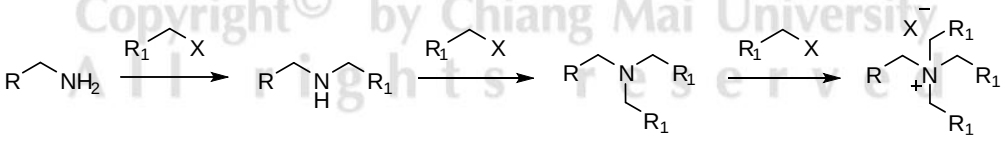
CHAPTER 3

Development of One-Pot *In Situ* Oxidation/Reductive Amination of Benzyl Halides under Solventless and Ultrasonic Irradiation

3.1 Introduction

Amines are very important organic compound that are widely used in both laboratory research and industrial production [239,240]. Amines and their derivatives are popularly used as building blocks for a vast organic substrates [241], essential starting material for pharmaceuticals [242,243], complex catalyst [244,245], and biological active compounds [246].

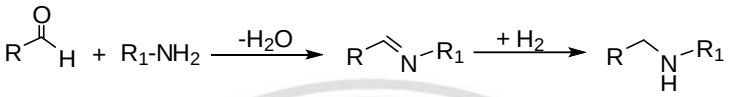
Although alkylation of amines with alkyl halides is the most simple and straightforward route toward *N*-alkylated amines, competing overalkylation often gives rise to product mixtures which complicates purification and results in low product yield (Scheme 3.1) [247]. While several attempts have been made to suppress the problem [239], selectivity of monoalkylation remains difficult to control with highly reactive alkylating agents or strongly nucleophilic amines [247-251].



Scheme 3.1 *N*-alkylation of amine

Reductive amination is the most applicable methods for preparation secondary or tertiary amines [252-255]. Generally, reductive amination is described as a reaction of the carbonyl compound and amine in the present of a reducing agent (Scheme 3.2). Common reducing agents that used in such reaction are borohydride based in the presence of Brønsted or Lewis acids. These reported reagent system include

$NaBH_4$/acetic acid [256], $NaBH_4/H_2SO_4$ [257], $NaBH(OAc)_3$/acetic acid [253], $NaBH_3CN$ [258,259], $NH_3BH_3/Ti(O^iPr)_4$ [260], *N*-methylpyrrolidine zinc borohydride [261], $NaBH_4$/ cellulose sulfuric acid [262], $NaBH_4$/silica phosphoric acid [263], $NaBH_4$/silica chloride [264], $NaBH_4$/Amberlyst 15 [265] and $NaBH_4$/Montmorillonite clays [266].



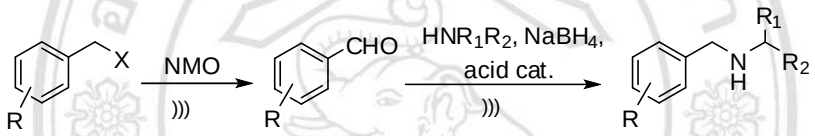
Scheme 3.2 Reductive amination

The above mentioned methods are mostly developed for only a pair of starting carbonyl compounds and amines which proceed directly within one step. A special case of reductive amination using other functional organic compounds beyond an aldehyde type is rare. Taylor and co-workers reported the one-pot oxidation-imine formation/reduction sequence for conversion of alcohols into amines. They carried out MnO_2 as oxidizing agent for imine formation and used polymer-supported cyanoborohydride in the present of acetic acid additive as reducing system [267]. This method is also established as the first report for the combination of a chemical oxidation and reduction in the preparation of amine compounds. Recently, Saxena and co-workers also developed a one-pot oxidation/reduction sequence for conversion of alcohol into amine. This route comprised of an in *situ* oxidation of alcohol using the 4-hydroxy-2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO)−[bis(acetoxy)iodo]-benzene (BAIB) as oxidizing system and reductive amination using Hantszch ester (HEH)−BINOL-derived phosphoric acid in 1,3-dimethyl-3,4,5,6-tetrahydro-2-pyrimidinone (DMPU) as reducing system [268]. In connection with efforts to use a combination of chemical oxidation and reduction, there are no reports of the use of organic halide involving with one-pot oxidation/reductive amination to produce amine compounds. It is much attention to desired a protocol that required more green manipulation which using cheap and environmental friendly reducing agent, no need of organic solvent, allowing to minimize reaction time and simple reaction work-up.

In the last decades, ultrasound-assisted organic synthesis has emerged as “green” methodology which is applied in many organic synthetic routes. Sonochemistry

enhances or promotes chemical reactions and mass transfer by cavitational collapsed phenomena [98]. It may thus increase reaction rates in heterogeneous or partially-miscible substrates reactions make this reduce mass transfer limitations. Many organic reactions have been reported to proceed efficiently under a combination of solvent-free conditions and ultrasonic irradiation [220,269-271]. This methodology led to noticeable advantages for high efficiency, reduction in the reaction time, low cost, low waste and low energy requirements, which could be considered as an economic and eco-friendly approach (green chemistry).

In this present work therefore report a new one-pot and solvent-free *in situ* oxidation/ reductive amination for conversion of benzylic halides into amines under ultrasonic irradiation together with a range of amines (Scheme 3.3).



Scheme 3.3 Ultrasonic-assisted synthesis of amines by *in situ* oxidation/reductive amination from benzylic halides

3.2 Experimental

3.2.1 Chemicals

The chemical were purchased and used without further purification; Aniline (98.5%, BDH, England), Anisidine (99%, Aldrich, Germany), Benzylamine (99%, Sigma-Aldrich, Germany), Benzyl bromide (98%, Aldrich, Germany), Benzyl chloride (≥99%, MERCK, Switzerland), Butylamine (99%, BDH, England), Celite 545 (Fluka, Switzerland), 4-Chlorobenzyl chloride (95%, Aldrich, India), 1-(Chloromethyl) naphthalene (≥97%, Aldrich, USA), Cyclopropylamine (≥98%, Fluka, Germany), Cyclohexylamine (99%, BDH, England), Isobutylamine (99%, ACROS, Belgium), 4-Methoxybenzyl chloride (98%, Aldrich, Germany), 3-Methoxybenzyl chloride (97%, Aldrich, USA), 2-Methylbenzyl chloride (99%, Aldrich, China), 3-Methylbenzyl chloride (98%, Aldrich, Belgium), 4-Methylbenzyl chloride (99%, Aldrich, Germany), 4-Methymorpholine *N*-oxide (NMO, 97%, Aldrich, USA), *N*-Methylmorpholine (>98%, Fluka, Switzerland), Montmorillonite K-10 clay (Aldrich, Germany), Morpholine,

≥99% (Fluka, Switzerland), 4-Nitroaniline (98.5%, Loba Chemie, India), 4-Nitrobenzyl chloride (99%, Aldrich, USA), Piperidine (99%, Sigma-Aldrich, Germany), Potassium idodide (KI, ≥99%, Sigma-Aldrich, Germany), Silica gel 60 (70-230 mesh, MERCK, Switzerland) and Sodium borohydride ($NaBH_4$, ≥96%, Fluka, Switzerland). Dichloromethane (DCM, Commercial grade, RCI Labscan, Thailand), Ethyl acetate (EtOAc, Commercial grade, RCI Labscan, Thailand), Hexane, Commercial grade (RCI Labscan, Thailand) and Methanol (MeOH, Commercial grade, Fluka, Switzerland) were purchased and were purified by distillation at normal pressure before use.

3.2.2 Instruments

Ultrasonic bath (Elma, S 30H Elmasonic, Germany). Analytical thin-layer chromatography (TLC) was performed with silica gel 60 F254 aluminum sheets (MERCK, Switzerland). NMR measurements were conducted on a Bruker AVANCTM (100 and 400 MHz for ^{13}C and ^{1}H, respectively) using chloroform-d ($CDCl_3$) as the solvent and tetramethylsilane (TMS) as an internal standard. Chemical shifts were reported in parts per million (ppm, δ) downfield from TMS. Splitting patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br), and doublet of doublet (dd). The Gas chromatography (GC) analysis was equipped with an HP model 6890A equipped with an HP-INNOWAX Polyethylene Glycol capillary column (30 m x 0.25 mm i.d., film thicknes 0.25 µm, temp 40-260/270 °C, Agilent Technologies, USA) with FID detector. The Gas Chromatography–Mass Spectrometry (GC-MS) analysis was perform with an HP model 6850 gas chromatograph equipped with an HP-5MS (5% phenyl-polymethylsiloxane) capillary column (30 m x 0.25 mm i.d., film thickness 0.25 µm, Agilent Technologies, USA) interfaced to an HP model 5973 mass-selective detector. EI mass spectra were collected at 70 eV ionization voltages over the range of m/z 35-350 and electron multiplier voltage was 2000 V. The mass spectra were compared with mass spectra of individual components with the reference mass spectra in the Wiley 275 and NIST 98 databases.

3.2.3 NMO Oxidation of Benzyl Chloride under Solventless and Ultrasonic Irradiation

All reaction were performed by sonication of a mixture containing benzyl chloride (0.046 ml, 0.4 mmol), KI (6.6 mg, 0.04 mmol) with various amount of NMO (0.1, 1.5, 2.0 and 3.0 mmol) at 80 °C for prescribed time. The crude mixtures were then analyzed by gas chromatography technique to obtain the %conversion of reaction.

3.2.4 Optimization of Oxidative/Reductive Amination of Benzyl Chloride with Various Acid Catalysts

In a glass sealed vessel, benzyl chloride (0.046 ml, 0.4 mmol), NMO (0.070 g, 0.6 mmol) and KI (6.6 mg, 0.04 mmol) were mixed and irradiated with ultrasonic bath at 80 °C for 30 min. The complete formation of aldehyde was monitored by TLC (1:9 ethyl acetate/hexane). A 100 mg of Montmorillonite K-10 was then added to the same reaction vessel followed by addition of benzylamine (0.065 ml, 0.6 mmol) and $NaBH_4$ (0.030 g, 0.8 mmol). The reaction was accomplished by incubated in ultrasonic bath at 80 °C for further 30 min. The reaction mixture was then allowed to cool at room temperature. The crude mixture was collected and purified by short column chromatography on silica gel (1:9 ethyl acetate/hexane) to give pure amine product.

3.2.5 Synthesis of Amines by *In Situ* Oxidative/Reductive Amination under Solventless and Ultrasonic Irradiation

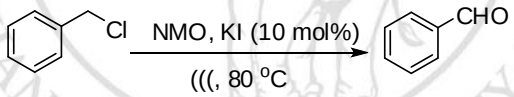
Unless otherwise specified, halide compound (0.4 mmol), NMO (0.6 mmol), and KI (0.04 mmol) were mixed in a 5 mL glass vial. The mixture was then irradiated in a water bath of the 37 kHz ultrasonic cleaner (Elmasonic S 30H) at 80 °C for 30 min. After that, Montmorillonite K-10 (100 mg), amine (0.6 mmol), and $NaBH_4$ (0.030 g, 0.8 mmol) were added, followed by sonication at 80 °C for further 30 min. After cooling down to room temperature, the crude mixture was purified by applied directly to a short column chromatography (1:9 ethyl acetate/hexane) to afford pure product. All known products were characterized by ^{1}H-NMR, IR and GC-MS techniques and their spectroscopic data were consistent with those reported in the literature.

3.3 Results and Discussion

3.3.1 NMO Oxidation of Benzyl Chloride under Solventless and Ultrasonic Irradiation

We have described the rapid conversion of benzyl halides into corresponding aldehydes using NMO in an ionic liquid in the present of KI catalyst under microwave irradiation [272] in Chapter 1. In this chapter, the oxidation of benzyl chloride was first investigated under solventless and ultrasonic irradiation. Therefore, the oxidation of benzyl halide with NMO under neat conditions was optimized in order to obtain the optimum amount of NMO to achieve high conversion within a reasonable time. Oxidation of benzyl chloride was chosen as the model reaction. Typically, a mixture of benzyl chloride, 10 mol% of KI, with various amounts of NMO was sonicated at 80 °C and the progress of the reaction was monitored by GC analysis.

Table 3.1 Optimization for NMO oxidation of benzyl halide using solventless condition under ultrasonic irradiation[a]

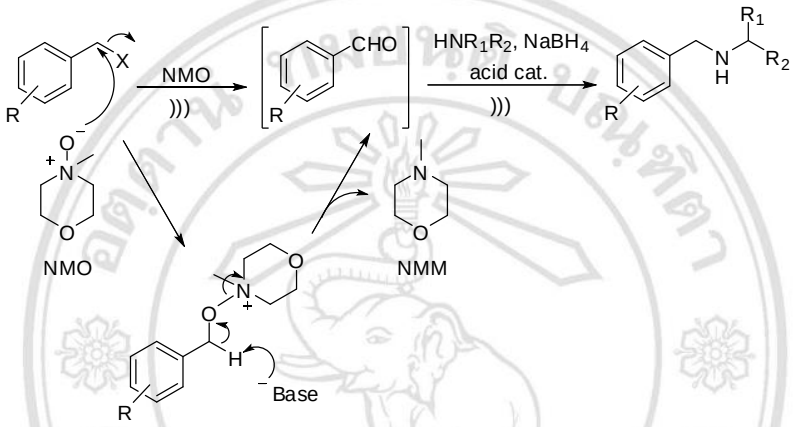


Entry	NMO (equiv.)	Time (min)	Conversion (%)[b]
1	1.0	90	74
2	1.5	30	100
3	2.0	15	97
4	3.0	5	98

[a] Reaction condition: 0.4 mmol benzyl chloride, stoichiometric amount of NMO, KI (10 mol), sonication at 80 °C.
[b] GC conversion

As can be seen in Table 3.1, it was found that the mole equivalent of NMO was played an important role in the kinetic of oxidation reaction of benzyl chloride. Three-fold excess of NMO, the reaction proceed rapidly within 5 min, whereas the reaction rate was much slower with 1 equiv. of NMO (> 90 min). Nevertheless, since the oxidation

of benzyl chloride with NMO will be released *N*-methylmorpholine (NMM) which well-known as organic base as a by-product. Therefore, use of excess amount of NMO leading to release high amount of NMM in the reaction mixture which will be the interference in the subsequent reductive amination (Scheme 3.4). According to NMM may disturb the acidic condition in the next step formation of imine intermediate. This is thus reasonable to minimize the amount of NMO in the reaction. For this case, 1.5 mole equivalent of NMO was selected with an acceptable reaction time.



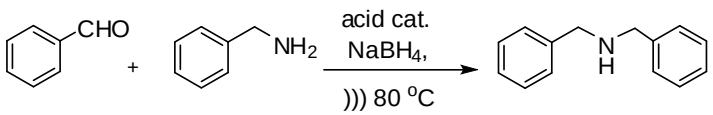
Scheme 3.4 Proposed mechanism of solvent-free *in situ* oxidation/reductive amination for conversion of benzyl halides into amines

3.3.2 Examination of Oxidation/Reductive Amination of Benzyl Chloride with Various Acid Catalysts

In continuation of my work, the next experiment was therefore investigated the *in situ* oxidation/reductive amination for conversion of benzyl halides into amines using NMO as oxidizing agent to generate aldehyde. The reaction is then continuously formed imine intermediate and was reduced by a system of $NaBH_4$ and Lewis acid catalyst to give amine product. To test the viability of this idea, the reaction of benzyl chloride and benzylamine was selected as model reaction.

With the optimized condition of an in *situ* oxidation of benzyl chloride in hand, our attention turned to combining the sequence with a reductive amination. The successful reductive amination is mostly undergone by acid catalyzed mechanism. It is noted that the selection of an appropriate acids catalyst is desirable. Therefore, different acidic solid catalysts were next examined (Table 3.2).

Table 3.2 Optimization for reductive amination using solventless condition under ultrasonic irradiation [a]



Entry	Catalyst	Isolated yield (%)
1	Amberlyst 15	77
2	Silica gel	70
3	Montmorillonite K-10	88
4	Celite	44
5	-	16

[a] Reaction condition: benzyl chloride (0.4 mmol), KI (10 %mol), NMO (0.6mmol), Benzylamine (0.6 mmol), $NaBH_4$ (0.8 mmol) and 100 mg of solid catalyst.

In typically, benzyl chloride was *in situ* oxidized with NMO under solventless and irradiation at 80 °C for 30 min. The completion of oxidation was detectable by TLC. And then, 100 mg of solid catalyst was added into same reaction vessel, followed addition of benzylamine and $NaBH_4$. The reaction vessel was established in ultrasonic bath at 80 °C and kept for 30 min to complete reaction. As the results shown in Table 2, the use of Amberlyst 15 and silica gel provided 70% and 77% yield of dibenzylamine, respectively. Celite was worse to catalyze the reaction which allowed only 44% yield. The highest yield was observed with Montmorillonite K-10 clay, gave 88% yield of dibenzylamine product. Interestingly, in the absence of acid catalyst, reaction was failed to produce desired amine product.

3.3.3 Synthesis of Amines by Solventless and One-pot *In Situ* Oxidation/Reductive Amination from Benzylic Halides

Having established the optimum condition for one-pot *in situ* oxidation/reductive amination sequence, further investigation on the scope and generality of the reaction was performed by reacting a range of benzyl halides (X = Cl, Br) with a variety of amines including benzylic, aliphatic, and aromatic amines. A certained amount of halide compound, NMO, and KI (0.04 mmol) were mixed in a 5 mL glass vial. The

mixture was then irradiated in a water bath of the ultrasonic bath at 80°C for 30 min. After that, Montmorillonite K-10 (100 mg), amine and $NaBH_4$ were added, followed by sonication at 80 °C for further 30 min. The crude mixture was purified by applied directly to a short column chromatography to afford pure amine product.

According to Table 3.3, benzyl chloride together with a series of primary, secondary and aliphatic amines were smoothly converted to corresponding secondary and tertiary amines products in good to excellent yields (entries 1-6) under solvent-free condition and ultrasonic irradiation. Side products from overalkylation and aldehyde reduction were not observed. Unfortunately, under the standard condition, the reaction of benzyl chloride with less reactive aromatic amine; aniline, *p*-methoxyaniline and *p*-nitroaniline gave relative low yields of the monoalkylated amines. They gave only 53%, 52% and 48% yield of *N*-benzylaniline, *N*-benzyl-4-methoxyaniline and *N*-benzyl-4-nitroaniline, respectively. This may due to the electronic property of aniline and electro-poor aniline make them be less nucleophilicity.

The yield of *N*-benzylaniline was greatly improved from 53% to 87% with prolonged reaction time for reductive amination step using twice fold-excess of amine (entry 7). Under similar condition, *N*-benzyl-4-methoxyaniline was also obtained in good yield (88%, entry 8). However, due to the strong electronwithdrawing effect of nitro substituted group, the least reactive 4-nitroaniline gave the desired *N*-benzyl-4-nitroaniline only 55% yield along with 40% of benzyl alcohol by product (entry 9). It can be explained that low reaction rate of 4-nitroaniline allowed the free benzaldehyde molecule in the reaction tended to react with reducing agent, $NaBH_4$, caused the obtaining of reduced product alcohol. Slightly better product yields were obtained with the more reactive benzyl bromide. Since benzyl bromide is a good substrate for NMO oxidation, addition of KI catalyst is not necessary. The corresponding amine products obtained from reaction of benzyl bromide with a range of amine were found to be high yield (entries 10-11).

In agreement with my previous study (chapter 2), the rate of benzyl halide oxidation was depended on electronic nature of the substituents on aromatic ring. Substrates with electron-donating groups were more reactive than those containing electron-withdrawing groups. Benzyl chlorides with electron-donating groups such as $–OCH_3$

and $-CH_3$ were converted readily to the corresponding aldehydes leading to relatively high yield of amine products (entries 14-28). However, the oxidation of 4-nitrobenzyl chloride was rather sluggish and only 77% yield of desired amine was obtained even prolonged oxidation step (entry 29). 1-(Chloromethyl) naphthalene was also investigated with benzylamine and n-butyl amine, obtained *N*-(naphthalen-1-ylmethyl)butylamine and *N*-(naphthalen-1-ylmethyl)benzylamine in 83% and 91%, respectively.

Table 3.3 Synthesis of amines *via in situ* oxidation/reductive amination of benzylic halides

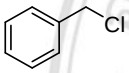
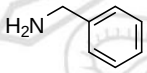
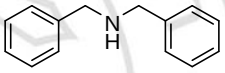
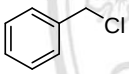
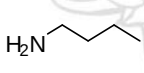
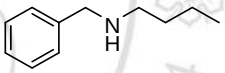
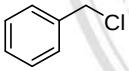
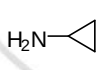
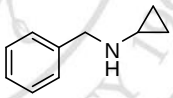
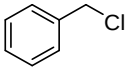
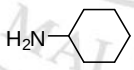
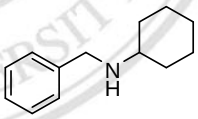
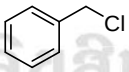
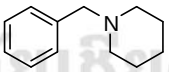
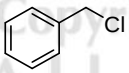
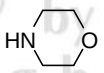
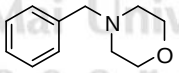
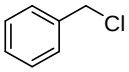
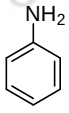
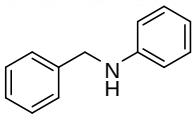
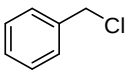
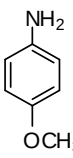
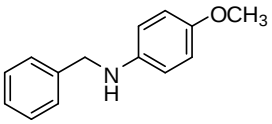
Entry	Halides	Amines	Products	Yield (%)
1				89
2				88
3				85
4				87
5				86
6				96
7				87[a]
8				88[a]

Table 3.3 Synthesis of amines *via* in *situ* oxidation/reductive aminationof benzylic halides (continued)

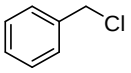
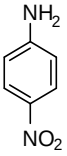
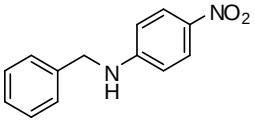
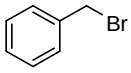
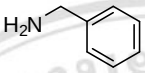
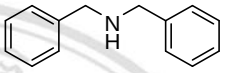
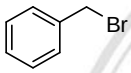
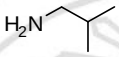
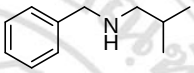
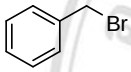
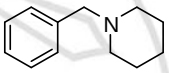
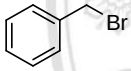
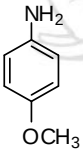
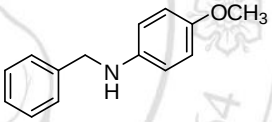
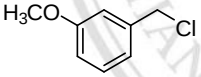
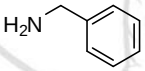
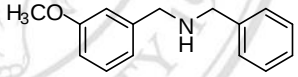
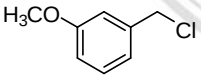
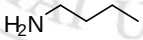
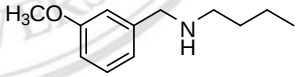
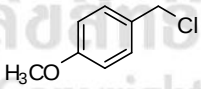
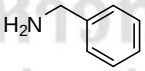
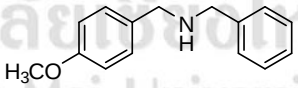
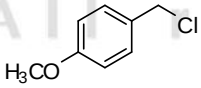
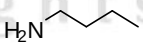
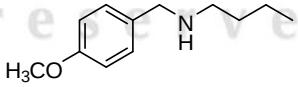
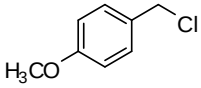
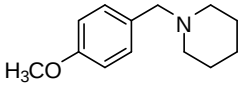
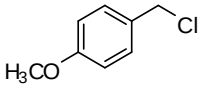
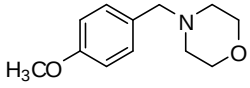
Entry	Halides	Amines	Products	Yield (%)
9				55[a]
10				91[b]
11				86[b]
12				91[b]
13				93[a,b]
14				80
15				94
16				92
17				92
18				95
19				92

Table 3.3 Synthesis of amines *via* in *situ* oxidation/reductive amination of benzylic halides (continued)

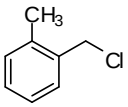
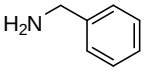
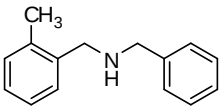
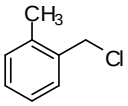
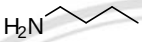
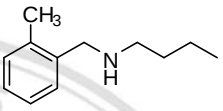
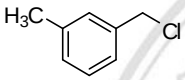
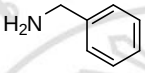
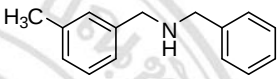
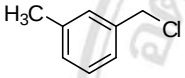
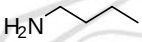
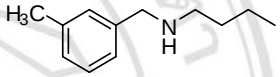
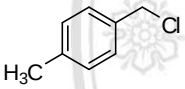
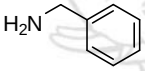
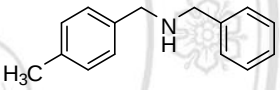
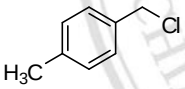
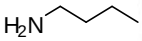
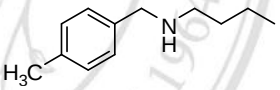
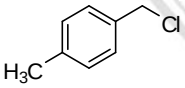
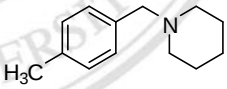
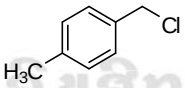
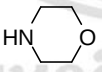
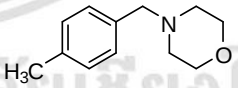
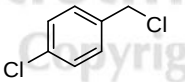
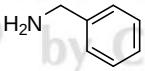
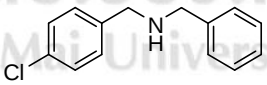
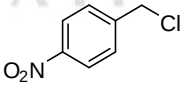
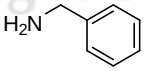
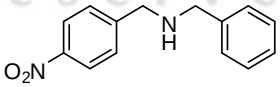
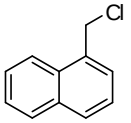
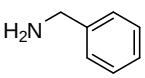
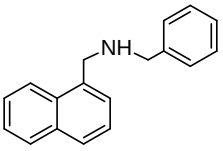
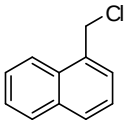
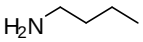
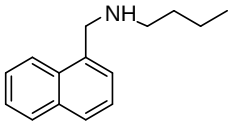
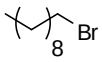
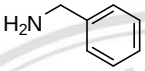
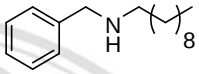
Entry	Halides	Amines	Products	Yield (%)
20				83
21				86
22				82
23				89
24				80
25				86
26				88
27				92
28				82
29				77
30				83

Table 3.3 Synthesis of amines *via* in *situ* oxidation/reductive amination of benzylic halides (continued)

Entry	Halides	Amines	Products	Yield (%)
31				91
32				91[c]

[a] Reductive amination was performed at 80°C for 60 min using amine 0.8 mmol.
[b] KI was not added
[c] Based on conversion of dodecyl bromide

It is noted that although this sequence reaction can be performed with other less reactive primary aliphatic halides, the reaction rate of oxidation step is much slower that the primary benzylic halides and generally requires longer reaction times for completion of the oxidation reaction. For example, dodecyl bromide was oxidized with 3.0 equiv. of NMO under ultrasonic irradiation at 80 °C for 60 min, occurring 54% conversion of dodecaldehyde was obtained. After that, the reaction was subsequently reacted with benzylamine under solventless reductive amination condition at 80 °C for 60 min leading to 91% yield of *N*-benzyldodecan-1-amine could be isolated based on conversion of dodecyl bromide (entry 32).

Nevertheless, attempt to perform the solvent-free *in situ* oxidation/reductive amination sequence with secondary halides such as cyclohexyl bromide and 3-bromocyclohene failed to give satisfactory result due to competitive elimination during NMO oxidation.