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A fast and highly efficient method for the synthesis of tertiary amines in aqueous medium

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A facile and highly efficient method for the synthesis of tertiary amines by the reaction of secondary amines with benzylic bromides and 1,1′-dibromo *p/o*-xylenes in aqueous dioxane and NaOH is described. The reactions are dually promoted by the base in short time (15 min.) at ambient conditions in aqueous medium.

Keywords: Secondary amines, benzylic bromides, dibromoxylenes, sodium hydroxide, tertiary amines

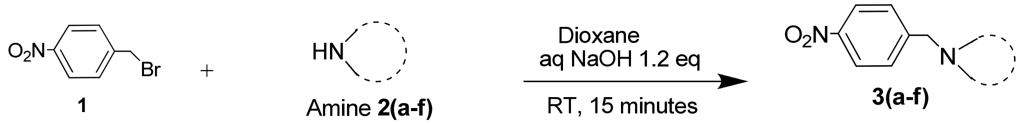
N-Alkylation of secondary amines continues to be focus for numerous studies[1]. Amines are of fundamental interest in many fields of chemistry, as evidenced by rapid increase in modern methods now available for their synthesis[2-5]. The direct alkylation of secondary amines with alkyl halides or alcohols is a straight forward method for the synthesis of tertiary amines[6-8]. These methods receive less attention due to the requirement of the specialized microwave equipment[6] or formation undesired products[7]. Although some significant achievements in the copper and palladium catalyzed arylation of amines have been made[3,4,9], the drawbacks of these catalyst systems, such as requirement of extremely anhydrous conditions, air sensitivity, high cost and toxicity, limits their applications. Use of solid supports are an alternate methods have been reported[10]. While these methods are apparently useful for constructing libraries of secondary and tertiary amines, they are obviously not practical for large scale preparations. Other alternate and general methods include reductive amination[11], Mannich and Petasis reactions[12], and metal induced amination of alkenes and alkynes[13]. Perhaps these methods are quite reliable, but practical success has been relatively limited since concomitant over alkylations are the common impediment. Therefore, the search for milder and more efficient systems for *N*-alkylation of primary and secondary amines is the subject of recent focus[3,14]. In continuation of our recent work on synthesis of 2,3-dihydro-1*H*-isoindole, under aqueous conditions[15], we found that tertiary amines can be efficiently synthesized under the same conditions in a short reaction time of 15 min. Therefore we report herein, an efficient base promoted synthesis of tertiary amines by the reaction of benzyl bromides with various secondary amines at RT are described.

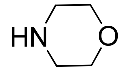
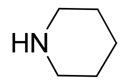
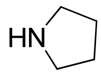
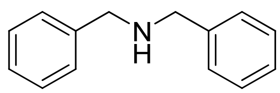
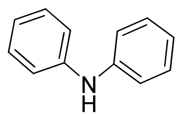
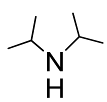
Results and Discussion

Initially, the reactivity of *p*-nitrobenzylbromide **1** with various secondary amines **2a-f** in presence of aqueous NaOH was screened out and results are summarized in **Table I**. Under the optimized conditions the reactions were completed with in 15 minutes when 1.2 equivalents of NaOH is used at room temperature (**Table I**, entries 1-3). The progress of the reaction was monitored by TLC, which shows intense spot of tertiary amines in iodine. These results are very significant compared to the reported procedures which normally need long reaction time. All the reactions proceeded smoothly, without significant loss of yields except in **2d** (**Table I**, entries 4) at RT rather than the microwave irradiation[6] where it needs high energy to promote reactions. The reaction of **1** with diphenyl amine **2e** (**Table I**, entries 5) is sluggish under the same conditions even reaction continued up to 60 minutes. However, the reaction with diisopropyl amine **2f** (**Table I**, entries 6) showed 33% desired product formation by GC analysis after 3 hr.

Encouraged by the results of **Table I**, the present methodology was extended to a wide range of benzylic

Table I — Reaction of *p*-nitrobenzyl bromide **1** with various secondary amines **2**



Entry	Amine **2**	Product **3**	Yield (%)[a]
1	 **2a**	**3a**	97
2	 **2b**	**3b**	95
3	 **2c**	**3c**	93
4	 **2d**	**3d**	49
5[b]	 **2e**	**3e**	--
6	 **2f**	**3f**	33[c]

[a]Isolated yields. [b]No reaction even with 60 minutes. [c]GC yield of desired product **3f** along with 7.0% 4-nitrobenzyl alcohol and the rest is unreacted starting substrate **1**,with reaction period 3 hr.

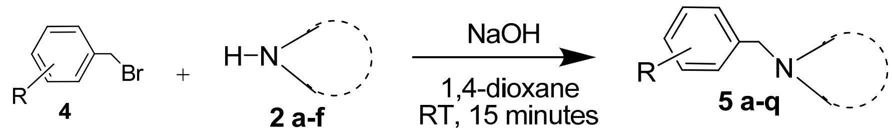
bromides, the corresponding tertiary amines were obtained in good yields without any appreciable side products at RT in a short period of time (15 minutes). The results are summarized in **Table II**. As evidenced from the results of **Table II**, the benzyl bromides with electron withdrawing substitutents in the phenyl ring provided excellent yields of tertiary amines with cyclic secondary amines as well as dibenzylamine (**Table II**, entries 1-6). Similarly the reactions of various chloro substituted benzyl bromides reacted smoothly with different secondary amines and provided good to high yields (67-94%) of corresponding tertiary amines (**Table II**, entries 7-12). Under the same conditions, the reaction of benzyl bromide with different secondary amines provided good yields of tertiary amines (**Table II**, entries 13-17).

In order to explore the scope and limitations of the present procedure for the *N*,*N*-bis(amination) of 1,1′-dibromo-*p*- and *o*-xylenes, with representative secondary amines were carried out (**Table III**). For instance the treatment of 1,1′-dibromo-*o*-xylene with dibenzylamine resulted a complex mixture. However 1,1′-dibromo-*p*-xylene underwent smoothly without much deterioration of yields and time with two equivalents of secondary amines under similar experimental conditions to provide the corresponding *N, N*-bis(amination) of 1,1′-dibromo-*p*- and *o*-xylenes in 72-99% isolated yields. The experimental procedure is very simple and pure products could be obtained by short column chromatography on silica gel.

Experimental Section

General. ^{1}H NMR spectra were recorded on Bruker-200 MHz FT-NMR DPX-200 in $CDCl_3$ with TMS as an internal standard and ^{13}C NMR at 50 MHz. FT-IR spectra were recorded on Perkin-Elmer GX-2000 spectrometer. Mass spectra were recorded

Table II — Synthesis of various tertiary amines **5**



Entry	**R**	Amine **2**	Product **5**	Yield (%)[a]
1	3-NO_2	**2a**	**5a**	95
2	3-NO_2	**2b**	**5b**	98
3	3-NO_2	**2c**	**5c**	80
4	2-NO_2	**2a**	**5d**	93
5	2-NO_2	**2b**	**5e**	97
6	2-NO_2	**2c**	**5f**	92
7	4-Cl	**2a**	**5g**	94
8	4-Cl	**2b**	**5h**	76
9	4-Cl	**2d**	**5i**	71
10	2-Cl	**2a**	**5j**	81
11	2-Cl	**2b**	**5k**	67
12	2-Cl	**2d**	**5l**	68
13	H	**2a**	**5m**	65
14	H	**2b**	**5n**	61
15	H	**2c**	**5o**	39
16	H	**2d**	**5p**	75
17	H	**2f**	**5q**	55[b]

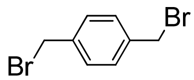
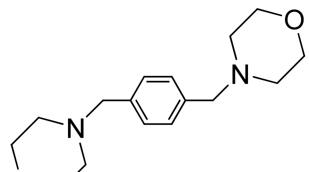
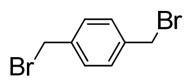
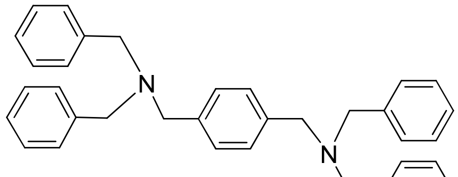
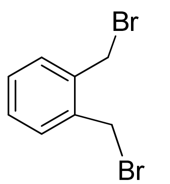
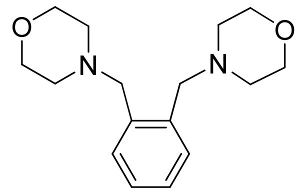
[a] Isolated yields after column chromatography. [b]GC yield of desired product with 90 minutes reaction time.

on micromass Q–Tof micro™ ES + ve mode. Melting points were recorded on Veego capillary instrument and may be uncorrected. Analytical TLC were performed on Aluchrosep Silica Gel 60/UV_{254} with UV light. Purification of the reaction products was carried out by column chromatography using silica gel 100-200 mesh.

General Procedure for synthesis of tertiary amines (Table I, entry 1, 3a). In a round bottom flask equipped with magnetic stir bar was charged with the 4-nitrobenzylbromide (0.926 mmol, 0.2 g), morpholine (0.926 mmol, 0.0805 g), 5 mL 1,4-dioxane. To the above mixture 2.2 mL of 0.5 *M* NaOH (1.11 mmol) was added under stirring at RT. The progress of the reaction was monitored by TLC after every 5 min, the reaction was completed within 15 min. After completion of the reaction, the mixture was extracted with ethyl acetate (3 × 15 mL). The organic layers were combined and dried over anhydrous sodium sulphate and concentrated under reduced pressure. The resulting residue was separated by column chromatography using 20% ethyl acetate in hexane to afford 4-(4-nitrobenzyl)morpholine **3a** (0.200 g, 0.901 mmole) 97.0% yield as pale yellow crystalline solid. The observed melting point is 75-77°C. Analytical data: ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.44-2.48 (t, *J* = 4.4, 4H,), 3.59 (s, 4H), 3.70-3.74 (t, *J* = 4.6, 4H), 7.51-7.55 (d, *J* = 8.4, 2H,), 8.15-8.19 (d, *J* = 8.2, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 54.28, 63.12, 67.54, 124.16, 130.14, 140.31; IR (KBr): 3425, 2970, 2935, 2895, 2862, 2818, 2800, 1604, 1517, 1446, 1344, 1320, 1207, 1110, 1070, 1008, 911, 864, 803, 743, 699, 650 cm^{-1}; LRMS for $C_{11}H_{14}N_2O_3$ $(M + H)^+$: Calcd: 223.11, Found: 223.09 The analytical data for new products **3d, 5i, 5l, 6, 7** and **8** are provided, the rest of all compounds are known their spectroscopic data was consistent with that reported in the literature[16].

Dibenzyl-(4-nitrobenzyl)amine 3d: ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.54 (s, 4H), 3.60 (s, 2H,), 7.22-7.39 (m,10 H), 7.51-7.55 (d, *J* = 8.6, 2H), 8.10-8.15 (d, *J* = 8.8, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 57.83, 58.78, 124.03, 127.76, 128.93, 129.29, 129.74, 130.32,

Table III — *N*,*N*-bis (amination) of 1,1′-dibromo-*p*-and *o*-xylenes [a]

Entry	Substrate	**2** (Equiv.)	Product (No.)	Yield (%)[b]
1		**2a**(2.0)	 **6**	76
2		**2d**(2.0)	 **7**	99
3		**2a**(2.0)	 **8**	72

[a]Conditions as under **Table I**, with 2.0 equivalents of NaOH. [b]Isolated yields after column chromatography.

139.42, 148.40; IR: (Neat): 3063, 3030, 2925, 2802, 1602, 1518, 1494, 1452, 1345, 1245, 1110, 1073, 973, 859, 843, 745, 699 cm^{-1}; LRMS for $C_{21}H_{20}N_2O_2$ (M^+): Calcd: 332.15, Found: 332.58.

Dibenzyl-(4-chlorobenzyl])amine 5i: ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.48 (s, 2H), 3.52 (s, 4H), 7.20-7.38 (m, 14H); ^{13}C NMR (50 MHz, $CDCl_3$): 57.82, 58.56, 127.64, 128.93, 129.01, 129.38, 130.69, 138.81, 139.94, 140.04; IR (Neat): 3029, 2927, 2799, 1491, 1451, 1370, 1092, 1015, 833 cm^{-1}; LRMS for $C_{21}H_{20}$ClN $(M + H)^+$: Calcd: 322.14, Found: 322.15.

Dibenzyl-(2-chlorobenzyl)amine 5l: ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.58 (s, 4H), 3.68 (s, 2H), 7.19-7.40 (m, 14H); ^{13}C NMR (50 MHz, $CDCl_3$): 55.27, 58.86, 127.35, 127.56, 128.49, 128.87, 129.35, 129.54, 129.92, 130.89, 140.01; IR (Neat): 3062, 3028, 2925, 2797, 1493, 1445, 1370, 1242, 1120, 1051, 971, 750, 698 cm^{-1}; LRMS for $C_{21}H_{20}$ClN $(M)^+$: Calcd: 321.13; Found: 321.82%.

1, 1′-bis(4-Morpholine)-*p*-xylene 6: ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.40-2.45 (t, *J* = 4.6, 8H), 3.47 (s, 4H), 3.67-3.72 (t, *J* = 3.8, 8H), 7.26 (s, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 54.25, 63.80, 67.63, 129.16, 129.74, 130.07, 137.27; IR (KBr): 2928, 2865, 2804, 1449, 1349, 1312, 1265, 1113, 1071, 1006, 910, 864, 791, 769 cm^{-1}; LRMS for $C_{16}H_{24}N_2O_2$ $(M + H)^+$; Calcd: 277.19, Found: 277.17.

1, 1′-bis(Dibenzyl amine)-*p*-xylene 7: ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.53 (s, 12H), 7.18-7.41 (m, 24H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 58.37, 58.62, 127.49, 128.86, 129.27, 129.42, 138.84, 140.09, 140.36; IR: (KBr) 3025, 2923, 2800, 1493, 1449, 1364, 1240, 1116, 1073, 1026, 976, 961, 911, 875, 825, 772, 751, 737 cm^{-1}; LRMS for $C_{36}H_{36}N_2$ $(M + H)^+$: Calcd: 497.30, Found: 497.30.

1, 1′-bis(4-morpholine)-*o*-xylene 8: ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.39-2.43 (t, *J* = 4.6, 8H), 3.61 (s, 4H), 3.63-3.68 (t, *J* = 4.6, 8H), 7.16-7.22 (m, 2H), 7.25-7.32 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 54.27, 61.07, 67.61, 127.34, 130.84, 137.57; IR: (Neat) 2956, 2852, 2807, 1453, 1395, 1351, 1308, 1281, 1265, 1118, 1070, 1034, 1006, 914, 867, 804, 752 cm^{-1}; LRMS for $C_{16}H_{24}N_2O_2$ $(M + H)^+$,Calcd: 277.19, Found: 277.33.

Conclusion

In conclusion, a highly efficient method for synthesis of various tertiary amines including *N*,*N*-

bis(amination) of 1,1′-dibromo-*p*- and *o*-xylenes, are developed. The simplicity, generality, reagents used for the current transformation are inexpensively available in a common chemical laboratory. These reactions are dually promoted under ambient conditions, without use of heavy metal catalysts and solid supports[10] are the advantages of the present procedure for the synthesis of tertiary amines.

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