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Tetrahedron Letters 47 (2006) 2797–2801
Tetrahedron Letters

Synthetic utilities of ionic liquid-supported NHPI complex

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Received 27 January 2006; revised 10 February 2006; accepted 10 February 2006
Available online 3 March 2006

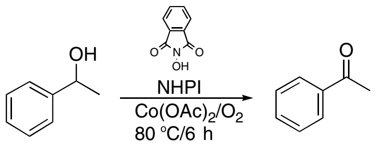
Abstract—Ionic liquid (IL)-supported NHPI complex for the oxidation and/or nitration was prepared. Synthetic utilities of the complex as recoverable and recyclable system in ionic liquid were described.

The concept of recoverable and recyclable catalysts has become extremely important from both the environmental and economical points of view.[1] Further, there is a growing interest in the development of the greener chemical processes that do not lead to three major sources of waste: organic solvents, catalysts and any hazardous by-products.[2] Especially, nucleophilic and/or oxidation reactions have been recognized as being useful in organic synthesis, their reactions commonly employ organic solvents (such as DMF, CH_3CN, DMSO, etc.), and in many cases they are removed from the final reaction mixture by a water quench which leads to an aqueous waste stream. Further, reusable media (ionic liquids) are having an important impact on organic reactions,[3] and various kinds of reactions in ionic liquids have been reported until now.[4] In this field, it has been recognized that ionic liquid (IL)-supported catalyst system is the major advantage in the homogeneous catalytic processes as recoverable and recyclable system.[5] To date, synthetic applications using ionic liquid (IL)-supported materials have been based on a few methods: (1) Rh-complex for the ring-closing reaction,[6] (2) Baylis–Hillman reaction,[7] (3) Fructose-derived ionic liquids,[8] (4) IL-supported TEMPO or NHPI complex for oxidation.[9] Furthermore, in spite of the above mentioned pioneering complexes, their scope and limitation of synthesis and synthetic utilities are an unsolved problem.

In this letter, we would like to describe the utilities of ionic liquid (IL)-supported NHPI complexes as recoverable and recyclable system for the oxidation and nitration with HNO_3.

Catalytic oxidation of carbohydrates using the stable phthalimide *N*-oxy (PINO) radical has become one of the most promising procedures to convert carbinols into the corresponding carbonyl compounds.[11–14] It is known that *N*-hydroxy-phthalimide (NHPI) acts as a catalyst for the transformation of alkanes to alcohols, ketones, carboxylic acids, and/or nitroalkanes under mild oxidation conditions.[13,14] In our results of the oxidation reaction from 1-phenyl ethanol to acetophenone in the NHPI–$Co(OAc)_2$–O_2 system shown in Table 1, the fluorinated ionic liquids are efficient for the oxidation reaction using NHPI as a catalyst. However, yields

Table 1. Sovelt effect in the oxidation with NHPI



Entry	Solvent	Yield[a] (%)
1	[bmim][PF_6]	93
2	[bmim][CF_3SO_3]	80
3	[bmim][BF_4]	78
4	[bmim][$(CF_3SO_2)_2N$]	78
5	[bmim][NO_3]	65
6	[bmim][CH_3SO_3]	33
7[b]	Ethyl acetate	92

[a] Yields were determined by ^1H NMR integral intensities using $C_6H_5CF_3$ as an internal standard.

[b] The reaction was carried out under reflux.

Keywords: Ionic liquid; Supported complex; Oxidation reaction.

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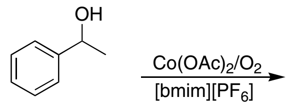
doi:10.1016/j.tetlet.2006.02.077

Table 2. Reuse of catalyst and solvent system



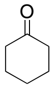
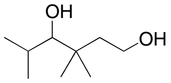
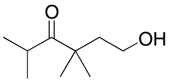
	Run: yield (%)				
	1	2	3	4	5
NHPI (6 h)	93	80	26		
IL-NHPI **4** (2 h)	98	99	96	98	97

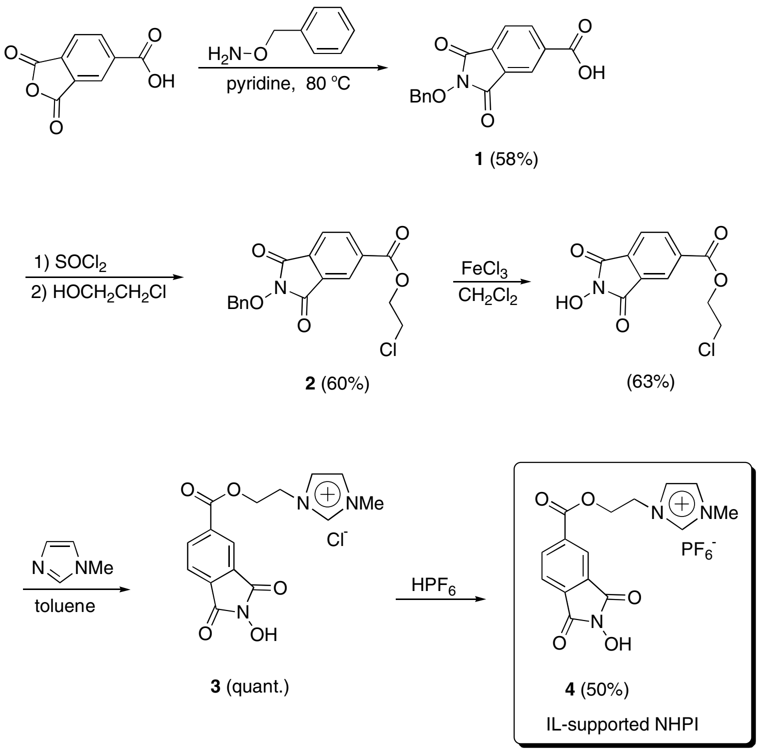
drastically decreased from the first cycle (93%) to the second (80%) and the third cycles (26%) shown in Table 2.

From these results, we have found that NHPI is separated smoothly from ionic liquid with organic solvents, and that it is impossible to construct the reusable reaction system because of the disappearance of NHPI as a catalyst. Therefore, we have designed the ionic liquid-supported NHPI complex which offers several benefits in comparison to homogeneous and/or heterogeneous catalysts, including easier product isolation and purification and the possibility to reuse the system. Ionic liquid (IL)-supported NHPI was prepared via the synthetic routes shown in Scheme 1. The structure of this complex was confirmed by the ^{1}H and ^{13}C NMR spectra.

In the literature,[15] the crystal structure of 1-ethyl-3-methylimidazolium hexafluorophosphate indicates PF_6 unit related by symmetry elements, and then the report for signal of ^{19}F NMR spectrum suggests a simple pattern (doublet with a coupling constant: $J_{F-P} = 700$–730 Hz).[10] In the ^{19}F NMR spectrum of the above complex **4**, a signal of PF_6 appears at δ 92.4 ppm (**4**) from ext. C_6F_6, and the coupling pattern of a signal of PF_6 was doublet (**4**, d, $J_{F-P} = 716.5$ Hz). From the results of the ^{1}H, ^{19}F, and ^{13}C NMR spectra, the structure of this complex was identified. From the results of the oxidation reaction from 1-phenyl ethanol to acetophenone shown in Table 2, we have found that the system using by the IL-NHPI (10 mol %)–$Co(OAc)_2$–O_2 in ionic liquid ([bmim][PF_6]; made in NIPPON GOHSEI (The Nippon Synthetic Chemical Industry Co. Ltd)) is reusable. In the same system, various types of carbinols are transformed into the corresponding aldehydes and/or ketones in good yield shown in Table 3. Obviously, secondary hydroxy group is selectively oxidized in this system (entry 5).

Table 3. Oxidation with complex **4** and $Co(OAc)_2$ system in [bmim][PF_6]

Entry	Substrate	Product	Time (h)	Yield (%)
1	Heptanol	Heptanal	10	Trace
2	2-Nonanol	2-Nonanon	2	84
3	PhCH(Me)OH	PhCOMe	2	98
4	*cyclo*-$C_6H_{11}OH$		2	80
5			2	78

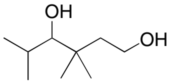
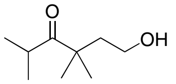


Scheme 1.

The above reactions commonly employ organic solvents (diethyl ether, methylene dichloride, etc.) for the extraction of the product, and in the above cases they are removed from the final reaction product. However, from the point of view on the greener chemical processes, it is important that they do not lead to three major sources of waste: organic solvents, catalysts and any hazardous by-products.[2] Therefore, instead of the organic solvents for the extraction process, we examined other extraction method. As it is well known that the supercritical carbon dioxide is a useful medium for organic reaction and extraction solvent, we examined the extraction of oxidation products in IL-supported NHPI complex-ionic liquid [bmim][PF_6] with supercritical carbon dioxide. At first, we have examined the relationship with temperature and percentage of extracted acetophenone in ionic liquid [bmim][PF_6]. From the results shown in Figure 1, we have found that the extraction proceeded smoothly at 35 °C. Therefore, the oxidation reactions in the pressure steel vessel were carried out at 80 °C. After heating for 5 h, the product was extracted with supercritical carbon dioxide at 35 °C shown in Figure 2, and then successive reuse of the recovered IL-supported NHPI complex-ionic liquid system and in the same reaction yielded amounts of product as high as in the first cycle. In the third cycle, reuse of reaction system recovered from the second cycle is possible to produce the same material in the same reaction. The results in supercritical carbon dioxide extraction system are shown in Table 4.[16]

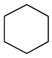
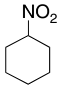
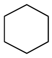
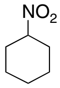
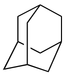
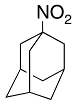
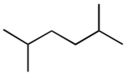
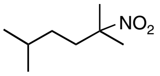
In the next step, we examined the direct nitration of carbon–hydride bond. Nitration is an important process in

Table 4. Extraction with supercritical carbon dioxide

Entry	Substrate	Product	Yield[a] (%)
1	PhCH(Me)OH	PhCOMe	89
2	PhCH(Me)OH	PhCOMe	95[b]
3	PhCH(Me)OH	PhCOMe	86[c]
4	2-Nonanol	2-Nonanon	97
5	*cyclo*-$C_6H_{11}OH$	*cyclo*-Hexanone	77
6			63

[a] Reaction condition: 1-phenyl ethanol (0.5 mmol), ionic liquid (5 mL), IL-NHPI complex (0.05 mmol), 80 °C.
[b] Second cycle.
[c] Third cycle.

Table 5. Nitration with HNO_3 in IL-complex **4** system[a]

Entry	Alkane	Product	Time (h)	Yield (%)
1			10	49
2[b]			10	40
3			10	70
4			10	50

[a] Reaction was carried out at 80 °C with 40% IL-supported NHPI complex and 1.5 equiv HNO_3.
[b] Second cycle.

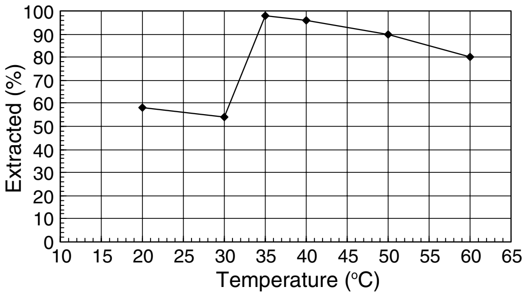


Figure 1.

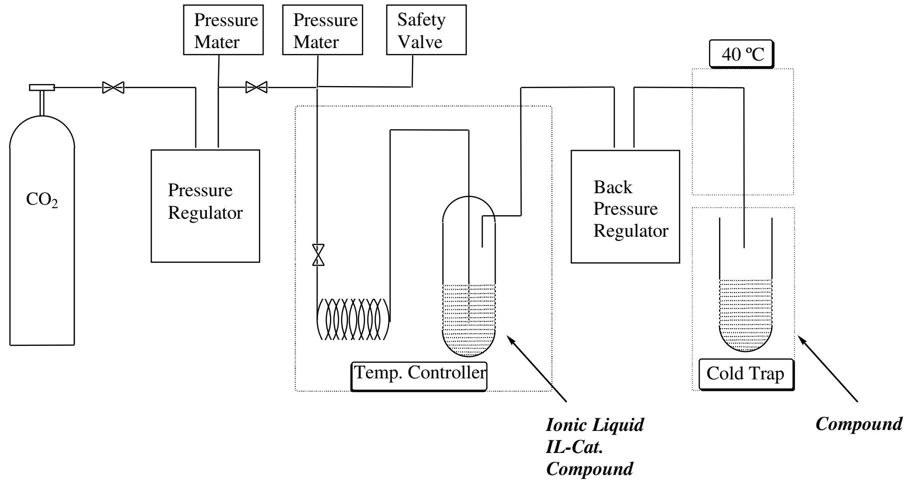


Figure 2.

the organic synthesis.[14] However, the temperature (250–400 °C) for the nitration of alkanes using nitric acid and/or NO_2 is not convenient for the greener chemistry.[15] Therefore, we examined the nitration of alkanes in IL-supported NHPI complex (25 mol %)–HNO_3–ionic liquid [bmim][PF_6] system. From the results shown in Table 5, this reaction system is reusable (entries 1 and 2), and then the nitrations proceed at 80 °C smoothly.

In conclusion, ionic liquid-supported systems are convenient reaction reuse systems to accelerate the various types of organic reactions.

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16. *Ionic liquid-supported NHPI complex* **4**.

(a) 2-Chloroethyl 2-(benzyloxy)-1,3-dioxoisoindoline-5-carboxylate **2**.

A mixture of compound **1** (0.60 g, 2 mmol) and $SOCl_2$ (6 ml) was stirred for 1 h at 50 °C, and then the excess $SOCl_2$ was removed under vacuum. Into the residue, 2-chloroethanol (0.16 g, 2 mmol), pyridine (0.02 g, 0.2 mmol) and CH_2Cl_2 (10 ml) were added. After the mixture was refluxed for 2 h, the solvent was removed under vacuum. Product was extracted with ethyl acetate, and the whole was washed with 1 N-HCl. After drying over anhydrous $MgSO_4$, the product was purified by column chromatography on silica gel using a mixture of ethyl acetate–hexane (1:5), giving the title material **2** (yield. 60%) as a colorless oil.

^{1}H NMR ($CDCl_3$): δ 3.84 (2H, t, $J = 5.8$ Hz), 4.63 (2H, t, $J = 5.8$ Hz), 5.23 (1H, s), 5.29 (1H, s), 7.38 (5H, m), 7.91 (1H, d, $J = 8.5$ Hz), 8.45 (1H, d, $J = 8.5$ Hz), 8.50 (1H, s). ^{13}C NMR ($CDCl_3$): δ 37.4, 66.5, 73.5, 118.4, 119.8, 121.4, 122.6, 123.8, 124.5, 125.2, 128.1, 128.6, 130.6, 131.2, 131.5, 157.6 (2c), 159.2.

(b) 4-(2-Chloroethyl)carboxyl-*N*-hydroxy-phthalimide. A mixture of compound **2** (0.30 g, 0.8 mmol) and iron chloride (0.51 g, 3.2 mmol) in CH_2Cl_2 was stirred for 4 h at room temperature. Product was extracted with ethyl acetate, and the whole was washed with 1 N HCl, and dried over $MgSO_4$. The product was purified by column chromatography on silica gel (AcOEt/Hex = 1:1), giving 4-(2-chloroethyl)carboxyl-*N*-hydroxy-phthalimide in 63% yield.

^{1}H NMR ($CDCl_3$): δ 3.86 (2H, t, $J = 5.5$ Hz), 4.58 (2H, t, $J = 5.5$ Hz), 7.86 (1H, d, $J = 7.8$ Hz), 8.32 (1H, s), 8.39 (1H, d, $J = 7.8$ Hz). ^{13}C NMR ($CDCl_3$): δ 37.0, 60.7, 118.5, 119.0, 124.8, 128.2, 130.3, 130.8, 151.5, 158.1, 159.2.

(c) 4-(2-Chloroethyl)carboxyl-*N*-hydroxy-phthalimide 3-methyl-3*H*-imidazol-1-ium chloride **3**.

A mixture of 4-(2-chloroethyl)carboxyl-*N*-hydroxy-phthalimide (0.36 g, 1.3 mmol) and methylimidazole (0.10 g, 1.2 mmol) in toluene (10 ml) was refluxed for 2 h, and then the solvent was removed. The product was extracted with water, and the aqueous layer was concentrated under vacuum. The product was purified by column chromatography on silica gel ($CHCl_3$–MeOH = 1:1), giving the compound **3** as an oil.

^{1}H NMR (DMSO-d_6): δ 3.75 (3H, s), 4.03 (2H, t, $J = 6.6$ Hz), 4.65 (2H, t, $J = 6.6$ Hz), 6.99 (1H, s), 7.15 (1H, s), 7.76 (1H, s), 8.00 (1H, d, $J = 7.8$ Hz), 8.29 (1H, s), 8.43 (1H, d, $J = 7.8$ Hz). ^{13}C NMR (DMSO-d_6): δ 28.9, 38.2, 61.4, 116.5, 118.7, 119.0, 123.0, 125.6, 129.0, 130.6, 131.1, 133.5, 159.2 (2c), 159.8.

(d) Compound **4**.

To the above material **3**, hexafluorophosphonic acid (1.2 mmol), and water (10 ml) were added, and the whole was stirred for 2 h at room temperature. The layer was washed with water, and then concentrated under vacuum, affording the material **4** in 50%.

^{1}H NMR (DMSO-d_6): δ 3.87 (3H, s), 4.02 (2H, t, $J = 5.7$ Hz), 4.61 (2H, t, $J = 5.7$ Hz), 7.66 (1H, s), 7.68 (1H, s), 7.99 (1H, d, $J = 8.0$ Hz), 8.32 (1H, s), 8.38 (1H, d, $J = 8.0$ Hz), 9.03 (1H, s). ^{13}C NMR (DMSO-d_6): δ 31.1, 38.2, 61.1, 115.3, 118.4, 118.7, 119.1, 125.0, 128.3, 130.1, 130.9, 131.3, 152.0, 158.8, 159.5. ^{19}F NMR (DMSO-d_6): δ 92.4 (d, $J = 716.5$ Hz) ppm from ext. C_6F_6.

General procedure for aerobic oxidation reaction.

A mixture of 1-phenyl ethanol (0.12 g, 1 mmol), IL-supported THPI complex **4** (0.04 g, 0.1 mmol) and

$Co(OAc)_2$ (0.003 g, 0.02 mmol) in [bmim][PF_6] (2 ml) was heated at 80 °C under an atmosphere of O_2. After stirring for 5 h at that temperature, the vessel was set to 35 °C, and then $scCO_2$ (10 MPa at 1 ml/min) was bubbled through the reaction mixture in ionic liquid, venting through a back-pressure regulator in a cold trap (−78 °C). The recovered reaction system containing IL-supported THPI complex **4**, $Co(OAc)_2$ and [bmim][PF_6] was used in the second cycle.

General procedure for nitration. A mixture of cyclohexane (0.18 g, 1 mmol), IL-supported NHPI complex **4** (0.185 g, 0.4 mmol) and HNO_3 (0.186 g, 3 mmol) in [bmim][PF_6] (6 ml) was heated at 80 °C. After stirring for 10 h at that temperature, the organic materials were extracted with diethyl ether, and the ethereal layer was dried over anhydrous $MgSO_4$. On removal of the solvent, nitrocyclohexane was obtained.