Aqueous *N*-alkylation of amines using alkyl halides: direct generation of tertiary amines under microwave irradiation

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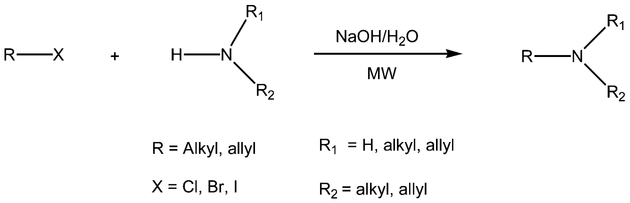
Received 3rd February 2004, Accepted 20th February 2004
First published as an Advance Article on the web 17th March 2004

Direct formation of tertiary amines *via* *N*-alkylation of amines by alkyl halides occurs in aqueous media under microwave irradiation. This greener alternative is also a useful and powerful method to construct C–N bond without using any transition metal catalysts.

Introduction

C–N bond formation is one of the most important transformations in organic synthesis. Amines are widely used as intermediates to prepare solvents, fine chemicals, agrochemicals, pharmaceuticals and catalysts for polymerization.[1] The nucleophilic attack of alkyl halides by primary and secondary amines is useful for the preparation of tertiary amines but the reaction requires longer reaction time and gives rise to a mixture of secondary and tertiary amines;[2] thermal reaction between alkyl halides and amines in the presence of base requires longer reaction time period and affords lower yields of desired products.[3,4] Although the relatively similar Ullmann and Goldberg reaction using copper catalysts,[5,6] and the Pd catalyzed Buchwald–Hartwig reaction have been studied,[7] transition metal-free microwave-assisted amination of electron-rich benzylic halides has been largely unexplored.[8]

Microwave (MW) irradiation has attracted considerable attention for rapid synthesis of a variety of organic compounds because of the selective absorption of microwave energy by polar molecules.[9] MW irradiation has been successfully utilized in the formation of a variety of carbon–heteroatom and carbon–carbon bonds.[10] During our ongoing efforts to explore organic syntheses using microwave irradiation,[11] we envisioned that the nucleophilic substitution reaction of alkyl halides with amines might be accelerated by microwave energy because of their polar nature. We wish to report herein an environmentally-friendlier synthesis of tertiary amines *via* direct *N*-alkylation of primary and secondary amines by alkyl halides under microwave irradiation that proceeds in water without any phase transfer reagent[12] (Scheme 1).

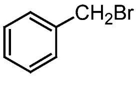
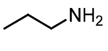
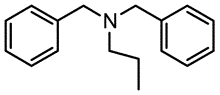
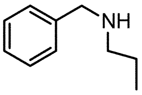
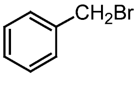
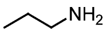
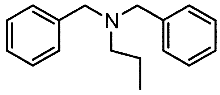
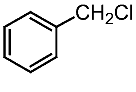
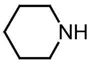
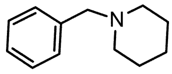
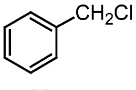
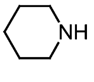
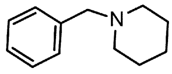


Scheme 1

Results and discussion

In order to ascertain the comparative effectiveness of microwave heating with respect to conventional heating, a few representative reactions were conducted using conventional heating in an oil bath. Mixtures of alkyl halides and amines, in the presence of one equivalent of aqueous NaOH, were heated in a round-bottom flask for a period of 12 hours. On the other hand, the same reactions proceeded to completion under microwave irradiation condition within 20 minutes (Table 1). Further, it was observed that under conventional heating mixtures of products were formed (entry 1) in

Table 1 *N*-Alkylation of amines by alkyl halides using MW and conventional heating

Entry	Halide	Amine	Reaction conditions	Products and yields[a]
1			Heated at 50 °C, 12 h	 45 %  20 %
2			MW, 45–50 °C, 20 mins	 95 %
3			Heated at 95 °C, 12 h	 70 %
4			MW, 95–100 °C, 20 mins	 92 %

[a] Benzyl alcohol was observed by GC/MS analysis in entry 1 and entry 3.

DOI: 10.1039/b401620c

addition to small amounts of side products such as benzyl alcohol (entries 1 and 3) as a result of hydrolysis of the alkyl halides in alkaline medium.[13]

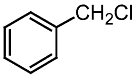
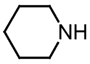
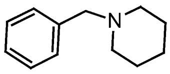
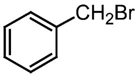
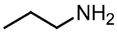
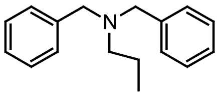
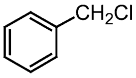
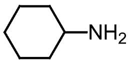
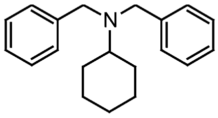
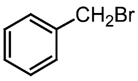
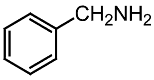
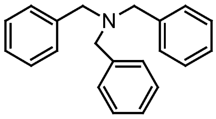
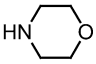
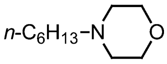
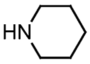
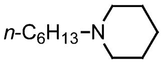
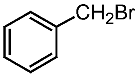
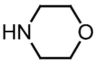
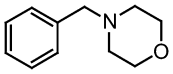
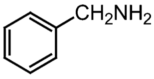
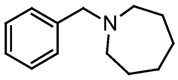
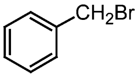
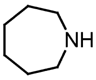
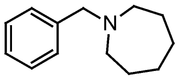
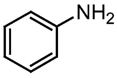
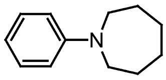
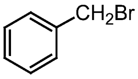
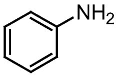
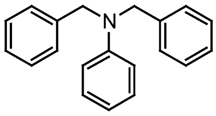
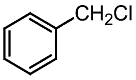
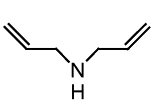
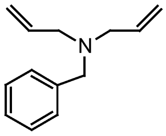
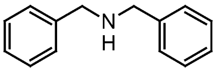
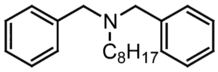
The microwave-assisted reaction was also examined under solventless conditions using water, polyethylene glycol with an average molecular weight of 300 (PEG 300) and acetonitrile as the reaction medium. Reactions under solventless conditions afforded very low yield (less than 20%) because of the insolubility of the base; volatile acetonitrile as reaction medium only gave rise to moderate products yields (50–70%); PEG 300 is a promising medium to replace volatile organic solvents for green chemical synthesis under microwave irradiation[14] but more expensive compared to water. Water is a good absorber for microwave energy[15] and has been successfully employed as solvent for various organic syntheses,[16] it turned out to be one of the best choices in view of its relatively environmentally-friendly characteristics.

The reaction is general in nature and is applicable to aliphatic halides and both aromatic and aliphatic amines as summarized in Table 2. Interestingly, the intramolecular double-alkylation of primary amines occurs in reaction with dihalides such as 1,6-dibromohexane thus providing a potentially useful approach to assemble cyclic amines in a single step (entries 8 and 10, Table 2).

Conclusion

In summary, a direct *tert*-amine forming protocol has been developed that proceeds rapidly *via* microwave-assisted *N*-alkylation of amines by alkyl halides. Shorter reaction times, higher product yields and aqueous reaction medium are some of the relevant advantages that render this procedure a greener alternative to conventional chemical synthesis.

Table 2 Aqueous *N*-Alkylation of amines using microwave irradiation[a]

Entry	Halide	Amine	Product amine[b]	Isolated yields (%)[c]
1				92
2				95
3				86
4				87
5	n-$C_6H_{13}Br$			70
6	n-$C_6H_{13}Br$			74
7				70
8	$Br(CH_2)_6Br$			71
9				90
10	$Br(CH_2)_6Br$			75
11				84
12				60
13	n-$C_8H_{17}I$			73

[a] All reactions were carried out at 1 mmol scale, MW power 250–300 Watt for 20–30 mins. [b] The NMR spectra of all synthesized amines are in accord with the literature. [c] Isolated yields based on starting halides (for entries 2, 3, 4, and 11, a halide : amine ratio of 2 : 1 has been used; 2 equivalents of base were used for entries 2, 3, 4, 8, 10 and 11).

Experimental

General

All the starting amines and alkyl halides were obtained from Aldrich Chemical Co. and were used as such. The synthesized products were identified by GC/MS qualitative analysis based on the Wiley library database using an HP 6890 GC system with an HP 5872 Mass selective detector. The identities were further confirmed by ^{1}H and ^{13}C NMR spectra that were recorded for the pure products in chloroform-*d* ($CDCl_3$) with TMS as internal reference using a Bruker 300 MHz NMR spectrometer.

Typical procedure

The representative experimental procedure is as follows: 1 mmol benzyl chloride (0.127 g), 1 mmol piperidine (0.085 g) and 1.1 mmol NaOH in water (2.20 mL 0.5 M solution) were placed in a round-bottom glass flask equipped with a condenser and a magnetic stirrer. The flask was placed in a CEM Discover Focused Microwave Synthesis System, and subjected to MW irradiation at 80–100 °C (power 250 Watt) for 25 minutes. After completion of the reaction (monitored by TLC), the product was extracted into ethyl acetate. Removal of the solvent under reduced pressure, followed by flash column chromatography using hexane–ethyl acetate (4/1) as eluent afforded 1-benzylpiperidine (0.161 g, 92%) as product as confirmed by satisfactory ^{1}H and ^{13}C NMR spectra.

Acknowledgments

We wish to thank Tom Deinlein, Julius Enriquez, Albert Foster and Amy Zhao for their assistance. This research was supported, in part, by the Postgraduate Research Program at the National Risk Management Research Laboratory administered by the Oak Ridge Institution for Science and Education through an interagency agreement between the U.S. Department of Energy and the U.S. Environmental Protection Agency.

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