A Simple Route to *N*-Methylarylamines

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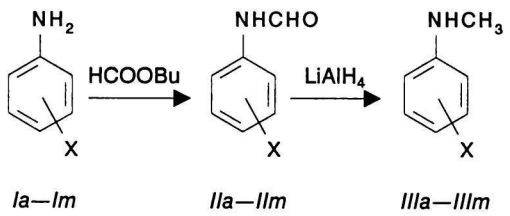
Thirteen ring-substituted anilines were transformed into corresponding formanilides by the action of n-butyl formate in the presence of trifluoroacetic acid and then reduced with lithium aluminium hydride to *N*-methylanilines in total yields 40—70 %. The method can be employed for methylation of primary and secondary amino groups bound to aromatic and heteroaromatic systems provided that they are neither sterically hindered nor strongly conjugated with other substituents.

The general method of *N*-alkylamines preparation, *i.e.* alkylation with alkyl halides or inorganic acids esters and reductive alkylations with carbonyl compounds are of limited value as regards synthesis of *N*-methylaniline and its derivatives. Reaction of aniline with methyl iodide affords the quaternary ammonium salt [1], with less reactive methyl sulfate a mixture of compounds is obtained from which *N*-methylaniline can be isolated as the *N*-nitroso derivative [2]. Methylation of *N*-tosylaniline presents no such problems but the cleavage of the sulfonamide bond requires very severe conditions [3], hence only some aniline derivatives can be *N*-methylated in this way.

Reductive methylation of anilines having substituted the most reactive sites in the benzene ring gives *N*,*N*-dimethyl derivatives but other substrates, when methylated according to the Eschweiler—Clark procedure yield mainly resins [4, 5]. Polycondensation can be excluded if sodium borohydride is used as the reducing agent but again *N*-methylaniline cannot be obtained in such a way [6].

In this report we describe a simple method of *N*-methylarylamines preparation involving formylation of the arylamine with subsequent reduction of the corresponding formanilide (Scheme 1).



Ia—Im *IIa—IIm* *IIIa—IIIm*

I—III	*a*	*b*	*c*	*d*	*e*	*f*	*g*
X	2-Me	4-Me	2,6-Me_2	benzo[2,3]	4-NMe_2	2-OMe	3-OMe
	h	*i*	*j*	*k*	*ℓ*	*m*	
X	4-OMe	3-Cl	4-Cl	4-Br	3-NO_2	4-NO_2	

Scheme 1

EXPERIMENTAL

The starting amines were commercial reagents, pure, used without purification. The progress of reactions was followed by the TLC method (Silufol; Kavalier, Votice) using PhMe—AcOEt (φ_r = 2 : 1) and $CHCl_3$—MeOH (φ_r = 24 : 1 to 5 : 1) mixtures as the developing systems; the plates were sprayed with 1 % rhodamine B and observed under the UV lamp.

All the compounds gave satisfactory elemental analyses. The purity of *N*-methylarylamines was controlled on the gas chromatograph 900 (Perkin—Elmer) equipped with the flame ionization detector and the 2.4 m × 2 mm column packed with the silicone oil OV-17 (3 %) on Chromosorb G-AW-DMCS (0.149—0.177 mm). The analyses were performed under isothermal conditions at 200 °C; purity of a product was 98—99 % unless stated otherwise.

Electron impact (70 eV) mass spectra were registered on the MX 1321 spectrometer (Scientific Instruments, USSR). ^1H and ^{13}C NMR spectra were recorded on the spectrometer BS 567A (Tesla) (2.3 T) in $CDCl_3$ with TMS as the standard. The infrared spectra were recorded on the Specord IR 75 instrument (Zeiss, Jena) in the KBr pellets or as a liquid film.

Substituted Formanilides *IIa—IIm*

The mixture of a ring-substituted aniline *I* (0.10 mol) and the appropriate amount (Table 1) of n-butyl formate with a drop of trifluoroacetic acid was refluxed for 0.5 to 3 h. The solution was left overnight in an ice-box, the precipitate was collected by filtration and purified by crystallization from a proper solvent. If the precipitate was not formed, the solution was heated to the boiling point, diluted with the equal volume of n-hexane and cooled again below 0 °C. The crude product was collected and recrystallized giving a pure formanilide *II*. The yields and

melting points of pure products are collected in Table 1.

Substituted *N*-Methylanilines *IIIa—IIIm* and Their Tosylates

A ring-substituted formanilide *II* (0.10 mol) was dissolved in absolute tetrahydrofuran (50 cm^3) and the solution was slowly dropped into intensely stirred suspension of lithium aluminium hydride (3.80 g; 0.10 mol) in tetrahydrofuran (50 cm^3). The mixture was stirred at room temperature for *ca.* 1 h and decomposed. Acetone (50 cm^3) was cautiously dropped in and then 50 % aqueous potassium hydroxide was added in small portions until the aluminates were precipitated. The mixture was filtered, the precipitate washed with tetrahydrofuran and discarded. The combined filtrates were evaporated and the residue distilled in vacuum. Solid residues (*IIIf*, *IIIh*, *IIIℓ*, *IIIm*) were purified by crystallization. The results are collected in Table 3.

N-Methylaniline *III* (1 cm^3, *ca.* 5 mmol) was dissolved in 8 cm^3 of the 1 M solution of tosyl chloride in methylene chloride. 2 M aqueous potassium hydroxide (8 cm^3) was added and the mixture shaken for 15 min. The precipitate was collected by filtration and crystallized from n-hexane or methanol. The melting points of the ring-substituted *N*-methyl-*N*-tosylanilines are given in Table 3.

RESULTS

Formylation of the primary, ring-substituted anilines *I* was carried out using n-butyl formate as the acylating agent. It should be mentioned that carefully purified ester, free of formic acid is inactive and the reaction must be catalyzed with trifluoroacetic acid. Minimum amounts of the formate were used sufficiently to obtain homogeneous reaction mixtures. Most of the formanilides (*cf.* Tables 1 and 2) crystallized from cold reaction mixtures, in some cases (*e.g. IIb*, *IIf*, *IIg*) the solutions were diluted with the

Table 1. Characterization of Formanilides

Compound	n(R)/n(S)[a]	Reaction time/h	Yield %	M.p./°C (Solvent)	M.p./°C	Ref.
IIa	1.3	1	80	56—59 (PhMe)	56.5—57.5	[7]
IIb	1.3	0.5	70	53—54 (MeOH)	52	[7]
IIc	2.5	0.1	47	166—167 (EtOH)	164—165	[8]
IId	9.0	2	88	140—141 (PhMe)	138.5	[7]
IIe	7.0	0.1	82	147—148 (PhMe)	–	
IIf	2.8	1	84	83—84 (PhMe)	83.5	[9]
IIg	1.3	0.5	89	58—60 (MeOH)	57	[10]
IIh	3.0	0.5	69	78—79 (Octane)	80—81	[11]
IIi	3.8	1	86	56—58 (PhH)	57—58	[12]
IIj	3.7	3	63	103—105 (PhH)	102	[13]
IIk	4.9	2	87	116—117 (PhMe)	119	[13]
IIℓ	3.5	3	83	134—135 (AcEt)	134	[14]
IIm	4.0	2	77	199—200 (AcEt)	194—195	[15]

a) The amount of substance ratio of n-butyl formate to the aniline.

Table 2. Spectral Characteristics of Formanilides

Compound	IR, $\tilde{\nu}$/cm^{-1} Amide bands	Mass spectra, m/z (I_r/%)
IIa	1550, 1665, 3240	135 (M^+, 28), 118 (6), 107 (22), 106 (59), 79 (11), 77 (18), 29 (100)
IIb	1520, 1690, 3190	135 (M^+, 98), 107 (36), 106 (100), 79 (14), 77 (23), 51 (11), 29 (6)
IIc	1525, 1655, 3230	149 (M^+, 62), 132 (26), 120 (100), 106 (60), 91 (35), 29 (3)
IId	1540, 1655, 3220	171 (M^+, 68), 143 (88), 116 (33), 115 (100), 89 (17), 29 (47)
IIe	1530, 1630	164 (M^+, 3), 136 (100), 121 (15), 120 (6), 93 (4), 29 (5)
IIf	1530, 1655, 3250	151 (M^+, 32) , 123 (15), 108 (66), 80 (100), 65 (20), 29 (20)
IIg	1520, 1680, 3200	151 (M^+, 100), 123 (80), 108 (4), 94 (77), 80 (62), 29 (19)
IIh	1510, 1655, 3240	151 (M^+, 6), 122 (4), 108 (18), 80 (16), 29 (100)
IIi	1595, 1695, 3200	157 (25), 155 (M^+, 81), 129 (31), 127 (100), 92 (32), 29 (100)
IIj	1540, 1620, 3250	157 (25), 155 (M^+, 75), 129 (28), 127 (100), 92 (32), 29 (7)
IIk	1530, 1670, 3280	201 (99), 199 (M^+, 100), 173 (69), 171 (73), 92 (82), 65 (61)
IIℓ	1545, 1680, 3260	166 (M^+, 100), 138 (25), 120 (6), 92 (76), 65 (74), 29 (27)
IIm	1550, 1680, 3255	166 (M^+, 100), 138 (9), 136 (3), 108 (24), 92 (32), 64 (74)

Table 3. Characterization of *N*-Methylanilines and Their Tosylates

Compound	Yield	B.p./°C (*p*/hPa)	*N*-Tosyl derivatives		
	%	M.p./°C (Solvent)	M.p./°C (Solvent)	M.p./°C	Ref.
IIIa	90	70 (7)	73—74 (Hexane)	86	[16]
IIIb	69	75 (11)	62—63 (Hexane)	60	[16]
IIIc	70	65 (5)	122—123 (MeOH)	–	
IIId	83	97 (0.7)	127—128 (Hexane)	124—125	[17]
IIIe	72	102 (3)	91—92 (Hexane)	–	
IIIf	45	80 (5)	104—105 (Hexane)	100	[6]
		33—34 (Hexane)[a]			
IIIg	88	108 (9)	58—59 (MeOH)	–	
IIIh	84	109 (11)	72—73 (MeOH)	68—69	[16]
		35—36 (Hexane)[b]			
IIIi	91	99 (5)	80—81 (Hexane)	–	
IIIj	65	74 (0.7)	96—97 (MeOH)	96	[16]
IIIk	63	96 (0.5)[c]	88—89 (Hexane)	–	
IIIℓ	68	63—64 (aq. EtOH)[d]	112—113 (Hexane)	139	[18]
IIIm	42	151—152 (EtOH)[e]	178—179 (AcEt)	188—189	[16]

Ref. give m.p.'s: *a*) 33—33.5 °C [9]; *b*) 37 °C [11]; *c*) 11 °C [19]; *d*) 65—66 °C [20]; *e*) 150—151 °C [21].

Table 4. ^{13}C NMR Spectral Data (δ) of *N*-Methylanilines

Compound	C-1	C-2	C-3	C-4	C-5	C-6	N—CH_3	CH_3
IIIa	14 7.2	121.8	129.9	116.8	127.2	109.1	30.7	17.3
IIIb	147.2	112.6	129.7	126.3	129.7	112.6	31.0	20.4
IIIc	147.4	128.2	128.8	121.8	128.8	128.2	35.3	18.4
IIId	144.5	115.3	134.2	117.2	119.8	103.6	30.8	*a*
IIIe	143.9	115.9	113.8	141.9	113.8	115.9	31.6	42.0[b]
IIIf	139.3	146.9	109.2	116.4	121.3	109.4	30.4	55.4
IIIg	147.5	98.2	160.8	102.2	129.9	105.6	31.6	55.0
IIIh	143.6	114.9	113.7	152.1	113.7	114.9	31.6	55.8
IIIi	150.4	111.8	134.9	116.9	130.1	110.8	30.5	–
IIIj	147.9	113.4	128.9	121.5	128.9	113.4	30.6	–
IIIk	148.2	113.9	131.8	108.7	131.8	113.9	30.7	–
IIIℓ	149.9	106.0	149.6	111.9	129.7	118.7	30.6	–
IIIm[c]	155.2	110.4	126.2	135.5	126.2	110.4	29.1	–

a) Carbons of the unsubstituted ring give signals at δ = 124.5, 125.6, 126.6, and 128.6. *b*) The peaks of the methyl groups are overlapped. *c*) In DMSO-d_6.

equal volume of n-hexane before cooling to – 20 °C. *N*,*N*-Dimethyl-1,4-phenylenediamine (*Ie*) and xylidine (*Ic*) react instantaneously at room temperature, toluidines (*Ia*, *Ib*) and anisidines (*If*—*Ih*) were formylated at the boiling point, halo- and nitroanilines required prolonged heating. 2,4,6-Tribromoaniline cannot be formylated in such a way (*ca.* 90 % recovery of the substrate).

The reductions of the formanilides *II* to the corresponding *N*-methylanilines *III* (*cf.* Tables 3 and 4) were performed using equimolar amounts of lithium aluminium hydride in absolute ethyl ether or tetrahydrofuran; lithium and sodium borohydrides were unreactive. Typically, a concentrated solution of formanilide was slowly dropped into intensely stirred suspension of the hydride, sparingly soluble formanilides as *IIm* were added all at once as the solids. In most cases the reduction was completed after 1 h at the boiling point, however, chromatographic control of the reaction seemed to be necessary. Small samples (*ca.* 1 cm^3) of a reaction mixture were pipetted, diluted with methanol and chromatographed using the starting amine *I* as the reference compound. When the primary amine was absent in a sample, the aluminium complexes were decomposed and precipitated, and *N*-methylaniline was purified by vacuum distillation and/or crystallization.

Surprisingly the nitro group in the corresponding derivatives (*ℓ*, *m*) appeared to be resistant to the action of lithium aluminium hydride. Several unsuccessful attempts were made to obtain *N*,*N*,*N*′-trimethyl-1,4-phenylenediamine (*IIIe*) from *IIe*. Reduction of the formyl to methyl group was accompanied with deformylation, consequently the crude product contained 35—40 % of *IIIe* and 60—65 % of *Ie* according to GC analyses. The amines could not be separated due to their instability. The crude mixture was tosylated and the *N*-tosyl derivatives of *Ie* and *IIIe* were separated by the flash chromatography.

Table 5. Characterization of *N*-Formyl Derivatives

Compound	M.p./°C (Solvent)	Yield %	IR, $\tilde{\nu}$/cm^{-1} Amide bands	^{13}C NMR, δ C-1	C-2	C-3	C-4	C-5	C-6	CHO
N-Methyl-4′-chloroformanilide[a]	53—54 (n-Hexane)	91	1670	141.0	129.3	123.2	130.1	123.2	129.3	161.8
N,2′-Dimethylformanilide[b]	Oil	82	1680	140.8	135.0	131.2	128.0	127.7	127.1	161.7
N,*N*-Diphenylformamide[c]	76—77 (n-Hexane)	44	1665	142.8	145.6	142.1	143.0	141.0	145.1	177.7
N-Benzylformanilide[d]	49—50 (n-Hexane)	85	1675	140.8	123.0	129.3	126.0	129.3	123.0	162.1
2-Formamidopyridine	72—73 (PhH)	46	1670, 3300	159.7	–	108.7	137.0	119.5	150.4	163.4
3-Formamidopyridine	93—95 (PhMe)	75	1695 1545, 3250	140.5	134.3	–	127.1	125.0	144.9	160.4
9-Formamidocarbazole	253—254 (MeOH)	81	1680, 3150	139.6	120.0	120.2	120.7	126.0	108.6	160.4
N,*N*′-Diformyl-1,3-phenylenediamine	156—157 (MeOH—PhMe)	96	1680 1540, 3250	138.6	110.3	138.6	114.7	130.2	114.7	159.4

a) *N*-Methyl group, δ = 31.0; *b*) *N*-methyl group, δ = 32.6 and C-methyl group, δ = 17.3; *c*) Due to the steric hindrance rotation along the Ar—N bond is restricted, consequently C-2 and C-6, resp. C-3 and C-5 are not magnetically equivalent; *d*) Methylene bridge, δ = 47.0 and remaining aromatic carbons, δ = 137.0, 138.3, 127.3, and 127.1.

Table 6. Characterization of *N*-Methylamines

Compound	M.p./°C (Solvent) B.p./°C (*p*/hPa)	Yield %	Mass spectra, *m*/*z* (I_r/%)
N,*N*-Dimethyl-4-chloroaniline	33—34 (Hexane) 89—90 (11)	78	157 (30), 156 (32), 155 (M^+, 95), 154 (100), 141 (3), 140 (6), 139 (12), 138 (11), 111 (10), 77 (17)
2,*N*,*N*-Trimethylaniline	Liquid 86—87 (11)	82	136 (3), 135 (M^+, 29), 134 (2), 121 (11), 120 (100), 118 (8), 104 (13), 103 (4), 91 (12), 77 (16)
N-Methyldiphenylamine	Liquid 106—107 (5)	80	184 (16), 183 (M^+, 100), 182 (46), 168 (13), 167 (13), 166 (10), 103 (20), 91 (14), 83 (9), 77 (74)
3-(Methylamino)pyridine	Liquid 119—120 (15)	84	109 (7), 108 (M^+, 100), 107 (91), 93 (5), 77 (34), 66 (18), 51 (28)
9-(Methylamino)carbazole	54—55 (Hexane)	47[a]	197 (14), 196 (M^+, 86), 182 (14), 181 (100), 167 (16), 166 (34), 154 (5), 152 (11), 139 (20)
N,*N*′-Dimethyl-1,3-phenylenediamine	Liquid 126—130 (11)	59	137 (11), 136 (M^+, 100), 135 (82), 134 (18), 121 (4), 107 (18), 106 (25), 105 (20), 93 (20), 79 (14)

a) Carbazole (39 %) was also isolated, m.p. and mixed m.p. = 254 °C.

The method worked out on primary anilines was then examined on some other arylamines. Secondary *N*-alkylanilines were formylated under similar conditions boiling with an excess of n-butyl formate for 4—8 h. Diphenylamine appeared to be even less reactive; after 20 h boiling the reaction mixture was evaporated and the residue containing nearly equal amounts of the substrate and *N*,*N*-diphenylformamide was worked up by the flash chromatography. Diphenylamine analogues as *N*,*N*′-diphenyl benzidine, phenothiazine, and carbazole could not be formylated with n-butyl formate. Reaction of 9-aminocarbazole occurs instantaneously at the boiling point of the ester. 3-Amino- and 2-aminopyridine require 6 h heating but only the former gives the corresponding formamide in a good yield. 4-Aminopyridine cannot be formylated by this method; it produces multicomponent reaction mixture from which only unchanged substrate can be isolated in a pure state. 1,3-Phenylenediamine is formylated on the both amino groups rapidly and quantitatively (Table 5).

N-Methylformanilides were reduced with lithium aluminium hydride to the corresponding *N*,*N*-dimethylanilines while *N*-benzylformanilide produced mainly *N*-benzylaniline (76—80 % according to GC analyses) regardless of the reaction conditions. 2-Formamidopyridine behaved similarly, the recovery of the primary amine was *ca.* 80 %. On the contrary, 3-methylaminopyridine was obtained in a good yield without difficulties. Reduction of 9-formamidocarbazole was accompanied with the cleavage of the N—N bond. 9-Methylaminocarbazole was separated from carbazole by extraction with 6 M hydrochloric acid from the ethereal solution of the crude product. Unstable *N*,*N*′-dimethyl-1,3-phenylene-

diamine was prepared in a good yield and contained no detectable amounts of the primary amines (Table 6).

DISCUSSION

Formylation of arylamines with n-butyl formate is a reversible process; the rate and conversion is determined with the steric and electronic factors.

Two bromine atoms in the *ortho* positions shield the amino group and make formylation of 2,4,6-tribromoaniline impossible although other *N*-acyl derivatives can be prepared by the action of anhydrides of carboxylic acid in the presence of boron trifluoride. The methyl groups in *Ic* disturb formylation, the reaction is rather fast but a significant part of the substrate remains unchanged. In the mass spectra of *IIa* and *IIc* the peaks of $[M - OH]^+$ indicate sterical interaction between the formamido and methyl groups. The alkyl substituents on the amino nitrogen slow down the formylation but do not influence the yield.

Within the aniline series the electron-donating substituents, which increase basicity of the amino nitrogen, facilitate formylation. It should be pointed out that alkylamines cannot be formylated in this way. They are much stronger bases than anilines and, probably they react with protonated ester molecules rather as proton acceptors than as nucleophiles. Aminopyridines, diarylamines and their heterocyclic analogues do not react or react with difficulty due to the distribution of the lone electron pair between nitrogen atom and aromatic rings. Strong interaction between the pyridine nitrogen and the amino group in conjugated position decreases nucleophilic reactivity of the amino nitrogen, retards formamide formation and facilitates some side reactions. On the contrary, 3-aminopyridine behaves like an aniline bearing an electron-accepting substituent. Planarity of the carbazole molecule favours delocalization of the pyrrole nitrogen unshared pair to the outer rings, hence carbazole is much less basic and nucleophilic than structurally related diphenylamine.

The second step of the preparation, *i.e.* reduction of formamides, provides further limitation of the method under discussion. The reaction occurs in two clearly separated steps. The first one, in which the amide is reduced to the corresponding aminomethanol, is almost instantaneous. The work up of the reaction mixture at this moment gives the primary amine and formaldehyde. The next step is much slower and in the case of *IIe* and 2-formamidopyridine never occurs to the end. Tertiary formamides are less prone to the reduction than secondary ones. Sterical factors seem to play a role in this case since preparation of *N*,*N*-dimethylanilines presents no problem while reduction of *N*-benzyl-*N*-phenylformamide produces a mixture of *N*-benzylaniline and its *N*-methyl derivative.

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