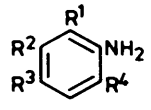
Selective Reactions in the Triazene Series. Part 2.[1] Protodediazoniation of Arenediazonium Salts with Formamide

Michael D. Threadgill * and Adrian P. Gledhill
Cancer Research Campaign Experimental Chemotherapy Group, Pharmaceutical Sciences Institute, Aston University, Aston Triangle, Birmingham B4 7ET

Treatment of preformed arenediazonium tetrafluoroborates or arenediazonium trifluoroacetates (formed *in situ*) with formamide and base effects reduction to the corresponding arene in moderate to good yield in cases where an electron-withdrawing substituent is present on the aromatic ring. Other functionalities remain unaffected. The mechanism of the protodediazoniation is shown to involve transfer of the formyl hydrogen atom to the substrate and may proceed *via* a 1-aryl-3-formyltriazene.

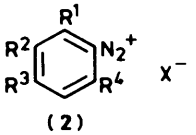
It has recently been shown that many *N*-methyl-containing compounds are metabolised by a preparation of murine liver to the corresponding *N*-hydroxymethyl derivatives[2] and, in the case of *N*-methylbenzamide, oxidised further to the N–CHO compound, *N*-formylbenzamide.[3] 1-Aryl-3,3-dimethyltriazenes are known antitumour agents but require prior oxidative metabolism for activity,[4] 3-(hydroxymethyl)triazenes being implicated as intermediates. In order to be able to test the hypothesis that these latter triazenes could be further metabolised, like the benzamides, to *N*-formyl analogues, a synthetic programme towards the preparation of 1-aryl-3-formyltriazenes was initiated. However, during this programme, the sole identifiable product (in moderate yield) from treatment of



(1)

a; $R^1 = R^2 = R^4 = H$, $R^3 = CO_2Me$
b; $R^1 = R^2 = R^4 = H$, $R^3 = CO_2Et$
c; $R^1 = R^2 = R^4 = H$, $R^3 = NO_2$
d; $R^1 = R^3 = H$, R^2 = 2,4-diamino-6-ethylpyrimidin-5-yl, $R^4 = Cl$
e; $R^1 = R^3 = H$, $R^2 = NO_2$, $R^4 = Me$
f; $R^1 = CN$, $R^2 = R^3 = R^4 = H$
g; $R^1 = OMe$, $R^2 = R^4 = H$, $R^3 = NO_2$
h; $R^1 = R^2 = R^4 = H$, $R^3 = Ac$
i; $R^1 = Ac$, $R^2 = R^3 = R^4 = H$
j; $R^1 = CO_2Me$, $R^2 = R^3 = R^4 = H$
k; $R^1 = Me$, $R^2 = R^3 = R^4 = H$
l; $R^1 = Me$, $R^2 = R^4 = H$, $R^3 = NO_2$
m; $R^1 = R^2 = R^4 = H$, $R^3 = OMe$
n; $R^1 = R^2 = R^4 = H$, $R^3 = Me$
o; $R^1 = R^2 = R^4 = Br$, $R^2 = H$
p; $R^1 = R^2 = R^4 = H$, $R^3 = Br$

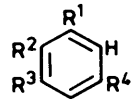
4-methoxycarbonylbenzenediazonium tetrafluoroborate (**2a**) with formamide and base was methyl benzoate (**3a**). Several agents have been reported to reduce arene diazonium salts to



(2)

$R^1,R^2R^3R^4$ as (1)
a—**f**; X = BF_4
g—**p**; X = CF_3CO_2

the corresponding arene, including tetrahydrofuran,[5] formaldehyde,[6] hypophosphorous acid,[7] *NN*-dimethylformamide[8] (DMF), and alcohols,[9] although problems have been encountered with each method. For example, biphenyls have been observed[9] as important by-products in the ethanol reduction. Formamide has once been claimed[8] to reduce a diazonium salt but the yield was reported to be markedly inferior to that achieved when the substrate was treated with DMF.



(3)

a; $R^1 = R^2 = R^4 = H$, $R^3 = CO_2Me$
b; $R^1 = R^2 = R^4 = H$, $R^3 = CO_2Et$
c; $R^1 = R^2 = R^4 = H$, $R^3 = NO_2$
d; $R^1 = R^3 = H$, R^2 = 2,4-diamino-6-ethylpyrimidin-5-yl, $R^4 = Cl$
e; $R^1 = R^3 = H$, $R^2 = NO_2$, $R^4 = Me$
f; $R^1 = CN$, $R^2 = R^3 = R^4 = H$
g; $R^1 = OMe$, $R^2 = R^4 = H$, $R^3 = NO_2$
h; $R^1 = R^2 = R^4 = H$, $R^3 = Ac$
i; $R^1 = Me$, $R^2 = R^4 = H$, $R^3 = NO_2$
j; $R^1 = R^3 = R^4 = Br$, $R^2 = H$
k; $R^1 = R^2 = R^4 = H$, $R^3 = Br$

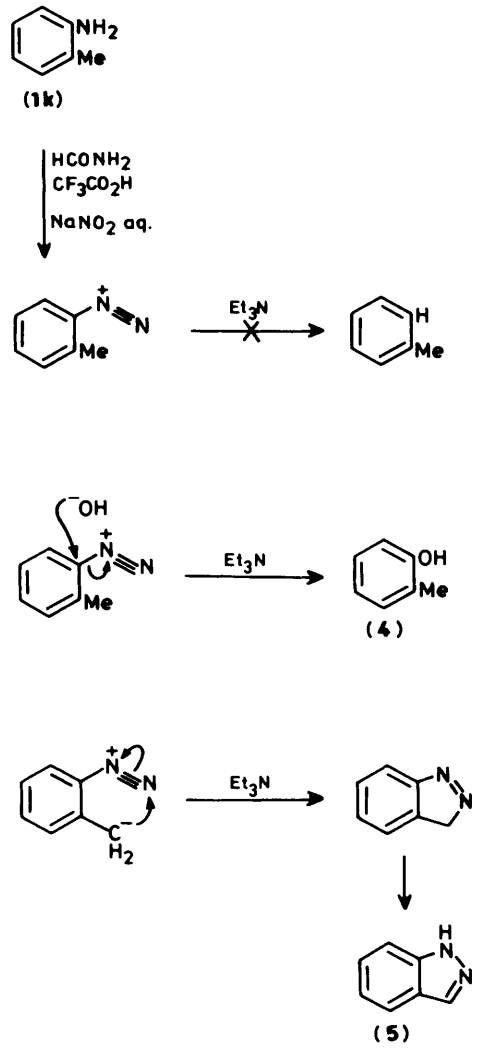
In order to investigate the generality of the reduction of (**1a**) by formamide, nitroaniline (**1c**) and 5-(3-amino-4-chlorophenyl)-6-ethylpyrimidine-2,4-diamine (**1d**) were diazotised in the usual way with sodium nitrite in aqueous tetrafluoroboric acid. The diazonium salts were isolated and dried before being dissolved in anhydrous formamide and treated with triethylamine. In both cases, good yields of the protodediazoniated product (**3c**,**d**) were obtained.

The method can be made into a true 'one-pot' synthetic reaction by carrying out the diazotisation with the formamide as solvent. Trifluoroacetic acid serves as the acid catalyst required. The intermediate diazonium trifluoroacetates were not isolated but the success of the sodium nitrite diazotisation step was indicated routinely by the formation of a bright orange-red azo-dye on treatment of a withdrawn aliquot with 2-naphthol and aqueous potassium carbonate. Addition at this stage of a large excess of triethylamine caused the rapid evolution of nitrogen gas characteristic of the reaction. Many arylamines were found to be deaminated by this facile process, as shown in the Table.

Substrates bearing only electron-donating substituents in the *para*-position, such as methoxy and methyl as in (**1m**) and (**1n**),

did not give the expected arene, only tarry materials resulting. However, where an electron-withdrawing substituent was present in substrate (**1g**) along with an electron-withdrawing moiety, protodediazoniation was achieved.

When 2-methylaniline (**1k**) was diazotised and treated with formamide and triethylamine according to the general one-pot procedure, the expected reduction product, toluene, was not observed by t.l.c. analysis of the reaction mixture. Here the isolated products were 2-methylphenol (**4**) and a trace of indazole (**5**). As with the diazonium salts (**2m,n**), 2-methylbenzenediazonium (**2k**) is insufficiently electrophilic to be reduced by the formamide but undergoes base-catalysed cyclisation to indazole (Scheme 1) and nucleophilic substitution by



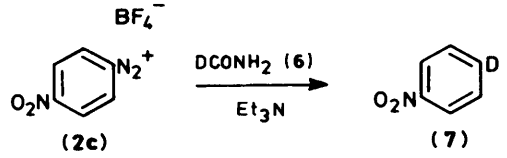
Scheme 1. Diazotisation of 2-methylaniline in formamide, followed by reaction with triethylamine gives products of substitution and cyclisation, not reduction

water to give the phenol. Indazole formation has been widely reported to be the outcome of attempted protodediazoniation of 2-methylbenzenediazonium salts; for example, the treatment of 2-methylanilines with pentyl nitrite and dioxane or tetrahydrofuran has been reported[5] to give indazoles as the sole products. When a powerful electron-withdrawing moiety, such as nitro, is present attached to the aromatic ring as in the cases of (**1e**) and (**1l**), we find indazole and phenol formation to be suppressed and good yields of the reduction products are obtained. This is consistent with Marx's observation[10] that 5-nitroindazole is not a product of the interaction of 2-methyl-4-nitrobenzenediazonium tetrafluoroborate with dimethylformamide.

Steric hindrance in the form of one *ortho*-substituent, as in the cases of the salts (**2b,e—g,i,j,l**) does not interfere with the progress of the reaction as shown by the moderate to good yields using these substrates or intermediates. However, where two bulky (bromo) substituents are present *ortho* to the diazonium function in salt (**2o**), the yield drops to 16%.

Mechanistic Studies.—The hydrogen atom which replaces the diazonium group on the arene could, at first sight, be derived from any of a number of sources including the formyl and NH_2 protons of the formamide, the triethylamine, or water. Water has been shown not to be the hydrogen source in a deuterium labelling study by Doyle *et al.*[8] in which 2,4,6-trichloroaniline was diazotised with t-butyl nitrite and then reduced by $HCONMe_2$ in the presence of one equivalent of D_2O. However, the tertiary amines tribenzylamine and *NN*-dimethylbenzylamine have been reported[11] to be the hydrogen source when 2,4,6-trichlorobenzenediazonium tetrafluoroborate was treated with the amines. In considering the formamide, Doyle *et al.*[8] also suggest that, since *NNN'N'*-tetramethylurea is as effective a reducing agent towards arenediazonium salts as is *NN*-dimethylformamide, then the formyl group is not the hydrogen source. This proposal is, however, weakened by their comparative study using *NN*-dimethylacetamide which was totally ineffective in reducing 4-nitrobenzenediazonium tetrafluoroborate (**2c**), whereas DMF gave a good yield of nitrobenzene.

In the present work, a sample of formamide deuteriated in the formyl group but not at the NH_2 function was prepared in a straightforward manner from 99 atom% methyl deuterioformate (DCO_2Me) and ammonia in anhydrous methanol. Insufficiently rigorous exclusion of moisture was found to lead to extensive hydrolysis of the starting ester. Treatment of the diazonium salt (**2c**) with this regiospecifically labelled formamide (**6**) and triethylamine furnished 4-deuterionitrobenzene (**7**) in which no pentaprotio compound could be detected by ^1H n.m.r. or mass spectroscopy. Hence, the formyl group is the sole hydrogen source under the conditions employed here (Scheme 2). This method using a relatively simply prepared isotopomer

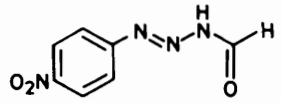


Scheme 2. Reaction of diazonium salt (**2c**) with deuterioformamide

of formamide may prove to be a useful method for the regiospecific labelling of aromatic compounds.

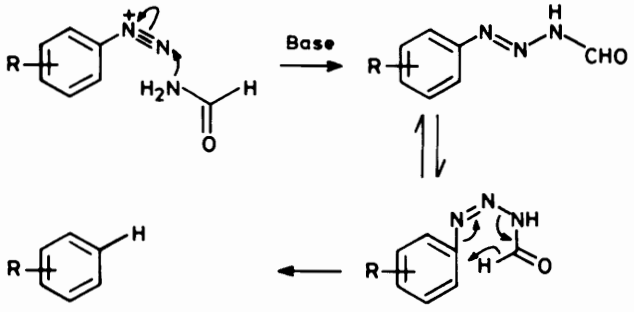
The question now arises as to whether the reduction process involves intermolecular hydride or H• transfer from formamide to arene or, alternatively, is the originally sought 1-aryl-3-formyltriazene formed *in situ* as an intermediate followed by intramolecular hydride transfer (Scheme 3). In their comparative study of aryl diazocyanides and aryl diazoisocyanides, Ignasiak *et al.*[12] prepared 1-aryl-3-formyltriazenes in low yield by treatment of solid arene diazonium chlorides and formamide in ether with aqueous sodium hydrogen carbonate. In the present study, the tetrafluoroborate (**2c**) was subjected to similar treatment, giving, in low yield, 3-formyl-1-(4-nitrophenyl)triazene (**8**) accompanied by a quantity of the reduction

product, nitrobenzene (**3c**). Interestingly, Ignasiak reports the crude formyl triazenes to be oily solids; perhaps the liquid components were the corresponding reduction products. Reaction of (**8**) with triethylamine effected reduction smoothly to give (**3c**), thus implying that compound (**8**) is an intermediate



(**8**)

in the protodediazoniation reaction and that hydride transfer is intramolecular (Scheme 3). The absence of biphenyl derivatives from the products of these reactions is indicative that radical processes (*e.g.* H$^{\bullet}$ transfer) are not involved, unlike in cases where hypophosphorous acid[13] and alcohols[14] are the reductants.



Scheme 3. Proposed pathway of the reduction reaction

The identities of co-products arising from the reducing agent formamide have not been established. Consideration of the proposed reaction pathway would suggest that isocyanate ($^{-}$NCO) should be formed. However, attempts to trap it as 4-chlorophenylurea[15] by treatment of the mixture arising from (**2c**), formamide, and triethylamine with an excess of acetic acid and 4-chloroaniline were unsuccessful. Furthermore, the cyclic trimer, cyanuric acid (2,4,6-trihydroxy-1,3,5-triazine) was shown by t.l.c. to be absent.

In conclusion, a method for the efficient protodediazoniation of arenediazonium salts bearing electron-withdrawing substituents has been developed. The facility of this reaction may explain why *N*-formyltriazenes have not been reported as metabolites of the antitumour *N*-methyltriazenes in marked contrast to the situation in the benzamide series.[3]

Experimental

The following methods are illustrative. M.p.s are uncorrected. N.m.r. spectra were obtained at 60 MHz using a Varian EM360A spectrometer and a Perkin-Elmer 1310 instrument furnished the i.r. data.

Method A: Nitrobenzene (**3c**) *from* 4-*Nitrobenzenediazonium Tetrafluoroborate* (**2c**).—Triethylamine (375 mg, 3.7 mmol) was added to 4-nitrobenzenediazonium tetrafluoroborate (474 mg, 2.0 mmol) in formamide (2.0 ml). After the evolution of nitrogen had ceased (5 min), the red mixture was stirred at ambient temperature for a further 30 min. An ethyl acetate extract (20 ml) of the mixture was washed with water (4 × 25 ml), 2M-hydrochloric acid (2 × 20 ml), saturated aqueous sodium hydrogen carbonate (20 ml), and saturated brine (15 ml) before being dried (Na_2SO_4), filtered, and the solvent evaporated to give a dark oil. Preparative layer chromatography (silica gel, diethyl ether) furnished nitrobenzene (202 mg, 82%) as a very pale yellow oil.

Table. Methods and yields of protodediazoniation products

Substrate	Method	Product[a]	Yield (%)
(**2a**)	A	(**3a**)	58[b]
(**2b**)	A	(**3b**)	21[c]
(**2c**)	A	(**3c**)	82[b]
(**2d**)	A	(**3d**)	64[b]
(**2e**)	A	(**3e**)	78[c]
(**2f**)	A	(**3f**)	35[c]
(**1g**)	B	(**3g**)	67
(**1h**)	B	(**3h**)	25
(**1i**)	B	(**3h**)	29
(**1k**)	B	(**3a**)	73.5
(**1j**)	B	(**4**)[d]	20
		(**5**)[d]	Trace
(**1l**)	B	(**3i**)	53
(**1m**)	B		0
(**1n**)	B	*e*	0
(**1o**)	B	(**3j**)	16
(**1p**)	C	(**3k**)	60.5

[a] Products were characterised by n.m.r. and mass spectroscopy and had m.p.s or b.p.s consistent with reported values ('CRC Handbook of Chemistry and Physics', ed. R. C. Weast, CRC Press, Cleveland, Ohio, U.S.A., 1979, 58th edn.; P. B. Russell and G. H. Hitchings, *J. Am. Chem. Soc.*, 1951, **73**, 3763; P. H. Griffiths, W. A. Walkey, and H. B. Watson, *J. Chem. Soc.*, 1934, 631). [b] Yield based on isolated arenediazonium tetrafluoroborate. [c] Yield based on starting aniline. [d] Toluene shown by t.l.c. to be absent. [e] Starting material (**1n**) (79%) recovered.

Method B: 3-*Methoxynitrobenzene* (**3g**) *from* 2-*Methoxy*-4-*nitroaniline* (**1g**).—Trifluoroacetic acid (2.0 g, 17.5 mmol) was added to 2-methoxy-4-nitroaniline (1.68 g, 10 mmol) in formamide (20 ml), followed by sodium nitrite (700 mg, 10 mmol) in water (1.3 ml) and the pale brown solution was stirred at ambient temperature for 20 min. Triethylamine (3.0 g, 30 mmol) was added and the deep red effervescing mixture was stirred for a further 20 min before being partitioned between ethyl acetate (100 ml) and water (50 ml). The organic portion was washed with 2M-hydrochloric acid (70 ml), water (4 × 50 ml), and saturated brine (50 ml), and then dried (Na_2SO_4) and filtered. The solvent was carefully evaporated to give a dark red oil which was chromatographed [silica gel, toluene–redistilled light petroleum (b.p. 60—80 °C); 1:1] to give 3-methoxynitrobenzene (1.03 g, 67%) as pale yellow crystals.

Method C: Bromobenzene (**3k**) *from Bromoaniline* (**1p**).—4-Bromaniline (1.72 g, 10 mmol) was treated as in Method B except that the crude product was distilled (Kugelrohr) to afford bromobenzene (950 mg, 60.5%) as a colourless liquid.

Deuterioformamide (**6**).—Anhydrous methanol (15 ml) (freshly distilled from magnesium methoxide) was saturated with ammonia at 0 °C. Methyl deuterioformate (99 atom %; Aldrich Chemical Co. Ltd.; 1.22 g, 20 mmol) was added and the mixture was stirred at ambient temperature in a tightly stoppered vessel for 16 h before careful evaporation of the solvent and excess ammonia gave deuterioformamide (890 mg, 97%) as a colourless liquid, b.p. 215 °C (lit.,[16] b.p. 111 °C at 20 mmHg for protio compound) $\nu_{max.}$ (liquid film) 3 300, 2 150 (C-D stretch), and 1 650 cm^{-1}; $\delta(D_2O)$ 5.2 (HOD); *m/z* 46 (M^+).

4-*Deuteronitrobenzene* (**7**).—4-Nitrobenzenediazonium tetrafluoroborate (**2c**) (237 mg, 1 mmol) was treated as for

Method A above except that deuterioformamide (**6**) (0.8 ml) and triethylamine (190 mg, 1.9 mmol) were employed. 4-Deuterionitrobenzene (96 mg, 77%) was obtained as a pale yellow liquid, $\nu_{max.}$ 2 950 (C-H stretch), 2 150 (C-D stretch), 1 520, and 1 330 cm^{-1}; $\delta(CDCl_3)$ 7.6 (2 H, *ca.* d, *J* 8 Hz, Ar 3- and 5-H), and 8.3 (2 H, d, *J* 8 Hz, Ar 2- and 6-H); *m/z* 124 (M^+).

3-*Formyl*-1-(4-*nitrophenyl*)*triazene* (**8**).—4-Nitrobenzenediazonium tetrafluoroborate (**2c**) (1.19 g, 5 mmol), formamide (900 mg, 20 mmol), water (10 ml), and diethyl ether (20 ml) were heated to reflux. Aqueous sodium hydrogen carbonate (8.4% w/v; 2.0 ml, 2 mmol) was added and the whole stirred under reflux for 15 min. The ether layer was removed and replaced by fresh ether (20 ml) and the $NaHCO_3$ addition/ether replacement cycle was repeated 5 times. The combined ethereal extracts were washed with water, dried, and the solvent evaporated to give an oily solid. This solid was triturated with light petroleum (b.p. 60—80 °C). The light petroleum supernatant was separated and the solvent was evaporated to give nitrobenzene (230 mg, 37%). The pale brown solid residue was characterised as 3-formyl-1-(4-nitrophenyl)triazene (280 mg, 29%) which decomposed when gently heated and failed to give a satisfactory CHN analysis although it appeared to be pure by t.l.c. (silica gel, toluene, and silica gel, light petroleum–dichloromethane; 2:1) $\nu_{max.}$(Nujol) 3 250, 1 710, 1 520, and 1 340 cm^{-1}; $\delta[(CD_3)_2SO]$ 6.2 (1 H, br, NH), 7.8 (2 H, *ca.* d, *J* 8 Hz) and 8.3 (2 H, d, *J* 8 Hz) (ArH), and 8.5 (1 H, br, CHO); *m/z* 194, 138, and 123.

Nitrobenzene (**3c**) *from* 3-*Formyl*-1-(4-*nitrophenyl*)*triazene* (**8**).—3-Formyl-1-(4-nitrophenyl)triazene (**8**) (194 mg, 1 mmol), was treated with triethylamine (2 ml) at ambient temperature for 4 h. Careful evaporation of the excess of reagent gave a dark residue which, on preparative layer chromatography (silica gel, diethyl ether) afforded nitrobenzene (81 mg, 66%) as a pale yellow oil.

Acknowledgements

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