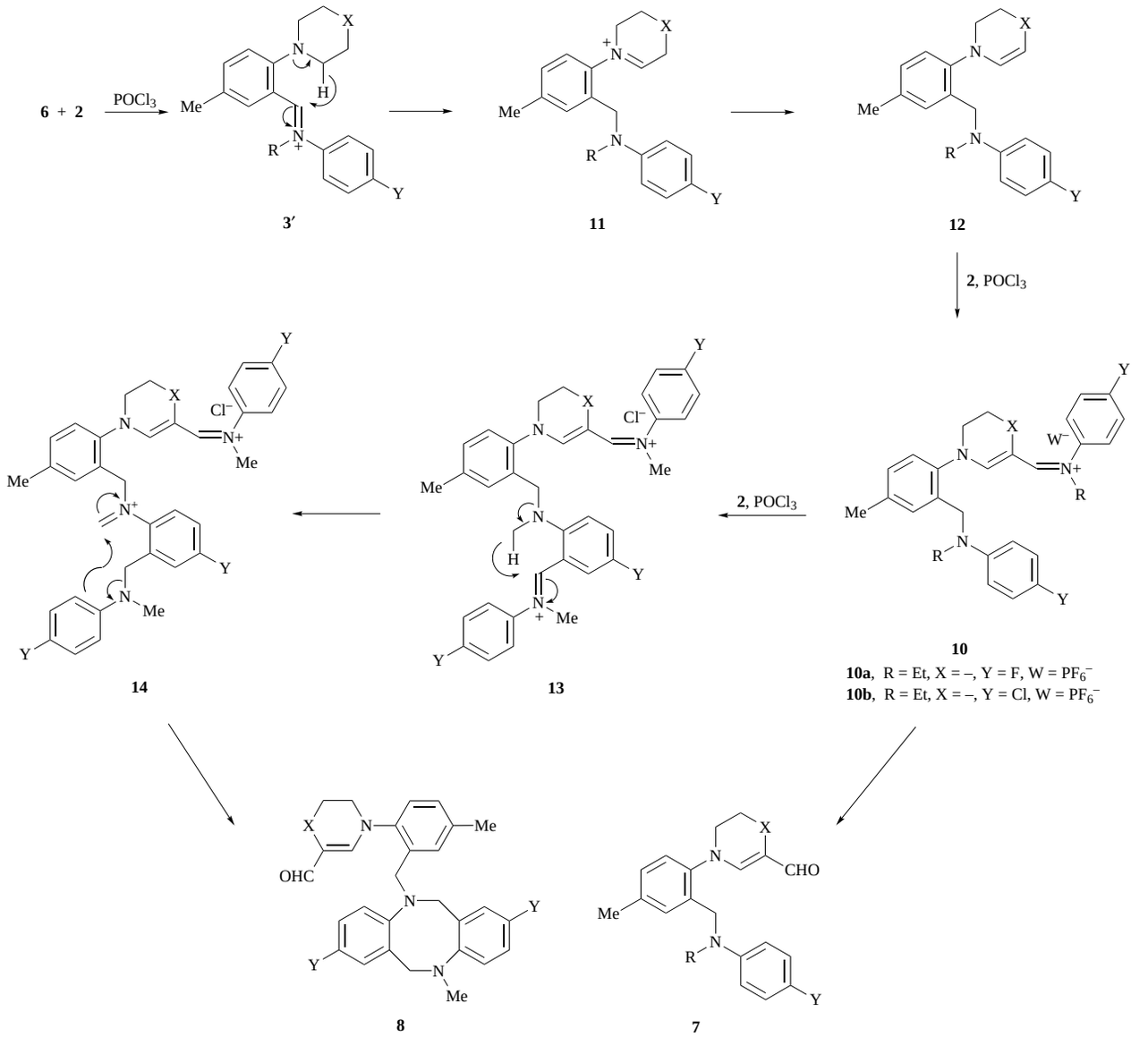
found in most cases, albeit in low yield (1–13%). An *N*-formylated dibenzo[*b*,*f*][1,5]diazocine **9** was also isolated in very poor yield in some cases (Table 1). It is worth noting that the iminium salt precursors **10a**,**b** of the aldehydes **7** were stable and easily extracted with dichloromethane and could even be chromatographed on silica. They were surprisingly resistant to hydrolysis but gave the corresponding aldehyde **7** in high yield after 1–2 hours in warm sodium hydroxide. In order to put the structures beyond doubt, the crystal and molecular structure of **8b** was determined by X-ray crystallography.[11] The chemical yields of the enamino aldehydes **7** were improved significantly by use of prolonged reaction times (Entries 2, 4, 6 and 8 in Table 1). Five- and seven-membered *tert*-anilines tended to give higher yields of enamino aldehyde **7** than their six-membered analogues (Entries 1–6). In a manner similar to the formation of **5c**, an enamino aldehyde derivative **7i** was obtained, resulting from a second formylation of the aniline ring. The diazocines **8** were isolated in low yields which decreased as reaction time increased.

We explain the origin of these products as follows. Vilsmeier formylation of the cyclic *tert*-anilines **6** yields the iminium salt **3′** which undergoes hydride migration with the formation of new iminium intermediate **11**. In contrast to the cases of the dimethylanilines discussed above, iminium ion **11** is stabilised by a rapid loss of a proton from the β-position of the ring rather than by intramolecular cyclisation. The resulting cyclic enamine **12**, being highly reactive towards the Vilsmeier reagent, forms the iminium salt **10**. This newly generated iminium ion **10** contains a *tert*-aniline moiety which is also susceptible to *ortho*-formylation and, *via* intermediates **13** and **14**, gives rise to the diazocine **8** (Scheme 3) on work-up; in a similar manner hydrolysis of the isolable salts **10** with alkali afforded aldehyde **7**. The *N*-formylated diazocine **9** was formed most probably from diazocine **8** by formylative *N*-debenzylation.

The key feature of all of the reactions of the *tert*-anilines with *N*-alkylformanilides in $POCl_3$ is the 1,5-sigmatropic transfer of hydride from the α-position of a tertiary amine to an unsaturated *ortho*-substituent, in these cases the iminium moiety. This is a new example of the '*t*-amino effect'.

Formylation of 4-substituted dimethylanilines with *N*-formylated heterocycles

When *N*-formyltetrahydroquinoline (NFTHQ) was used as the Vilsmeier reagent to formylate *N*,*N*-dimethyl-*p*-toluidine, surprisingly no diazocine formed but the reaction stopped at the



Scheme 3

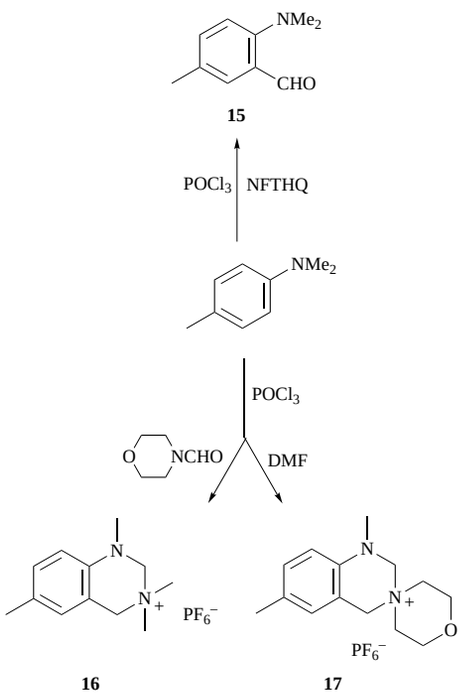
ortho-formylation step, to give 2-formyl-4-methyl-*N*,*N*-dimethylaniline **15** in 56% yield (Scheme 4). To our surprise the analogous attempted formylation utilising *N*-formylindoline was totally without effect, even after raising the reaction temperature to 100 °C for 3 hours. It would seem that the iminium salt intermediate derived from the bulkier reagent, *N*-formyltetrahydroquinoline lies out-of-plane with respect to the dimethylaniline ring, thus not allowing the concerted sigmatropic H-shift to take place. The almost planar Vilsmeier reagent derived from *N*-formylindoline appears to be incapable of approaching the more sterically crowded *ortho*-position of the 4-methyl-*N*,*N*-dimethylaniline. We have found that this reagent is a powerful formylating agent in other applications.[12]

Formylation of 4-substituted dimethylanilines with *N*-formylated aliphatic secondary amines

Finally we have studied briefly the effect of Vilsmeier reagents derived from simple aliphatic *N*,*N*-disubstituted formamides on 4-substituted dimethylanilines. Using DMF and $POCl_3$ with 4-methyl-*N*,*N*-dimethylaniline, a ready reaction ensued which was monitored by ^{1}H NMR spectroscopy. In the event, a quinazolinium salt **16** was formed in 31% yield, isolated by precipitation of its PF_6^- salt. This compound is derived by *ortho*-formylation followed by the usual '*t*-amino effect' transfer of hydride, whereupon the new iminium salt cyclises onto the basic aliphatic amine appendage (Scheme 4). A similar product **17** was derived from *N*-formylmorpholine and 4-methyl-*N*,*N*-dimethylaniline in 49% yield. Bulky formamides such as diisopropylformamide were ineffective in this process. These quinazolinium salts are the presumed intermediate in the already noted debenzylation of a 4-substituted *N*-benzyl-*N*-alkylaniline,[6] where the *ortho*-dimethylaminomethylated derivative was isolated as the final product.

Experimental

Melting points, which are uncorrected, were determined using a Reichert Kofler hot-stage apparatus. Infrared spectra were obtained on a Unicam Research Series 1 FTIR instrument as KBr discs or liquid films. NMR spectra were recorded in $CDCl_3$ solution with $SiMe_4$ as internal standard on JEOL 270 and Varian Unity 200 spectrometers. Chemical shifts are reported in ppm while the coupling constant *J* values are in Hz. Mass spectra were measured on a Kratos MS8ORF mass spectrometer and microanalyses were carried out at Newcastle University, UK and at the Institute of Chemistry, Academia Sinica, Beijing. Thin layer chromatography (TLC) was performed with Merck silica $60F_{254}$ plates and Janssen silica (35–70 μm) was used for flash chromatography. Light petroleum refers to that of bp 60–80 °C.



Scheme 4

General procedure for the preparation of dibenzo[*b*,*f*][1,5]-diazocines 5

In a dry flask, the *N*-methylformanilide **2** (11 mmol) was mixed with $POCl_3$ (10 cm^3) and the mixture was warmed at 70 °C for about 10 minutes. The resulting red solution then cooled in an ice bath, and to it was added *tert*-anilines **1** (10 mmol) slowly under nitrogen. The deep red mixture was kept stirring at 70–80 °C for 4 h. After cooling to room temperature, the reaction mixture was poured into ice–water (*ca*. 100 g), basified with aqueous NaOH (20%) and extracted with dichloromethane (4 × 50 cm^3). The organic phase was dried over $MgSO_4$ and filtered quickly through a silica pad. The product precipitated after removal of most of the solvent, and recrystallisation from ethyl acetate gave the diazocine **5** as colourless prisms as follows.

5,6,11,12-Tetrahydro-2-methoxy-5,8,11-trimethyldibenzo[*b*,*f*]-[1,5]diazocine 5a. Mp 141.5–143 °C (Found: C, 76.7; H, 8.1; N, 9.9. $C_{18}H_{22}N_2O$ requires C, 76.6; H, 7.85; N, 9.9%); ν_{max}/cm^{-1} 2850, 1600, 1500 and 1480; δ_H 2.27 (3H, s, CH_3), 2.78 (3H, s, CH_3) 2.82 (3H, s, CH_3), 3.77 (3H, s, CH_3), 4.20 (4H, s, CH_2) and 6.71–7.01 (6H, m, aromatic H); δ_C 20.4, 39.5, 39.9, 55.6, 55.7, 112.5, 115.6, 117.1, 117.2, 117.3, 127.5, 127.7, 128.4, 129.5, 131.9, 145.2, 148.6 and 152.2; *m*/*z* (EI) 282 (M^+, 100%) and 266 (55).

5,6,11,12-Tetrahydro-2,5,8,11-tetramethyldibenzo[*b*,*f*][1,5]-diazocine 5b. Mp 152–153.5 °C (Found: C, 81.1; H, 8.7; N, 10.55. $C_{18}H_{22}N_2$ requires C, 81.2; H, 8.3; N, 10.5%); ν_{max}/cm^{-1} 2870, 1500 and 1480; δ_H 2.27 (6H, s, CH_3), 2.80 (6H, s, CH_3), 4.22 (4H, s, CH_2) and 6.76–7.00 (6H, m, aromatic H); δ_C 20.4, 39.4, 58.6, 115.4, 127.0, 127.3, 128.4, 131.9, 145.2 and 148.5.

5,6,11,12-Tetrahydro-2-formyl-5,8,11-trimethyldibenzo[*b*,*f*]-[1,5]diazocine 5c (Y = CHO). Mp 226–228 °C (Found: C, 76.8; H, 7.2; N, 9.8. $C_{18}H_{20}N_2O$ requires C, 77.1; H, 7.2; N, 10.0%); ν_{max}/cm^{-1} 1660 and 1590; δ_H 2.29 (3H, s, CH_3), 2.78 (3H, s, CH_3), 2.94 (3H, s, CH_3), 4.40 (4H, broad s, $2CH_2$), 6.76–6.70 (6H, m, aromatic H) and 9.78 (1H, s, CHO); δ_C 38.3, 38.4, 40.8, 57.2, 57.6, 113.1, 114.3, 123.8, 125.0, 125.3, 126.1, 128.5, 130.6, 131.8, 132.9, 147.0, 154.5 and 189.4; *m*/*z* (EI) 280 (M^+, 100%), 146 (61) and 132 (69).

5,6,11,12-Tetrahydro-2-chloro-5,8,11-trimethyldibenzo[*b*,*f*]-[1,5]diazocine 5d. Mp 152.5–153.5 °C (Found: C, 71.3; H, 6.7; N, 9.8. $C_{17}H_{19}N_2Cl$ requires C, 71.2; H, 6.7; N, 9.8%); ν_{max}/cm^{-1} 2947, 2867, 1510 and 1497; δ_H 2.28 (3H, s, CH_3), 2.80 (3H, s, CH_3), 2.81 (3H, s, CH_3), 4.22 (4H, broad s, CH_2) and 6.74–7.15 (6H, m, aromatic H); δ_C 20.3, 39.1, 39.2, 58.1, 58.2, 115.5, 116.1, 122.1, 126.5, 127.2, 127.6, 128.5, 128.6, 130.8, 131.9, 148.1 and 149.1; *m*/*z* (EI) 286 (M^+, 100%), 271 (95), 166 (70), 146 (92), 134 (95) and 132 (90).

5,6,11,12-Tetrahydro-2,8-dichloro-5,11-trimethyldibenzo[*b*,*f*]-[1,5]diazocine 5e. Mp 195.5–198 °C (Found: C, 62.5; H, 5.0; N, 9.05. $C_{16}H_{16}N_2Cl_2$ requires C, 62.55; H, 5.25; N, 9.1%); ν_{max}/cm^{-1} 2868, 1592 and 1498; δ_H 2.79 (6H, s, CH_3), 4.21 (4H, s, CH_2) and 6.75–7.15 (6H, m, aromatic H); δ_C 39.1, 58.0, 116.7, 122.7, 127.9, 128.1, 130.9 and 149.0; *m*/*z* (EI) 308 (M + 2, 70), 306 (M^+, 95%), 166 (99) and 154 (100).

5,6,11,12-Tetrahydro-2-chloro-8-methoxy-5,11-dimethyl-dibenzo[*b*,*f*][1,5]diazocine 5f. Mp 158.5–160 °C (Found: C, 67.3; H, 6.25; N, 9.4. $C_{17}H_{19}N_2ClO$ requires C, 67.4; H, 6.3; N, 9.25%); ν_{max}/cm^{-1} 2861, 1591 and 1499; δ_H 2.79 (3H, s, CH_3), 2.83 (3H, s, CH_3) 3.77 (3H, s, OCH_3), 4.22 (4H, s, CH_2) and 6.70–7.13 (6H, m, aromatic H); δ_C 39.0, 39.3, 39.7, 55.7, 58.4, 112.8, 116.3, 116.4, 117.2, 117.4, 122.6, 127.6, 127.8, 128.7, 130.8, 149.2 and 152.3; *m*/*z* (EI) 302 (M^+, 100%).

Reaction of cyclic *tert*-anilines 6 with *N*-alkylformanilides 2

Using the same procedure as for the preparation of diazocines **5**, cyclic *tert*-anilines **6** (10 mmol) were reacted with *N*-alkyl-formanilides **2** (30 mmol) in $POCl_3$ (10 cm^3) until ^1H NMR spectroscopy indicated completion of reaction (Table 1). The cooled reaction mixture was poured into ice–water (*ca*. 100 g) and worked up following one of two methods.

Method A. NH_4PF_6 (10 mmol) was added to the aqueous solution and the mixture was stirred vigorously for 10 minutes. Extraction with dichloromethane (3 × 50 cm^3) gave, after drying over Na_2SO_4 and removal of the solvent, a residue which was subjected to column chromatography using ethyl acetate and light petroleum (3:1) as eluent to give iminium salt **10** as follows.

10a. (40%) Mp 198–200 °C (Found: C, 57.4; H, 5.4; N, 6.9. $C_{29}H_{32}N_3F_8P$ requires C, 57.5; H, 5.3; N, 6.9%); ν_{max}/cm^{-1} 1631, 1562, 1504 and 838; δ_H 1.04 (3H, t, *J* 7.0, CH_3), 1.25 (3H, t, *J* 7.3, CH_3), 2.35 (3H, s, CH_3), 2.84 (2H, t, *J* 8.9, $=CCH_2$), 3.25 (2H, q, *J* 7.0, NCH_2CH_3), 3.79 (2H, q, *J* 7.3, $N^+CH_2CH_3$), 3.88 (2H, t, *J* 8.9, NCH_2CH_2), 4.29 (2H s, NCH_2Ar), 6.67–7.20 (11H, m, aromatic H), 7.86 (1H, s, N–CH=C), and 7.90 (1H, s, N^+=CH); δ_C 29.3, 29.6, 29.9, 30.3, 30.4, 30.6, 30.9, 31.2, 40.3, 43.2, 50.2, 55.1, 74.9, 80.3, 87.8, 145.3, 145.6, 145.8, 145.9, 146.3, 147.3, 155.6, 159.2, 159.9, 160.7, 163.9, 165.5, 169.8 and 183.2; *m*/*z* (electrospray) 460 (M^+, 100%).

10b. (41%) Mp 197–199 °C (Found: C, 54.4; H, 4.9; N, 6.5. $C_{29}H_{32}N_3Cl_2F_3P$ requires C, 54.6; H, 5.05; N, 6.6%); ν_{max}/cm^{-1} 1629, 1594, 1554 and 836; δ_H 1.05 (3H, t, *J* 6.8, CH_3), 1.23 (3H, t, *J* 7.3, CH_3), 2.34 (3H, s, CH_3), 2.85 (2H, t, *J* 8.9, $=CCH_2$), 3.26 (2H, q, *J* 7.3, NCH_2CH_3), 3.78 (2H, q, *J* 7.3, $N^+CH_2CH_3$), 3.88 (2H, t, *J* 8.9, NCH_2CH_2), 4.34 (2H, s, NCH_2Ar), 6.68 (2H, dd, *J* 8.4, aromatic H), 7.06–7.19 (7H, m, aromatic H), 7.44 (2H, dd, *J* 8.4, aromatic H), 7.83 (1H, s, N–CH=C) and 7.86 (1H, s, N^+=CH); *m*/*z* (electrospray) 492 (M^+, 100%).

Method B. The aqueous phase was basified with aqueous NaOH (20%) in an ice-bath and then extracted with dichloromethane (3 × 50 cm^3). After removal of the solvent the residue was hydrolysed in aqueous NaOH (20%) at *ca*. 50–60 °C for 1 h, the mixture cooled, and extracted with dichloromethane (3 × 50 cm^3) and dried ($MgSO_4$). After removal of the solvent the residue was purified by column chromatography eluting with light petroleum containing gradually increasing amounts of ethyl acetate and finally pure ethyl acetate to give the following products.

7a. Mp 123–125 °C (Found: C, 70.5; H, 6.15; N, 8.2. $C_{20}H_{21}N_2ClO$ requires C, 70.6; H, 6.2; N, 8.2%); ν_{max}/cm^{-1} 2856, 2790, 1621, 1598 and 1573; δ_H 2.30 (3H, s, CH_3), 2.97 (3H, s, CH_3), 2.97 (2H, t, *J* 10, $=CCH_2$), 3.95 (2H, t, *J* 10, NCH_2), 4.41 (2H, s, NCH_2Ar), 6.60–7.21 (8H, aromatic H and N=CH=C)

and 9.37 (1H, s, CHO); δ_C 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 and 182.9; *m*/*z* (EI) 340 (M^+, 18%), 199 (90), 172 (100) and 170 (70).

7b. Oil (Found: 354.1485. $C_{21}H_{23}N_2ClO$ requires 354.1499); ν_{max}/cm^{-1} 2850, 2711, 1648, 1596 and 1500; δ_H 1.98 (2H, quintet, *J* 6.2, $CH_2CH_2CH_2$), 2.31 (3H, s, CH_3), 2.40 (2H, t, *J* 6.2, CH_2CH_2C=), 2.98 (3H, s, CH_3), 3.52 (2H, t, *J* 6.2, NCH_2), 4.39 (2H, s, NCH_2Ar), 6.60–7.20 (8H, m, aromatic H and N−CH=C) and 8.99 (1H, s, CHO); *m*/*z* (EI) 354 (M^+, 10%), 214 (100) and 185 (85).

7c. Oil (Found: 368.1668. $C_{22}H_{25}N_2ClO$ requires 368.1655); ν_{max}/cm^{-1} 2857, 2707, 1652, 1598 and 1498; δ_H 1.65 (2H, m, $CH_2CH_2CH_2$), 1.95 (2H, m, $CH_2CH_2CH_2$), 2.30 (3H, s, CH_3), 2.56 (2H, t, *J* 6.5, CH_2), 2.98 (3H, s, CH_3), 3.64 (2H, t, *J* 5.7, NCH_2), 4.42 (2H, s, NCH_2Ar), 6.60–7.20 (8H, m, aromatic H and N−CH=C) and 8.95 (1H, s, CHO); *m*/*z* (EI) 368 (M^+, 18%), 228 (100) and 198 (60).

7d. Oil (Found: 356.1285. $C_{20}H_{21}N_2ClO_2$ requires 356.1292); ν_{max}/cm^{-1} 2881, 2825, 1733, 1660, 1617 and 1500; δ_H 2.23 (3H, s, CH_3), 2.89 (3H, s, CH_3), 3.56 (2H, t, *J* 4.3, NCH_2), 4.13 (2H, t, *J* 4.3, OCH_2), 4.33 (2H, s, NCH_2Ar), 6.51–7.09 (8H, m, aromatic H and N−CH=C) and 8.60 (1H, s, CHO); *m*/*z* (EI) 356 (M^+, 40%), 216 (100), 158 (80) and 143 (80).

7e. Mp 115–117 °C (Found: C, 74.15; H, 6.52; N, 8.51. $C_{20}H_{21}N_2FO$ requires C, 74.04; H, 6.53; N, 8.64%); ν_{max}/cm^{-1} 3036, 2935, 2884, 2789, 1621 and 1572; δ_H 2.31 (3H, s, CH_3), 2.91 (3H, s, CH_3), 2.95 (2H, t, *J* 10.8 $=CCH_2$), 3.95 (2H, t, *J* 10.8, NCH_2), 4.34 (2H, s, NCH_2Ar), 6.65–7.22 (8H, m, aromatic H and N−CH=C) and 9.35 (1H, s, CHO); δ_C 21.0, 25.1, 39.0, 54.4, 55.2, 114.3, 114.4, 115.3, 115.6, 119.9, 124.2, 128.9, 129.7, 133.0, 136.9, 137.9, 146.4, 146.5, 154.1, 156.5, 157.7 and 182.7; *m*/*z* (EI) 324 (M^+, 28%), 172 (100) and 105 (90).

7f. Oil (Found: 338.1802 $C_{21}H_{23}N_2FO$ requires 338.1794); ν_{max}/cm^{-1} 2850, 2715, 1675, 1648, 1598 and 1511; δ_H 1.99 (2H, quintet, *J* 6.2, $CH_2CH_2CH_2$), 2.32 (3H, s, CH_3), 2.39 (2H, t, *J* 6.2, CH_2), 2.93 (3H, s, CH_3), 3.50 (2H, t, *J* 6.2, NCH_2), 4.34 (2H, s, NCH_2Ar), 6.60–7.20 (8H, m, aromatic H and N−CH=C) and 8.97 (1H, s, CHO); *m*/*z* (EI) 338 (M^+, 15%), 214 (100) and 184 (80).

7g. Mp 128–130 °C (Found: C, 74.0; H, 6.95; N, 8.1. $C_{21}H_{23}N_2FO$ requires C, 74.5; H, 6.85; N, 8.3%); ν_{max}/cm^{-1} 2867, 2784, 1631, 1573 and 1511; δ_H 1.15 (3H, t, *J* 7.0, CH_3), 2.97 (2H, t, *J* 10, $=CCH_2$), 2.31 (3H, s, CH_3), 3.38 (2H, q, *J* 7.0, CH_2CH_3), 3.97 (2H, t, *J* 10, NCH_2), 4.34 (2H, s, NCH_2Ar), 6.59–7.09 (7H, m, aromatic H), 7.25 (1H, s, N−CH=C) and 9.35 (1H, s, CHO); δ_C 11.7, 21.1, 25.1, 45.6, 51.5, 55.1, 114.6, 114.8, 115.3, 115.5, 115.8, 119.9, 124.2, 128.8, 129.5, 133.2, 136.9, 137.8, 144.9, 156.7, 182.8; *m*/*z* (EI) 338 (M^+, 9%), 201 (100) and 172 (80).

7h. Oil (Found: 368.1665. $C_{22}H_{25}N_2ClO$ requires 368.1656); ν_{max}/cm^{-1} 2861, 2709, 1649, 1616 and 1594; δ_H 1.19 (3H, t, *J* 7.3, CH_3), 2.00 (2H, quintet, *J* 5.7, $CH_2CH_2CH_2$), 2.32 (3H, s, CH_3), 2.42 (2H, t, *J* 6.2, $=CCH_2$), 3.43 (2H, q, *J* 7.3, NCH_2CH_3), 3.55 (2H, t, *J* 5.7, NCH_2CH_2), 4.37 (2H, s, NCH_2Ar), 6.25–7.15 (m, 8H, alkenic and aromatic H) and 9.00 (s, 1H, CHO); *m*/*z* (EI) 368 (M^+, 9%), 214 (100) and 184 (80).

7i. Oil (Found: C, 75.56; H, 7.28; N, 7.68. $C_{23}H_{26}N_2O_2$ requires C, 76.20; H, 7.23; N, 7.73%); ν_{max}/cm^{-1} 2854, 2726, 1664, 1592 and 1527; δ_H 1.88 (2H, m, $CH_2CH_2CH_2$), 1.97 (2H, m, $CH_2CH_2CH_2$), 2.18 (3H, s, CH_3), 2.57 (2H, t, *J* 5.7, $=CCH_2$), 3.16 (3H, s, CH_3), 3.69 (2H, t, *J* 5.4, NCH_2CH_2), 4.59 (2H, s, NCH_2Ar), 6.69–7.75 (8H, m, aromatic and N−CH=C), 8.98 (1H, s, CHO) and 9.75 (1H, s, CHO); *m*/*z* (EI) 362 (M^+, 9%) and 228 (100).

8a. Mp 217–219 °C (Found: C, 68.4; H, 5.1; N, 8.3. $C_{28}H_{27}N_3Cl_2O$ requires C, 68.4; H, 5.5; N, 8.55%); ν_{max}/cm^{-1} 2859, 2763, 1623, 1567 and 1598; δ_H 2.36 (3H, s, CH_3) 2.79 (2H, t, *J* 9.7, $=CCH_2$), 2.83 (3H, s, CH_3), 3.76 (2H, t, *J* 9.7, NCH_2), 4.20 (2H, s, NCH_2Ar), 4.22 (2H, s, NCH_2Ar), 4.27 (2H, s, NCH_2Ar), 6.50–7.20 (10H, m, aromatic H and N−CH=C) and 9.16 (1H, s, CHO); δ_C 21.2, 25.0, 39.2, 52.6, 55.0, 58.3, 115.5, 118.7, 119.9, 122.8, 123.6, 124.4, 127.9, 128.3, 129.5, 131.0, 131.2, 131.4, 136.4, 138.6, 148.7, 148.8, 156.5 and 183.0; *m*/*z* (EI) 491 (M^+, 5%), 291 (40), 201 (100) and 172 (30).

8b. Mp 137–139 °C (Found: 505.1685. $C_{29}H_{29}N_3Cl_2O$ requires 505.1688); ν_{max}/cm^{-1} 2867, 1614, 1590 and 1502; δ_H 1.78 (2H, quintet, *J* 5.7, $CH_2CH_2CH_2$), 2.28 (2H, t, *J* 5.7, $=CCH_2$), 2.34 (3H, s, CH_3), 2.84 (3H, s, CH_3), 3.30 (2H, t, *J* 5.7, NCH_2), 4.28 (2H, s, NCH_2Ar), 4.34 (2H, s, NCH_2Ar), 4.40 (2H, s, NCH_2Ar), 6.50–7.20 (10H, m, aromatic H and N−CH=C) and 8.86 (1H, s, CHO); δ_C 17.8, 20.8, 21.2, 38.9, 50.6, 51.9, 55.1, 58.0, 113.7, 115.9, 119.4, 122.9, 124.4, 126.2, 126.9, 128.1, 128.2, 129.2, 129.8, 130.0, 131.0, 131.3, 133.6, 137.6, 142.8, 148.8, 149.1, 153.5 and 187.8; *m*/*z* (EI) 505 (M^+, 3%), 293 (70), 291 (100), 215 (90), 214 (80) and 184 (60).

8c. Mp 245–247 °C (Found: 519.1871. $C_{30}H_{31}N_3Cl_2O$ requires 519.1844); ν_{max}/cm^{-1} 2863, 2790, 1673, 1614, 1592 and 1500; δ_H 1.75 (4H, m, $CH_2CH_2CH_2CH_2$), 2.30 (3H, s, CH_3), 2.47 (2H, t, *J* 5.9, $=CCH_2$), 2.85 (3H, s, CH_3), 3.46 (2H, t, *J* 5.1, NCH_2), 4.17 (2H, s, NCH_2Ar), 4.20 (2H, s, NCH_2Ar), 4.29 (2H, s, NCH_2Ar), 6.51 (1H, s, N−CH=C), 6.70–7.10 (9H, m, aromatic H) and 8.87 (1H, s, CHO); δ_C 21.3, 23.2, 26.2, 28.6, 38.9, 51.5, 55.9, 57.8, 60.3, 115.6, 117.5, 119.0, 122.6, 123.9, 126.2, 128.0, 128.1, 128.4, 128.6, 129.1, 129.4, 130.9, 131.3, 137.6, 145.2, 158.9, 161.8 and 190.8; *m*/*z* (EI) 519 (M^+, 2%), 293 (65), 291 (100), 229 (90) and 228 (65).

8d. Mp 212–214 °C (Found: C, 65.7; H, 5.2; N, 8.1. $C_{28}H_{27}N_3Cl_2O_2$ requires C, 66.25; H, 5.4; N, 8.2%); ν_{max}/cm^{-1} 2883, 1616 and 1598; δ_H 2.34 (3H, s, CH_3), 2.83 (3H, s, CH_3), 3.38 (2H, t, *J* 4.3, NCH_2CH_2), 3.99 (2H, t, *J* 4.3, OCH_2), 4.15 (2H, s, NCH_2Ar), 4.22 (2H, s, NCH_2Ar), 4.24 (2H, s, NCH_2Ar), 6.27 (1H, s, N−CH=C), 6.59–7.14 (9H, m, aromatic H) and 8.57 (1H, s, CHO); *m*/*z* (EI) 507 (M^+, 70%), 291 (100) and 217 (60).

8f. Mp 212–214 °C (Found: C, 73.55; H, 6.05; N, 8.8. $C_{29}H_{29}N_3F_2O$ requires C, 73.5; H, 6.2; N, 8.9%); ν_{max}/cm^{-1} 2854, 2809, 1646, 1598, 1577 and 1500; δ_H 1.74 (2H, quintet, *J* 5.7, $CH_2CH_2CH_2$), 2.27 (2H, t, *J* 6.5, $=CCH_2$), 2.34 (3H, s, CH_3), 2.83 (3H, s, CH_3), 3.23 (2H, t, *J* 5.7, NCH_2), 4.12 (2H, s, NCH_2Ar), 4.16 (2H, s, NCH_2Ar), 4.21 (2H, s, NCH_2Ar), 6.30–7.25 (10H, m, aromatic H and N−CH=C) and 8.85 (1H, s, CHO); δ_C 17.7, 20.7, 21.2, 39.3, 50.3, 52.5, 55.0, 58.4, 113.1, 114.2, 114.3, 114.5, 114.6, 115.8, 115.9, 117.1, 117.4, 117.6, 117.9, 120.5, 120.6, 126.2, 129.0, 130.3, 133.8, 137.6, 142.6, 153.8 and 187.8; *m*/*z* (EI) 473 (M^+, 5%), 259 (100), 215 (49) and 214 (50).

9a. Mp 249–251 °C (Found: C, 59.5; H, 4.3; N, 8.7. $C_{16}H_{14}N_2Cl_2O$ requires C, 60.0; H, 4.4; N, 8.75%); ν_{max}/cm^{-1} 2863, 2798 and 1673; δ_H 2.83 (3H, s, CH_3), 4.18 (2H, s, CH_2) 4.71 (2H, s, CH_2), 6.87–7.35 (6H, m, aromatic H) and 8.32 (1H, s, CHO); δ_C 38.0, 38.3, 38.6, 38.9, 39.2, 39.5, 39.8, 48.3, 57.0, 116.8, 125.1, 126.8, 127.2, 129.0, 130.5 and 160.4; *m*/*z* (EI) 322 (70), 320 (M^+, 100%) and 166 (80).

Formylation of *N*,*N*-dimethyl-*p*-toluidine utilising *N*-formyl-1,2,3,4-tetrahydroquinoline and *N*-formylindoline

N,*N*-Dimethyl-*p*-toluidine (1.35 g, 10 mmol) and *N*-formyl-1,2,3,4-tetrahydroquinoline (3.02 g, 20 mmol) in $POCl_3$ (5 cm^3) were heated at 80 °C for 3 h after which the mixture was poured onto ice and basified with aqueous sodium hydroxide (5 M) and warmed on a water bath for 30 min. The cooled mixture was extracted with dichloromethane (3 × 50 cm^3), dried ($MgSO_4$) and evaporated and the resulting red oil subjected to flash chromatography using petroleum–ethyl acetate (50:50) as eluent. The first band (R_f 0.16) gave 2-*formyl*-4,N,N-*trimethylaniline* **15** as a pale yellow solid (0.91 g, 56%), mp 71 °C (Found: *m*/*z* 163.0995. $C_{10}H_{13}NO$ requires *m*/*z* 163.0997); ν_{max}/cm^{-1} 1671; δ_H 2.79 (3H, s, CH_3), 3.62 (6H, s, 2 × NCH_3), 7.88 (1H, dd, *J* 1.6 and 8.1, H-5), 8.10 (1H, *J* 1.6, H-3), 8.14 (1H, *J* 8.1, H-6) and 10.12 (1H, s, CHO).

A similar reaction with *N*-formylindoline in place of

formyltetrahydroquinoline resulted in unchanged dimethyl-*p*-toluidine, even after prolonged heating at 100 °C.

Formylation of *p*-substituted *tert*-anilines using aliphatic formamides

N,*N*-Dimethyl-*p*-toluidine (1.35 g, 10 mmol) and the formamide (10 mmol) in $POCl_3$ (5 cm^3) were heated at 80 °C for 3 h after which the reaction mixture was poured onto ice and ammonium hexafluorophosphate (1.63 g, 10 mmol) was added. If no precipitate formed, the solution was basified with sodium carbonate and extracted with ethyl acetate (3 × 40 cm^3) and the extract dried ($MgSO_4$) and evaporated to give the salt as follows.

From dimethylformamide was obtained 1,2,3,4-*tetrahydro*-1,3,3,6-*tetramethylquinazolinium hexafluorophosphate* **16** (1.04 g, 31%) as a pale brown solid by extraction. Recrystallisation from acetonitrile and ethyl acetate gave the product as pale buff needles, mp 223 °C (Found: C, 43.0; H, 5.7; N, 8.3. $C_{12}H_{19}F_6N_2P$ requires C, 42.9; H, 5.7; N, 8.3%); ν_{max}/cm^{-1} 838 (PF_6); δ_H 2.26 (3H, s, CH_3) 3.23 (3H, s, CH_3), 3.35 (6H, s, 2 × NCH_3), 4.77 (2H, s, CH_2), 4.84 (2H, s, CH_2), 6.92 (1H, d, *J* 8.6, H-8), 6.96 (1H, br s, H-5) and 7.17 (1H, br d, *J* 8.6, H-7).

From *N*-formylmorpholine was isolated by precipitation *morpholinium*-4-*spiro*-3′-1′,2′,3′,4′-*tetrahydro*-1′,6′-*dimethylquinazolinium hexafluorophosphate* **17** as pale yellow needles from acetonitrile and ethyl acetate, mp 192–193 °C (Found: C, 44.5; H, 5.55; N, 7.3. $C_{14}H_{21}F_6N_2OP$ requires C, 44.4; H, 5.6; N, 7.4%); ν_{max}/cm^{-1} 838 (PF_6); δ_H 2.25 (3H, s, CH_3), 3.24 (3H, s, CH_3), 3.67 (4H, m, NCH_2CH_2), 4.18 (4H, t, *J* 5.0, OCH_2) 4.97 (2H, s, NCH_2N^+), 5.07 (2H, s, N^+CH_2Ar), 6.90 (1H, d, *J* 8.4, H-8′), 7.00 (1H, br s, H-5′) and 7.16 (1H, dd, *J* 1.4, 8.4, H-7′).

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