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Highly specific N-monomethylation of primary aromatic amines

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Abstract—A synthetic methodology for the specific conversion of primary aromatic amines into their *N*-monomethyl derivatives under very mild conditions is presented. Anilines are treated with 4-nitrobenzenesulfonyl (nosyl) chloride to generate the corresponding sulfonamides **2** in high yields. The subsequent N-methylation reaction of the sulfonamides **2** with a solution of diazomethane is rapid and quantitative. Removal of the nosyl protecting group is readily carried out using the reagent system mercaptoacetic acid/1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) affording the *N*-monomethylated aromatic amines **4**. The procedure is convenient, efficient, and gives rise to the *N*-monomethyl-anilines exclusively.

1. Introduction

N-Monomethylated aromatic amines are useful synthetic intermediates in preparative organic chemistry especially in the synthesis of pharmaceuticals and dyes.[1] Although various methods have been reported for the N-methylation of aniline derivatives, most of these procedures suffer from some limitations.

The direct base-promoted N-methylation of primary amines performed with traditional alkylating agents cannot be used because of the formation of mixtures of secondary and tertiary amines along with the corresponding ammonium salt that are difficult to separate.[2] The direct N-methylation of anilines using methanol and different catalysts,[3] solid bases,[4] or nonconventional methylating agents such as sulfur and bismuth derivatives,[5] suffers from lack of selectivity for monomethylation. Moreover, reaction products are obtained in very low yield. Many methods have been developed for the straightforward N-methylation of primary aromatic amines employing dimethyl sulfate or dimethyl carbonate over zeolites,[6] or methanol in either gas[7] or supercritical[8] phase. Nevertheless, these processes need very severe reaction conditions such as high temperature and high pressure, and they don't exclude the formation of by-products derived from further methylation even if only in a little yield.

The difficulties associated with direct N-monomethylation have led to the development of indirect N-methylation procedures through partially protected anilines. In fact, the use of blocking groups permits the N-monomethylation of primary aromatic amines without proceeding N-methylation beyond the desired stage. The indirect N-monomethylation is a multi-step process based on the synthesis of suitable aniline derivatives that are subjected to the N-methylation reaction, or alternatively to the reductive N-methylation. Finally the modified amine function is released. The most popular indirect method for the synthesis of *N*-methyl anilines is the one-pot reductive N-methylation[9] of primary aromatic amines. However, reduction of *N*-aryl methyleneamines using various reagents[9] furnishes the corresponding *N*,*N*-dimethylated by-products too. Besides, this methodology is sometimes limited when functional groups sensitive to reductants are present. Treatment of trifluoroacetanilides with methyl iodide over potassium hydroxide allows the N-monomethylation process[10] exploiting the weak binding of hydrogen to the trifluoroacetylamino-group. *N*-Methyl anilines are successively obtained by hydrolysis of the corresponding *N*-methyl trifluoroacetanilides. *N*-Arylaminomethylsuccinimides,[11] 1-(1′-arylaminomethyl)-benzotriazoles,[12] 3-methylbenzothiazol-2-(3*H*)-imines,[13] and iminophosphoranes[14] have also been used to prepare *N*-monomethyl anilines. Reduction of *N*-arylformamide[15] and *N*-arylformimidate[16] derivatives yields *N*-monomethylated anilines also without isolating the reaction intermediates before reduction.

Such a massive experimental effort indicates that a convenient and general procedure for the N-monomethylation of primary aromatic amines has long been of considerable interest.

2. Results and discussion

Using an appropriate *N*-protecting group, which is able to enhance the acidity of the amine proton could be a valid

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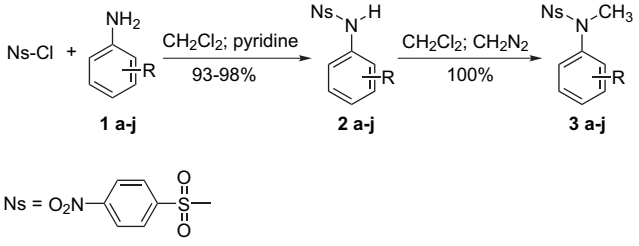
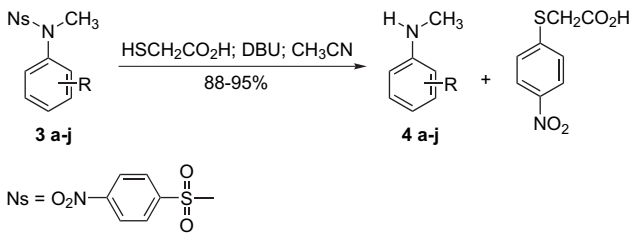
approach to the rapid N-methylation of aromatic primary amines with diazomethane. For this purpose we decided to use the 4-nitrobenzenesulfonyl (nosyl) protecting group to furnish a sulfonamide derivative of exceptional acidity.[17] The pK_a value of the 4-nitrobenzenesulfonamides ranges between 9 and 11;[17b–d] diazomethane could act on the acidic sulfonamide proton to generate the corresponding methyl diazonium ion, that is, the effective methylating agent. Moreover, the nosyl protecting group could preclude competitive over methylation.

In order to study the proceeding of the planned methodology, preliminary reactions were carried out using aniline as a test substrate. Treatment of aniline **1a** with nosyl chloride in dry CH_2Cl_2 and in the presence of pyridine as base (Scheme 1) afforded after work-up the corresponding sulfonamide **2a** as a crystalline solid in 96% overall yield. The subsequent N-methylation reaction, carried out using a solution of diazomethane in dichloromethane, reached completion in only 10 min at room temperature affording the *N*-methylated sulfonamide **3a** as the sole reaction product. The dichloromethane solution of diazomethane was prepared from *N*-methyl-*N*-nitrosourea without distillation, thus avoiding the most dangerous operation in other preparations of diazomethane.[18] After the solvent was removed, **3a** was recovered as a solid in 100% yield without need for further purification.



Scheme 1. Synthesis of *N*-methyl-*N*-nosyl sulfonamides **3a**–**j**.

At last, removal of the nosyl protecting group was readily performed in 15 min using the reagent system mercaptoacetic acid/1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) in dry acetonitrile (Scheme 2). *N*-Methyl aniline **4a** was recovered in 93% yield after flash chromatography. The thioether formed as coproduct at the end of the deprotection step was easily removed by washing the reaction mixture with an aqueous solution of Na_2CO_3. The chromatographic purification was just served to remove the excess of DBU.



Scheme 2. Removal of the nosyl group.

In order to assess the synthetic validity of the proposed methodology, the same procedure tested for aniline **1a** was then extended to anilines **1b**–**j** bearing different functional groups on the aromatic ring (Table 1).

Table 1. Isolated yield based on substrate **1**

4	R	Yield (%)
a	H	89
b	*o*-CH_3	85
c	*m*-CH_3	87
d	*p*-OCH_3	86
e	*o*-F	81
f	*o*-I	86
g	*p*-NO_2	85
h	*p*-$COCH_3$	88
i	*p*-CO_2CH_3	87
j	*m*-CN	84

In all cases, the *N*-monomethylated anilines **4b**–**j** were obtained as the sole reaction product in overall yields ranging from 81–88% calculated based on the starting anilines **1b**–**j**.

Nosyl protecting group was already employed to prepare various secondary amines under Mitsunobu conditions or under more conventional conditions.[19] The novelty of the proposed methodology is represented by the use of diazomethane as efficient methylating agent. Furthermore, our procedure has an advantage over the ones reported in literature in that the work-up of the *N*-methylation reaction is very simple and rapid. In fact, the N-methylated nosyl anilines were recovered quantitatively by evaporation of the solvent.

3. Conclusion

In contrast to several other methods currently used for the N-monomethylation of anilines the novel adopted methodology presents some inalienable advantages. The application of this methodology permits the specific and high yielding N-monomethylation of primary aromatic amines. The synthetic procedure is accomplished under very mild conditions and all reaction steps are carried out at room temperature. The proposed strategy appears quite general and compatible with a wide range of functional groups.

4. Experimental

4.1. General

All reagents were purchased from Sigma–Aldrich Co. All solvents were purified and dried by standard procedures and distilled prior to use. NMR characterization of all compounds was performed on a Bruker Avance 300 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz, respectively, using $CDCl_3$ or DMSO-d_6 as solvent and tetramethylsilane as an internal standard. ^{19}F NMR spectra were recorded at 470 MHz on a Bruker Avance 500 spectrometer using $CDCl_3$ or DMSO-d_6 as solvent and trichlorofluoromethane as an internal standard. Chemical shift values (δ) are expressed in parts per million. Melting points (mp) were determined on a Kofler hot-stage apparatus and are uncorrected. GC–MS analyzes were carried out using a 30 m HP-35MS capillary column with a 0.25 mm internal diameter and a 0.25 mm film thickness. The mass detector was operated in an electron impact ionization mode (EIMS) at an electron energy of 70 eV. Elemental analyzes

were performed on a Perkin–Elmer Elemental Analyzer. IR spectra were obtained with a Perkin–Elmer FT paragon 1000 PC spectrometer. Reaction mixtures were monitored by TLC using silica gel 60-F_{254} precoated glass plates, purchased from Merck. Short column flash chromatography (SCFC) was performed on Kieselgel 60 H without gypsum. All reactions were carried out under an inert atmosphere (N_2). The dichloromethane solution of diazomethane was prepared from *N*-methyl-*N*-nitrosourea. The concentration of the diazomethane solution (0.66 M) was obtained by a back-titration performed with a standard benzoic acid solution.[20] Dichloromethane solutions of diazomethane are stable for long period if stored on KOH pellets at −20 °C.

4.2. Synthesis of *N*-nosyl anilines 2a–j

4.2.1. General procedure. A solution of nosyl chloride (1.0 mmol) in dry CH_2Cl_2 (15 mL) was added dropwise over 15 min to a magnetically stirred solution of the appropriate aromatic amine **1a–j** (1.1 mmol) and pyridine (1.1 mmol) in dry CH_2Cl_2 (15 mL). The resulting mixture was stirred at room temperature for 2–3 h, monitoring the conversion of **1a–j** by TLC analysis (chloroform/methanol 95:5 v/v, or diethyl ether/light petroleum 60:40 v/v). A 1 M HCl solution was added, then the acidified aqueous phase (pH≅2) was separated and extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were washed with brine, then dried over Na_2SO_4, and evaporated to dryness to afford *N*-nosyl anilines **2a–j** as solids (93–98% overall yields).

4.2.1.1. *N*-Nosyl-aniline[21] (2a). Yield 96%, pale yellow solid, mp 174–176 °C. GC–MS (EI): *m/z* 278 [$M^{\bullet+}$, 24%]; 167 (3); 122 (3); 92 (100); 76 (5); 65 (28). ^{1}H NMR (DMSO-d_6): δ 7.02–7.12 (m, 3H, Ar–H); 7.20–7.28 (m, 2H, Ar–H); 7.95–8.02 (m, 2H, Ar–H); 8.33–8.40 (m, 2H, Ar–H); 10.61 (br s, 1H, N–H). ^{13}C NMR (DMSO-d_6): δ 121.11; 125.11; 125.24; 128.73; 129.81; 137.34; 145.31; 150.28. Anal. Calcd for $C_{12}H_{10}N_2O_4S$: C, 51.79; H, 3.62; N, 10.07; S, 11.52. Found: C, 51.67; H, 3.60; N, 10.11; S, 11.49. IR (KBr): ν_{max} 3308, 3076, 1602, 1525, 1349, 1168 cm^{-1}.

4.2.1.2. *N*-Nosyl-*o*-toluidine (2b). Yield 94%, pink solid, mp 157–159 °C. GC–MS (EI): *m/z* 292 [$M^{\bullet+}$, 11%]; 106 (100); 79 (10); 77 (17). ^{1}H NMR ($CDCl_3$): δ 2.02 (s, 3H, CH_3); 6.74 (br s, 1H, N–H); 7.11–7.21 (m, 3H, Ar–H); 7.25–7.30 (m, 1H, Ar–H); 7.88–7.95 (m, 2H, Ar–H); 8.25–8.32 (m, 2H, Ar–H). ^{13}C NMR ($CDCl_3$): δ 17.69; 124.28; 125.09; 127.25; 127.33; 128.45; 131.20; 132.19; 133.20; 145.28; 150.19. Anal. Calcd for $C_{13}H_{12}N_2O_4S$: C, 53.42; H, 4.14; N, 9.58; S, 10.97. Found: C, 53.51; H, 4.16; N, 9.55; S, 10.92. IR (KBr): ν_{max} 3313, 3074, 1598, 1524, 1347, 1169 cm^{-1}.

4.2.1.3. *N*-Nosyl-*m*-toluidine (2c). Yield 95%, orange solid, mp 138–139 °C. GC–MS (EI): *m/z* 292 [$M^{\bullet+}$, 27%]; 106 (100); 79 (29); 77 (25). ^{1}H NMR ($CDCl_3$): δ 2.28 (s, 3H, CH_3); 6.86–7.01 (m, 3H, Ar–H, N–H); 7.12–7.19 (m, 2H, Ar–H); 7.93–8.00 (m, 2H, Ar–H); 8.24–8.31 (m, 2H, Ar–H). ^{13}C NMR ($CDCl_3$): δ 21.36; 119.06; 122.81; 124.31; 127.22; 128.56; 129.44; 135.25; 139.85; 144.59; 150.20. Anal. Calcd for $C_{13}H_{12}N_2O_4S$: C, 53.42; H, 4.14; N, 9.58; S, 10.97. Found: C, 53.34; H, 4.16; N, 9.53; S, 10.94. IR (KBr): ν_{max} 3327, 3068, 1597, 1524, 1345, 1168 cm^{-1}.

4.2.1.4. *N*-Nosyl-*p*-anisidine (2d). Yield 93%, pale violet solid, mp 187–189 °C. GC–MS (EI): *m/z* 308 [$M^{\bullet+}$, 8%]; 122 (100); 108 (3); 95 (9). ^{1}H NMR (DMSO-d_6): δ 3.64 (s, 3H, OCH_3); 6.76–6.82 (m, 2H, Ar–H); 6.93–6.99 (m, 2H, Ar–H); 7.86–7.92 (m, 2H, Ar–H); 8.32–8.38 (m, 2H, Ar–H); 10.27 (s, 1H, N–H). ^{13}C NMR (DMSO-d_6): δ 55.60; 114.91; 124.56; 125.01; 128.76; 129.59; 145.30; 150.16; 157.43. Anal. Calcd for $C_{13}H_{12}N_2O_5S$: C, 50.64; H, 3.92; N, 9.09; S, 10.40. Found: C, 50.78; H, 3.90; N, 9.08; S, 10.36. IR (KBr): ν_{max} 3286, 3101, 1609, 1524, 1345, 1253, 1183 cm^{-1}.

4.2.1.5. *N*-Nosyl-*o*-fluoroaniline[22] (2e). Yield 93%, yellow solid, mp 164–166 °C. GC–MS (EI): *m/z* 296 [$M^{\bullet+}$, 23%]; 122 (4); 110 (100); 83 (41); 76 (6). ^{1}H NMR ($CDCl_3$): δ 6.92–7.03 (m, 2H, Ar–H, N–H); 7.12–7.21 (m, 2H, Ar–H); 7.58–7.64 (m, 1H, Ar–H); 7.92–7.98 (m, 2H, Ar–H); 8.26–8.33 (m, 2H, Ar–H). ^{13}C NMR ($CDCl_3$): δ 115.67; 115.93; 124.33; 124.69; 125.10; 125.15; 127.57; 127.67; 128.50; 144.43. ^{19}F NMR ($CDCl_3$): δ −46.87. Anal. Calcd for $C_{12}H_9FN_2O_4S$: C, 48.65; H, 3.06; F, 6.41; N, 9.46; S, 10.82. Found: C, 48.77; H, 3.05; F, 6.38; N, 9.42; S, 10.79. IR (KBr): ν_{max} 3271, 3119, 1607, 1522, 1340, 1259, 1162 cm^{-1}.

4.2.1.6. *N*-Nosyl-*o*-iodoaniline (2f). Yield 94%, yellow solid, mp 141–143 °C. GC–MS (EI): *m/z* 404 [$M^{\bullet+}$, 28%]; 219 (15); 218 (100); 91 (76); 76 (7); 64 (17). ^{1}H NMR ($CDCl_3$): δ 6.89–6.97 (m, 2H, Ar–H, N–H); 7.35–7.42 (m, 1H, Ar–H); 7.65–7.72 (m, 2H, Ar–H); 7.87–7.93 (m, 2H, Ar–H); 8.25–8.31 (m, 2H, Ar–H). ^{13}C NMR ($CDCl_3$): δ 93.61; 124.29; 128.20; 128.80; 129.87; 131.02; 136.35; 139.41; 144.46; 150.40. Anal. Calcd for $C_{12}H_9IN_2O_4S$: C, 35.66; H, 2.24; I, 31.40; N, 6.93; S, 7.93. Found: C, 35.75; H, 2.24; I, 31.43; N, 6.91; S, 7.90. IR (KBr): ν_{max} 3296, 3099, 3063, 1606, 1531, 1469, 1349, 1176, 1089 cm^{-1}.

4.2.1.7. *N*-Nosyl-*p*-nitroaniline[21a] (2g). Yield 93%, yellow solid, mp 177–179 °C. GC–MS (EI): *m/z* 323 [$M^{\bullet+}$, 70%]; 186 (69); 122 (100); 107 (7); 92 (19); 91 (21); 76 (28); 75 (23); 64 (27); 63 (21). ^{1}H NMR ($CDCl_3$): δ 7.24–7.30 (m, 3H, Ar–H, N–H); 8.04–8.10 (m, 2H, Ar–H); 8.15–8.21 (m, 2H, Ar–H); 8.33–8.38 (m, 2H, Ar–H). ^{13}C NMR ($CDCl_3$): δ 119.40; 124.73; 125.62; 128.54; 134.91; 137.93; 146.82; 153.88. Anal. Calcd for $C_{12}H_9N_3O_6S$: C, 44.58; H, 2.81; N, 13.00; S, 9.92. Found: C, 44.69; H, 2.80; N, 12.98; S, 9.88. IR (KBr): ν_{max} 3245, 3105, 2947, 1599, 1529, 1514, 1475, 1346, 1293, 1160, 1087 cm^{-1}.

4.2.1.8. *N*-Nosyl-*p*-aminoacetophenone (2h). Yield 98%, pale pink solid, mp 192–194 °C. GC–MS (EI): *m/z* 320 [$M^{\bullet+}$, 31%]; 305 (100); 134 (5); 122 (6); 119 (35); 106 (23); 92 (13); 91 (12); 79 (11); 77 (12); 64 (13). ^{1}H NMR (DMSO-d_6): δ 2.45 (s, 3H, CH_3); 7.20–7.26 (m, 2H, Ar–H); 7.81–7.87 (m, 2H, Ar–H); 8.03–8.10 (m, 2H, Ar–H); 8.34–8.42 (m, 2H, Ar–H); 11.20 (s, 1H, N–H). ^{13}C NMR (DMSO-d_6): δ 26.90; 118.97; 125.32; 128.77; 130.39; 132.95; 141.88; 144.96; 150.48; 196.98. Anal. Calcd for $C_{14}H_{12}N_2O_5S$: C, 52.49; H, 3.78; N, 8.75; S, 10.01.

Found: C, 52.57; H, 3.75; N, 8.71; S, 10.00. IR (KBr): ν_{max} 3163, 3080, 2927, 2861, 1675, 1602, 1537, 1354, 1278, 1157, 1091 cm^{-1}.

4.2.1.9. Methyl *N*-nosyl-*p*-aminobenzoate (2i). Yield 93%, pale pink solid, mp 201–203 °C. GC–MS (EI): *m/z* 336 [$M^{\bullet+}$, 54%]; 305 (31); 150 (100); 122 (95); 119 (16); 92 (19); 91 (11); 76 (21); 64 (20). ^1H NMR (DMSO-d_6): δ 3.73 (s, 3H, OCH_3); 7.20–7.27 (m, 2H, Ar–H); 7.81–7.86 (m, 2H, Ar–H); 8.02–8.08 (m, 2H, Ar–H); 8.34–8.41 (m, 2H, Ar–H); 11.14 (s, 1H, N–H). ^{13}C NMR (DMSO-d_6): δ 52.45; 119.26; 125.92; 125.55; 128.76; 131.22; 142.01; 144.93; 150.49; 166.01. Anal. Calcd for $C_{14}H_{12}N_2O_6S$: C, 50.00; H, 3.60; N, 8.33; S, 9.53. Found: C, 50.15; H, 3.57; N, 8.30; S, 9.49. IR (KBr): ν_{max} 3199, 3108, 3027, 2952, 2873, 1702, 1609, 1539, 1512, 1350, 1318, 1298, 1165, 1091 cm^{-1}.

4.2.1.10. *N*-Nosyl-*m*-aminobenzonitrile (2j). Yield 94%, pale orange solid, mp 202–204 °C. GC–MS (EI): *m/z* 303 [$M^{\bullet+}$, 100%]; 273 (7); 186 (74); 156 (26); 122 (68); 117 (73); 92 (24); 90 (39); 76 (29); 75 (25). ^1H NMR (DMSO-d_6): δ 7.38–7.57 (m, 4H, Ar–H); 8.01–8.06 (m, 2H, Ar–H); 8.34–8.40 (m, 2H, Ar–H); 11.12 (s, 1H, N–H). ^{13}C NMR (DMSO-d_6): δ 112.72; 118.61; 123.32; 125.25; 125.33; 128.70; 128.78; 131.42; 138.42; 144.70; 150.51. Anal. Calcd for $C_{13}H_9N_3O_4S$: C, 51.48; H, 2.99; N, 13.85; S, 10.57. Found: 51.61; H, 2.99; N, 13.80; S, 10.55. IR (KBr): ν_{max} 3169, 3081, 2964, 2245, 1606, 1587, 1535, 1415, 1351, 1178, 1089 cm^{-1}.

4.3. Preparation of diazomethane from *N*-methyl-*N*-nitrosourea

Dichloromethane (100 mL) was added to a 40% aqueous potassium hydroxide solution (30 mL). The mixture was cooled to 4 °C, and *N*-methyl-*N*-nitrosourea (10.0 g, 97.0 mmol) was added with shaking, and the reaction temperature was maintained below 5 °C. After 20 min, the organic phase was separated and stored over pellets of pure potassium hydroxide at −20 °C.

4.4. Methylation of *N*-nosyl anilines 2a–j

4.4.1. General procedure. A 0.66 M solution of diazomethane in CH_2Cl_2 (3.0 mmol) was added dropwise over 5 min to a solution of the appropriate *N*-nosyl aniline **2a–j** (1.0 mmol) in CH_2Cl_2 (15 mL). The reaction mixture was stirred at room temperature for 10 min. After this time, TLC analysis (chloroform/methanol 99:1 v/v, or diethyl ether/light petroleum 60:40 v/v) showed complete conversion of the precursor. Evaporation of the solvent under reduced pressure gave *N*-methyl-*N*-nosyl anilines **3a–j** as solids (100% overall yields).

4.4.1.1. *N*-Methyl-*N*-nosyl-aniline[23] (3a). Brown solid, mp 130–132 °C. GC–MS (EI): *m/z* 292 [$M^{\bullet+}$, 12%]; 228 (3); 122 (2); 106 (100); 79 (15); 77 (39). ^1H NMR ($CDCl_3$): δ 3.23 (s, 3H, CH_3); 7.05–7.11 (m, 2H, Ar–H); 7.32–7.36 (m, 3H, Ar–H); 7.70–7.75 (m, 2H, Ar–H); 8.27–8.34 (m, 2H, Ar–H). ^{13}C NMR ($CDCl_3$): δ 38.40; 124.04; 126.60; 128.02; 129.00; 129.28; 140.58; 142.24; 150.13. Anal. Calcd for $C_{13}H_{12}N_2O_4S$: C, 53.42; H, 4.14; N, 9.58; S, 10.97. Found: C, 53.33; H, 4.16; N, 9.53; S, 10.93. IR (KBr): ν_{max} 3078, 2977, 1607, 1526, 1350, 1128 cm^{-1}.

4.4.1.2. *N*-Methyl-*N*-nosyl-*o*-toluidine[23] (3b). Yellow solid, mp 126–128 °C. GC–MS (EI): *m/z* 306 [$M^{\bullet+}$, 9%]; 120 (100); 91 (26); 77 (5); 65 (7). ^1H NMR ($CDCl_3$): δ 2.39 (s, 3H, CH_3); 3.22 (s, 3H, N–CH_3); 6.52–6.57 (m, 1H, Ar–H); 7.05–7.12 (m, 1H, Ar–H); 7.23–7.34 (m, 2H, Ar–H); 7.87–7.93 (m, 2H, Ar–H); 8.34–8.39 (m, 2H, Ar–H). ^{13}C NMR ($CDCl_3$): δ 18.32; 39.15; 124.17; 126.71; 126.76; 128.89; 129.11; 131.86; 138.89; 139.39; 143.92; 144.20. Anal. Calcd for $C_{14}H_{14}N_2O_4S$: C, 54.89; H, 4.61; N, 9.14; S, 10.47. Found: C, 55.05; H, 4.58; N, 9.10; S, 10.42. IR (KBr): ν_{max} 3068, 2975, 1601, 1523, 1348, 1164 cm^{-1}.

4.4.1.3. *N*-Methyl-*N*-nosyl-*m*-toluidine[23] (3c). Yellow solid, mp 114–116 °C. GC–MS (EI): *m/z* 306 [$M^{\bullet+}$, 8%]; 242 (5); 201 (4); 120 (100); 92 (12); 91 (38); 77 (12); 65 (11). ^1H NMR ($CDCl_3$): δ 2.33 (s, 3H, CH_3); 3.22 (s, 3H, N–CH_3); 6.78–6.83 (m, 1H, Ar–H); 6.94–6.99 (m, 1H, Ar–H); 7.09–7.22 (m, 2H, Ar–H); 7.72–7.77 (m, 2H, Ar–H); 8.27–8.34 (m, 2H, Ar–H). ^{13}C NMR ($CDCl_3$): δ 21.34; 38.48; 123.19; 123.98; 127.63; 128.82; 128.97; 129.03; 139.37; 140.50; 142.41; 150.10. Anal. Calcd for $C_{14}H_{14}N_2O_4S$: C, 54.89; H, 4.61; N, 9.14; S, 10.47. Found: C, 54.76; H, 4.59; N, 9.11; S, 10.49. IR (KBr): ν_{max} 3065, 2976, 1599, 1525, 1349, 1158 cm^{-1}.

4.4.1.4. *N*-Methyl-*N*-nosyl-*p*-anisidine (3d). Brown solid, mp 147–149 °C. GC–MS (EI): *m/z* 322 [$M^{\bullet+}$, 10%]; 136 (100); 122 (6); 121 (12); 108 (5); 92 (6); 77 (4). ^1H NMR ($CDCl_3$): δ 3.20 (s, 3H, N–CH_3); 3.81 (s, 3H, OCH_3); 6.78–6.85 (m, 2H, Ar–H); 6.94–6.99 (m, 2H, Ar–H); 7.71–7.77 (m, 2H, Ar–H); 8.27–8.33 (m, 2H, Ar–H). ^{13}C NMR ($CDCl_3$): δ 38.72; 55.49; 114.38; 124.01; 128.06; 129.05; 133.08; 142.46; 154.46; 159.10. Anal. Calcd for $C_{14}H_{14}N_2O_5S$: C, 52.18; H, 4.38; N, 8.69; S, 9.95. Found: C, 52.01; H, 4.36; N, 8.66; S, 9.99. IR (KBr): ν_{max} 3122, 2977, 1606, 1527, 1350, 1252, 1185 cm^{-1}.

4.4.1.5. *N*-Methyl-*N*-nosyl-*o*-fluoroaniline (3e). Yellow solid, mp 115–117 °C. GC–MS (EI): *m/z* 310 [$M^{\bullet+}$, 10%]; 124 (100); 122 (9); 95 (8); 77 (43). ^1H NMR (DMSO-d_6): δ 3.19 (s, 3H, N–CH_3); 7.17–7.32 (m, 3H, Ar–H); 7.38–7.45 (m, 1H, Ar–H); 7.88–7.94 (m, 2H, Ar–H); 8.39–8.45 (m, 2H, Ar–H). ^{13}C NMR (DMSO-d_6): δ 38.74; 117.22; 125.16; 125.55; 129.43; 130.84; 131.10; 143.00; 150.55; 157.45; 160.77. ^{19}F NMR (DMSO-d_6): δ −40.03. Anal. Calcd for $C_{13}H_{11}FN_2O_4S$: C, 50.32; H, 3.57; F, 6.12; N, 9.03; S, 10.33. Found: C, 50.51; H, 3.54; F, 6.10; N, 9.07; S, 10.29. IR (KBr): ν_{max} 3108, 2942, 1606, 1526, 1492, 1355, 1179, 1105 cm^{-1}.

4.4.1.6. *N*-Methyl-*N*-nosyl-*o*-iodoaniline (3f). Yellow solid, mp 166–168 °C. GC–MS (EI): *m/z* 418 [$M^{\bullet+}$, 24%]; 291 (66); 233 (54); 232 (100); 202 (16); 120 (25); 105 (49); 104 (70); 90 (15); 64 (53). ^1H NMR ($CDCl_3$): δ 3.25 (s, 3H, N–CH_3); 7.04–7.12 (m, 2H, Ar–H); 7.31–7.38 (m, 1H, Ar–H); 7.88–7.93 (m, 1H, Ar–H); 7.96–8.02 (m, 2H, Ar–H); 8.35–8.41 (m, 2H, Ar–H). ^{13}C NMR ($CDCl_3$): δ 39.03; 100.61; 124.32; 129.21; 129.46; 129.73; 130.51; 140.67; 142.71; 144.73; 150.20. Anal. Calcd for

$C_{13}H_{11}IN_2O_4S$: C, 37.34; H, 2.65; I, 30.34; N, 6.70; S, 7.67. Found: C, 37.48; H, 2.67; I, 30.20; N, 6.66; S, 7.71. IR (KBr): ν_{max} 3101, 2951, 1607, 1530, 1472, 1355, 1177, 1081 cm^{-1}.

4.4.1.7. *N*-Methyl-*N*-nosyl-*p*-nitroaniline (3g). Yellow solid, mp 169–181 °C. GC–MS (EI): *m/z* 337 [$M^{\bullet+}$, 22%]; 186 (9); 151 (43); 122 (24); 105 (100); 92 (8); 90 (10); 76 (17); 63 (9). ^1H NMR ($CDCl_3$): δ 3.30 (s, 3H, N–CH_3); 7.33–7.38 (m, 2H, Ar–H); 7.74–7.77 (m, 2H, Ar–H); 8.20–8.26 (m, 2H, Ar–H); 8.32–8.37 (m, 2H, Ar–H). ^{13}C NMR ($CDCl_3$): δ 37.90; 124.43; 124.66; 126.07; 128.82; 134.24; 137.73; 146.26; 153.26. Anal. Calcd for $C_{13}H_{11}N_3O_6S$: C, 46.29; H, 3.29; N, 12.46; S, 9.51. Found: C, 46.12; H, 3.27; N, 12.40; S, 9.47. IR (KBr): ν_{max} 3098, 2964, 1602, 1532, 1512, 1498, 1477, 1347, 1318, 1291, 1162, 1085 cm^{-1}.

4.4.1.8. *N*-Methyl-*N*-nosyl-*p*-aminoacetophenone (3h). Pale yellow solid, mp 172–175 °C. GC–MS (EI): *m/z* 334 [$M^{\bullet+}$, 26%]; 319 (25); 148 (100); 133 (13); 132 (20); 122 (3); 106 (18); 105 (27); 91 (8); 77 (11); 76 (7). ^1H NMR ($CDCl_3$): δ 2.59 (s, 3H, $COCH_3$); 3.24 (s, 3H, N–CH_3); 7.21–7.26 (m, 2H, Ar–H); 7.69–7.74 (m, 2H, Ar–H); 7.91–7.96 (m, 2H, Ar–H); 8.28–8.33 (m, 2H, Ar–H). ^{13}C NMR ($CDCl_3$): δ 26.70; 37.96; 124.25; 125.88; 128.88; 129.36; 135.86; 141.82; 144.70; 150.29; 196.94. Anal. Calcd for $C_{15}H_{14}N_2O_5S$: C, 53.88; H, 4.22; N, 8.38; S, 9.59. Found: C, 53.71; H, 4.25; N, 8.35; S, 9.55. IR (KBr): ν_{max} 3109, 3076, 2978, 1675, 1602, 1538, 1357, 1270, 1174 cm^{-1}.

4.4.1.9. Methyl *N*-methyl-*N*-nosyl-*p*-aminobenzoate (3i). Yellow solid, mp 185–187 °C. GC–MS (EI): *m/z* 350 [$M^{\bullet+}$, 11%]; 319 (3); 164 (100); 132 (18); 120 (5); 105 (13); 104 (15); 92 (6); 91 (5); 77 (13); 76 (7). ^1H NMR ($CDCl_3$): δ 3.24 (s, 3H, N–CH_3); 3.92 (s, 3H, OCH_3); 7.15–7.22 (m, 2H, Ar–H); 7.67–7.83 (m, 2H, Ar–H); 7.96–8.04 (m, 2H, Ar–H); 8.27–8.34 (m, 2H, Ar–H). ^{13}C NMR ($CDCl_3$): δ 37.99; 52.41; 124.20; 125.75; 128.88; 129.24; 130.60; 141.80; 144.6; 150.27; 166.10. Anal. Calcd for $C_{15}H_{14}N_2O_6S$: C, 51.42; H, 4.03; N, 8.00; S, 9.15. Found: C, 51.60; H, 4.01; N, 7.97; S, 9.19. IR (KBr): ν_{max} 3107, 3064, 2970, 1701, 1609, 1540, 1351, 1315, 1296, 1168, 1087 cm^{-1}.

4.4.1.10. *N*-Methyl-*N*-nosyl-*m*-aminobenzonitrile (3j). Yellow solid, mp 149–151 °C. GC–MS (EI): *m/z* 317 [$M^{\bullet+}$, 33%]; 253 (24); 212 (10); 186 (8); 131 (100); 122 (13); 104 (14); 102 (22); 77 (10); 76 (13). ^1H NMR ($CDCl_3$): δ 3.24 (s, 3H, N–CH_3); 7.38–7.52 (m, 3H, Ar–H); 7.59–7.64 (m, 1H, Ar–H); 7.71–7.77 (m, 2H, Ar–H); 8.32–8.37 (m, 2H, Ar–H). ^{13}C NMR ($CDCl_3$): δ 38.01; 113.55; 117.60; 124.40; 128.91; 129.63; 130.30; 130.78; 131.28; 141.59; 141.65; 150.44. Anal. Calcd for $C_{14}H_{11}N_3O_4S$: C, 52.99; H, 3.49; N, 13.24; S, 10.10. Found: 53.16; H, 3.48; N, 13.19; S, 10.07. IR (KBr): ν_{max} 3110, 3072, 2943, 2233, 1605, 1532, 1356, 1190, 1165, 1067 cm^{-1}.

4.5. Deprotection of *N*-nosyl-*N*-methyl anilines 3a–j

4.5.1. General procedure. A solution of the appropriate *N*-methyl-*N*-nosyl aniline **3a–j** (1.0 mmol) in dry CH_3CN (10 mL) was added to a solution of mercaptoacetic acid (2.0 mmol) and 1,8-diazabicyclo-[5.4.0]undec-7-ene (4.0 mmol) in dry CH_3CN (10 mL). The resulting mixture was stirred at room temperature for 10–15 min, monitoring the conversion of **3a–j** by TLC analysis (chloroform/methanol 99:1 v/v, or diethyl ether/light petroleum 60:40 v/v). The solvent was evaporated under reduced pressure and the residue was dissolved in 9% aqueous Na_2CO_3 (10 mL) and CH_2Cl_2 (15 mL). The organic layer was separated, washed with 9% aqueous Na_2CO_3 (5 mL), dried over Na_2SO_4, and then evaporated under vacuum to give a crude reaction product. The subsequent chromatographic purification (diethyl ether/light petroleum 50:50 v/v) afforded *N*-methyl anilines **4a–j** (88–95% overall yields).

4.5.1.1. *N*-Methyl-aniline[24] (4a). Yield 93%, brown oil. GC–MS (EI): *m/z* 107 [$M^{\bullet+}$, 81%]; 106 (100); 79 (15); 77 (24); 65 (7). ^1H NMR ($CDCl_3$): δ 2.83 (s, 3H, N–CH_3); 6.59–6.67 (m, 2H, Ar–H); 6.71–6.78 (m, 1H, Ar–H); 7.18–7.25 (m, 2H, Ar–H). ^{13}C NMR ($CDCl_3$): δ 30.32; 112.27; 117.05; 129.07; 149.22. Anal. Calcd for C_7H_9N: C, 78.46; H, 8.47; N, 13.07. Found: C, 78.17; H, 8.45; N, 13.02. IR (liquid film): ν_{max} 3422, 3058, 2932, 2821, 1601, 1511, 1320, 1172 cm^{-1}.

4.5.1.2. *N*-Methyl-*o*-toluidine[25] (4b). Yield 91%, brown oil. GC–MS (EI): *m/z* 121 [$M^{\bullet+}$, 100%]; 120 (62); 106 (72); 91 (26); 77 (13); 65 (12). ^1H NMR ($CDCl_3$): δ 2.21 (s, 3H, CH_3); 2.95 (s, 3H, N–CH_3); 3.50 (br s, 1H, N–H); 6.64–6.76 (m, 2H, Ar–H); 7.07–7.13 (m, 1H, Ar–H); 7.19–7.26 (m, 1H, Ar–H). ^{13}C NMR ($CDCl_3$): δ 17.46; 30.83; 109.16; 116.69; 121.92; 127.24; 129.95; 147.30. Anal. Calcd for $C_8H_{11}N$: C, 79.29; H, 9.15; N, 11.56. Found: C, 79.55; H, 9.11; N, 11.51. IR (liquid film): ν_{max} 3429, 3056, 2934, 2818, 1608, 1592, 1515, 1470, 1318, 1267, 1168 cm^{-1}.

4.5.1.3. *N*-Methyl-*m*-toluidine[26] (4c). Yield 92%, brown oil. GC–MS (EI): *m/z* 121 [$M^{\bullet+}$, 85%]; 120 (100); 201 (4); 120 (100); 106 (6); 92 (6); 91 (22); 77 (10); 65 (9). ^1H NMR ($CDCl_3$): δ 2.34 (s, 3H, CH_3); 2.86 (s, 3H, N–CH_3); 3.41 (br s, 1H, N–H); 6.44–6.51 (m, 2H, Ar–H); 6.57–6.62 (m, 1H, Ar–H); 7.10–7.17 (m, 1H, Ar–H). ^{13}C NMR ($CDCl_3$): δ 21.59; 30.73; 109.58; 113.12; 118.15; 129.02; 138.94; 149.34. Anal. Calcd for $C_8H_{11}N$: C, 79.29; H, 9.15; N, 11.56. Found: C, 79.50; H, 9.19; N, 11.50. IR (liquid film): ν_{max} 3426, 3054, 2930, 2821, 1610, 1598, 1517, 1462, 1325, 1170 cm^{-1}.

4.5.1.4. *N*-Methyl-*p*-anisidine[27] (4d). Yield 93%, brown oil. GC–MS (EI): *m/z* 137 [$M^{\bullet+}$, 65%]; 122 (100); 94 (13); 77 (5); 65 (9). ^1H NMR ($CDCl_3$): δ 2.81 (s, 3H, N–CH_3); 3.32 (br s, 1H, N–H); 3.77 (s, 3H, OCH_3); 6.58–6.65 (m, 2H, Ar–H); 6.80–6.86 (m, 2H, Ar–H). ^{13}C NMR ($CDCl_3$): δ 31.57; 55.75; 113.61; 114.79; 143.57; 152.02. Anal. Calcd for $C_8H_{11}NO$: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.29; H, 8.11; N, 10.16. IR (liquid film): ν_{max} 3428, 3046, 2936, 2830, 1616, 1604, 1508, 1467, 1323, 1240, 1162 cm^{-1}.

4.5.1.5. *N*-Methyl-*o*-fluoroaniline[28] (4e). Yield 88%, brown oil. GC–MS (EI): *m/z* 125 [$M^{\bullet+}$, 84%]; 124 (100); 96 (8); 95 (9); 83 (11); 77 (36). ^1H NMR ($CDCl_3$): δ 2.89 (s, 3H, N–CH_3); 6.59–6.75 (m, 2H, Ar–H); 6.93–7.08 (m, 2H, Ar–H). ^{13}C NMR ($CDCl_3$): δ 30.26; 111.49; 114.06; 114.29; 116.32; 116.43; 124.62. ^{19}F NMR ($CDCl_3$):

δ −14.68. Anal. Calcd for C_7H_8FN: C, 67.19; H, 6.44; F, 15.18; N, 11.19. Found: C, 67.01; H, 6.41; F, 15.23; N, 11.16. IR (liquid film): ν_{max} 3410, 3061, 2935, 1610, 1596, 1509, 1458, 1321 cm^{-1}.

4.5.1.6. *N*-Methyl-*o*-iodoaniline[29] (4f). Yield 92%, dark oil. GC–MS (EI): *m/z* 233 [$M^{\bullet+}$, 98%]; 232 (100); 203 (3); 127 (10); 106 (25); 105 (37); 104 (43); 91 (17); 79 (29); 77 (82); 64 (14); 63 (19). ^1H NMR ($CDCl_3$): δ 2.92 (d, 3H, N–CH_3, J=4.8 Hz); 4.25 (br s, 1H, N–H); 6.46–6.62 (m, 2H, Ar–H); 7.25–7.32 (m, 1H, Ar–H); 7.68–7.73 (m, 1H, Ar–H). ^{13}C NMR ($CDCl_3$): δ 29.97; 85.14; 109.98; 118.45; 129.47; 138.83; 148.11. Anal. Calcd for C_7H_8IN: C, 36.08; H, 3.46; I, 54.45; N, 6.01. Found: C, 36.21; H, 3.48; I, 54.67; N, 6.05. IR (liquid film): ν_{max} 3419, 3052, 2931, 1612, 1600, 1515, 1455, 1319 cm^{-1}.

4.5.1.7. *N*-Methyl-*p*-nitroaniline[30] (4g). Yield 92%, yellow solid, mp 149–151 °C. GC–MS (EI): *m/z* 152 [$M^{\bullet+}$, 100%]; 122 (53); 106 (33); 94 (17); 79 (46); 78 (30); 77 (84); 65 (49). ^1H NMR ($CDCl_3$): δ 2.94 (d, 3H, N–CH_3, J=4.9 Hz); 4.70 (br s, 1H, N–H); 6.50–6.56 (m, 2H, Ar–H); 8.07–8.13 (m, 2H, Ar–H). ^{13}C NMR ($CDCl_3$): δ 30.14; 110.69; 126.42; 137.90; 154.22. Anal. Calcd for $C_7H_8N_2O_2$: C, 55.26; H, 5.30; N, 18.41. Found: C, 55.18; H, 5.27; N, 18.34. IR (KBr): ν_{max} 3358, 1603, 1550, 1498, 1324, 1302 cm^{-1}.

4.5.1.8. *N*-Methyl-*p*-aminoacetophenone[31] (4h). Yield 90%, pale yellow solid, mp 106–108 °C. GC–MS (EI): *m/z* 149 [$M^{\bullet+}$, 56%]; 134 (100); 106 (15); 105 (27); 79 (10); 77 (14). ^1H NMR ($CDCl_3$): δ 2.51 (s, 3H, $COCH_3$); 2.89 (d, 3H, N–CH_3, J=5.0 Hz); 4.40 (br s, 1H, N–H); 6.55–6.61 (m, 2H, Ar–H); 7.82–7.89 (m, 2H, Ar–H). ^{13}C NMR ($CDCl_3$): δ 26.04; 30.07; 110.98; 126.39; 130.76; 153.09; 196.50. Anal. Calcd for $C_9H_{11}NO$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.22; H, 7.39; N, 9.44. IR (KBr): ν_{max} 3389, 3064, 1662, 1628, 1594, 1528, 1439, 1310, 1283 cm^{-1}.

4.5.1.9. Methyl *N*-methyl-*p*-aminobenzoate[32] (4i). Yield 95%, pale yellow solid, mp 86–88 °C. GC–MS (EI): *m/z* 165 [$M^{\bullet+}$, 99%]; 134 (100); 120 (5); 106 (23); 91 (4); 77 (13); 79 (16); 77 (22); 65 (9). ^1H NMR ($CDCl_3$): δ 2.88 (s, 3H, N–CH_3); 3.83 (s, 3H, OCH_3); 4.27 (br s, 1H, N–H); 6.52–6.59 (m, 2H, Ar–H); 7.84–7.91 (m, 2H, Ar–H). ^{13}C NMR ($CDCl_3$): δ 30.11; 51.52; 111.04; 118.03; 131.48; 152.90; 167.41. Anal. Calcd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.29; H, 6.74; N, 8.42. IR (KBr): ν_{max} 3394, 3073, 2948, 1692, 1608, 1583, 1517, 1445, 1264, 1244, 1174 cm^{-1}.

4.5.1.10. *N*-Methyl-*m*-aminobenzonitrile[33] (4j). Yield 90%, brown oil. GC–MS (EI): *m/z* 132 [$M^{\bullet+}$, 99%]; 131 (100); 104 (23); 102 (17); 90 (9); 77 (15); 76 (11); 75 (12). ^1H NMR ($CDCl_3$): δ 2.82 (s, 3H, N–CH_3); 3.73 (br s, 1H, N–H); 6.77–6.73 (m, 2H, Ar–H); 6.94–6.99 (m, 1H, Ar–H); 7.20–7.27 (m, 1H, Ar–H). ^{13}C NMR ($CDCl_3$): δ 30.34; 112.85; 114.42; 116.95; 119.61; 120.58; 129.83; 149.35. Anal. Calcd for $C_8H_8N_2$: C, 72.70; H, 6.10; N, 21.20. Found: C, 72.95; H, 6.07; N, 21.12. IR (liquid film): ν_{max} 3401, 3062, 2933, 2158, 1602, 1516, 1319, 1169 cm^{-1}.

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