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Aerobic oxidation with *N*-hydroxyphthalimide catalysts in ionic liquid

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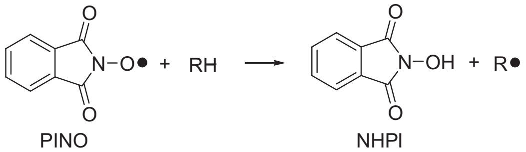
Abstract—*N*-Hydroxyphthalimide (NHPI)-catalyzed aerobic oxidations in the ionic liquids were examined for the first time. Both NHPI and its ionic derivative, 3-pyridinylmethyl-*N*-hydroxyphthalimide (Py-NHPI), were found to have better performance in the ionic liquid than in the conventional organic solvents for the aerobic oxidation of *N*-alkylamides to imides. On the other hand, Py-NHPI was found to be a much better catalyst than NHPI for the aerobic oxidation of benzylic compounds in the ionic liquid.

Ionic liquids (ILs) are usually salts of organic cations.[1] They are liquid at (or close to) room temperature with good thermal stability, yet they have essentially no vapor pressure. Being highly polar and non-coordinating, ILs can readily dissolve a variety of organic and organometallic compounds. It is also possible to perform a fine tuning of the miscibility of ILs with water and common organic solvents simply by changing the side chains or the nature of the organic cation and the inorganic anion. ILs appear very attractive as novel reaction media toward more environmentally benign processes in organic synthesis. Their unique properties have been reflected by their use in a wide range of stoichiometric and catalytic organic reactions.

Many hydrogenation, hydroformylation, dimerization, and C–C coupling reactions have been successfully performed in ILs,[1] but only few oxidation reactions in ILs have been reported. Little attention has been paid, to date, to performing aerobic oxidation reactions in room temperature ILs despite the economical and environmental importance of such reactions. In 2000, Howart reported the first example of an aerobic oxidation in IL.[2] It was found that several aromatic aldehydes could be oxidized using the catalyst [Ni(acac)$_2$] and oxygen at atmospheric pressure, as the oxidant, in the ionic liquid [bmim][PF$_6$] (bmim = 1-butyl-3-methyl-imidazolium). Later, Farmer and Welton[3] and Ansai and Gree[4] reported the aerobic oxidation of aromatic and aliphatic alcohols with TPAP/CuCl and CuCl/TEMPO in ILs. In 2002, Jacobs and co-workers[5] reported the aerobic oxidations of aliphatic and aromatic alcohols into the corresponding aldehydes and ketones with several ruthenium catalysts in various ILs under low oxygen pressure and without any co-catalyst. Very recently, Sun et al.[6] reported a highly interesting aerobic oxidation reaction of 2,3,6-trimethylphenol to trimethyl-1,4-benzoquinone with 2.5 mol% CuCl$_2$ as the catalyst in [bmim]Cl.

Herein we report a novel aerobic oxidation reaction in ILs using Ishii's *N*-hydroxyphthalimide (NHPI) as the catalyst.[7] Previous studies by Ishii's group and several others have shown that NHPI and some of its derivatives were effective catalysts for the oxidation of organic compounds by molecular oxygen under mild conditions.[8] It was proposed that hydrogen abstraction by phthalimide-*N*-oxyl radical (PINO), generated in situ, from C–H bonds (Scheme 1) played a key role in the oxidation reactions. The newly formed carbon centered radical then readily reacted with dioxygen to give ultimately oxygenated compounds. Up to now the solvent systems that have been explored for the



Scheme 1.

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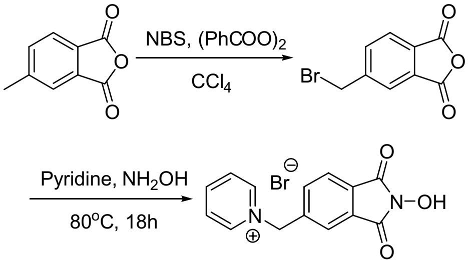
NHPI-dependent aerobic oxidation reactions include toluene, acetonitrile, cyanobenzene, and acetic acid. It remains an unanswered question whether these reactions can be carried out in ILs. Some other interesting questions include: what NHPI derivative is desirable for aerobic oxidation in ILs? Do NHPI-dependent aerobic oxidations proceed better in ILs than in the conventional solvents?

In the first stage of the investigation, we tried to use NHPI to catalyze aerobic oxidation of *N*-alkylamides to imides in [bmim][PF_6]. This transformation is of potential application for the synthesis of diverse imides from readily available starting materials. Previous studies by Minisci et al. have shown that the oxidation of *N*-alkylamides by O_2, catalyzed by NHPI and $Co(OAc)_2$, occurred in MeCN or AcOH, leading to a number of carbonyl products (imides, carboxylic acids, ketones/aldehydes).[9] We carried out the same oxidation reaction in [bmim][PF_6], using NHPI and $Co(OAc)_2$ as catalysts.[10] From GC–MS analysis, the reaction conversion was determined to be 92% (see Table 1). The yield for the desired product, that is, imide **4**, was 62%. We also observed the formation of benzaldehyde (**2**) with a yield of 12%. These results should be compared with Minisci et al.'s results.[9] In their report, the reaction conversion was found to be 43% in MeCN (60 °C) with a yield of 24% for the imide **4**. A higher reaction conversion (75%) was obtained when the oxidation was performed in AcOH (100 °C).[9] However, the major product under this condition was benzoic acid, whereas the yield for the imide **4** only equaled to 2.2%. Thus, the aerobic oxidation reaction in [bmim][PF_6] provided a significantly higher yield for the imide **4**.

Encouraged by the above finding, we then tried to utilize different metal salts to improve the yield of the imide. Thus, we tried $CoCl_2$, $Ni(OAc)_2$, $Cu(OAc)_2$, and $Mn(OAc)_2$, which led to the yields of 49%, 57%, 63%, and 31% for the imide **4**, respectively (see Table 1). We also synthesized $Co(PF_6)_2$ by reacting $CoCO_3·6H_2O$ with HPF_6. It was found that use of $Co(PF_6)_2$ as co-catalyst gave a yield of 70% for the imide **4** when the reaction was conducted in [bmim][PF_6]. Surprisingly, no reaction could be observed when the aerobic oxidation (using $Co(PF_6)_2$ as co-catalyst) was conducted in a different ionic liquid, [bmim][BF_4].

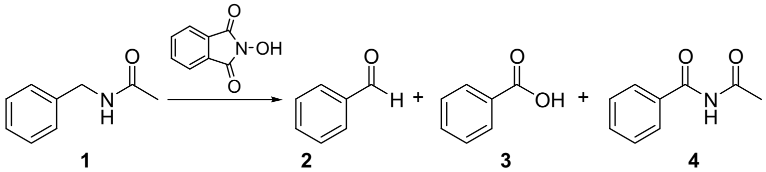
The above results indicated that the use of different cations and anions could have significant effects on the aerobic oxidation reactions in the ionic liquid. At this point, we hypothesized that a higher yield of the desired product could be obtained if we utilized an ionic catalyst in the ionic liquid. Thus, we designed the first ionic version of the NHPI family of catalysts, which we named Py-NHPI (see Scheme 2). Py-NHPI was successfully synthesized in two steps from the commercially available starting materials with an overall yield of 36%.[11] It is worth noting that in the previous studies a number of ionic versions of catalysts (e.g., ruthenium carbene catalysts with a designed ionic tag[12]) have also been reported. These ionic catalysts were usually found to have better performance than their corresponding standard, neutral catalysts for the catalytic reactions in ionic liquids.

The performance of the Py-NHPI catalyst for the aerobic oxidation of *N*-benzylacetamide in [bmim][PF_6] was



Scheme 2.

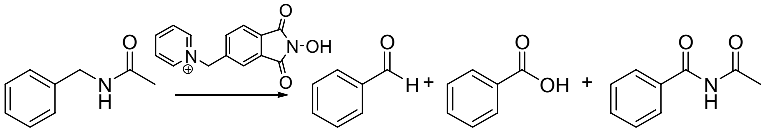
Table 1. Aerobic oxidation of *N*-benzylacetamide catalyzed by NHPI in [bmim][PF_6][a]



Entry	Salt	Conversion[b]	Yield[b] (%)		
			2	3	4
1	$Co(OAc)_2$	92	12	0	62
2	$CoCl_2$	90	9	0	49
3	$Ni(OAc)_2$	87	4	0	57
4	$Cu(OAc)_2$	74	5	0	63
5	$Mn(OAc)_2$	35	3	0	31
6	$Co(PF_6)_2$	94	10	5	70
7[c]	$Co(PF_6)_2$	0	0	0	0

[a] Reaction conditions: *N*-benzylacetamide (1 mmol), NHPI (10 mol%), salt (0.5 mol%), [bmim][PF_6] (3 mL), O_2 (1 atm), 75 °C, 24 h.
[b] GC–MS conversions and yields.
[c] Solvent = [bmim][BF_4].

Table 2. Aerobic oxidation of *N*-benzylacetamide catalyzed by Py-NHPI in [bmim][PF_6][a]



1 **2** **3** **4**

Entry	Temperature (°C)	Conversion[b]	Yield[b] (%)		
			2	**3**	**4**
1	45	37	5	0	21
2	55	59	2	0	32
3	65	85	3	0	70
4	70	88	5	0	71
5	75	95	10	5	71
6	85	97	3	4	57
7	95	95	0	12	30
8[c]	65	100	3	0	81[d]

[a] Reaction conditions: *N*-benzylacetamide (1 mmol), Py-NHPI (10 mol%), $Co(PF_6)_2$ (0.5 mol%), [bmim][PF_6] (3 mL), O_2 (1 atm), 24 h.

[b] GC–MS conversions and yields.

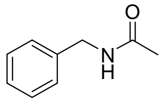
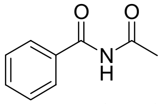
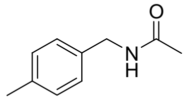
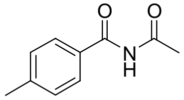
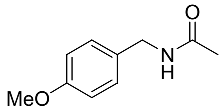
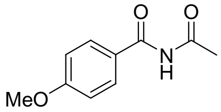
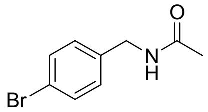
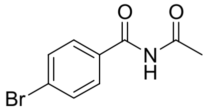
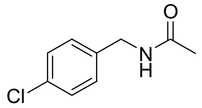
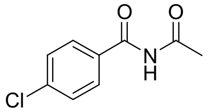
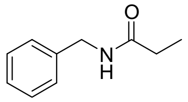
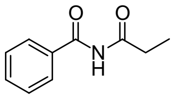
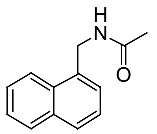
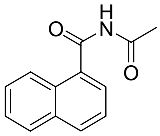
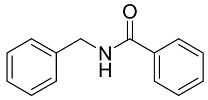
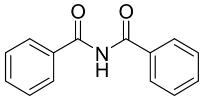
[c] Catalyst = 5 mol% Py-NHPI + 1 mol% $Co(PF_6)_2$.

[d] Isolated yields.

shown in Table 2. To our surprise, it was found that Py-NHPI gave almost the same results as NHPI for the oxidation at 75 °C. Next we used Py-NHPI to study the temperature effect on the oxidation (see Table 2). It was found that a higher temperature always produced a higher conversion in the range from 45 °C to 95 °C. Nevertheless, the maximum yield of the imide **4** was reached at 70–75 °C, because further increase of the temperature led to the formation of more unidentified byproduct. By using less Py-NHPI catalyst (5 mol%) but more $Co(PF_6)_2$ (1 mol%), we found that a 100% conversion (GC–MS value) of the starting material could be observed at 65 °C. An isolated yield of 81% (determined by weight) was then obtained for the formation of imide **4**.

It was indicated that the aerobic oxidation, carried out with 5 mol% of Py-NHPI and 1 mol% of $Co(PF_6)_2$ at 65 °C under 1 atm of O_2 in [bmim][PF_6], was a synthetically valuable method for the conversion of *N*-benzylacetamide to *N*-acetylbenzamide. Using the same reaction condition, we also tested the oxidation of a number of other *N*-alkylamides (see Table 3). It was found that the isolated yields for the oxidation of the amides of benzylamines with aliphatic carbonyls ranged from 57% to 83%. These yields are about 20–30% higher than the yields in Minisci's study.[9] Nevertheless, it was found that oxidation of the amide of naphthalenylmethanamine only gave a yield of 23% (GC–MS value). Furthermore, oxidation of the amide of benzylamine with an aromatic carbonyl (i.e., benzoyl) only gave a yield of 18% (GC–MS value).

Table 3. Aerobic oxidation of *N*-alkylamides catalyzed by Py-NHPI in [bmim][PF_6][a]

Entry	Reactant	Product	Yield[b]
1			81
2			78
3			57
4			66
5			74
6			83
7			23[c]
8[c]			18[c]

[a] Reaction conditions: *N*-alkylamide (1 mmol), Py-NHPI (5 mol%), $Co(PF_6)_2$ (1 mol%), [bmim][PF_6] (3 mL), O_2 (1 atm), 65 °C, 24 h.

[b] Isolated yields.

[c] GC–MS yield.

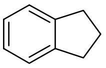
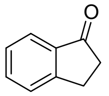
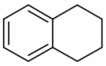
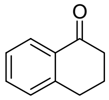
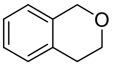
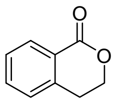
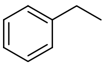
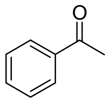
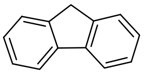
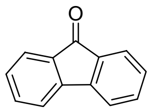
Having successfully oxidized *N*-alkylamides, we then studied the aerobic oxidation of benzylic compounds in ionic liquid. First we used the unmodified NHPI to oxidize indan in [bmim][PF_6] at 65 °C with $Co(PF_6)_2$ as the co-catalyst. From GC–MS analysis we observed the formation of 1-indanone with a yield of 28.3%. We also observed the formation of three other by-products (molecular weights = 150, 148, and 132) with yields of 22.7%, 22.1%, and 16.4%, respectively. Thus, the aerobic oxidation of indan catalyzed by NHPI was not selective for the desired product.

It was then discovered that by using Py-NHPI as the catalyst, indan could be exclusively oxidized to 1-indanone. The GC–MS yield was almost 100%, while the isolated yield was 84%. It is worth noting that in the previous study by Einhorn and co-workers, aerobic oxidation of indan catalyzed by the NHPI type of catalyst gave a yield of 77% in CH_3CN.[13] Furthermore, in 2003, Alsters and co-workers reported that benzylic oxidation of indan with dioxygen by metal/NHPI-catalyzed co-oxidation with benzaldehyde in AcOH gave a yield of 75% for 1-indanone.[14]

Some other benzylic compounds were also examined for the aerobic oxidation (see Table 4). The GC–MS yields ranged from 82% to 100%, while the isolated yields were from 47% to 96%. Thus, the Py-NHPI catalyzed aerobic oxidation of benzylic compounds in [bmim][PF_6] is also a synthetically valuable method. It is worth mentioning that in all of the above reactions the ionic liquid [bmim][PF_6] can be recovered after each oxidation reaction and then re-used in the next oxidation reaction.[10]

In summary, NHPI-catalyzed aerobic oxidations in the ionic liquids were examined for the first time. Both NHPI and its ionic derivative, Py-NHPI, were found to have better performance in the ionic liquid than in the conventional organic solvents for the aerobic oxidation of *N*-alkylamides to imides. On the other hand, Py-NHPI was found to be a much better catalyst than NHPI for the aerobic oxidation of benzylic compounds to the carbonyl compounds in the ionic liquid.

Table 4. Aerobic oxidation of benzylic compounds catalyzed by Py-NHPI in [bmim][PF_6][a]

Entry	Reactant	Product	Yield[b]
1			100 (84)
2			82 (63)
3			100 (86)
4			84 (47)
5			96 (96)

[a] Reaction conditions: Benzylic compound (3 mmol), Py-NHPI (5 mol%), $Co(PF_6)_2$ (1 mol%), [bmim][PF_6] (5 mL), O_2 (1 atm), 65 °C, 24 h.

[b] Yields outside parentheses are GC–MC yields. Yields in parentheses are isolated yields.

Acknowledgments

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10. Typical procedures for the aerobic oxidation of *N*-benzylacetamide: a two-necked flask was charged with *N*-benzylacetamide (149 mg, 1 mmol), Py-NHPI (16.7 mg, 0.05 mmol, 5 mol%), $Co(PF_6)_2$ (4.2 mg, 0.01 mmol, 1 mol%), and [bmim][PF_6] (3 mL). The reaction mixture was heated to 65 °C and stirred for 24 h under 1 atm of O_2. The resulting suspension was cooled to room temperature and extracted with ether a few times. After concentration of the ether solution, the residue was purified by chromatography to afford the pure product (the yields were shown in the previous Tables 1–4). To recycle the ionic liquid, we added 10 mL of dichloromethane to the remaining [bmim][PF_6] and then washed the mixture with water. The mixture was dried over anhydrous $MgSO_4$. After the solvent was removed [bmim][PF_6] could be used for the next reaction.
11. *Py-NHPI*: 1.62 g (10 mmol) of 5-methylisobenzofuran-1,3-dione, 2.7 g (15 mmol) of NBS, and 0.1 g of $(PhCOO)_2$

were dissolved in 60 mL of CCl_4. The reaction was refluxed for 6 h. After the mixture was filtered and the solvent was removed, the crude product was added to a flask containing 0.69 g (10 mmol) of $NH_2OH \cdot HCl$ and 10 mL of dry pyridine. The reaction was stirred at 80 °C for 18 h. After the solution was cooled to room temperature, white solid was obtained via filtration, which was washed with ethanol to yield 1.2 g of pure product (yield over two steps = 36%). Mp: 274.8–276.1 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.93 (s, 1H), 9.28 (d, 2H $J = 6.0$ Hz), 8.5 (t, 1H $J = 6.9$, 7.3 Hz), 8.21 (t, 2H $J = 6.7$, 6.8 Hz), 8.08 (s, 1H), 8.00 (d, 1H $J = 8.0$ Hz), 7.92 (d, 1H $J = 7.7$ Hz), 6.03 (s, 2H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 163.4, 146.2, 145.0, 140.3, 135.0, 129.6, 129.4, 128.5, 123.6, 123.5, 62.4 ppm; MS: m/z = 80.16, 176.10, 255.06 ($M^+ - Br$). IR (KBr): 3437.11, 3048.34, 2901.87, 2776.26, 1778.94, 1727.49, 1635.16, 1494.87 cm^{-1}.

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