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Use of an Ionic Liquid as a Co-solvent for Recyclable Pd/C-mediated *N*-Debenzylation†

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Benzyl group is a widely used protecting group for amino, hydroxyl and sulfurhydryl groups in peptide and carbohydrate chemistry.[1] Its popularity as a protecting group owes to its chemical stability under various reaction conditions including strongly acidic and basic environments. However, this robust character of the benzyl group sometimes turns out to be a liability when it comes to its deprotection. For the deprotection of the *N*-benzyl group, a variety of methods have been reported including hydrogenation with Pd/C at high or atmospheric pressure,[2] catalytic transfer hydrogenation in acidic media[3] or with ammonium formate,[4] oxidation with molecular oxygen,[5] use of Lewis acids, or employment of photosensitized single electron transfer reaction[6] and use of other reagents.[7] Except for the catalytic hydrogenation and transfer hydrogenation employing ammonium formate,[2-4] most of the methods require rather harsh reaction conditions for satisfactory yields of the debenzylation. From our continued interest in peptidomimetic chemistry, we were in search of mild and possibly recyclable deprotection methods for various *N*-benzyl and *N*,*N*-dibenzyl protected amino groups. If the reagents or catalysts for the debenzylation can be recycled, the process would be amenable to large scale, practical applications.[8]

Recently, ionic liquids, made of organic cations and various anions, have emerged as powerful solvents or catalysts due to their peculiar physical and chemical properties such as high polarity, low melting point, non-volatile character, poor coordination, and immiscibility with other organic solvents.[9] Recently various attempts have been made to use Pd nanoparticle catalysts in ionic liquid media.[10,11] It has been reported that the ionic liquids can be utilized to accelerate and enhance selectivities in a number of organic reactions. After several attempts of rather capricious deprotection of various *N*-benzyl- and *N*,*N*-dibenzylamino groups using Pd/C under atmospheric pressure of hydrogen, we have examined ionic liquids as a co-solvent for *N*-debenzylation, keeping in mind particularly a possibility of recycling through the immobilization of the catalyst in an ionic liquid. Herein, we wish to report on the mild and efficient debenzylation of various *N*-benzyl- and *N*,*N*-dibenzylamino derivatives using 1-*n*-butyl-3-methylimidazolium (bmim) salts as co-solvents and efficient recycling of Pd/C catalyst.

First we screened widely used, commercially available ionic liquids (**1a-e**) to select a proper solvent system for the debenzylation (Figure 1). Taking *N*-benzylpiperidine (**2**) as a representative substrate, reactions were carried out employing 50 wt % of Pd/C relative to starting material under 1 atm of H_2 in a combination of methanol and an ionic liquid for 16 h at room temperature. Then the reaction mixture was treated with $(Boc)_2O$ for 12 h at room temperature and the *N*-Boc protected product **3** was extracted with a mixture of EtOAc and *n*-hexane (1:1 v/v). The extracted organic layer was concentrated under reduced pressure and purified on a silica gel chromatographic column (EtOAc:*n*-hexane = 1:8 to 1:4 v/v). The results are shown in Table 1.

From Table 1, it became clear that yield of *N*-debenzylation was highly dependent upon the counter-anion of the ionic liquid. The reaction in methanol alone without the use of any ionic liquid provided a 77% yield of the desired product after protection with Boc group. Use of MeOH and [bmim]Cl (**1a**) mixture provided only 34% yield of **3** (entry 2). Some improvement (70% yield) was observed with the use of [bmim]OTf (**1b**) (entry 3). However, use of [bmim]SbF_6 (**1c**) and [bmim]PF_6 (**1d**) improved the yield noticeably to 82% and 93%, respectively (entries 4 and 5) and the best result was obtained using [bmim]BF_4 (**1e**) as co-solvent giving 96% yield of the desired product (entry 6).

Using the proper solvent system identified in Table 1, we

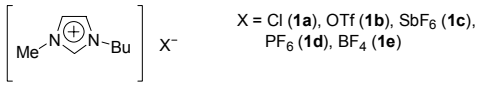
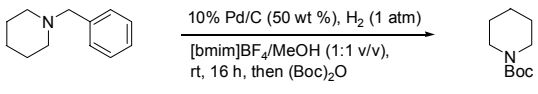


Figure 1. Various ionic liquids.

Table 1. Screening of ionic liquids for *N*-debenzylation



2 **3**

entry	ionic liquids used with methanol (1:1, v/v)	yield (%)[a]
1	MeOH only	77[b]
2	**1a**	34
3	**1b**	70
4	**1c**	82
5	**1d**	93
6	**1e**	96

[a]Yields after purification on silica gel column. [b]About 10% starting material remained.

†This paper is dedicated to Professor Sunggak Kim on the occasion of his honorable retirement.

Table 2. Screening the amount of the catalyst

entry	wt % of 10% Pd/C	yield (%)[a]
1	5	6
2	10	19
3	20	33
4	50	96

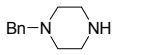
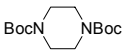
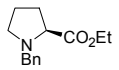
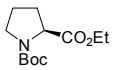
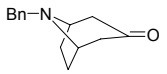
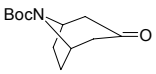
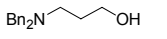
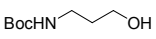
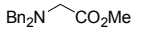
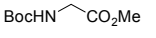
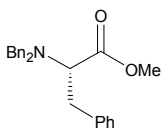
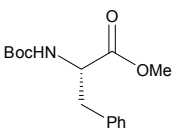
[a]Yields of Boc-protected amines after purification on silica gel column.

Table 3. Search for the best organic co-solvent system in combination with [bmim]BF_4

entry	solvent system (v/v)	time (h)	yield (%)[a]
1	**1e** : THF = 1:1	16	76
2	**1e** : EtOAc = 1:1	16	86
3	**1e** : DCM = 1:1	16	84
4	**1e** : MeOH = 1:1	16	96
5	**1e** : MeOH = 1:10	16	62
6	**1e** : MeOH = 1:5	16	59
7	**1e** : MeOH = 5:1	16	25

[a]Isolated yields after purification of Boc-protected amines on silica gel column.

Table 4. Result on the *N*-debenzylation using 50 wt % Pd/C in 1:1 methanol/[bmim]BF_4 followed by Boc-protection

entry	substrate	product	time (h)	yield (%)[a]
1			12	93
2			12	93
3			12	96
4			24	91
5			12	95
6			12	96

[a]Yields after purification on silica gel column.

then investigated the influence on the yield of the amount of activated Pd/C relative to that of the starting material using otherwise the same reaction conditions. As outlined in Table 2, use of less than 50 wt % of Pd/C proved to be not effective in the deprotection under given time period (16 h) at room temperature. In fact the yields were almost directly proportional to the amount of the catalyst system employed and use of 50 wt % of the catalyst was necessary to ensure the best result (96% yield, entry 4).

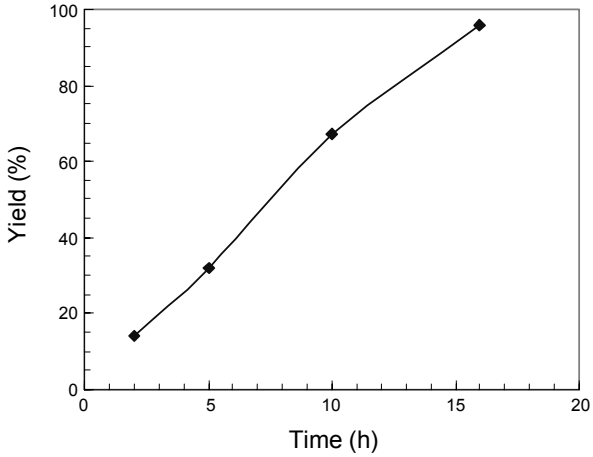


Figure 2. Yields of **3** at given reaction time.

We then examined reaction time required to complete the deprotection in [bmim]BF_4/MeOH (1:1 v/v) using 50 wt % of Pd/C, and the results are outlined in Figure 2. The production of the deprotected amine was almost linearly proportional to the reaction time and at least 16 h was required to furnish the best result.

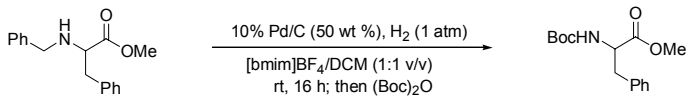
Examination of various organic co-solvents and their ratios in combination with **1e** was also carried out under otherwise identical reaction conditions. The less polar solvents examined in Table 3, i.e. THF, ethyl acetate and dichloromethane, turned out to be somewhat inferior to methanol (entries 1-3). The ratio of methanol to the ionic liquid was also found to be critical; a 1:1 mixture of methanol and [bmim]BF_4 was essential in ensuring the best yield of the deprotection (entry 4). Reactions in solvent systems employing 9% and 17% of the ionic liquid relative to methanol proceeded slowly (entries 5 and 6, respectively). Use of a large excess of ionic liquid did not provide satisfactory result either, presumably due to low solubility of the substrate in the solvent system (entry 7).

With the efficient *N*-debenzylation method using the ionic liquid in hand, we carried out debenzylation of various mono- and dibenzyl-protected amino derivatives as shown in Table 4.

Most of the *N*-benzyl derivatives of secondary amines and *N*,*N*-dibenzyl derivative of primary amines were successfully cleaved in the presence of [bmim]BF_4/MeOH (1:1 v/v) under 1 atm of H_2 atmosphere at room temperature in 12 ~ 24 h, providing more than 90% yields of the desired product after Boc-protection (entries 1-6). It is noteworthy that even *N*,*N*-dibenzyl derivative of sterically hindered L-phenylalanine methyl ester was cleanly converted to the corresponding Boc-protected amine in an excellent (96%) yield under atmospheric pressure of hydrogen (entry 6).

We then investigated recycling capability of the ionic liquid for debenzylation. For the recycling experiment, we discovered that dichloromethane proved to be a better co-solvent than

Table 5. Recycling investigation



cycle	1	2	3	4	5	6	7	8	9	10	11[b]
yield (%)[a]	92	94	79	74	82	81	84	65	29	2	93

[a]Yields after purification on silica gel column. [b]After 10th recycling, fresh Pd/C (50 wt %) was added.

MeOH since it gave better extraction profile. Therefore, the co-solvent was switched to dichloromethane to minimize the leaching out of palladium. After extraction with EtOAc/*n*-hexane (1:1 v/v) to separate the products from the reaction mixture, the residual black ionic liquid containing the Pd/C suspension was directly reused for the next debenzylation. The reaction was recycled without addition of further Pd/C and ionic liquid and the results are shown in Table 5. A slight drop in the yield after the 3rd recycling was observed, however, uniformly good yields were obtained from the 3rd to the 7th recycling. At the 8th recycling experiment, the yield dropped considerably and at the 9th, precipitously. This is presumably due to the leaching out of the palladium metal from the Pd/C complex.[12] Most of the starting material was recovered unchanged at the 10th recycling experiment. After 10th recycling experiment, a fresh batch of 10% Pd/C was added to the reaction mixture. In that case, a satisfactory yield (93%) was obtained, indicating that the integrity of the ionic liquid after 10th recycling experiment was still intact.

In summary, an efficient deprotection method for *N*-benzylamine derivatives has been developed employing [bmim]BF_4 as co-solvent under mild and non-acidic catalytic hydrogenation conditions. The best result was obtained for *N*-benzylpiperidine using 50 wt % of Pd/C in [bmim]BF_4/MeOH (1:1 v/v) at 1 atm of H_2 and room temperature. Using this protocol, *N*-benzyl group was successfully removed from various *N*-benzylamino derivatives in high yields. In recycling experiments, a slight, gradual decrease in yield was observed until a precipitous drop at the 8th recycle. The critical role of ionic liquid for this mild debenzylation and how to conserve the activity of Pd in ionic liquid are under investigation.

Experimental Section

General procedure for *N*-debenzylation. To a stirred mixture solution of methanol (1 mL) and ionic liquid (1 mL) were added *N*-benzyl derivative (100 mg) and 10 wt % Pd/C (50 mg). Resulting suspension was vigorously stirred for 16 h at room temperature under atmospheric pressure of H_2. Then Boc_2O (1.2 equiv) was added and the mixture stirred for 12 h. Methanol was evaporated under reduced pressure and the residue was extracted with a mixture of *n*-Hexane, EtOAc and Et_2O (5 times each of 1.0, 1.0, and 2.0 mL's, respectively). Combined organic phase was concentrated under reduced pressure. The crude product was purified through column chromatography on silica gel to afford the desired product.

For the repetition experiment, the ionic liquid phase after extraction with a mixture of organic solvents was reused for the next reaction.

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