SHORT PAPER

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Unusual aminations with tetramethylguanidine†

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Heating activated halobenzenes with 1,1,3,3-tetramethylguanidine affords mixtures of dimethylaminobenzenes and 2-aryl-1,1,3,3-tetramethylguanidines.

Keywords: nucleophilic aromatic substitution, tetramethylguanidine

The amination of aromatic and heterocyclic rings has attracted considerable attention in recent years.[1-4] Mention can be made of work describing nucleophilic halide displacement reactions (S_NAr) of substituted halobenzenes,[2] the use of enamines[3] and the recent introduction of transition metal promoted amination reactions.[4] In particular, amino substituted benzophenones, which may be obtained by the aforementioned routes, are valuable intermediates for the preparation of di- and triphenylmethane dyes,[5] photo-[6] and thermo-[7] chromic molecules, colour formers[8] and polymeric triarylamines.[9]

We now report an unusual nucleophilic aromatic substitution of halide on heating halobenzenes in 1,1,3,3-tetramethylguanidine (TMG).

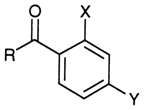
The displacement of chloride or fluoride from electron deficient aromatic compounds on heating either in neat amine or with an amine in a co-solvent (*e.g.* DMSO,[10] DMF[11] or tetramethylene sulfone[12]) has proved a fruitful route to aminobenzenes.[2] One function of particular interest to us was the guanidine unit. There are relatively few reports of S_NAr reactions using TMG. In all cases a halogen was displaced from a highly activated system *e.g.* 2-chloro-4,6-dimethoxy-1,3,5-triazine,[13] 2-chloropyrimidine[14] and 2,3,5,6-tetrabromo-1,4-benzoquinone,[15] and resulted in the formation of a 2-substituted TMG through displacement of the halogen by the imine N atom. We now report that heating 4-fluorobenzophenone in neat TMG at 100°C gave a new more polar pale yellow product that, surprisingly, was 4-dimethylaminobenzophenone, together with some intractable highly polar material after routine aqueous work-up and column chromatography. None of the desired benzophenone containing a TMG unit could be detected in the mixture by GC-MS. Repeating the procedure with other fluorobenzophenones (Table 1) revealed that this dimethylamination was a general reaction.

Dimethylamino group displacement of halides has been observed on heating activated chlorobenzenes at *ca* 200°C[16] and fluorobenzenes at *ca* 100°C[17] in DMF or hexamethylphosphoramide.[18] Also attempts to displace halogens with relatively non-nucleophilic amines *e.g.* diethanolamine, using DMF as solvent results in significant dimethylamination.[11]

A possible mechanism for this reaction is outlined in Scheme 1. Initial attack by the NMe_2 function of TMG is followed by re-aromatisation of the intermediate anion through loss of fluoride. Elimination of dimethylcyanamide completes the sequence. GC-MS analysis of several of the reaction mixtures confirmed that dimethylcyanamide was present and thus supports the proposed mechanism.

To further explore the generality of this reaction we investigated the displacement of halide from some halogenoarenes (Table 2). Thus warming 1-fluoro-2-nitrobenzene in TMG resulted in the formation of two bright yellow components

Table 1 Substituted benzophenones



Reactant				Product[a]				
No.	R	X	Y	R	X	Y	Yield/%[b]	M.p./b.p./°C (lit. value)
1	Ph	H	F	Ph	H	NMe_2	58	87–88 (87.5–89)[19]
2	Ph	F	H	Ph	NMe_2	H	51	105–109, 0.08 mm (141–142, 1.0mm)[20]
3	4-FC_6H_4	H	F	4-FC_6H_4	H	NMe_2	29	109–111
				4-$Me_2NC_6H_4$	H	NMe_2	27	170–172(172–172.3)[19]
4	2-FC_6H_4	H	F	2-FC_6H_4	H	NMe_2	25[c]	83.5–84
5	4-$MeOC_6H_4$	H	F	4-$MeOC_6H_4$	H	NMe_2	54	131–132 (131.4)[19]
6	2-thienyl	H	F	2-thienyl	H	NMe_2	55	91–93 (92–94)[21]

[a]All new compounds were fully characterised by ^1H NMR spectroscopy, HRMS and gave satisfactory elemental analysis. Known compounds had comparable spectroscopic data and physical properties with authentic material. [b]Isolated yields are unoptimised. [c]Entry 4 is particularly noteworthy because C-4 substitution was entirely regiospecific, no other aminated products could be isolated.

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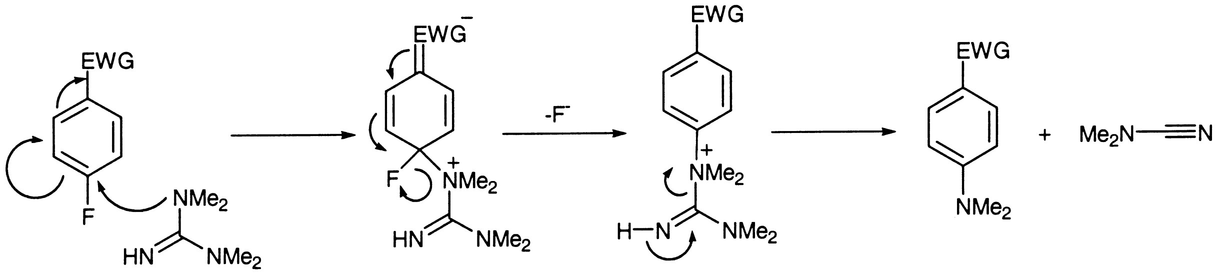
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*



Scheme 1

having markedly differing polarities. Separation by column chromatography gave the less polar minor fraction as 2-nitro-*N*,*N*-dimethylaniline (14%) and the more polar major 2-nitrophenyl substituted TMG (54%). Similar behaviour was observed with the chloronitrobenzotrifluoride (Table 2, entry 5). However, none of the TMG substituted product was obtained from the reaction of the isomeric chloronitrobenzotrifluoride (Table 2, entry 6) and only the dimethylamino substituted product was obtained. These results suggest that as the ability of the aromatic ring to stabilise the negatively charged σ-complex increases, attack by the imine nitrogen atom prevails.

The transformation of TMG, on heating with electron deficient aromatic halides, into 2-aryltetramethylguanidines provides a valuable alternative to the existing syntheses of these compounds, which are typically obtained from the reaction of an aniline with the chloroiminium salt derived from tetramethylurea and POCl$_3$.[25]

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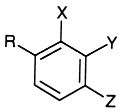
References

1 A.J. Belfield, G.R. Brown and A.J. Foubister, *Tetrahedron,* 1999, **55**, 11399.
2 F. Terrier, *Nucleophilic Aromatic Displacements: The Influence of the Nitro Group,* VCH Publishers Inc., New York, 1991; F.D. Bellamy, J.B. Chazan, P. Dodey, P. Dutartre, K. Ou, M. Pascal and J. Robin, *J. Med. Chem.,* 1991, **34**, 1545; G. L. Gravatt, B.C. Baguley, W.R. Wilson and W.A. Denny, *J. Med. Chem.,* 1991, **34**, 1552; E.A. Schmittling and J.S. Sawyer, *J. Org. Chem.,* 1993, **58**, 3229; H. Kotsuki, H. Sakai, H. Morimoto and H. Suenaga, *Synlett,* 1999, 1993; G.R. Brown, A.J. Foubister and P.D. Ratcliffe, *Tetrahedron Lett.,* 1999, **40**, 1219; D. Prim and G. Kirsch, *Tetrahedron,* 1999, **55**, 6511; A.J. Belfield, G.R. Brown, A.J. Foubister and P.D. Ratcliffe, *Tetrahedron,* 1999, **55**, 13285; E. Hendrickx, Y. Zhang, K.B. Ferrio, J.A. Herlocker, J. Anderson, N.R. Armstrong, E.A. Mash, A.P. Persoons, N. Peyghambarian and B. Kippelen, *J. Mater. Chem.,* 1999, **9**, 2251.
3 S.G.R. Guinot, J.D. Hepworth and M. Wainwright, *Dyes and Pigments,* 1998, **36**, 387.
4 J.F. Hartwig, *Synlett,* 1997, 329; J.P. Wolfe, S. Wagaw, J-F. Marcoux and S.L. Buchwald, *Acc. Chem. Res.,* 1998, **31**, 805; T. Ishiyama, H. Kizaki, T. Hayashi, A. Suzuki and N. Miyaura, *J. Org. Chem.,* 1998, **63**, 4726; I.P. Beletskaya, A.G. Bessmertnykh and R. Guilard, *Synlett,* 1999, 1459; E. Brenner, R. Schneider and Y Fort, *Tetrahedron,* 1999, **55**, 12829; B.H. Lipshutz, H. Ueda, *Angew. Chem., Int. Ed. Engl.,* 2000, **39**, 4492.
5 D.F. Duxbury, *Chem. Rev.,* 1993, **93**, 381.
6 D.A. Clarke, B.M. Heron, C.D. Gabbutt, J.D. Hepworth, S.M. Partington and S.N. Corns, International Patent Application PCT WO98/42695 and PCT WO 45281.
7 S.M. Burkinshaw, J. Griffiths and A.D. Towns, *J. Mater. Chem.,* 1998, **8**, 2677.
8 A.R. Katritzky, Z. Zhang, H. Lang, N. Jubran, L.M. Leichter and N. Sweeny, *J. Mater. Chem.,* 1997, **7**, 1399.
9 F.E. Goodson, S.I. Hauck and J.F. Hartwig, *J. Am. Chem. Soc.,* 1999, **121**, 7527.
10 G. Stefancich, R. Silvestri, S. Panico, M. Artico and M. Simonetti, *Arch. Pharm., (Weinheim),* 1990, **323**, 273.
11 Y.H. Cho and J.C. Park, *Tetrahedron Lett.,* 1997, **38**, 8331.
12 S.F. Beach, J.D. Hepworth, D. Mason, B. May and G. Hallas, *J. Chem. Soc., Perkin Trans. 2,* 1985, 107.

Table 2 Substituted benzenes



Reactant					Product^a					
No.	R	X	Y	Z	R	X	Y	Z	Yield/ %^{b}	M.p./b.p./°C (lit. value)
1	CN	H	H	F	CN	H	H	NMe$_2$	40	77–79 (80–81)[18]
2	CN	F	H	H	CN	NMe$_2$	H	H	47	68–71, 0.08 mm (58–65, 0.06 mm)[18]
3	CHO	H	H	F	CHO	H	H	NMe$_2$	47	73–75 (74)[22]
4	NO$_2$	F	H	H	NO$_2$	NMe$_2$	H	H	14	80–84, 0.08 mm (79–82, 0.08mm)[18]
					NO$_2$	N=C(NMe$_2$)$_2$	H	H	54	165–170, 0.3 mm
5	NO$_2$	H	CF$_3$	Cl	NO$_2$	H	CF$_3$	NMe$_2$	18	44–45 (44.5–45)[23]
					NO$_2$	H	CF$_3$	N=C(NMe$_2$)$_2$	58	94–95[24]
6	NO$_2$	CF$_3$	H	Cl	NO$_2$	CF$_3$	H	NMe$_2$	71	90.5–91

[a]All new compounds were characterised by ^{1}H NMR spectroscopy, HRMS and gave satisfactory elemental analysis. Known compounds had comparable spectroscopic data and physical properties with authentic material. [b]Isolated yields are unoptimised.

13 Z.J. Kamiński, P. Paneth and J. Rudziński, *J. Org. Chem,* 1999, **63**, 4248.

14 B.C. Elmes, G. Holan, G.T. Wernert and D.A. Winkler, *Aust. J. Chem.,* 1996, **49**, 573.

15 M. Dworniczak and A. Jarczewski, *Pol. J. Chem.,* 1999, **73**, 1739.

16 J.-M. Dumont and P. Rumpf, *Bull. Soc. Chim. Fr.,* 1962, 1213; S.G. Sibrikov, V.N. Kazin, V.V. Kopeikin, G.S. Mironov and T.N. Orlova, *J. Org. Chem. USSR, (Engl. Transl.),* 1991, **27**, 325.

17 T. Watanabe, Y. Tanake, K. Sekiya, Y. Akita and A. Ohta, *Synthesis,* 1980, 39; D. Badone, R. Cecchi and U. Guzzi, *J. Org. Chem.,* 1992, **57**, 6321.

18 J.T. Gupton, J.P. Idoux, G. Baker, C. Colon, A.D. Crews, C.D. Jurss and R.C. Rampi, *J. Org. Chem.,* 1983, **48**, 2933.

19 M. Matsui, H. Nakabayashi, K. Shibata and Y. Takase, *Bull Chem. Soc. Jpn.,* 1984, **57**, 3312.

20 P. Grammaticakis, *Bull Chem. Soc. Fr.,* 1953, 93.

21 I. Stahl, *Chem. Ber.,* 1987, **120**, 135.

22 F.A. Bell, P. Beresford, L.J. Kricka, and A. Ledwith, *J. Chem. Soc. Perkin Trans. 1,* 1974, 1788.

23 J.D. Hepworth, P. Jones and G. Hallas, *Synthesis,* 1974, 874.

24 Typical experimental procedure: A solution of 2-chloro-5-nitrobenzotrifluoride (4.5 mmol) in TMG (10 cm^3) was stirred at RT for 30 minutes and then gradually heated to 100°C and maintained at this temperature until TLC indicated that no aromatic halide remained. The mixture was cooled to room temperature and then poured into water (200 cm^3) and then partially neutralised with HCl (2M aq.). The resulting solution was extracted with EtOAc (4 × 30 cm^3). The combined extracts were washed with water (2 × 50 cm^3), dried and evaporated to afford the crude product. Elution from silica with 40% EtOAc in hexane gave two fractions. Fraction 1; 2-dimethylamino-5-nitrobenzotrifluoride (18%) as a bright orange solid, m.p. 44-45°C [lit m.p. 44.5–45°C[23]] and Fraction 2; 2-(4-nitro-2-trifluoromethylphenyl)-1,1,3,3-tetramethylguanidine (58%) as bright yellow cubes from hexane and EtOAc, m.p. 94–95°C, δ_H 2.80 (12H, s, 2(NMe_2)), 6.36 (1H, d, *J* 9.0, 6-H), 8.13 (1H, dd, *J* 9.0, 2.7, 5-H), 8.44 (1H, d, *J* 2.7, 3-H), (Found: MH^+, 305.1227; C, 47.3; H, 5.0; N, 18.2. $C_{12}H_{15}F_3N_4O_2$ requires MH^+, 305.1225(3); C, 47.4; H, 5.0; N, 18.4%).

25 H. Kessler, D. Leibfritz, and C. Burk, *Tetrahedron,* 1970, **26**, 1805; P. Pruszynski, *Can. J. Chem.,* 1987, **65**, 626.