Transfer Hydrogenation in Ionic Liquids under Microwave Irradiation

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Received 7 June 2002

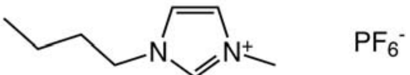
Dedicated to Jenny Berthold for her lifework.

Abstract: Catalytic transfer hydrogenation (CTH) of different homo- or heteronuclear organic compounds was performed in a room temperature ionic liquid (RTIL) *N*-butyl-*N'*-methylimidazolium hexafluorophosphate, ($[BMIM]^+$ $[PF_6]^-$) (**1**) as solvent heated by microwave irridiation. Formate salts such as ammonium formate and triethylammonium formate were used as a hydrogen source in the reaction catalyzed by palladium on carbon. Essentially pure products could be isolated in moderate to excellent yields by simple liquid-liquid extraction with methyl *tert*-butyl ether (MTBE). Recycling of the catalyst/solvent system was possible.

Key words: microwaves, room temperature ionic liquid, catalytic transfer hydrogenation, unsaturated compounds, formate salts

The advantages of using microwave dielectric heating for performing organic reactions has been realized by many different groups over the recent decade.[1a–e] The most compelling features of microwave irradiation in chemical synthesis are dramatically accelerated reaction rates and improved yields, selectivity, and purity of the products in many cases. Generally, the reaction can be run in a solvent as a homogeneous or heterogeneous mixture or solvent-free on solid supports like silica gel, alumina or clays. The latter methodology has been developed originally to circumvent potential hazards of uncontrolled microwave heating of flammable, toxic and volatile organic liquids (VOLs), especially when domestic microwave ovens have been employed.[2a,b]

Nevertheless, avoiding or replacing VOLs in organic synthesis is currently a major goal in designing 'greener' and environmentally benign processes in industry.[3] Very recently room temperature ionic liquids (RTILs) have drawn much attention to overcome many of these environmental issues, due to their unique physicochemical properties profile, as they are nonflammable, nontoxic (as far as known), nonvolatile, recyclable, extremely high boiling, and thermally and chemically stable. Their purely ionic character makes them excellent solubilizers for a wide range of inorganic as well as organic substrates, thus substituting polar aprotic solvents. RTILs are 'tuneable' concerning miscibility with other solvents (VOLs, water, $scCO_2$ etc.) via a proper choice of the counter anion, consequently offering interesting options for workup and extraction procedures.[4a,b] With regard to microwave-assisted synthesis their extremely high dielectric constant makes them ideally suited to be rapidly heated in a microwave field.[5a–d] Catalytic transfer hydrogenation (CTH) is a versatile reaction for the reduction of homo or heteroatomic sp or sp2 bonds present in alkenes, alkynes, nitriles, nitro and carbonyl compounds as well as for reductive dehalogenation of haloarenes.[6a–d] The reactions have been conducted preferably in a microwave field using a range of solvents like DMSO, ethylene glycol or propane-1,3-diol and with different catalysts (i.e., palladium/carbon, Raney nickel, and Wilkinson's catalyst) using formic acid and its salts as a hydrogen source.[7a,b] While ionic liquids have already found broad application as solvent-cum-catalysts in a wide range of synthetic transformations[8a,5d] including catalytic hydrogenations with molecular hydrogen,[8b–j] CTH with salts of formic acid in ionic liquids under microwave irradiation has not been reported to date. Herein, we report our results using the ionic liquid (IL) *N*-butyl-*N'*-methylimidazolium hexafluorophosphate ($[BMIM]^+$ $[PF_6]^-$) (**1**) (Figure) as a solvent and 10% palladium/carbon as a catalyst for the catalytic transfer hydrogenation of various organic substrates. We have chosen **1** based on its physicochemical properties (i.e., exceptionally high thermal stability and immiscibility with organic as well as aqueous solvents).



1

Figure The structure of *N*-butyl-*N'*-methylimidazolium hexafluorophosphate.

In a first trial, we reduced 4-nitrobenzoic acid methyl ester (**2**) applying the conditions reported by Bose et al.[7a] (i.e., 10% Pd/C and ammonium formate at 120 °C using propane-1,3-diol as the solvent). A 70% yield of 4-aminobenzoic acid methyl ester (**2a**) was obtained after microwave irradiation with 300 W for 7 minutes. In a second experiment, propane-1,3-diol was replaced by the ionic liquid **1**. The yield of essentially pure product **2a** increased to 92% after simple liquid-liquid extraction. Encouraged by these results, we applied the conditions to (*E*)-methyl cinnamate

Synthesis 2002, No. 11, Print: 22 08 2002.
Art Id.1437-210X,E;2002,0,11,1607,1610,ftx,en;C02802SS.pdf.

ISSN 0039-7881

(**3**). However, for complete conversion the reaction conditions had to be modified. Eventually a linear temperature gradient over 10 minutes to the final temperature of 150 °C, subsequent heating over 70 minutes at 150 °C and active cooling to 50 °C over 30 minutes was applied to the reduction of various organic functionalities (Table 1).

Interestingly, monitoring of the internal pressure allowed us to estimate the progress of the reaction. After having reached a constant pressure of about 0.9 to 1.5 MPa the reaction was complete. According to the observations of Sasson et al.,[11] gas evolution occurred when a stock solution of ammonium formate and Pd/C in **1** was warmed to 50 °C in the absence of a hydrogen acceptor. Consequently, all solutions were freshly prepared. The unsatisfactory results (Table 1, entries 4, 5, and 6) and loss of ammonium formate due to sublimation prompted us to replace ammonium formate by triethylamine formate[6b,7b] by simply adding an equimolar cold mixture of Et_3N and formic acid in a five fold excess. The results are shown in Table 2.

To test the recyclability of the ionic liquid/catalyst system, five subsequent cycles of the reduction of **4** to **4a** were performed. After each cycle, the ionic liquid phase was exhaustively extracted with MTBE and recharged with **4** and a five molar excess of equimolar amounts of triethylamine and formic acid. The results are shown in Table 3.

Table 1 CTH Route A with Ammonium Formate, 10% Pd/C, IL **1**, 150 °C via Microwave Irradiation (Max. 300 Watt)

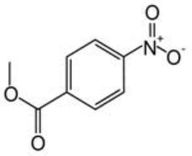
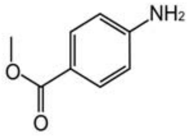
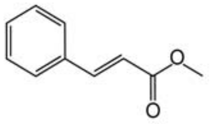
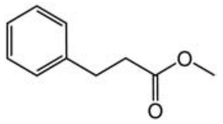
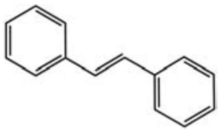
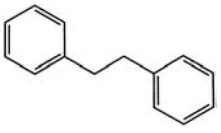
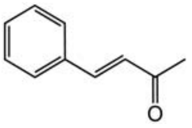
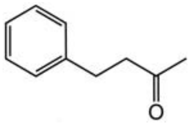
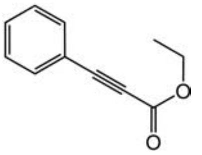
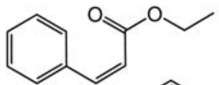
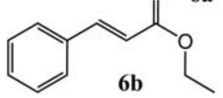
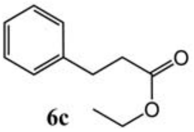
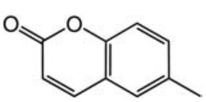
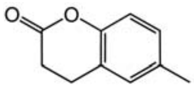
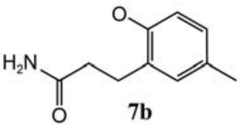
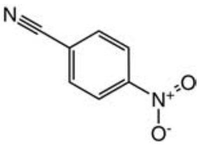
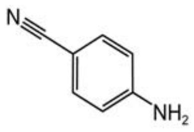
Entry	Substrate	Product	Yield (%)[a]
1	 **2**	 **2a**	92[b] (97)[6b]
2	 **3**	 **3a**	99 (90)[7b]
3	 **4**	 **4a**	84 (37)[6d]
4	 **5**	 **5a**	byproducts
5	 **6**	 **6a**  **6b**  **6c**	50% conversion **6a**:**6b**:**6c** = 6:1:1
6	 **7**	 **7a**  **7b**	0 of **7a** 30 of **7b**[9]
7	 **8**	 **8a**	67[b,c]

Table 2 CTH Route B with Triethylamine Formate, 10% Pd/C, IL **1**, 150 °C via Microwave Irradiation (Max. 300 Watt)

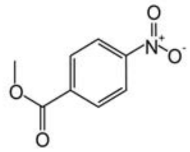
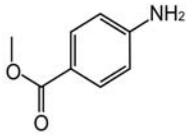
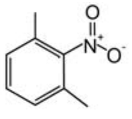
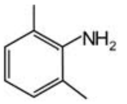
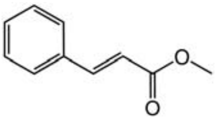
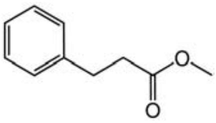
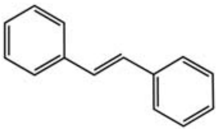
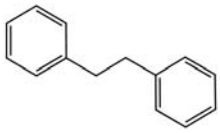
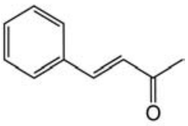
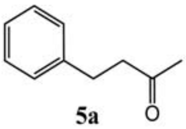
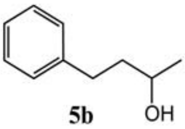
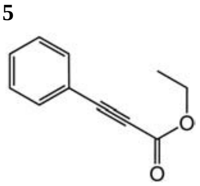
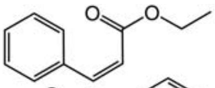
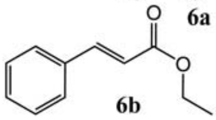
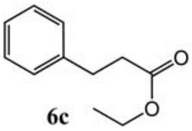
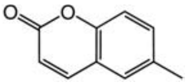
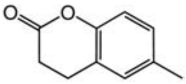
Entry	Substrate	Product	Yield (%)[a]
1	 **2**	 **2a**	83
2	 **9**	 **9a**	92[b] (48)[6d]
3	 **3**	 **3a**	83[c] (90)[6b]
4	 **4**	 **4a**	98 (37)[6d]
5	 **5**	 **5a**  **5b**	97[d] **5a**:**5b** = 97:3[7b,6d]
6	 **6**	 **6a**  **6b**  **6c**	97 only **6c**
7	 **7**	 **7a**	no conversion

Table 3 Recyclability of the Catalytic System with Constant Reaction Time

Entry	Recovery (%)	Yield **4a** (%)
1	99	100
2	99	91
3	102	68
4	96	56
5	100	59
Average	99	75

Similar results were obtained, when the reaction was terminated after reaching a constant pressure (Table 4).

In conclusion, various functional groups (i.e., nitro, alkene, alkyne) have been cleanly reduced in ionic liquid 1 under microwave irradiation and conveniently isolated by simple liquid/liquid extraction with MTBE in high yields and purity. Alternatively, the aniline 9a could be isolated by aqueous acidic extraction from **1**, thus exploiting the useful properties of 1 to form ternary phases with aqueous and organic solvents. Yields were similar or better than previously reported. Reductive dehalogenation of haloarenes (results not shown) was successful, but occurred under partial de-methylation of 1, forming *N*-butylimidazole as a contaminant.[5b,12] In contrast to previous re-

Table 4 Recyclability of the Catalytic System with Respect to Time

Entry	Time of Run (min)[b]	Recovery (%)	**4a** (%)
1	32	98	100
2	50	100	90
3	60	100	79
4	72	101	67
5	90	100	59
1–5 averaged	61	100	79
6[a]	43	100	92

[a] After addition of ca. 40% (92 mg, 0.86 mmol) of the original amount of dry 10% Pd/C to the reaction mixture of entry 5, catalytic activity was almost restored.

[b] Including the temperature ramp to reach 150 °C.

ports,[10] reduction of aryl nitriles was unexpectedly sluggish. This observation was utilized for the selective reduction of a nitro group in presence of a nitrile (Table 1, entry 7). Recyclability of the solvent/catalyst system has been demonstrated. After five repetitive catalytic cycles a 40% loss in catalytic activity was observed, which could almost be restored by adding a corresponding amount of fresh catalyst (Table 4).

^{1}H NMR spectra were obtained on a Bruker AVANCE 300 instrument at 300 MHz. Irradiations were performed in a multimode reactor (MLS ETHOS 1600 Milestone Inc.). All experiments were carried out in sealed 100 mL PTFE reaction vessels. Magnetic stirring with teflon-coated stirring bars was used in all operations. During the experiments, time, pressure (APC-80 pressure sensor), microwave power and internal temperature (ATC-FiberOptic) were monitored/controlled.

Chemicals were purchased from the following suppliers: From Fluka **1**; from Aldrich **3**, **4**, **7**, **8**, **9**, formic acid 96% and dry 10% Pd/C; from Acros **5**, **6**, and Et_3N; from Janssen **2**; from Merck-Schuchart ammonium formate. All reagents were used as purchased. Ammonium formate was handled under exclusion of moisture in an argon atmosphere. All experiments were run in 100 mL Teflon bombs equipped with Teflon® coated stirring bars. IL **1** was handled preferably with plastic lab ware.

Catalytic Tranfer Hydrogenation; General Procedures

Route A (Table 1, Entries 1–7): Substrates (3.27 mmol to 3.85 mmol) were dissolved in the ionic liquid **1** (3 mL) and 10% Pd/C (50 mg/mmol substrate) was added. A five molar excess of finely ground ammonium formate was added and the vessel sealed. The vessel was irradiated with microwaves of max. 300 W with a temperature ramp to reach 150 °C within 10 min, retaining this temperature until the total time of 80 min had been expired. After cooling, the reaction mixture was exhaustively extracted with MTBE and checked by TLC (hexane–EtOAc, 80:20). The collected organic phases were filtered through a short plug of silica gel to remove traces of catalyst and evaporated. No further purification of the products was required, since purity was typically >95% as checked by NMR spectroscopy.

Route B: (Table 2, Entries 1–7): The experiments were run under identical conditions as described for route A, except that ammonium formate was replaced by a freshly prepared, cold mixture of Et_3N and 96% formic acid.

Study of the Recycleability

The procedure was performed exactly as described in route B. After extraction, traces of MTBE were removed by bubbling a gentle stream of argon through the heated (80–100 °C) mixture of **1** and the used catalyst (Tables 3 and 4).

Acknowledgment

We are indebted to Prof. Eric Carreira, ETH Zürich, and Drs. Gerd Ruehter, Mark J. Tebbe and Macharri Vorndran-Jones, Eli Lilly Research Laboratories for helpful discussions.

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