

Microwave-promoted mono-*N*-alkylation of aromatic amines in water: a new efficient and green method for an old and problematic reaction

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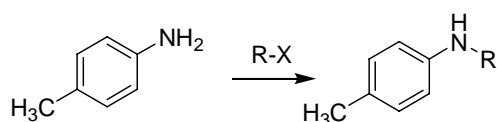
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EXPERIMENTAL

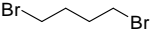
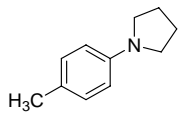
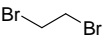
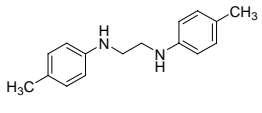
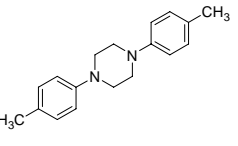
All commercial chemicals and solvents used were analytical grade and were used without further purification. Syntheses were performed in a CEM Discover® monomode reactor with the temperature monitored by a built-in infrared sensor. Melting points were determined on a Gallenkamp MFB-595-010M melting point apparatus and are uncorrected. Analytical TLC was performed on pre-coated 60 F₂₅₄ silica gel plates (0.25 mm; Merck) developing with a CH₂Cl₂/MeOH mixture (9:1). Preparative column chromatography was performed using silica gel 60 (0.063-0.100 mm; Merck), eluting with CH₂Cl₂. ¹H NMR spectra were recorded on a Bruker AMX300 spectrometer with TMS as internal standard. Chemical shift values are reported in ppm and coupling constants are reported in Hz. HRMS spectra were obtained using an ESI-TOF Mariner 5220 (Applied Biosystem) mass spectrometer with direct injection of the sample and collecting data in the positive ion mode. Elemental analyses were performed on a Perkin-Elmer 2400 Analyser and are within ±0.4% of theoretical values.

General procedure. A mixture of aryl amine (3 mmol) and alkyl halide (6 mmol) in H₂O (1 mL) was microwave irradiated at 150°C (power set point 150 W; ramp time 1 min; hold time 20 min). After cooling, the mixture was diluted with water (500 mL), neutralised with NaHCO₃, and fractionally distilled at atmospheric pressure through an efficient column, discarding the first fraction (corresponding to a mixture of the unreacted starting amine and a little amount of alkylated products) and then collecting the pure final product. If the first fraction was redistilled, the final yield could be increased as much as 5%. Alternatively, the mixture was diluted with water (10 mL), neutralised with NaHCO₃, and extracted with CH₂Cl₂ (3 x 10 mL); the organic phase was evaporated under reduced pressure, and the residue was purified by column chromatography to give the final product. The yields of the two methods were comparable (considering the redistillation of the first fraction). Yields, ¹H-NMR, HRMS and elemental analyses are reported in the tables below.

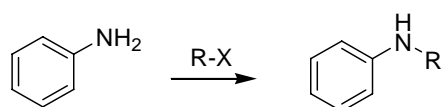
1. Synthesis of *N*-alkyl-4-toluidines


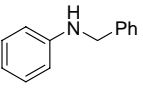


R-X	Final Product	Yield	¹ H-NMR	HRMS ESI-TOF (M + H ⁺)	Elem. Anal.	
					Calcd.	Found
		82%	CDCl ₃ : 7.49-7.36 (m, 5 H, Harom); 7.10 (d, J=8.4, 2 H, Harom); 6.66 (d, J=8.4, 2 H, Harom); 4.39 (s, 2 H, CH ₂); 2.36 (s, 3 H, 4-CH ₃)	C ₁₄ H ₁₅ N + H ⁺ Calcd.: 198.1283 Found: 198.1277	C 85.24 H 7.66 N 7.10	C 85.22 H 7.61 N 7.17
		85%	CDCl ₃ : 6.99 (d, J=8.1, 2 H, Harom); 6.54 (d, J=8.1, 2 H, Harom); 3.14 (q, J=7.2, 2 H, CH ₂ CH ₃); 2.24 (s, 3 H, 4-CH ₃); 1.24 (t, J=7.2, 3 H, CH ₂ CH ₃)	C ₉ H ₁₃ N + H ⁺ Calcd.: 136.1126 Found: 136.1202	C 79.95 H 9.69 N 10.36	C 79.99 H 9.73 N 10.28
		88%		C ₉ H ₁₃ N + H ⁺ Calcd.: 136.1126 Found: 136.1122	C 79.95 H 9.69 N 10.36	C 79.90 H 9.66 N 10.44
		73%	CDCl ₃ : 7.03 (d, J=8.3, 2 H, Harom); 6.79 (d, J=8.3, 2 H, Harom); 3.41-3.30 (m, 1 H, CHCH ₃); 2.27 (s, 3 H, 4-CH ₃); 1.79-1.44 (m, 2 H, CH ₂ CH ₃); 1.21 (d, J=6.4, 3 H, CHCH ₃); 0.94 (t, J=7.0, 3 H, CH ₂ CH ₃)	C ₁₁ H ₁₇ N + H ⁺ Calcd.: 164.1439 Found: 164.1450	C 80.93 H 10.50 N 8.57	C 80.95 H 10.48 N 8.57
		68%	CDCl ₃ : 6.97 (d, J=7.1, 2 H, Harom); 6.70 (d, J=7.1, 2 H, Harom); 2.22 (s, 3 H, 4-CH ₃); 1.28 (s, 9 H, CCH ₃)	C ₁₁ H ₁₇ N + H ⁺ Calcd.: 164.1439 Found: 164.1422	C 80.93 H 10.50 N 8.57	C 80.97 H 10.50 N 8.54
		66%	CDCl ₃ : 7.02 (d, 8.1, 2 H, Harom); 6.66 (d, J=8.1, 2 H, Harom); 3.83 (t, J=5.0, 2 H, CH ₂ OH); 3.30 (t, J=5.0, 2 H, NHCH ₂); 2.25 (s, 3 H, 4-CH ₃)	C ₉ H ₁₃ NO + H ⁺ Calcd.: 152.1075 Found: 152.1088	C 71.49 H 8.67 N 9.26	C 71.60 H 8.63 N 9.22
		90%	CDCl ₃ : 6.99 (d, J=8.3, 2 H, H arom); 6.59 (d, J=8.3, 2 H, H arom); 3.35 (t, J=5.8, 2 H, NHCH ₂); 2.88 (t, J=5.8, 2 H, CH ₂ N(CH ₃) ₂); 2.53 (s, 6 H, N(CH ₃) ₂); 2.23 (s, 3 H, 4-CH ₃)	C ₁₁ H ₁₈ N ₂ + H ⁺ Calcd.: 179.1548 Found: 179.1566	C 74.11 H 10.18 N 15.71	C 74.08 H 10.16 N 15.76

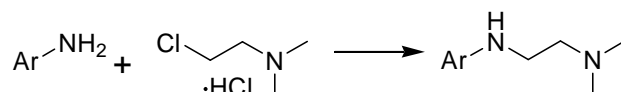
		85%	CDCl ₃ : 7.03 (d, J=8.3, 2 H, H arom), 6.50 (d, J=8.3, 2 H, H arom), 3.30-3.15 (m, 4 H, 2'-H and 5'-H), 2.26 (s, 3 H, 4-CH ₃), 2.02-1.95 (m, 4 H, 3'-H and 4'-H).	C ₁₁ H ₁₅ N + H ⁺ Calcd.: 162.1283 Found: 162.1296	C 81.94 H 9.38 N 8.69	C 81.95 H 9.43 N 8.60
		20	CDCl ₃ : 7.00 (d, J=8.2, 4 H, H arom); 6.59 (d, J=8.2, 4 H, H arom); 3.36 (s, 4 H, NHCH ₂); 2.24 (s, 6 H, CH ₃)	C ₁₆ H ₂₀ N ₂ + H ⁺ Calcd.: 241.1705 Found: 241.1700	C 79.96 H 8.39 N 11.66	C 80.01 H 8.41 N 11.58
		20	CDCl ₃ : 7.10 (d, J=8.1, 4 H, H arom); 6.91 (d, J=8.1, 4 H, H arom); 3.28 (s, 8 H, N(CH ₂) ₂); 2.24 (s, 6 H, CH ₃)	C ₁₈ H ₂₂ N ₂ + H ⁺ Calcd.: 267.1861 Found: 267.1888	C 81.16 H 8.32 N 10.52	C 81.20 H 8.38 N 10.57

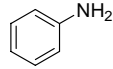
2. Synthesis of *N*-benzylaniline

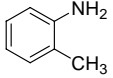
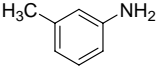
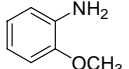
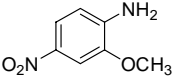
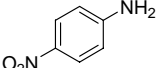
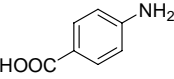
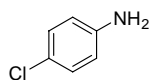
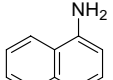
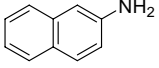


R-X	Final Product	Yield	¹ H-NMR	HRMS ESI-TOF (M + H ⁺)	Elem. Anal.	
					Calcd.	Found
		75%	CDCl ₃ : 7.35-7.29 (m, 4 H, Harom); 7.24-7.20 7.10 (m, 1 H, Harom); 7.13 (t, J=7.5, 2 H, Harom); 6.68 (t, J=7.5, 1 H, H arom); 6.58 (d, J=7.5, 2 H, H arom); 4.26 (s, 2 H, CH ₂)	C ₁₃ H ₁₃ N + H ⁺ Calcd.: 184.1126 Found: 184.1155	C 85.21 H 7.15 N 7.64	C 85.22 H 7.12 N 7.59

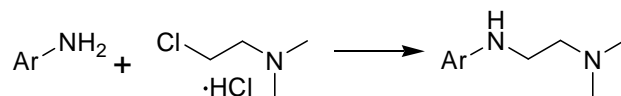
3. Synthesis of *N,N*-dimethyl-*N'*-arylethylene-1,2-diamines

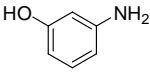
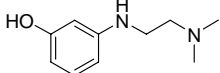
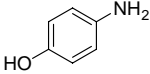
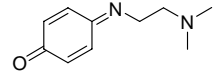
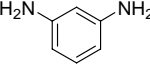
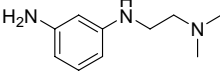
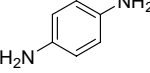
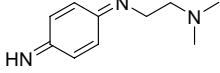


Ar-NH ₂	Yield	¹ H-NMR	HRMS ESI-TOF (M + H ⁺)	Elem. Anal.	
				Calcd.	Found
	89%	CDCl ₃ : 7.19 (t, J=8.1, 2 H, 3-H and 5-H); 6.71 (t, J=8.1, 1 H, 4-H); 6.64 (d, J=8.1, 2 H, 2-H and 6-H); 3.17 (t, J=6.1, 2 H, NHCH ₂); 2.59 (t, J=6.1, 2 H, CH ₂ N(CH ₃) ₂); 2.28 (s, 6 H, N(CH ₃) ₂)	C ₁₀ H ₁₆ N ₂ + H ⁺ Calcd.: 165.1392 Found: 165.1374	C 73.13 H 9.82 N 17.05	C 73.20 H 9.79 N 17.01

	74%	CDCl ₃ : 7.14 (t, J=8.2, 1 H, 5-H); 7.04 (d, J=8.2, 1 H, 5-H); 6.72 (t, J=8.2, 1 H, 4-H); 6.61 (d, J=8.2, 1 H, 3-H); 3.21 (t, J=5.9, 2 H, NHCH ₂); 2.64 (t, J=5.9, 2 H, CH ₂ N(CH ₃) ₂); 2.29 (s, 6 H, N(CH ₃) ₂); 2.18 (s, 3 H, 2-CH ₃)	C ₁₁ H ₁₈ N ₂ + H ⁺ Calcd.: 179.1548 Found: 179.1572	C 74.11 H 10.18 N 15.71	C 74.02 H 10.23 N 15.75
	82%	CDCl ₃ : 7.08 (t, J=7.5, 1 H, 5-H); 6.54 (d, J=7.5, 1 H, 4-H); 6.50-6.44 (m, 2 H, 2-H and 6-H); 3.17 (t, J=6.0, 2 H, NHCH ₂); 2.59 (t, J=6.0, 2 H, CH ₂ N(CH ₃) ₂); 2.29 (s, 9 H, N(CH ₃) ₂ and 2-CH ₃)	C ₁₁ H ₁₈ N ₂ + H ⁺ Calcd.: 179.1548 Found: 179.1523	C 74.11 H 10.18 N 15.71	C 74.20 H 10.17 N 15.63
	72%	CDCl ₃ : 6.87 (td, J=7.7, J=1.4, 1 H, 5-H or 4-H); 6.77 (dd, J=7.7, J=1.4, 1 H, 6-H or 3-H); 6.67 (td, J=7.7, J=1.4, 1 H, 5-H or 4-H); 6.61 (dd, J=7.7, J=1.4, 1 H, 6-H or 3-H); 3.85 (s, 3 H, OCH ₃); 3.23 (t, J=6.4, 2 H, NHCH ₂); 2.62 (t, J=6.4, 2 H, CH ₂ N(CH ₃) ₂); 2.31 (s, 6 H, N(CH ₃) ₂)	C ₁₁ H ₁₈ N ₂ O + H ⁺ Calcd.: 195.1497 Found: 195.1486	C 68.01 H 9.34 N 14.42	C 67.95 H 9.36 N 14.44
	20%	CDCl ₃ : 7.91 (dd, J=8.9, J=2.3, 1 H, 5-H); 7.62 (d, J=2.3, 1 H, 3-H); 6.50 (d, J=8.9, 1 H, 6-H); 3.94 (s, 3 H, OCH ₃); 3.49 (t, J=6.2, 2 H, NHCH ₂); 2.86 (t, J=6.2, 2 H, CH ₂ N(CH ₃) ₂); 2.51 (s, 6 H, N(CH ₃) ₂)	C ₁₁ H ₁₇ N ₃ O ₃ + H ⁺ Calcd.: 240.1348 Found: 240.1367	C 55.22 H 7.16 N 17.56	C 55.34 H 7.20 N 17.48
	10%	CDCl ₃ : 8.07 (d, J=9.2, 2 H, 3-H and 5-H); 6.55 (d, J=9.2, 2 H, 2-H and 6-H); 3.22 (t, J=6.0, 2 H, NHCH ₂); 2.57 (t, J=6.0, 2 H, CH ₂ N(CH ₃) ₂); 2.25 (s, 6 H, N(CH ₃) ₂)	C ₁₀ H ₁₅ N ₃ O ₂ + H ⁺ Calcd.: 210.1243 Found: 210.1259	C 57.40 H 7.23 N 20.08	C 57.27 H 7.19 N 20.16
	35%	CDCl ₃ : 7.17 (d, J=7.6, 2 H, 3-H and 5-H); 6.64 (d, J=7.6, 2 H, 2-H and 6-H); 3.23 (t, J=5.7, 2 H, NHCH ₂); 2.71 (t, J=5.7, 2 H, CH ₂ N(CH ₃) ₂); 2.38 (s, 6 H, N(CH ₃) ₂)	C ₁₁ H ₁₆ N ₂ O ₂ + H ⁺ Calcd.: 209.1290 Found: 209.1310	C 63.44 H 7.74 N 13.45	C 63.33 H 7.76 N 13.60
	67%	CDCl ₃ : 7.11 (d, J=8.7, 2 H, 3-H and 5-H); 6.55 (d, J=8.7, 2 H, 2-H and 6-H); 3.12 (t, J=5.7, 2 H, NHCH ₂); 2.57 (t, J=5.7, 2 H, CH ₂ N(CH ₃) ₂); 2.27 (s, 6 H, N(CH ₃) ₂)	C ₁₀ H ₁₅ ClN ₂ + H ⁺ Calcd.: 199.1002 Found: 199.1018	C 60.45 H 7.61 Cl 17.84 N 14.10	C 60.50 H 7.62 Cl 17.78 N 14.10
	75%	CDCl ₃ : 7.95-7.89 (m, 1 H, Harom); 7.82-7.76 (m, 1 H, Harom); 7.48-7.41 (m, 2 H, Harom); 7.35 (t, J=7.7, 1 H, 3-H); 7.23 (d, J=7.7, 1 H, 4-H); 6.58 (d, J=7.7, 1 H, 2-H); 3.23 (t, J=6.2, 2 H, NHCH ₂); 2.75 (t, J=6.2, 2 H, CH ₂ N(CH ₃) ₂); 2.34 (s, 6 H, N(CH ₃) ₂)	C ₁₄ H ₁₈ N ₂ + H ⁺ Calcd.: 215.1548 Found: 215.1607	C 78.46 H 8.47 N 13.07	C 78.55 H 8.42 N 13.03
	78%	CDCl ₃ : 7.67 (d, J=8.5, 1 H, 5-H); 7.62 (d, J=8.5, 2 H, 4-H and 8-H); 7.36 (t, J=8.5, 1 H, 7-H); 7.19 (t, J=8.5, 1 H, 6-H); 6.94 (dd, J=8.5, J=2.2, 1 H, 3-H); 6.81 (d, J=2.2, 1 H, 1-H); 3.28 (t, J=6.1, 2 H, NHCH ₂); 2.65 (t, J=6.1, 2 H, CH ₂ N(CH ₃) ₂); 2.31 (s, 6 H, N(CH ₃) ₂)	C ₁₄ H ₁₈ N ₂ + H ⁺ Calcd.: 215.1548 Found: 215.1555	C 78.46 H 8.47 N 13.07	C 78.42 H 8.45 N 13.13

4. Synthesis of *N,N*-dimethylethylene derivatives of hydroxyanilines and phenylenediamines



Ar-NH ₂	Final Product	Yield	¹ H-NMR	HRMS ESI-TOF (M + H ⁺)	Elem. Anal.	
					Calcd.	Found
		45%	DMSO: 6.82 (t, J=8.1, 1 H, 5-H); 6.04-5.91 (m, 3 H, Harom); 4.32 (t, J=5.2, 1 H, NH); 3.45 (td, J=7.2, J=5.2, 2 H, NHCH ₂); 3.05 (t, J=7.2, 2 H, CH ₂ N(CH ₃) ₂); 2.24 (s, 6 H, N(CH ₃) ₂)	C ₁₀ H ₁₆ N ₂ O + H ⁺ Calcd.: 181.1341 Found: 181.1400	C 66.63 H 8.95 N 15.54	C 66.66 H 9.01 N 15.47
		n.d.	Structure identified by HRMS analysis.	C ₁₀ H ₁₄ N ₂ O + H ⁺ Calcd.: 179.1184 Found: 179.1200		
		32%	CDCl ₃ : 6.97 (t, J=7.7, 1 H, 5-H); 6.12 (dd, J=7.7, J=2.8, 2 H, 4-H e 6-H); 5.99 (t, J=2.8, 1 H, 2-H); 3.14 (t, J=7.2, 2 H, NHCH ₂); 2.57 (t, J=7.2, 2 H, CH ₂ N(CH ₃) ₂); 2.27 (s, 6 H, N(CH ₃) ₂)	C ₁₀ H ₁₇ N ₃ + H ⁺ Calcd.: 180.1501 Found: 180.1487	C 67.00 H 9.56 N 23.44	C 66.87 H 9.62 N 23.51
		n.d.	Structure identified by HRMS analysis.	C ₁₀ H ₁₅ N ₃ + H ⁺ Calcd.: 178.1344 Found: 178.1367		

n.d. = not determined.