A Simple Method for Preparation of Secondary Aromatic Amines

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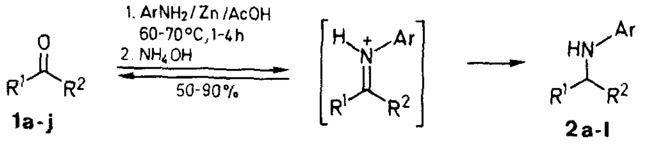
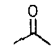
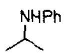
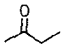
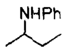
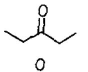
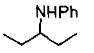
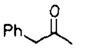
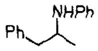
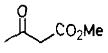
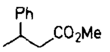
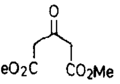
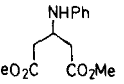
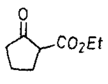
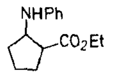
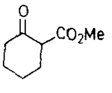
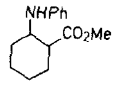
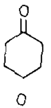
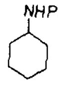
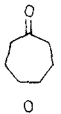
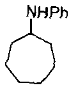
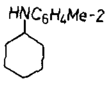
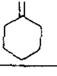
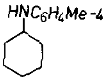
A simple and efficient method for the preparation of secondary *N*-alkylarylamines via reductive amination of ketones with primary aromatic amines using activated zinc/acetic acid is described. It requires only equimolar amounts of the starting compounds and affords good yields of the corresponding amines (50–90%). It is not applicable to aldehydes nor aliphatic amines.

A large number of methods have been developed to transform a carbonyl moiety to the corresponding amine.[1] Some of the more commonly used procedures involve reduction of carbonyl derivatives, such as imines,[2-7] enamines,[8-9] or oximes,[10-15] either catalytically or with metal hydrides. Alternatively, a carbonyl compound/amine mixture can often be reduced directly to the corresponding secondary or tertiary amine, utilizing catalytic hydrogenation,[16] formic acid (Leucart–Wallace reaction)[17-19] or certain metal hydrides.[8,9,20-25] In the latter instance sodium cyanoborohydride appears to be the most convenient reagent due to wide applicability.[26] However, most of the aforementioned procedures require elevated pressure or expensive and toxic reagents. Few aldehydes and acetone have been reductively aminated albeit in low yields with the



Scheme

Table 1. Physical Characteristics of Amines **2a–l** Prepared

Substrate	Amine	Time (h)	Product		Yield (%)	bp (°C)/ Torr	Molecular Formula or Lit. bp (°C)/Torr
	**1a** $PhNH_2$	1		**2a**	90	93–94/12	212–213/760[34]
	**1b** $PhNH_2$	2		**2b**	85	106–108/12	224–225/765[34]
	**1c** $PhNH_2$	4		**2c**	48	115–117/12	114/14[36]
	**1d** $PhNH_2$	2		**2d**	80	140–142/0.05	[a]
	**1e** $PhNH_2$	2		**2e**	84	118–120/0.05	144–146/9[38]
	**1f** $PhNH_2$	4		**2f**	82	148–150/0.05	$C_{13}H_{17}NO_4$[b] (251.3)
	**1g** $PhNH_2$	4		*cis/trans*-**2g**	84[c]	130–132/0.05	137/0.06[39]
	**1h** $PhNH_2$	4		*cis/trans*-**2h**	80[c]	130–132/0.05	$C_{14}H_{19}NO_2$[d] (233.3)
	**1i** $PhNH_2$	2		**2i**	90	102–104/0.05	146–148/16[40]
	**1j** $PhNH_2$	4		**2j**	50	120–123/0.05	156–156/11[41]
	**1k** $2\text{-}MeC_6H_4NH_2$	4		**2k**	60	80–82/0.05	230/30[42]
	**1l** $4\text{-}MeC_6H_4NH_2$	4		**2l**	81	90–92/0.05	180/30[42,e]

[a] Lit.[37], bp not reported.

[b] Satisfactory microanalysis obtained: C + 0.21, H + 0.21, N + 0.12.

[c] Diastereoisomeric ratio; **2g**: *cis/trans* (8 : 2) (cap. GS); **2h**: *cis/trans* (8 : 2) (cap. GS, ^1H-NMR).

[d] Satisfactory microanalysis obtained: C + 0.13, H + 0.27, N + 0.06; mp 65–77 °C.

[e] mp 41–42 °C.

simpler and inexpensive zinc amalgam and hydrochloric acid,[27,28] but to our knowledge, it has not been generally applied to carbonyl compounds. It can also effect hydrolysis of various functional groups and decarboxylate β-keto esters. An intramolecular reductive amination of keto anilines to tetrahydroquinolines has been effected by zinc, and 37% hydrobromic acid in acetic acid.[29]

We have found[30] that various ketones and β-keto esters can be reductively aminated with primary aromatic amines, in good yields utilizing activated zinc dust[31] and acetic acid. It is more applicable than zinc/hydrochloric acid, gives better yields, and it is particularly well suited for preparation of β-arylamino esters. The reaction proceeds rapidly, being complete in 1-4 hours, at 60-70 °C and requires only stoichiometric amounts of the reagents. In some instances, where shorter reaction times were used, the intermediate imines could be isolated (IR band at 1650 cm^{-1}), thus providing the general mechanism as shown in the Scheme. Temperature control was found to be important since zinc reacts rapidly with acetic acid at elevated temperatures.

Yields were dependent upon the structure of both the ketone and amine. More sterically hindered ketones give lower yields, probably because of slower intermediate imine formation. For example, cyclohexanone gave *N*-cyclohexylaniline (**2i**) in 90% yield, while cycloheptanone afforded only 50% of *N*-cycloheptylaniline (**2j**). Similar differences in reactivity were noted between methyl ethyl ketone and diethyl ketone. On the other hand, β-keto esters furnished excellent yields (80-85%) of the corresponding β-*N*-phenylamino esters. Some conformationally rigid ketones, like tropinone failed to react at all, and only acetanilide ensued. Aldehydes gave

Table 2. Spectroscopic Data of Amines **2a-l**

Compound	IR (film) ν (cm^{-1})	^{1}H-NMR (CDCl$_3$/TMS) δ, *J* (Hz)	^{13}C-NMR (CDCl$_3$/TMS) δ
2a	3392, 3089, 3051, 3020, 2966, 2929, 2870, 1603, 1506, 1465, 1429, 1402, 1384, 1366, 1318, 1256, 1179, 1153, 750, 693, 505	1.25 (d, 6H, *J* = 6.9), 3.25-3.85 (m, 2H), 6.50-6.90 (m, 3H), 7.05-7.35 (m, 2H)	21.91, 43.09, 112.39, 115.93, 128.3, 146.73
2b	3400, 3086, 3052, 3020, 2965, 2929, 2875, 1603, 1506, 1458, 1429, 1402, 1377, 1320, 1274, 1166, 1153, 749, 693, 504	0.95 (t, 3H, *J* = 6.9), 1.15 (d, 3H, *J* = 7), 1.30-1.75 (m, 2H), 3.30 (br s, 1H), 3.35 (sext, 1H, *J* = 6.4), 6.50-6.75 (m, 3H), 7.0-7.30 (m, 2H)	10.21, 20.32, 29.90, 50.08, 113.50, 117.01, 129.28, 148.10
2c	3401, 3084, 3052, 3019, 2964, 2932, 2875, 1603, 1505, 1461, 1430, 1381, 1321, 1280, 1246, 1180, 1155, 1077, 1032, 997, 867, 776, 748, 693, 507, 407	0.90 (t, 6H, *J* = 6.9), 1.30-1.80 (m, 4H), 3.05-3.50 (m, 2H), 6.50-6.80 (m, 3H), 7.0-7.30 (m, 2H)	9.58, 26.37, 54.89, 112.52, 128.68, 147.90
2d	3402, 3084, 3053, 3026, 2966, 1602, 1506, 1454, 1430, 1402, 1377, 1319, 1284, 1256, 1180, 1154, 749, 694, 506, 419	1.15 (d, 3H, *J* = 6.9), 2.55-3.10 (m, 2H), 3.45 (br s, 1H), 3.75 (sext, 1H, *J* = 6.5), 6.55-6.75 (m, 3H), 7.05-7.30 (m, 7H)	20.20, 42.54, 49.46, 113.61, 117.27, 126.2, 128.26, 129.29, 129.42, 138.70, 147.49
2e	3392, 3100, 3053, 3023, 2971, 2953, 2930, 1734, 1603, 1509, 1455, 1436, 1403, 1381, 1367, 1298, 1258, 1196, 1180, 1153, 1093, 1008, 752, 695	1.30 (d, 3H, *J* = 7), 2.55 (m, 2H), 3.70 (s, 3H), 3.70-4.05 (m, 2H), 6.55-6.85 (m, 3H), 7.05-7.30 (m, 2H)	19.22, 39.51, 44.68, 50.14, 112.39, 116.30, 128.09, 145.85, 170.94
2f	3381, 3054, 3025, 2953, 1735, 1604, 1510, 1500, 1438, 1371, 1290, 1259, 1202, 1180, 1117, 1070, 1029, 995, 929, 754, 695, 512	2.65 (d, 4H, *J* = 6.9), 3.65 (s, 6H), 4.20 (m, 2H), 6.55-6.85 (m, 3H), 7.0-7.25 (m, 2H)	36.9, 46.21, 50.15, 112.67, 116.79, 127.97, 145.24, 170.38
2g	3395, 3053, 3022, 2962, 2873, 1723, 1603, 1508, 1475, 1438, 1398, 1377, 1351, 1313, 1281, 1191, 1155, 1099, 1029, 750, 693	1.30-2.10 (m), 2.70-2.95 (m), 3.55 (s), 3.60 (s), 4.0-4.30 (m), 6.50-6.75 (m), 7.0-7.25 (m)	13.98, 14.16, 22.52, 23.54, 27.89, 28.63, 32.93, 33.64, 47.20, 51.29, 57.04, 58.60, 60.23, 60.49, 113.34, 117.22, 117.36, 129.09, 147.55, 174.21, 175.14
2h	3398, 2936, 2858, 1729, 1602, 1506, 1450, 1435, 1373, 1338, 1312, 1255, 1212, 1192, 1176, 1136, 1126, 1096, 1075, 1032, 1003, 750, 694, 508	1.25-2.0 (m), 2.85 (m), 3.55 (s), 3.60 (s), 4.20 (m), 6.50-6.80 (m), 7.0-7.25 (m)	24.57, 24.96, 27.50, 30.51, 45.66, 52.13, 52.21. 112.27, 112.38, 115.84, 127.34, 144.68, 170.86
2i	3400, 3084, 3051, 3019, 2928, 2853, 1602, 1559, 1505, 1464, 1450, 1432, 1402, 1367, 1321, 1256, 1179, 1148, 1118, 1072, 1029, 994, 889, 866, 852, 693, 621, 506, 464	1.0-2.20 (m, 10H), 3.10-3.45 (m, 2H), 6.40-6.80 (m, 3H), 7.0-7.30 (m, 2H)	24.55, 25.50;, 32.94, 51.10, 112.67, 116.28, 128.70, 146.97
2j	3403, 3084, 3051, 3019, 2927, 2854, 1602, 1505, 1460, 1445, 1431, 1402, 1320, 1278, 1253, 1178, 748, 693	1.15-2.20 (m, 12H), 3.45 (br s, 2H), 6.40-6.80 (m, 3H), 7.0-7.30 (m, 2H)	24.59, 28.44, 35.09, 53.84, 113.50, 116.85, 129.21, 147.67
2k	3426, 3056, 3037, 3017, 2928, 2853, 1606, 1587, 1512, 1478, 1464, 1449, 1402, 1378, 1368, 1345, 1313, 1258, 1160, 1150, 1128, 1090, 1050, 979, 889, 745, 716	1.0-2.10 (m, 10H), 2.15 (s, 3H), 3.15-3.55 (m, 2H), 6.50-6.75 (m, 2H), 6.90-7.25 (m, 2H)	17.27, 24.83, 25.86, 33.43, 51.26, 110.04, 116.13, 121.32, 126.85, 130.05, 145.10
2l	3413, 3102, 3016, 2927, 2853, 1619, 1589, 1520, 1483, 1450, 1406, 1368, 1318, 1303, 1255, 1234, 1181, 1148, 1126, 1105, 890, 807, 509	1.0-2.20 (m, 10H), 2.25 (s, 3H), 3.10-3.50 (m, 2H), 6.45-6.65 (m, 2H), 6.90-7.10 (m, 2H)	22.17, 26.74, 27.67, 34.97, 52.82, 112.2, 124.3, 127.88, 142.81

a mixture of secondary and tertiary amines, as did α-keto esters. Attempted condensation of aniline with succinic dialdehyde (prepared by acid hydrolysis of 2,5-dimethoxytetrahydrofuran) gave mainly *N*-phenylpyrrole,[32] while glutaric dialdehyde gave only a tar.

Variation of the amino component also demonstrated steric influence, i.e., *o*-toluidine gave a substantially lower yield than *p*-toluidine in reactions with cyclohexanone. Aliphatic amines failed to give the desired product, although they formed the corresponding imines under the reaction conditions. Apparently, these imines do not undergo reduction with zinc/acetic acid.

Workup of the reaction mixture includes removal of the acetic acid under reduced pressure, and treatment of the residue with excess ammonia. The latter complexes the zinc(II) ions and prevents precipitation of a gelatinous zinc hydroxide unlike other bases such as sodium hydroxide and sodium carbonate. This greatly improves the isolation procedure and affords far better yields.

Physical characteristics of the products are listed in Table 1, while spectroscopic data are provided in Table 2.

Activated Zn dust was prepared with 5 % HCl.[31] Aniline, *o*- and *p*-toluidine were purified by reduced pressure distillation from Zn/HCl before use. Methyl 2-oxocyclohexanecarboxylate was prepared according to a literature procedure.[33] Reagent quality solvents were used without further purification, and other reagents were used as supplied, by Aldrich Chemical Co. and Fluka Chemical Co. Melting points were taken with a Mel-Temp apparatus and are uncorrected. Microanalyses were obtained with Pregl elemental analyzer, IR spectra with a Perkin-Elmer FT IR 1725 X spectrometer, ^{1}H-NMR spectra and ^{13}C-NMR spectra with Varian FT-80 A spectrometer at 80 MHz and 20 MHz, respectively. In the case of β-keto esters, glacial AcOH was used instead of 90 % AcOH.

N-Cyclohexalaniline (2i); Typical Procedure:
Into a 500 mL, three necked flask equipped with mechanical stirrer, reflux condenser and thermometer are combined AcOH (250 mL), H_2O (25 mL), activated Zn dust (78.45 g, 1.20 mol), aniline (27.94 g, 27.3 mL, 0.30 mol) and cyclohexanone (29.44 g, 31.3 mL, 0.30 mol). Stirring is initiated and after the moderately exothermic reaction subsides (ca. 30 min), the mixture is heated on a water bath (2 h, 60–70 °C). After cooling, the mixture is diluted with MeOH (100 mL), and filtered with a sinter funnel. The solids are washed with MeOH (2 × 100 mL), and the combined filtrates are concentrated at 50 °C with a rotary evaporator. Crushed ice (100 g), and CH_2Cl_2 (200 mL), are added to the residue with shaking, followed with excess 25 % NH_4OH until the pH is ca. 10. The organic layer is separated, the aqueous layer is extracted with CH_2Cl_2 (2 × 100 mL), and the combined extracts dried ($MgSO_4$). The residue is distilled (bp 102–104 °C/0.05 Torr) to afford pure *N*-cyclohexylaniline; yield: 47.4 g (90 %).

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