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New N-Permethylations and Introduction of Deuterium Labelled Methyl Groups into Primary and Secondary Amines

Angelo G. Giumanini, Giancarlo Verardo and Maria H. Gei

Department of Chemistry, University of Udine, I-33100 Udine

Lucia Lassiani

Department of Pharmaceutical Chemistry, University of Trieste, I-34100 Trieste

Summary

The extension of the N-permethylation reaction of amines to aromatic amines with strong electron withdrawing substituents in o- and p- positions is reported. A comparison of this method with other "best" last step synthetic methods reported in literature is given. The reaction could be extended to the syntheses of N-permethyl-derivatives of amines of the type $CH_{3-n}D_n$ by use of formaldehyde, dideuteroformaldehyde, sodium borodeuteride and -hydride. Label conservation in the reaction is complete: the final step in the reaction involves H^- (or D^-) transfer from the reducing agent to a reactive species. The MS of the labelled compounds revealed extensive label excange in the ionization chamber. A new homogeneous procedure for the N-permethylation, especially suited for larger scale preparations, is described.

Key Words: N-Permethylation, N-Per(deuteromethylation), Amines, Mass Spectrometry, Mechanism

We wish to report some useful extensions of our N-permethylation reaction of amines[1], using sodium borohydride (1), aqueous formaldehyde (2) and sulphuric acid and the experimental confirmation of part of the proposed reaction mechanism.

The first extension widens the scope of the reaction to substrates with strong electron withdrawing groups, even when they are located in sterically significant positions, depressing strongly the basicity of the nitrogen center.

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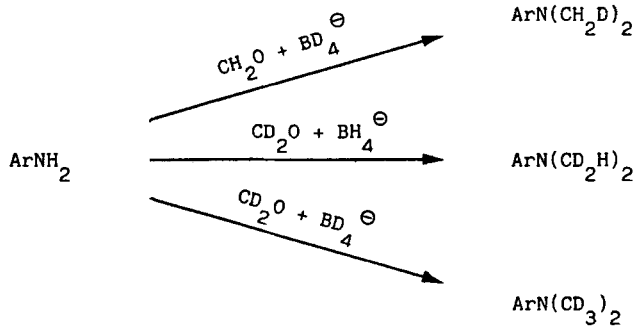
Thus, not only 4-nitro-benzeneamine (3), but also 3-nitrobenzeneamine (4) and 2-nitrobenzeneamine (5) could be N-permethylated in essentially quantitative yield. Moreover, the reaction was equally successful with 2- and 4-aminobenzoic acid methyl esters (6 and 7), 2- and 4-aminobenzonitrile (8 and 9) and 4-phenylazobenzeneamine (10), which all underwent smooth methylation. Functions other than amino were left intact. The present procedure strongly contrasts with the usually very poor yields of the desired product, by and large accompanied by lesser and overmethylated side products of the reaction of the most popular methylating agents with these substrates.

The second extension here proposed opens up an easy access to introduce N-monodeuteromethyl and dideuteromethyl groups in the N-permethylation reaction in a selective way with an isotopic purity apparently reflecting only that of the reducing agent and of the dideuteroformaldehyde precursor used, respectively. In fact, when sodium borodeuteride (11) and formaldehyde were used in the reaction of 4 and 3, the final products were N-permonodeuteromethylated amines 12 and 13.

SCHEME I



On the other hand, when polymeric dideuteroformaldehyde (14, paraformaldehyde) was used in connection with 1 on amines 3 and 4, the corresponding N-perdideuteromethylated amines 15 and 16 were analogously obtained. N-Trideuteromethylation may also be achieved on reactive nucleophiles with the commercially available trideuteroiodomethane, but the usual drawbacks would come by with amines, when they do react. Our reaction worked beautifully with compounds such as 5 to yield 2-nitro-N,N-di(trideuteromethyl)benzeneamine (17), obtained in quantitative yield (Scheme I).

Procedures and product identifications

The standard methylation[1] of anthranilic acid methyl ester (6) yielded a single product 18 (97.5% yield as average of 3 experiments). Its p-isomer, namely 7 behaved similarly (19, 96.9% yield as average of 3 experiments). The product obtained were GC homogeneous. Compound 18 was isolated as a colorless, fragrant oil whose ^{1}H - NMR and IR indicated the absence of hydrogens on nitrogen: the IR spectrum of 18 exhibited the same pattern as the parent compound in the out-of-plane (o.o.p.) bending region and increased absorption in the CH stretching region and was coincidental with that reported in the literature[2] for the N,N-dimethylderivative of 6. Its NMR spectrum confirmed this structural attribution. Compound 19 was analogously identified as the N,N-dimethylderivative of 7 also from the practical coincidence of the observed and reported melting points[3]. The mass spectra (EI-positive ions) of 18 and 19 are strikingly different as to peak relative intensities: the p-isomer spectrum is dominated by the same peak at m/z 148 (CH_3O loss from the parent ion), whereas extensive fragmentations with apparent skeletal rearrangements characterize the spectral pattern of 18. The o-effect produces a tremendous steric acceleration of the N-methyl expulsion from the parent ion, but it is still strongly felt, as shown by an N-methyl loss, after a methoxyl radical elimination from the parent ion in a competitive route. Intriguing peaks show up at m/z 91 and 77 (C_7H_7 and C_6H_5) as a result of a migration of an N-methyl group into the aromatic ring (Scheme II).

Perusal of the relevant literature about the two esters 6 and 7 did not reveal any successful attempt of their methylation: one reference[4] was found to a preparation of 18 from the N-methyl derivative of 6 with iodomethane at 95°C in sealed tube.

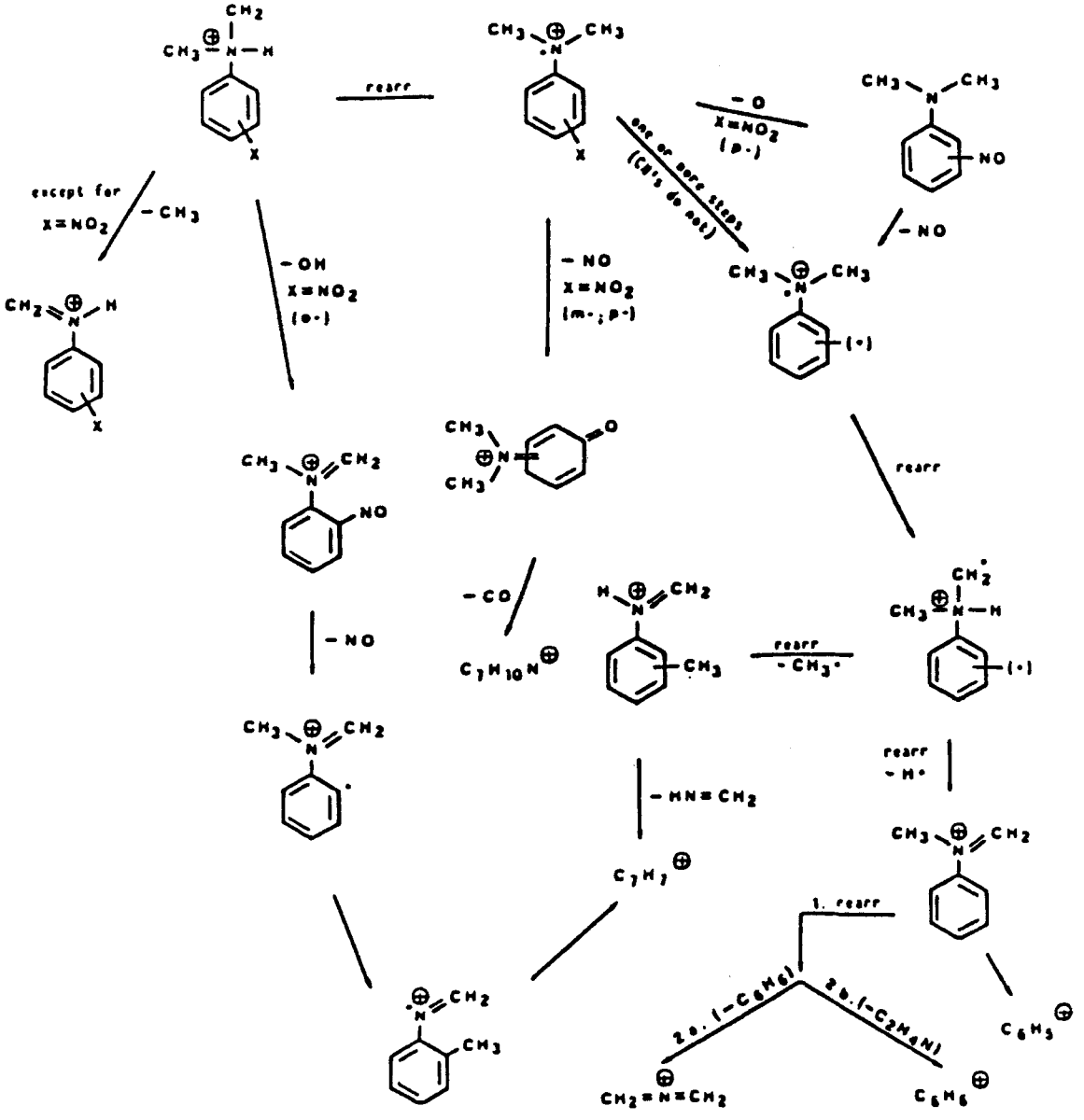
The best final step synthesis of 2-N,N-dimethylaminobenzonitrile (20) reported in the literature[5] employs 2-chlorobenzonitrile and hexamethylphosphotriamide, which were refluxed at 200°C during 48 h (yield: 64%). The 4-isomer (21) was obtained by reaction of p-dimethylaminobenzaldehyde with hydroxylamine hydrochloride (8 h reflux, yield: 86%). No direct methylation procedure of either isomer 8 and 9 was ever reported.

Product 20 (yield: 94.5%) of the reaction of 8 with 1 and 2 exhibited an IR spectrum indicating the presence of an intact nitrile function ($\nu_{C=N}$ 2200 cm^{-1}) and the expected o.o.p. pattern for artho substitution; the ν_{NH} absorption was completely deleted. The NMR spectrum gave a singlet for the N-methyl

SCHEME II

Some Characteristic Electron Impact Induced Fragmentations

of Aromatic N-Methylamines



group introduced into 8 in the 3:2 ratio with integral for the aromatic protons multiplet. These spectroscopic features were similarly found for the corresponding product 21 from 9. The parent ions of 20 and 21, obtained by electron impact at 70 eV, behaved quite similarly and appeared rather stable: both lost a hydrogen atom; the operation of the steric compression is made evident in the o-product by a more copious loss of the N-methyl group from the parent ion.

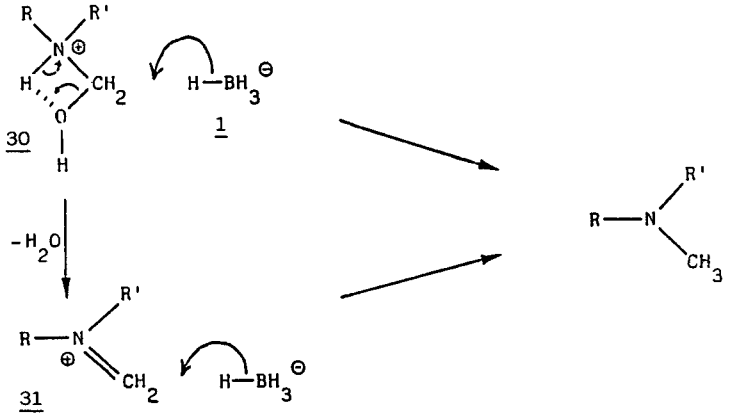
The best last step to the preparation of 2-nitro-N,N-dimethylbenzeneamine (22) reported in the literature[6] requires refluxing 2-nitrobromobenzene with dimethylamine during 10 h. No direct methylation of 5 was ever reported. Repeating the successful N-methylation of 3[1], 22 was obtained in excellent yield by our method. Besides the IR and ^1H - NMR evidences, the MS showed the correct molecular ion.

Two aromatic amines, namely 3, 4 and p-methylbenzeneamine (23), were tested for the introduction of the N-monodeuteromethyl group using 11 and 2 according to the usual procedure. The expected products 13, 12 and p,N,N-trimethylbenzeneamine (24) showed a quantitative deuterium incorporation as indicated ^1H - NMR spectrometry: the methyl protons are spin coupled with the deuteron giving rise to a characteristic triplet. Their mass spectra exhibited the expected mass shifts (M^+ at m/z 168): comparison of the spectra of 23 and of the p-nitro-N,N-dimethylbenzeneamine[7] allows to discard significant losses of hydrogen from the parent ions of 12 and 13: the actual ions at m/z 167 and 166 are to be considered as originated by D-H excange in the ionization chamber. Interestingly the base peaks at m/z 42 in the spectra of undeuterated amines were party shifted to m/z 43 (base peaks, C_2H_3DN) and 44 ($C_2H_2D_2N$).

N-Perdideuteromethylation was effected with 1 and 14 (prior its complete depolymerization in acidic solution) on 3. The ^1H - NMR signal for the methyl group of 15 was a quintuplet. A single band was present in the $\nu_{CH\text{-}sat}$ region (2922 cm^{-1}), whereas the $\nu_{C\text{-}D}$ was centered at 2115 cm^{-1}. Analogous results were found from 4 obtaining 16: the mass spectrum showed intense peaks at m/z 44, 45, 46 whose total intensity referred to that of the parent ion (M^+ at m/z 170) nicely matched the ratio of the intensity of the ion at m/z 42 over that at m/z 166 (M^+) for 3-nitro-N,N-dimethylbenzeneamine (25).

The N-pertrideuteromethylation of 5 (yielding 17) and diphenylamine (26) (yielding 27) was achieved with equal ease by using 11 in connection with depolymerized 14. The IR stretching patterns of the 2-nitro-N,N-di(trideuteromethyl)benzeneamine 17 and its undeuterated counterpart (22) are shown in Fig. 1.

other than that present in the original methylene of the formaldehyde precursor, indicated that the reduction step involves the transfer of a hydride ion to a reactive substrate (of type 30 in an S_N2 reaction or 31, as formerly proposed[1].



Although we did not perform any N-permethylation with tritiated reagents, it is expected that our procedures may be extended to such derivatives.

Experimental

Equipment. - Gas chromatography (CG) was performed with a HRGC Erba (Milan, Italy) with capillary columns and a Dani Gas Chromatograph (Milan, Italy) using packed columns. Standard siliconic and FFAP phases (on Chrmosorb P for packed columns) were used; flame ionization detectors allowed to monitor the eluates. Quantitative GC determinations were made by the internal standard technique with weight-area precalibration. GC-mass spectrometry (MS) was performed with a Finnigan 1020 (OWA, United States) with automatic data acquisition and quadrupole filter, operating at 70 eV. All spectra were recorded from capillary GC eluates with background substraction. Due care was given to ascertain peak homogeneity by repetitive scanning. Scheme II (see next page) reports characteristic fragmentations. Infrared spectra (IR) were recorded with a JASCO model 702 Spectrophotometer on neat samples between KBr windows. Solid samples were analyzed by the KBr pellet technique.

^1H - Nuclear magnetic resonance spectra (NMR) were recorded with a Brucker model WP-80 SY, with automatic data acquisition. Resonance locations are given in δ-values (ppm, from tetramethylsilane) and coupling constants are given in Hz.

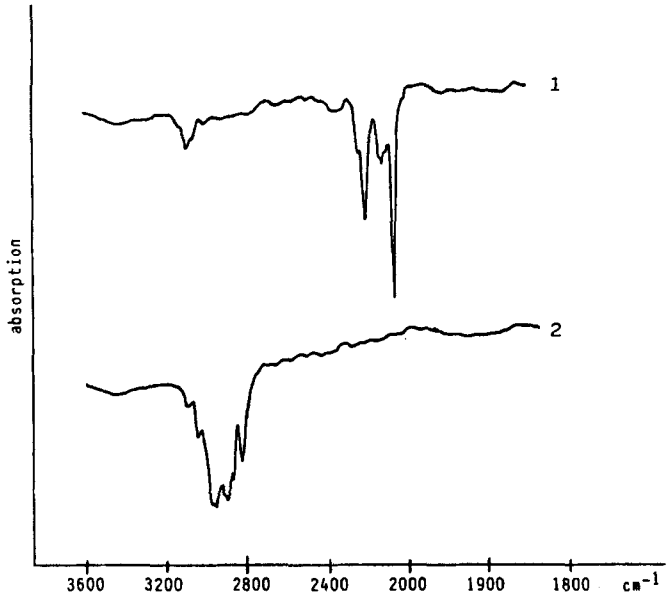


Figure 1.- The C-D and C-H stretching bands of 2-nitro-N,N--di(trideuteromethyl)benzeneamine (17), profile 1) and 2-nitro--N,N-dimethylbenzeneamine (22), profile 2).

The mass and H - NMR spectra of 17 and N-trideuteromethyldiphenylamine (27) were in agreement with the obvious expectations.

In view of developing a more convenient handling of larger preparations of N-permethylated products, we have made a preliminary investigation in order to avoid the addition of the sodium borohydride slurry. We found that an excellent solvent for both the aromatic amine - benzeneamine (28) was the test compound - - and the inorganic salt 1 was ethyleneglycol monomethylether, where 1 is moderately stable at room temperature: the yield of N,N-dimethylaniline (29) was quantitative.

Conclusions

Our N-permethylation procedure has been thus applied to the preparation of H-labelled N-methylamines. In view of the unreactivity of many amines with iodomethane and other methylating agents and/or the production of complex mixtures, the present method affords a very convenient alternative. Moreover, in any case, monodeuteroiodomethane is not commercially available and its synthesis involves starting with C-monodeuteromethanol and the yield is far from quantitative[8,9].

These isotopic syntheses had an interesting mechanistic fallout. The clean introduction of a label (better than 96% of theoretical deuterium in crude 24)

Melting points (uncorrected) were determined with a Büchi Schemelzpunktbestimmungsapparat nach Tottoli; boiling points are rather approximate due to the tiny quantities distilled for preparative purposes in relatively large apparatuses. Yields and main physical data on deuterated compounds are collected in table I.

Elemental analyses were satisfactory for all new compounds.

Materials. - All aromatic amines 1 were commercially available (Erba, Milan, Italy) and were used without purification (except for 26, distilled before use). Sodium borodeuteride (11, 99% D) and D_2-parafomaldehyde (14, 98% D) were obtained from Stohler Isotope Chemicals, U.S.A.. The achieved label introduction was better than 96% D (NMR-data), corresponding to a label transfer better than 99%.

General procedure. - A slurry made up of a solution of the primary amine (1.37 mmol) in tetrahydrofuran (10 mL, freshly distilled from lithium aluminum hydride) and finely powdered sodium borohydride (5.76 mmol) was slowly added to an aqueous solution of 37% formaldehyde (9.6 mmol) and 3M aqueous sulphuric acid (ca. 4 mL) admixed with tetrahydrofuran under careful temperature control of the exothermal rapid reaction. The pH of the solution was monitored to constantly provide an acidic medium. The organic solvent provided a non reactive, volatile dispersion medium for the reducing agent, an excellent solvent for the amine and was itself soluble in water, until, when needed, the mixture was salted out. At the end of the addition, the reaction mixture was made strongly alkaline with excess 40% aqueous sodium hydroxide. The organic phase separated in a clear layer. Two 5 mL tetrahydrofuran extracts of the aqueous phase were then combined with the original organic layer and dried over sodium sulphate. After quantitative GC and GC-MS analyses, the obtained product was separated in pure form for elemental, IR and NMR analyses and the determination of mp and mixed mp, when suitable.

A small amount of N-monomethylated product was found only in the preparations of N,N-dimethyl-2-nitrobenzeneamine (4) (less than 1%) and -2-cyanobenzeneamine (7, 3%). Table I collects data about the newly synthetized products.

Homogeneous reductive methylation procedure. - Benzeneamine (28, 1.83 mmol) and sodium borohydride (1, 1.00 mmol) were dissolved at room temperature in commercial ethyleneglycol monomethylether (5 mL). This solution was slowly added under magnetic stirring to a solution of 0.56 mL 37% aqueous formaldehyde (2)

TABLE I

N-Per(CH_nD_{3-n})tion of Aromatic Amines X-PhNHY

					Properties		
X,Y	n	numera	yield %	mp or bp (°C/torr)	IR***	MS	NMR**
	3	**22**	97		2800-3050 (m, mult.), 1515 (s, broad), 1440 (m, doub.), 960 (m) and 740 (s, unres'd mult.) cm^{-1}	91(100), 77(47), 104(40), 149(27), 119 (27), 105(27), 42(23), 118(21), 51(21), 78(17), 166(14)*, 121(10), 120(6) and 134(3)	2.90 (s, 6H) and 7.30 (m, 4H)
	2	**32**	97		2900 (w, broad), 2140 (w), 1210 (w), 985 (w) and 990 (w) cm^{-1}	43(100), 168(66)*, 78(38), 44(35), 50 (31), 63(29), 167(28), 106(28), 77(27), 105(26), 122(21), 121(19) and 166(9)	3.00 (t, 4H) and 7.40 (m, 4H)
2-NO_2,H				bp 146/20			
	1	**33**	97		2900 (vw, broad), 2090 (w), 1200 (w), 980 (w), 880 (w) and 840 (m) cm^{-1}	44(100), 45(88), 170(70)*, 79(40), 63 (40), 46(37), 107(34), 78(34), 50(33), 124(30), 169(18) and 168(10)	3.00 (m, 2H) and 7.40 (m, 4H)
	0	**17**	97		2200 (w), 2100 (vw), 2060 (m), 1510 (s), 1485 (s), 1450 (m), 1130 (m), 940 (vw), 900 (w), 820 (m), 760 (m) and 735 (s) cm^{-1}	94(100), 154(63), 122(61), 106(54), 172 (43)*, 108(35), 78(27), 107(19), 126(17), 46(16), 138(6) and 136(3)	7.20 (m, 4H)
	3	**25**	97.4		2900 (m, broad), 1420 (w), 1230 (m), 1190 (w), 1060 (m), 990 (m), 970 (w), 870 (s), and 840 (s) cm^{-1}	42(100), 166(34)*, 77(28), 50(24), 51 (19), 63(18), 104(15), 78(14), 105(13), 120(12), 108(3) and 136(1)	3.00 (s, 6H) and 7.40 (m, 4H)
3-NO_2,H				mp 56-7			
	2	**12**	97.4		2900 (w, broad), 2140 (w), 1210 (w), 985 (w), 990 (w) and 840 (m) cm^{-1}	43(100), 168(66)*, 78(38), 44(35), 50 (31), 63(29), 167(28), 106(28), 77(27) 105(26), 122(21), 121(19) and 166(9)	3.00 (t, 4H) and 7.40 (m, 4H)

(to be continued at next page)

					Properties		
X,Y	n	numera	yield %	mp or bp (°C/torr)	IR***	MS	NMR**
3-NO_2,H	1	**16**	97.4	mp 56-7	2900 (vw, broad), 2090 (w), 1200 (w), 980 (w), 880 (w) and 840 (m) cm^{-1}	44(100), 45(88), 170(70)*, 79(40), 63 (40), 78(38), 46(37), 107(34), 50(33), 124(30), 169(18) and 168(10)	3.00 (quint., 2H) and 7.40 (m, 4H)
	3	**34**	97.5		2930 (w, broad), 1380 (m), 1235 (w), 1070 (w) and 940 (w) cm^{-1}	42(100), 166(80)*, 136(49), 77(36), 119 (31), 50(29), 51(25), 102(22), 105(21), 63(21), 120(13) and 150(3)	3.10 (s, 6H) and 7.30 (q, 4H)
4-NO_2,H	2	**13**	97.5	mp 160-2	2920 (vw, broad), 2140 (vw) and 1400 (w) cm^{-1}	168(100)*, 43(99), 138(54), 121(38), 78 (38), 44(38), 167(34), 50(34), 120(28), 51(27) and 166(7)	3.10 (t, 4H) and 7.30 (q, 4H)
	1	**15**	97.5		2920 (w), 2120 (vw) and 1400 (w) cm^{-1}	44(100), 45(85), 140(74), 170(73)*, 63 (47), 79(45), 78(41), 50(41), 107(40), 81(29), 124(18), 168(9) and 154(3)	3.00 (quint., 2H) and 7.30 (m, 4H)
2-CN,H	3	**20**	94.5	bp 137/14	3030 (w), 2940 (m, broad), 2200 (s), 1595 (s), 1560 (m), 1500 (s), 1430 (s), 1340 m, broad), 1280 (m), 1180 (m), 1160 (m), 1040 (m), 940 (s) and 745 (s) cm^{-1}	145(100), 146(72)*, 131(64), 103(24), 102(19), 77(19), 76(16), 42(14), 91 (13), 75(12), 119(2) and 115(1)	3.03 (s, 6H) and 7.20 (m, 4H)
4-CN,H	3	**21**	97.1	mp 74-5	2900 (w), 2200 (s), 1600 (s), 1520 (s), 1440 (m), 1370 (m), 1170 (m) and 810 (s) cm^{-1}	145(100), 146(53)*, 102(19), 129(16), 130(11), 42(11), 75(9), 76(8), 51(8), 50(6), 131(3) and 101(2)	3.00 (s, 6H) and 6.90 (q, 4H)
2-$COOCH_3$,H	3	**18**	97.5	mp 18-9 bp 130-1/11	2980 (s), 1725 (s), 1605 (s), 1520 (m), 1505 (s), 1435 (s), 1350 (m), 1300 (m) and 1250 (s) cm^{-1}	132(100), 164(91), 148(89), 91(74), 77 (73), 118(66), 44(58), 146(48), 74(43), 179(41)*, 104(37) and 178(22)	2.85 (s, 6H), 3.89 (s, 3H) and 7.25 (m, 4H)

4-$COOCH_3$,H	3	**19**	96.9	mp 96-8	3020 (w), 2950 (m, broad), 1705 (s), 1620 (s), 1530 (m), 1440 (s), 1380 (s), 1280 (s), 1230 (m), 1180 (s), 1110 (s), 960 (m), 945 (m), 820 (s) and 760 (s) cm^{-1}	148(100), 179(60)*, 178(35), 74(28), 77 (27), 104(17), 118(13), 105(13), 78 (13), 76(12), 132(12) and 136(3)	3.00 (s, 6H), 3.85 (s, 3H) and 7.25 (q, 4H)
H,C_6H_5	3	**35**	99.9	bp 100/1	3030 (w), 2970 (w), 1595 (s), 1500 (s), 1345 (s), 1255 (m), 1195 (w), 745 (s) and 690 (s) cm^{-1}	183(100)*, 77(85), 182(67), 51(50), 167 (38), 104(36), 91(26), 90(24), 184(17), 39(17), 142(8) and 115(7)	3.30 (s, 3H) and 7.00 (m, 10H)
	0	**27**	99.9		2050 (w), 1335 (s), 975 (w) and 785 (m) cm^{-1}	186(100)*, 77(99), 51(82), 167(67), 185 (58), 184(51), 105(37), 39(35), 92(28), 93(27), 168(20), 142(17), 166(16) and 115(13)	7.01 (m, 10H)
4-Ph-N=N,H	3	**36**	98.6	mp 117-8	2920 (vw), 1600 (s), 1515 (m), 1405 (m), 1370 (m), 1225 (m), 1135 (s), 1060 (w), 815 (s) and 755 (s) cm^{-1}	42(100), 77(93), 120(66), 51(64), 105 (23), 104(22), 78(22), 79(19), 50(18) 225(16)*, 91(16) and 148(12)	3.10 (s, 6H) and 7.45 (m, 9H)
4-CH_3,H	2	**24**	97.4	bp 211	2900 (m), 2180 (w), 2100 (w), 1620 (s), 1570 (w), 1520 (s), 1455 (m), 1370 (m), 1325 (w), 1270 (m), 1190 (m), 1040 (m), and 800 (s) cm^{-1}	136(100), 137(82)*, 135(58) 91(37), 119 (24), 120(19), 65(19), 92(15), 39(14) and 118(12)	2.22 (s, 3H), 2.85 (t, 4H) and 6.80 (q, 4H)

* Parent ion

** Recorded in $CDCl_3$ solution

*** Recorded as neat liquids or with the pellet technique (solids). The most significant bands are reported; the bands at variance with the undeuterated compounds are reported for the deuterated methylamines

and 0.41 mL 3M aqueous sulphuric acid at 0-20°C. At the end of the addition a highly concentrated solution of sodium hydroxide was added till the pH became strongly basic: the aqueous phase was extracted with ether and dried over sodium sulphate. The GC yield of N,N-dimethylbenzeneamine (29) was 100%.

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