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OBSERVATIONS ON THE VILSMEIER REACTION Part 1

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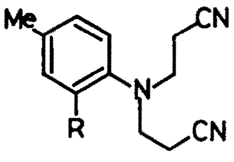
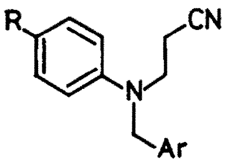
Abstract: The reaction of N,N-disubstituted-4-methylaniline derivatives under Vilsmeier conditions afforded products derived from an intramolecular hydride shift when one N-substituent was benzyl or 4-chlorobenzyl.

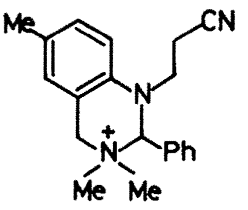
The Vilsmeier reaction$^{1-3}$ has found widespread application in synthesis as a method for the introduction of a formyl group into electron-rich aromatic systems. We have investigated the Vilsmeier reaction of N,N-disubstituted-4-methylaniline derivatives **(1)**-**(3)** and, for comparison, N,N-disubstituted aniline derivatives **(4)** and **(5)**.



(1) R=H
(6) R=CHO



	R	Ar
(2)	Me	phenyl
(3)	Me	4-chlorophenyl
(4)	H	phenyl
(5)	H	4-chlorophenyl
(8)	CHO	phenyl
(9)	CHO	4-chlorophenyl



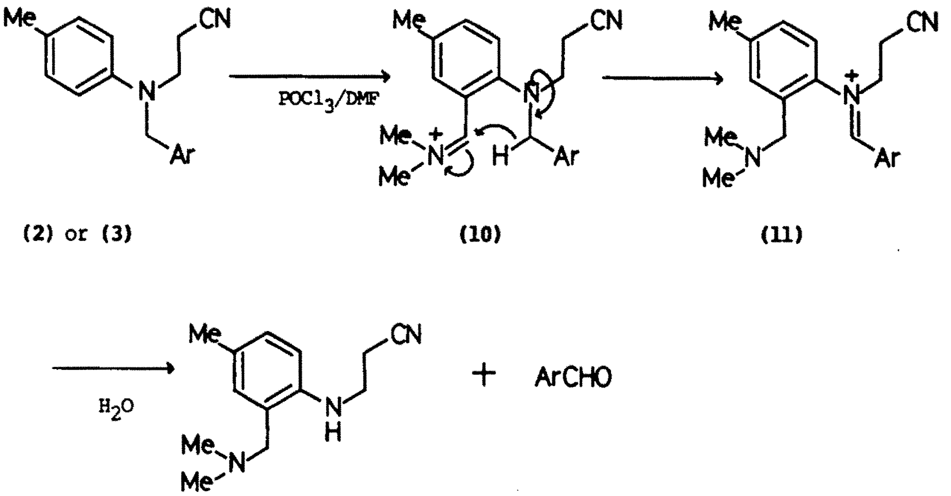
(12)

Preparation of Compounds (1)-(5)

N,N-Di(2-cyanoethyl)-4-methylaniline **(1)** was prepared by cyanoethylation of 4-methylaniline^{4}. Compounds **(2)**-**(5)** were all prepared by a similar cyanoethylation procedure. Thus, N-benzyl-4-methylaniline afforded N-benzyl-N-(2-cyanoethyl)-4-methylaniline **(2)** (46% yield), N-(4-chlorobenzyl)-4-methylaniline afforded N-(4-chlorobenzyl)-N-(2-cyanoethyl)-4-methylaniline **(3)** (48% yield), N-benzylaniline afforded N-benzyl-N-(2-cyanoethyl)aniline **(4)** (61% yield) and N-(4-chlorobenzyl)aniline afforded N-(4-chlorobenzyl)-N-(2-cyanoethyl) aniline **(5)** (60% yield). Compounds **(2)-(5)** all exhibited spectral and microanalytical data consistent with their proposed structures.

Vilsmeier Reaction of Compounds **(1)-(5)**

When compound **(1)** was reacted under Vilsmeier conditions [$POCl_3$- dimethylformamide (DMF)], 2-(N,N-di-2-cyanoethyl)amino-5-methyl- benzaldehyde **(6)** (95% yield) was obtained as expected. However, when compound **(2)** was reacted under similar conditions N-(2-cyanoethyl)-2- dimethylaminomethyl-4-methylaniline **(7)** (71% yield) and benzaldehyde (94 % yield) were isolated. Compound **(7)** was an oil and its proposed structure was supported by its spectral data. A plausible explanation for this transformation **(2)**⟶**(7)** + benzaldehyde is presented in the Scheme. Treatment of compound **(2)** with $POCl_3$- DMF affords the intermediate **(10)** which undergoes an intramolecular hydride shift (facilitated by the formation of a conjugated system between both aromatic rings) giving intermediate **(11)**. Hydrolysis of this intermediate **(11)** then yields compound **(7)** and benzaldehyde. We have also considered the possibility of a second intermediate **(12)** in this reaction which is formed by intramolecular cyclisation of compound **(11)**. In a similar manner compound **(3)** afforded compound **(7)** (67% yield) and 4-chlorobenzaldehyde (80% yield) under Vilsmeier conditions.



(2) or **(3)** **(10)** **(11)**

(7)

Scheme

In comparison to compounds **(2)** and **(3)**, compounds **(4)** and **(5)** afforded the expected products 4-[N-benzyl-N-(2-cyanoethyl)]aminobenzaldehyde **(8)** (100% yield) and 4-[N-(4-chlorobenzyl)-N-(2-cyanoethyl)]aminobenzaldehyde **(9)** (91 % yield) when they were reacted under Vilsmeier conditions. In these cases an intramolecular hydride shift is not possible.

Acknowledgements

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EXPERIMENTAL

Melting points are uncorrected. Proton NMR spectra (60MHz) were determined in deuterochloroform solution using tetramethylsilane as an internal standard. Infra-red spectra were determined as KBr discs unless otherwise stated.

Preparation of Compounds **(2)**-**(5)** : General Method

A mixture of *N*-substituted aniline derivative (see below), acrylonitrile and CuCl in acetic acid (15-30ml) were heated under reflux (5-15hrs). The reaction mixture was allowed to cool to room temperature and then poured into an excess of aqueous ammonia solution. The mixture was extracted several times (dichloromethane or ether) and the combined organic extracts were washed with water, dried ($MgSO_4$) and evaporated under reduced pressure. The resulting oils or solids were crystallised from ethanol. By this method the following transformations were achieved:

N-Benzyl-4-methylaniline[5] (9.0g), acrylonitrile (18ml) and CuCl (2.75g) gave *N*-benzyl-*N*-(2-cyanoethyl)-4-methylaniline **(2)**(5.2g, 46%) as white needles, m.p 55-57°. [Found: C,81.7;H,7.2;N,11.2. $C_{17}H_{18}N_2$ requires C,81.6;H,7.2;N,11.2%]. V_{max}. 2250(-CN)cm^{-1}.δ 7.15 (5H,s,Ph-*H*), 6.95 (2H,d,*J* 8Hz,Ar-*H*), 6.55(2H,d,*J* 8Hz,Ar-*H*), 4.45(2H,s,-CH_2Ph), 3.60(2H,t,*J* 8Hz,>NCH_2CH_2CN), 2.45(2H,t,*J* 8Hz,>NCH_2CH_2CN) and 2.20(3H,s,-CH_3).

N-(4-chlorobenzyl)-4-methylaniline[6] (10.0g), acrylonitrile (18ml) and CuCl (2.75g) gave N-(4-chlorobenzyl)-N-(2-cyanoethyl)-4-methylaniline **(3)** (5.8g, 48%) as white needles, m.p 64-65°. [Found: C,72.0;H,6.0;N,9.9;Cl,12.6. $C_{17}H_{17}ClN_2$ requires C,71.7;H,6.0;N,9.9;Cl,12.4%]. V_{max}. 2250(weak,-CN).δ 7.15 (4H,s,Ar-*H*), 7.00 (2H,d,*J* 8Hz,Ar-*H*), 6.55(2H,d,*J* 8Hz,Ar-*H*), 4.45(2H,s,-CH_2Ar), 3.65(2H,t,*J* 7Hz,>NCH_2CH_2CN), 2.50(2H,t,*J* 7Hz,>NCH_2CH_2CN) and 2.20(3H,s,-CH_3).

N-Benzylaniline[7] (18.0g), acrylonitrile (36ml) and CuCl (5.50g) gave N-benzyl-N-(2-cyanoethyl)aniline **(4)**(14.1g, 61%) as light tan needles, m.p 102-103°. [Found: C,81.8;H,6.8;N,12.0. $C_{16}H_{16}N_2$ requires C,81.3;H,6.8 ;N,11.9%]. V_{max}. 2250(-CN)cm^{-1}. δ 7.20-6.50(10H,m,Ar-*H*), 4.45(2H,s,-CH_2Ar), 3.65(2H,t,*J* 7Hz,>NCH_2CH_2CN) and 2.50(2H,t,*J* 7Hz,>NCH_2CH_2CN).

N-(4-Chlorobenzyl)aniline[8] (10.0g), acrylonitrile (18ml) and CuCl (2.75g) gave N-(chlorobenzyl)-N-(2-cyanoethyl)aniline **(5)**(7.4g, 60%) as light tan needles, m.p 89-91°. [Found: C,70.9;H,5.5;N,10.5;Cl,13.3. $C_{16}H_{15}ClN_2$ requires C,71.0 ;H,5.6;N,10.3;Cl,13.1%]. V_{max}. 2250(weak,-CN)cm^{-1}.δ 7.35-6.55(9H,m,Ar-*H*), 4.50(2H,s,-CH_2Ar), 3.65(2H,t,*J* 7Hz,>NCH_2CH_2CN) and 2.50(2H,t,*J* 7Hz,>NCH_2CH_2CN).

Vilsmeier Reactions: General Method

To cooled (ice-bath) dimethylformamide (13-20ml) was added $POCl_3$ dropwise with stirring keeping the temperature below 15°C. The *N,N*-disubstituted aniline derivative (see below) was then added. The mixture was allowed to warm to room temperature, was heated (1.5-9hrs) at 80-100°C and allowed to cool to room temperature. In the reactions of compounds **(1)**,**(4)** and **(5)** the mixture was made basic by addition of dilute sodium hydroxide solution and the corresponding aldehydes **(6)**,**(8)** and **(9)** were isolated by extraction into dichloromethane or ether. In the reactions of compounds **(2)** and **(3)** the mixture was made acidic by addition of dilute hydrochloric acid and the benzaldehyde or 4-chlorobenzaldehyde was isolated by extraction into ether; the aqueous fraction was then basified with dilute sodium hydroxide solution and compound **(7)** was isolated by extraction into ether. In all of the above reactions the organic extracts were washed with water, dried ($MgSO_4$) and evaporated under reduced pressure to yield the reaction products. Formylated products were crystallised from ethanol. By this method the following transformations were achieved:

Compound **(1)** (2.0g) and $POCl_3$ (2.87g) gave 2-(N,N-di-2-cyanoethyl)amino-5-methylbenzaldehyde **(6)** (2.1g, 95%) as light tan needles, m.p 92-93°. [Found: C,69.9;H,6.3;N,17.6. $C_{14}H_{15}N_3O$ requires C,69.7;H,6.3;N,17.4%]. ν_{max}. 2250(weak,-CN) and 1680(-CHO)cm^{-1}. δ 10.50 (1H,s,$-C\underline{H}O$), 7.65(1H,d,*J* 2Hz,Ar-$\underline{H}$,), 7.45(1H,dd,*J* 7 and 2Hz,Ar-$\underline{H}$), 7.20(1H,d,*J* 7Hz,Ar-$\underline{H}$), 3.50(4H,t,*J* 7Hz,$>NCH_2C\underline{H}_2CN$), 2.50(4H,t,*J* 7Hz,$>NC\underline{H}_2CH_2CN$) and 2.40(3H,s,$-C\underline{H}_3$).

Compound **(2)** (1.0g) and $POCl_3$ (1.25g) gave N-(2-cyanoethyl)-2-dimethylaminomethyl-4-methylaniline **(7)** (0.62g,71%) as a light tan oil and benzaldehyde (0.40g,94%), identical with an authentic sample. Compound **(7)**: ν_{max}.(liquid film) 3220(>NH) and 2250(weak,-CN)cm^{-1}. δ 6.95(1H,broad d,*J* 8Hz,Ar-$\underline{H}$), 6.76(1H,broad s,Ar-$\underline{H}$), 6.38(1H,d,*J* 8Hz,Ar-$\underline{H}$), 6.05(1H,broad s,$>N\underline{H}$), 3.35(4H,m,$ArC\underline{H}_2NMe_2$ and $>CH_2C\underline{H}_2CN$), 2.55(2H,t,*J* 7Hz,$>NC\underline{H}_2CH_2CN$), 2.20(3H,s,Ar-$C\underline{H}_3$) and 2.16(6H,s,$-N\underline{Me}_2$). Compound **(7)** (0.1g) and methyl iodide (0.2g) were heated (10 mins) at reflux in ethyl acetate (10ml) giving a methiodide, m.p 174-176°. [Found:C,46.7;H,6.1;N,11.2;I,35.1. $C_{14}H_{22}\overset{+}{N_3}\,\overset{-}{I}$ requires C,46.8;H,6.2;N,11.7;I,35.3%].

Compound **(3)** (1.5g) and $POCl_3$ (1.65g) gave compound **(7)** (0.77g, 67%), identical with the sample prepared above and 4-chlorobenzaldehyde (0.59g, 80%), identical with an authentic sample.

Compound **(4)** (1.0g) and $POCl_3$ (1.30g) gave 4-[N-benzyl-N-(2-cyanoethyl)]aminobenzaldehyde **(8)** (1.1g, 100%) as tan needles , m.p 72-73°. [Found: C,76.9;H,6.0;N,10.5. $C_{17}H_{16}N_2O$ requires C,77.2;H,6.1;N,10.6%]. ν_{max}. 2250(weak,-CN) and 1660(-CHO)cm^{-1}. δ 9.50 (1H,s,$-C\underline{H}O$), 7.50(2H,d,*J* 8Hz,Ar-$\underline{H}$), 7.05(5H,broad s,Ph-$\underline{H}$), 6.60(2H,d,*J* 8Hz,Ar-$\underline{H}$), 4.55(2H,s,$-C\underline{H}_2Ph$), 2.70(2H,t,*J* 7Hz,$>NCH_2C\underline{H}_2CN$) and 2.55(2H,*J* 7Hz,$>NC\underline{H}_2CH_2CN$).

Compound **(5)** (1.5g) and $POCl_3$ (1.7g) gave 4-[N-(4-chlorobenzyl)-N-(2-cyanoethyl)]aminobenzaldehyde **(9)** (1.5g,91%) as pale yellow rhombs m.p 138-140°. [Found: C,68.1;H,5.0;N,9.2;Cl,11.9. $C_{17}H_{15}ClN_2O$ requires C,68.3;H,5.1;N,9.4;Cl,11.9%]. ν_{max}. 2250(weak,-CN) and 1665(-CHO)cm^{-1}. δ 9.75 (1H,s,$-C\underline{H}O$), 7.75(2H,d,*J* 8Hz,Ar-$\underline{H}$), 7.40-7.00(4H,m,Ar-$\underline{H}$), 6.75(2H,d,*J* 8Hz,Ar-$\underline{H}$), 4.70(2H,s,$-C\underline{H}_2Ar$), 3.85(2H,t,*J* 7Hz,$>NCH_2C\underline{H}_2CN$), and 2.70(2H,d,*J* 8Hz,$>NC\underline{H}_2CH_2CN$).

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