Notes

Convenient Procedure for N-Phenylation of Amines

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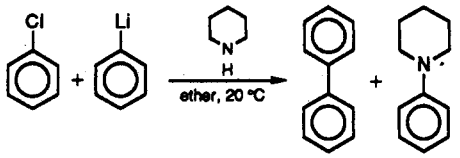
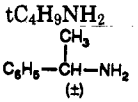
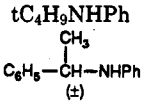
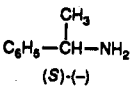
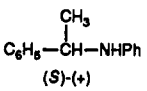
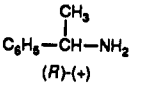
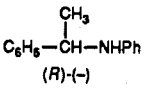
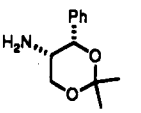
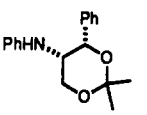
Although several methods have been reported for N-phenylation of amines in recent years,[1-3] the earlier method utilizing alkali metal (Li or Na), halobenzene, and the amine is the simplest for synthetic applications.[4-8] The reaction can be carried out in refluxing amine solvent or at room temperature.[4-8] In connection with our studies utilizing chiral *N*-phenylamines,[9] we were looking for a convenient method for the preparation of them. Unfortunately, the available methods require amine as solvent.[4-7] It has been reported that piperidine catalyzes the reaction of chlorobenzene and phenyllithium to give biphenyl along with *N*-phenylpiperidine.[10]



It occurred to us that a convenient method for N-phenylation of amines can be developed, based on this observation, using excess of halobenzene and lithium in relation to amine. Indeed, this has been the case. We have found that *N,N*-diethylaniline can be obtained in 82% yield by the reaction of bromobenzene (30 mmol), lithium (30 mmol), and diethylamine (10 mmol) in dry THF for 6 h at room temperature. The transformation is a general one (Table I).

The secondary amines give tertiary amines in reasonable yields (entries 1-5). Whereas aniline gives diphenylamine in 65% yield, the secondary phenylamines (entries 7 and 8) are not affected. Several primary amines can be converted to secondary amines (entries 6, 9, and 10), including some chiral amines (entries 11-13). Whereas 1-bromonaphthalene on reaction with pyrrolidine and lithium gave a mixture of 1- and 2-naphthylpyrrolidines, in accordance with the formation of the corresponding aryne intermediate, 1-bromo-2-methylnaphthalene yielded 2-methylnaphthalene as expected.[5]

Table I. N-Phenylation of Amines

entry no.	substrate[a]	product[b]	yield (%)[c]
1	$(C_2H_5)_2NH$	$(C_2H_5)_2NPh$	82
2	$(iC_3H_7)_2NH$	$(iC_3H_7)_2NPh$	78
3			86
4			80
5			81
6	$C_6H_5NH_2$	$(C_6H_5)_2NH$	65
7	$(C_6H_5)_2NH$	-	no reaction
8		-	no reaction
9	$tC_4H_9NH_2$	tC_4H_9NHPh	80
10	 (±)	 (±)	71
11	 (*S*)-(-)	 (*S*)-(+)	70[d]
12	 (*R*)-(+)	 (*R*)-(-)	70[e]
13			72[f]

[a] All reactions were carried out using 30 mmol of lithium dispersion in mineral oil (30%), 30 mmol of bromobenzene, and 10 mmol of amine in dry THF at room temperature. [b] All products were identified by IR, ^1H NMR, ^{13}C NMR, and physical constants data, and comparison with the data reported in literature. [c] Yields are of isolated and purified products. [d] Elemental analysis, Calcd: C, 85.24; H, 7.66; N, 7.10. Found: C, 85.39; H, 7.7; N, 7.15. $[\alpha]^{24}_D = +17°$ (*C* 1, CH_3OH); lit.[11] $[\alpha]^{24}_{578} = +18.5°$ (*C* 1, CH_3OH). [e] $[\alpha]^{24}_D = -16°$ (*C* 1, CH_3OH); lit.[11] $[\alpha]^{24}_{578} = -17.7°$ (*C* 1, CH_3OH). [f] Elemental analysis, calcd: C, 76.29; H, 7.47; N, 4.94. Found: C, 75.83; H, 7.40; N, 5.07. $[\alpha]^{24}_D = -86.5°$ (c 1.26, $CHCl_3$).

When sodium (30 mmol) was used in place of lithium and N-phenylation was carried out using bromobenzene (30 mmol) and piperidine (10 mmol) in THF for 24 h at room temperature, *N*-phenylpiperidine was obtained in 73% yield.

In conclusion, the procedure using excess of bromobenzene and lithium should be useful for the N-phenylation of primary and secondary amines, especially when the starting amines are valuable.

Experimental Section

Lithium powder suspended in mineral oil (30%) supplied by Alpha (Danvers) was used for all reactions. Bromobenzene was distilled before use. All amines were distilled over KOH prior to use. All reactions were carried out in THF freshly distilled over sodium benzophenone. (*R*)-(+)-α-Methylbenzylamine (98%)

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$[\alpha]^{20}_D = +30° \pm 2$ (*C* 10, ethanol), (*S*)-(−)-α-methylbenzylamine (98%) $[\alpha]^{20}_D = -30° \pm 2$ (*C* 10, ethanol), (4*S*,5*S*)-(+)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane (98%) $[\alpha]^{20}_D = +50° \pm 1$ (*C* 2, ethanol) supplied by Fluka, Switzerland, were utilized. Representative procedures for N-phenylation are given below.

N-Phenylation of Diisopropylamine. To a lithium powder suspension (30 mmol) in dry THF (20 mL) was injected diisopropylamine (10 mmol) under dry N_2 atmosphere. Bromobenzene (30 mmol) in THF (10 mL) was added slowly through a pressure equalizer during 15 min. The contents were further stirred at room temperature for 6 h. The reaction was quenched carefully with methanol (5 mL). The mixture was acidified with 20% HCl and the aqueous layer was separated. The amine was regenerated by the addition of aqueous KOH and extracted into ether (3 × 20 mL). The combined ether extract was dried over anhydrous Na_2SO_4. Evaporation of solvent afforded crude *N*,*N*-diisopropylaniline which was further purified by column chromatography over silica gel using hexane as eluent: yield 1.48 g (78%); bp 93 °C (10 mm), lit.[2] 95–96 °C (11 mm); ^{1}H NMR (100 MHz, $CDCl_3$) δ 1.2 (d, 12 H), 3.7 (m, 2 H), 6.8–7.3 (m, 5 H); ^{13}C NMR (25.0 MHz, $CDCl_3$) δ 21.3, 47.4, 118.4, 119.7, 128.5, 148.2.

N-Phenylation of (4*S*,5*S*)-(+)-5-Amino-2,2-dimethyl-4-phenyl-1,3-dioxane. To a lithium powder suspension (30 mmol) in dry THF (20 mL) was added amine (10 mmol) in THF (10 mL) using a cannula under nitrogen pressure. Bromobenzene (30 mmol) in THF (10 mL) was added slowly during 15 min. The reaction mixture was further stirred for 6 h at room temperature. The reaction was carefully quenched with methanol (5 mL), followed by water (10 mL). The organic layer was separated and the aqueous layer was extracted with ether (3 × 20 mL). Combined organic extract was washed with brine and dried over Na_2SO_4. Evaporation of solvent afforded crude *N*-phenyl secondary amine (entry 13, Table I), which was further purified by column chromatography on silica gel using hexane–ethyl acetate (95:5): yield 2 g (72%); ^{1}H NMR (100 MHz, $CDCl_3$) δ 1.6 (s, 6 H, 3.5 (br s, 1 H), 3.9–4.2 (m, 3 H), 5.2 (d, 1 H), 6.4–7.4 (m, 10 H); ^{13}C NMR (25.0 MHz, $CDCl_3$) δ 18.1, 29.2, 50.4, 63.1, 72.5, 99.0, 112.9, 116.7, 125.4, 127.0, 127.7, 128.6, 138.6, 146.7. Anal. Calcd: C, 76.29; H, 7.47; N, 4.94. Found: C, 75.83; H, 7.40; N, 5.07.