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The first Bischler–Napieralski cyclization in a room temperature ionic liquid

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Abstract—We have demonstrated the use of the room temperature ionic liquid, 1-butyl-3-methylimidazoliumhexafluorophosphate ([bmim]PF_6), as an environmentally benign solvent for the preparation of isoquinoline derivatives through Bischler–Napieralski cyclization under mild conditions with excellent purity and yields. The role of HF as a catalyst in the reaction was also investigated. © 2002 Elsevier Science Ltd. All rights reserved.

Room-temperature ionic liquids[1] such as [bmim]PF_6 **1** are finding growing applications as alternative reaction media for separations[2] and organic transformations.[3–11] Recent examples of such organic transformations include hydrogenations,[3] Friedel–Crafts reactions,[4] Diels–Alder reactions,[5] Heck reactions,[6] olefin hydrodimerizations/telomerizations,[7] olefin dimerizations,[8] cross-couplings,[9] hydroformylations[10] and oxidations.[11] The desirable advantages of ionic liquids such as the lack of vapor pressure, wide liquid range and thermal stability have made them exceptional reaction media and environmentally benign solvents. Accordingly, they are emerging as novel replacements for volatile organic compounds (VOCs) which are used as solvents in organic synthesis and transformations. They are especially promising solvents for catalysis where the activity, selectivity, and stability of catalysts are enhanced (Fig. 1).

In this communication we report an efficient and environmentally friendly preparation of isoquinoline derivatives using an ionic liquid as a substitute for chlorinated and high boiling solvents.

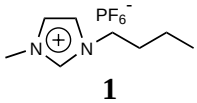

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Figure 1. [bmim]PF_6.

The isoquinoline nucleus is widespread in the alkaloid family and is found in many physiologically active compounds.[12] The most widely used methods for the synthesis of isoquinolines are relatively classical synthetic methods and include the Bischler–Napieralski,[13] and the Pictet–Spengler[14] reactions. The Bischler–Napieralski synthesis involves the cyclodehydration of β-phenylethanamides to 3,4-dihydroisoquinolines using a wide range of dehydrating agents.[15] The reaction often involves the use of toxic and hazardous chlorinated and high boiling point solvents (e.g. 1,2-dichloroethane, 1,1′,2,2′-tetrachloroethane, chlorobenzene, dioxane)[15d,16] at elevated temperatures. In our experience, under these conditions and with the use of phosphorus oxychloride as a dehydrating reagent, black gummy products are obtained. The products require extensive purification by chromatography and several recrystallizations with decolourising charcoal to bring them to acceptable purity. These difficulties are therefore limiting factors in such an important reaction.

The effectiveness of ionic liquids as solvents for the Bischler–Napieralski reaction was examined in the preparation of isoquinoline derivatives. We set out to examine the reaction in the most widely used ionic liquid, [bmim]PF_6 **1**, using phosphorus oxychloride as a dehydrating reagent and *N*-(3′,4′-dimethoxyphenethyl)-acetamide as the starting amide (entry **1**, Table 1). The reaction[18] was carried out by dissolving 0.80 g of the amide in 1.6 mL [bmim]PF_6 followed by dropwise

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† Ionic liquid sample prepared and supplied by Adam McCluskey.

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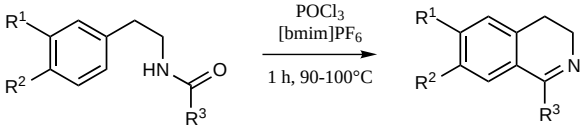
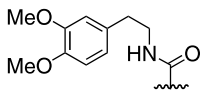
Table 1. Cyclization of substituted phenethylamides



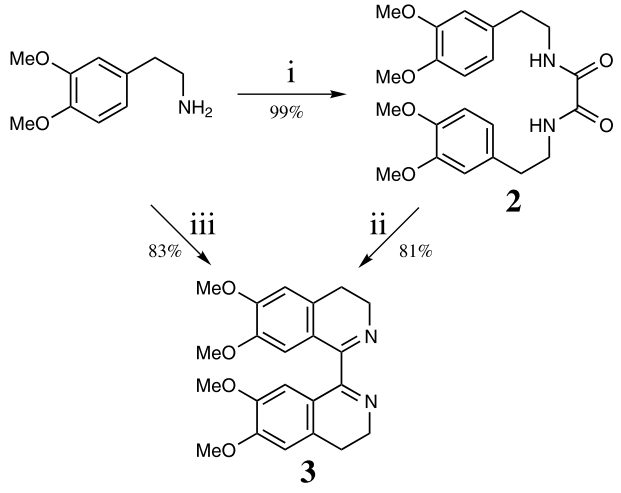
Entry	R^1	R^2	R^3	Using ionic liquid	Literature
				Yield (%)	Yield (%)
1	OMe	OMe	Me	87	61[15d,17]*
2	OMe	H	Me	83	64[16]*
3	H	H	Me	0	0[13a]
4	OMe	OMe		81	56[15d]*

*Reaction solvent: ethanol:1,1,2,2-tetrachloroethane (11:3) or ethanol:1,2-dichloroethane (3:11) or chlorobenzene.

addition of phosphorus oxychloride, then heating at 90–100°C for 1 h. The product was recovered by simple extraction as a white solid and the ionic liquid was recycled and reused. The purity of the product was confirmed by ^{1}H NMR spectroscopic analysis as no starting materials or decomposition products were observed and therefore no further purification of the product was needed. The yield (entry 1, Table 1) of the product was found to be much higher than in the case where other solvents were used. The black colour associated with the ionic liquid after the reaction could be removed by flash column chromatography using ethyl acetate as eluent. The process was extended to the cyclization of other amides (entries 2, 3 and 4, Table 1) employing similar conditions. The results were again excellent in terms of yields and product purity for entries 2 and 4,[19] while only the starting material was recovered in the case of entry 3. This is not surprising as the ease of the cyclization is greatly affected by the electron density (and therefore electron donating groups *meta* to the aminoethyl group) at the benzenoid carbon undergoing cyclization. A double Bischler–Napieralski reaction also proceeded under these conditions with excellent yields and purity (entry 4, Scheme 1). Therefore, bisoxamide **2** was subjected to cyclization in [bmim]PF_6 using $POCl_3$ to give bisimine **3**.

Alternatively, cyclization of bisoxamide **2** to give bisimine **3** could also be achieved in high yields (83%) in one pot using [bmim]PF_6 without the necessity of separating bisoxamide **2** (Scheme 1). The cyclization reactions using [bmim]PF_6 are significant from the viewpoint of pollution avoidance and excellent purity of the products obtained.

It is a well-known fact that [bmim]PF_6 ionic liquid undergoes slow hydrolysis when it comes into contact with water or humidity, producing hydrofluoric acid among other hydrolysis products. HF can also be formed during the preparation of [bmim]PF_6 and therefore can be present as a contaminant in the ionic liquid. The role of HF as a catalyst in the Bischler–Napieralski reaction was therefore studied and its effect on the yield was investigated. Two reactions for the cyclization of *N*-(3′,4′-dimethoxyphenethyl)acetamide with $POCl_3$ (entry 1, Table 1) using the same batch of ionic liquid were investigated under similar conditions, except that in one case, and prior to the reaction, the ionic liquid was extracted several times with water to ensure it contained no HF and was then dried under vacuum over molecular sieves. The reactions were performed under an inert atmosphere of nitrogen to exclude moisture. Since the two sets of reactions gave similar yields [86 and 84% (treated with H_2O and therefore HF free)], it was concluded that HF plays no catalytic part in the reaction.



Scheme 1. Double Bischler–Napieralski cyclization. *Reagents and conditions*: (i) $(C_2H_5O_2C)_2$, toluene, 2.5 h, reflux; (ii) $POCl_3$, [bmim]PF_6, 1 h, 90–100°C; (iii) (a) $(C_2H_5O_2C)_2$, [bmim]PF_6, 3 h, 90–100°C, (b) $POCl_3$, 1 h, 90–100°C.

In conclusion we have demonstrated that Bischler–Napieralski cyclization of phenethylamine derivatives to the corresponding isoquinoline derivatives can be achieved effectively using [bmim]PF_6 **1** to give higher yields and cleaner products in a shorter reaction time than otherwise achieved under the typical conditions employed for the Bischler–Napieralski cyclization.

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18. General procedure for the Bischler–Napieralski cyclization reaction in ionic liquid: $POCl_3$ (ca. 9 mol equiv.) was added dropwise to a suspension of the amide in the ionic liquid (ca. 0.8 mL ionic liquid per 0.40 g of the amide) at room temperature. After complete addition the mixture was stirred at room temperature for 10 min then heated to 90–100°C for 1 h whereupon the mixture turned black. The reaction mixture was cooled to room temperature then diluted with ethyl acetate and extracted with water. The aqueous layer was made basic (pH 10) using 10% aqueous K_2CO_3 and then extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and the solvent was removed in vacuo to give a white solid. The ionic liquid was recovered from the original ethyl acetate layer by evaporation under reduced pressure.
19. Preparation of 6,6′,7,7′-tetramethoxy-3,3′,4,4′-tetrahydro-1,1′-bisisoquinoline **3**: *N*,*N*′-Bis(3′,4′-dimethoxyphenethyl)oxamide **2** (0.65 g, 1.6 mmol) in [bmim]PF_6 (1.3 mL) was treated with $POCl_3$ (0.33 mL) according to the general procedure to give the product as off-white needles after crystallization from 95% ethanol (0.49 g, 81%) mp 201–203°C (198–202°C).[15d] ν_{max} (Nujol): 1605, 1565, 1510, 1455, 1405, 1375, 1350, 1320, 1280, 1260, 1240, 1215, 1200, 1190, 1120, 1030, 990, 940, 915, 860, 825, 805, 775 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.79 (4H, t, *J* 7.4 Hz, CH_2-4 and CH_2-4′), 3.72 (6H, s, OCH_3-7 and OCH_3-7′), 3.90 (4H, obscured triplet, CH_2-3 and CH_2-3′), 3.91 (6H, s, OCH_3-6 and OCH_3-6′), 6.73 (2H, s, H8 and H8′), 6.87 (2H, s, H5 and H5′). ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 25.5 (C4 and C4′), 47.3 (C3 and C3′), 55.9 (OCH_3-6, OCH_3-6′, OCH_3-7 and OCH_3-7′), 110.2 (C5 and C5′), 110.5 (C8 and C8′), 121.0 (C8a and C8′a), 131.4 (C4a and C4′a), 147.3 (C7 and C7′), 151.3 (C6 and C6′), 164.6 (C1 and C1′). Mass spectrum: *m*/*z* 380 (M^+, 15%), 379 (M−1, 13%), 349 (100), 192 (11).