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Rapid oxidation of organic halides with *N*-methylmorpholine N-oxide in an ionic liquid under microwave irradiation

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ABSTRACT

A simple and rapid method for the conversion of organic halides into carbonyl derivatives is developed via microwave-assisted oxidation with *N*-methylmorpholine N-oxide in an ionic liquid. A variety of halide substrates are oxidized to the corresponding products in good to excellent yields in short reaction times. The ionic liquid is recovered and reused in several reaction cycles without any significant loss in activity.

Direct oxidation of organic halides to the corresponding aldehydes and ketones is considered an important functional group transformation in organic synthesis, since the products are often important building blocks for the preparation of fine chemicals both in the laboratory and industrial applications. Currently, there are many methods available for such a conversion. The Hass–Bender[1] and Sommelet[2] reactions are two well-known classical methods, while oxidations with other reagents such as dimethyl sulfoxide (DMSO), namely the Kornblum reaction,[3–6] $NaIO_4$–DMF,[7] IBX,[8] H_5IO_6 in $[C_{12}mim][FeCl_4]$,[9] H_2O_2,[10,11] and amine N-oxide[12–17] have also been reported.

In many cases, carbonyl derivatives can be obtained in good yields, especially from reactive primary and secondary organic bromides (where R = allyl, benzyl). However, some limitations such as harsh reaction conditions, toxic reagents, long reaction times, and difficult work-ups and purifications still hinder the applicability of many protocols. Therefore, the development of a green and efficient method for the direct oxidation of organic halides with a broader substrate scope is highly desirable.

A combination of the two prominent green chemistry principles: microwaves (MW) and ionic liquids (IL) has received considerable attention.[18] Microwave-assisted synthesis has been proven to be an extremely effective method for a variety of organic reactions.[19] Compared to conventional heating, the use of microwaves for the activation of chemical reactions often dramatically shortens reaction times, increases product yields, and enhances the product selectivity and purity. However, microwave heating usually requires a polar solvent as the energy transfer medium to obtain uniform heating. ILs are alternative solvents which have been widely described as green synthetic media because of their negligible vapor pressure, high thermal stability, non-flammability, reusability, and good solvating ability.[20] Owing to their dipolar characteristics, ILs couple very efficiently with microwave energy. This effect offers significant advantages when using ILs as reaction media in microwave-assisted organic transformations.

Our interest in mild oxidations with *N*-methylmorpholine N-oxide (NMO) has led us to develop a facile and efficient protocol for the oxidation of organic halides using a combination of microwave heating and an ionic liquid. Similar to the Kornblum reaction, where DMSO was employed as the oxygen donor,[6] oxidation with an amine N-oxide proceeds via nucleophilic substitution of the organic halide with the oxygen of the amine N-oxide to form an *N*-alkoxy salt. Subsequent proton abstraction at the carbon carrying the oxygen leads to the formation of a carbonyl product.

According to the Ganem oxidation with an amine N-oxide oxidant,[14] DMSO was found to be the best solvent due to its ability to enhance nucleophilic substitution reactions. However, the high water solubility of this solvent and its high boiling point create problems in the separation and purification of the oxidized products. It is therefore rational that apart from the non-volatile and non-flammable properties which are suited to MW conditions, polar ILs facilitate nucleophilic displacement while offering additional benefits in facilitating work-up and purification.

In our preliminary studies to maximize the product yield, benzyl chloride was chosen as the substrate for optimization of the reaction

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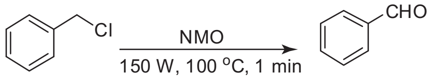
Table 1
Oxidation of benzyl chloride to benzaldehyde[a]



Entry	Solvent	Additive	Yield[b] (%)
1	DMSO	–	37
2	[emim]Cl	–	73
3	[emim]Cl	NaBr	85
4	[emim]Cl	NaI	86
5	[emim]Cl	KBr	83
6	[emim]Cl	KI	91
7	[emim]Cl	CuI	75
8	TBACl	KI	81
9	THPCl	KI	16
10	ChCl-urea	KI	64

[a] Reaction conditions: benzyl chloride (0.4 mmol), NMO (0.8 mmol), additive (10 mol %), DMSO (2 mL) or IL (0.4 g).
[b] Yield based on GC analysis.

conditions. The effects of solvent and additive on the reaction conversion were investigated and the results are summarized in Table 1. It was found that, in the presence of 1-ethyl-3-methylimidazolium chloride, [emim]Cl, the reaction proceeded smoothly to give a twofold product yield compared to DMSO (Table 1, entries 1 and 2). The conversion was further improved in the presence of additives and, the highest yield was obtained with KI (entry 6). Since KI has less ionic lattice energy compared to other salts (KI < KBr < NaI < NaBr < CuI),[21] this presumably allows the more reactive ionic salt to facilitate the S_N2 mechanism of NMO oxidation.

The effect of the ionic liquid type was also examined using tetrabutylammonium chloride (TBACl), trihexyl(tetradecyl)-phosphonium chloride (THPCl), and choline chloride urea (ChCl-urea) as the reaction media (entries 8–10). A relatively good yield of benzaldehyde was obtained in TBACl (entry 8), whereas a lower yield was observed in the case of ChCl-urea (entry 10). Only a trace amount of benzaldehyde was generated in THPCl (entry 9). It should be noted that THPCl incompletely dissolved NMO due to its low polarity. In addition, its electrophilic nature may lead to a competing reaction with the halide substrate in reactions with the oxygen of NMO under MW heating.[22]

The effect of microwave conditions was next investigated by varying the MW power and irradiation time. According to Table 2, an 84% yield of benzaldehyde was obtained using a low MW power in a short reaction time (entry 1). By increasing the MW power from 100 to 150 W (entry 2), the yield was significantly enhanced, representing a great improvement over the yield obtained via the microwave-assisted Kornblum oxidation with DMSO/$NaHCO_3$ (87%).[4] However, prolonged reaction at 150 W for five minutes or on increasing the MW power to 200 W resulted in a slight decrease in the yield, possibly due to leakage of the volatile starting halide and/or the product (entries 3–5).

In an attempt to minimize the amount of NMO used in the oxidation of benzyl chloride, it was found that the product yield decreased from 97% to 82% when decreasing the NMO content from 2 to 1.2 equiv. On consideration that NMO can be generated in situ by reacting *N*-methylmorpholine (NMM) with H_2O_2, the oxidation was also carried out using a combination of NMM (2 equiv) and H_2O_2 (2 equiv). However, only a 68% yield of benzaldehyde was obtained. In the absence of NMO, or in the presence of NMM, no oxidation product was observed indicating NMO to be the stoichiometric oxidant of choice.

Table 2
Effect of the microwave conditions on the oxidation of benzyl chloride[a]

Entry	Microwave power (W)	Exposure time (min)	Isolated yield (%)
1	100	2	84
2	150	2	97
3	150	5	90
4	200	2	92
5	200	1	87

[a] All reactions were carried out with benzyl chloride (0.4 mmol), NMO (0.8 mmol), and KI (10 mol %) in [emim]Cl (0.4 g) at 100 °C.

With optimized reaction conditions in hand, further investigations on the efficiency and the scope of the reaction were performed with a range of different organic halides, and the results are summarized in Table 3. It is clear that various types of primary benzylic halides, especially the less reactive chloride derivatives, could be rapidly oxidized to the corresponding aldehydes in good to excellent yields (entries 1–12). Notably, the reaction times using the microwave method were greatly reduced over those employing conventional heating or room temperature reactions. The reaction rate was also found to be dependent on the electronic nature of the substituents on the aromatic ring. Benzylic chlorides having electron-withdrawing groups on the aromatic ring were less reactive than those with electron-donating groups, and generally required longer times for completion of the reaction (entries 6 and 7). The relatively high yields of these products are noteworthy since they represent the best reported yields for amine N-oxide oxidation. Primary alkyl bromide substrates (entries 13 and 14) were also converted into the corresponding aldehydes in good yields, though longer MW irradiation times were required.

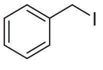
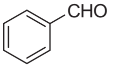
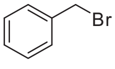
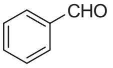
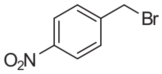
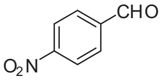
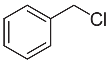
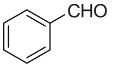
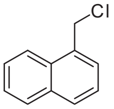
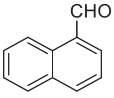
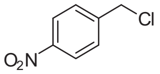
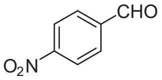
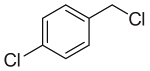
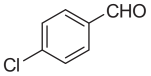
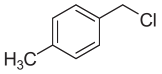
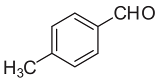
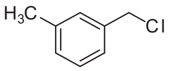
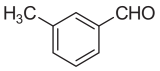
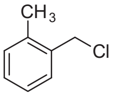
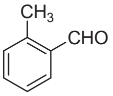
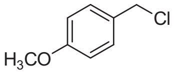
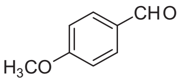
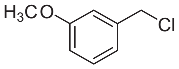
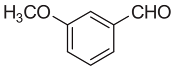
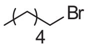
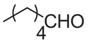
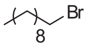
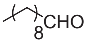
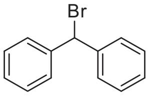
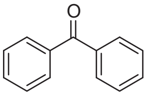
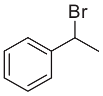
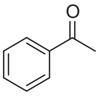
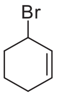
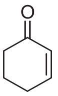
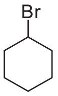
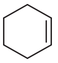
The secondary benzylic bromide, benzhydryl bromide (entry 15) was readily oxidized to benzophenone in high yield. However, the presence of a β-proton in 1-bromoethylbenzene (entry 16) allowed competing elimination to give styrene (44%) along with the desired acetophenone (51%) as detected by GC–MS analysis.

In the case of a secondary allylic bromide, 3-bromocyclohexene was converted into the oxidation product in a relatively low yield due to competing hydrolysis of the substrate to 2-cyclohexenol (entry 17). When these conditions were applied to the secondary alkyl bromide, cyclohexyl bromide (entry 18), cyclohexene was obtained exclusively as the product without formation of the desired ketone. It is plausible that MW irradiation at high temperature may facilitate elimination and hydrolysis of less reactive halides leading to low yields of the corresponding oxidation products.

One of the advantages of using an IL is its potential to function as a recyclable reaction medium. The reusability of [emim]Cl was thus examined in the oxidation of benzyl chloride. After each reaction cycle, the ionic liquid was treated with activated charcoal for decolorization, and was reused in subsequent reactions. According to Table 4, only a slight decrease in the isolated yield of benzaldehyde was observed after six consecutive runs, while [emim]Cl can be recovered effectively in good percentage. Although it has previously been observed that when heating above 200 °C, ionic liquids comprising an alkylimidazolium cation and a halide anion decompose to give an alkyl halide and an alkyl imidazole,[23] in our case, ^{1}H NMR analysis of the recovered IL after nine cycles indicated no such decomposition had occurred. The loss of its efficiency in the latter three runs was probably due to a change in the chemical composition of the IL, which alters its physical characteristics. Indeed, analysis of the chloride ion content by the Mohr method[24] revealed that the amount of chloride in the IL was reduced to 95% and 81% after being reused once and nine times, respectively.

In summary, a facile and efficient procedure for the NMO oxidation of organic halides to carbonyl derivatives has been developed using [emim]Cl as a recoverable solvent under microwave irradiation. Benzylic halides (chloride, bromide, and iodide) and primary alkyl bromides can be rapidly converted into the corresponding aldehydes in good to excellent yields. The use of the IL not only enhances the conversions of the less reactive chloride substrates, but also facilitates the reaction work-up and purification.

Table 3
MW-assisted oxidation of organic halides with NMO in [emim]Cl[a]

Entry	Halide	Product	Time (min)	Isolated yield (%)
1[b]			2	96
2[b]			2	95
3			3	85
4			2	97
5			2	91
6			5	83
7			5	89
8			2	94
9			2	90
10			2	92
11			2	95
12			2	92
13			5	94
14			5	80
15			2	90
16			2	51[c]
17			2	67[c]
18			5	96[c]

[a] All reactions were carried out with halide (0.4 mmol), NMO (0.8 mmol), and KI (10 mol %) in [emim]Cl (0.4 g) using a MW (150 W) at 100 °C.

[b] KI was not used.

[c] Yield based on GC–MS analysis.

General procedure for the microwave-assisted NMO oxidation

All the reactions were performed using a CEM Discover microwave system in a 10 mL microwave vessel. The halide (0.4 mmol), NMO (0.8 mmol), and [emim]Cl (0.4 g), with or without 10 mol % of an additive salt were irradiated at the specified power for the prescribed time. The mixture was allowed to cool, followed by extraction with 1:9 EtOAc/hexane (1 mL × 3). The combined organic layers were dried (Na_2SO_4) and then concentrated in vacuo. The crude material was purified by short column chromatography (silica gel, 1:9 EtOAc/hexane) to afford the pure product.

Table 4
The percentage yield of benzaldehyde and the recovery of [emim]Cl in the oxidation of benzyl chloride[a]

Run	1	2	3	4	5	6	7	8	9
Isolated yield (%)	97	95	91	92	90	89	85	82	82
Recovery of IL (%)	91	97	93	91	90	95	90	92	88

[a] All reactions were carried out with benzyl chloride (0.4 mmol), NMO (0.8 mmol), and KI (10 mol %) in [emim]Cl (0.4 g) using a MW (150 W) at 100 °C for 2 min.

Regeneration of the ionic liquid

The used ionic liquid (~0.4 g) was washed with EtOAc (1 mL × 2) and then stirred for 1 h with activated charcoal in 5 mL of hot EtOH. After cooling, the ammonium salt of NMM precipitated. The mixture was filtered and the filtrate concentrated in vacuo to give the pale-yellow ionic liquid. The obtained ionic liquid was then dried in an oven at 110 °C overnight and stored in a desiccator for further use.

Acknowledgments

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Supplementary data

Supplementary data (experimental details) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.01.131.

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