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IONIC LIQUID IN ORGANIC SYNTHESIS: THE PICTET-SPENGLER REACTION

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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 2-benzenesulfonyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid ethyl ester derivatives through Pictet-Spengler reaction using phenyliodine(III) bis(trifluoroacetate) (PIFA) under mild conditions.

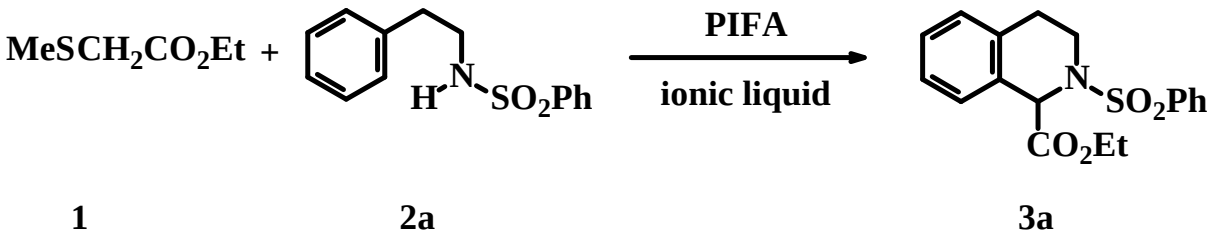
Room temperature ionic liquids (RTIL) are liquids that are composed entirely of ions. In fact, ionic liquids can now be produced which remain liquid at room temperature and below (even as low as -90 ℃) and appear to be undemanding and inexpensive to manufacture.[1] Ionic liquids offer an attractive alterative to conventional organic liquids for clean synthesis, as they are easy to recycle, lack flammability, and possess effectively no vapour pressure. Compared with classical molecular solvents, the ionic liquids are environmentally benign reaction media.[2] To date some of the more important reactions have been carried out and investigated in ionic liquids, for example, Friedel–Crafts reaction,[3] alkoxycarbonylation,[4] hydrogenation,[5] Diels–Alder reaction,[6] Wittig reaction,[7] Heck reaction,[8] Trost-Tsuji coupling,[9] Ring-closing metathesis (RCM),[10] Suzuki cross-coupling,[11] Fischer indole synthesis,[12] 1,3-dipolar cycloaddition reaction,[13] Beckmann rearrangement,[14] the Knoevenagel and Robinson annulation reactions,[15] etc.

The isoquinoline nucleus is widespread in the alkaloid family and is found in many physiologically active compounds.[16] The most widely used methods for the synthesis of isoquinolines are relatively classical synthetic methods and include the Bischler-Napieralski[17] and the Pictet-Spengler reactions.[18] The Pictet-Spengler synthesis occurs only when the ring-closure position is activated by electron donating substituents. However, β-phenethylamines bearing an electron withdrawing substituent on the benzene

ring afford 1,2,3,4-tetrahydroisoquinoline derivatives in poor yields or do not give any cyclized product. Modifications of the original strategy to increase the electrophilicity of the iminium intermediate, which employ electron withdrawing groups on the nitrogen such as acyl [19] or sulfonyl [20] moieties are known.

Recently, hypervalent iodine(III) reagents have generated considerable interest due to their low toxicity, ready availability, and easy handling.[21] As a part of our ongoing studies to utilize hypervalent iodine(III) reagents in organic synthesis, we report here a modified Pictet-Spengler cyclization of *N*-benzenesulfonyl-β-phenethylamines with α-acyl sulfide using phenyliodine(III) bis(trifluoroacetate) (PIFA) in the room temperature ionic liquid under mild conditions to prepare 2-benzenesulfonyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid ethyl estetr derivatives.

Firstly, we compared the efficacy of different ionic liquids in the reaction of α-acyl sulfide (**1**) with *N*-benzenesulfonyl-β-phenethylamine (**2a**) using PIFA (Scheme 1). We chose the most commonly and conveniently used ionic liquid, 1-butyl-3-methylimidazolium hexafluorophosphorate ([bmim]PF_6), 1-butyl-3-methylimidazolium tetrafluorophosphorate ([bmim]BF_4) and butylpyridinium tetrafluoroborate ($BPyBF_4$), as representatives for this reaction. The results summarized in Table 1 show that [bmim]PF_6 gave the best results in terms of yield and reaction time. When the reaction was conducted in the classical solvents, such as 1,2-dichloroethane, the preparation of 1,2,3,4-tetrahydroisoquinoline (**3a**) needs refluxing for 4 h.[22]



1 **2a** **3a**

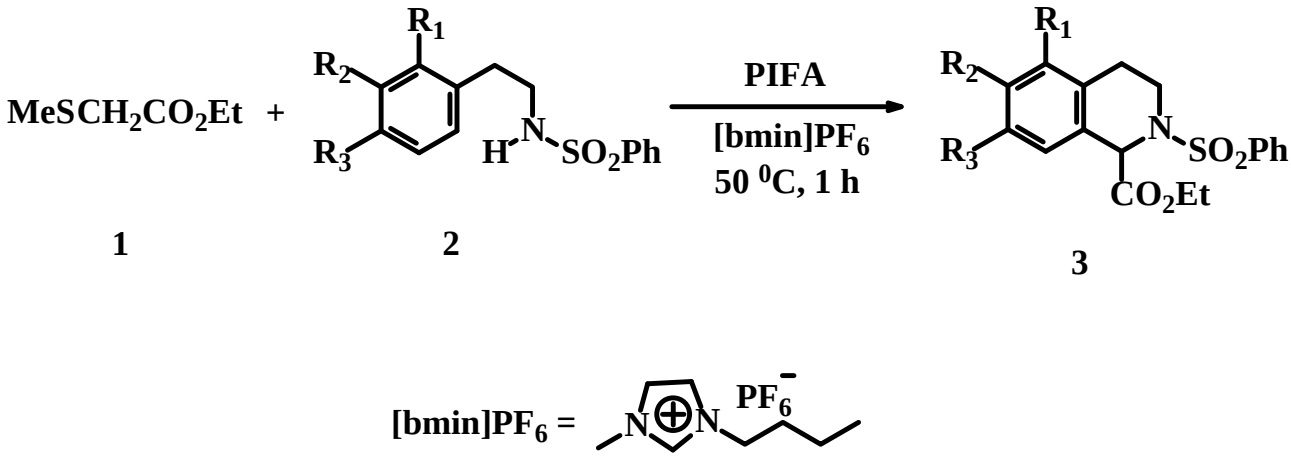
Scheme I

Table 1. Reaction of α-acyl sulfide (**1**) with *N*-benzenesulfonyl-β-phenethylamine (**2a**) in different ionic liquids to form **3a**

Entry	Ionic Liquid	Reaction Temp (℃)	Reaction Time (h)	Yield (%)
1	[bmim]PF_6	50	1	88
2	[bmim]BF_4	80	2	72
3	$BPyBF_4$	80	2	70

The scope of the reaction of α-acyl sulfide (**1**) with *N*-benzenesulfonyl-β-phenethylamines (**2**) using PIFA occured easily in ionic liquid [bmim]PF_6 at 50 ℃ for 1 h to form the corresponding

1,2,3,4-tetrahydroisoquinoline derivatives (**3**) (Scheme 2, Table 2). Interestingly, unlike the case of the sulfur-based reagent employed by Kohno,[23] no Friedel-Crafts reaction products were detected when activated β-phenethylamines were cyclized.[24]



Scheme II

Table 2. Reaction of α-acyl sulfide (**1**) with *N*-benzenesulfonyl-β-phenethylamines in ionic liquid [bmim]PF_6

Entry	Compd	R_1	R_2	R_3	Product	Yield (%)
1	**2a**	H	H	H	**3a**	88
2	**2b**	H	H	OMe	**3b**	78
3	**2c**	H	OMe	OMe	**3c**	85
4	**2d**	Cl	H	H	**3d**	73
5	**2e**	H	Cl	H	**3e**	72
6	**2f**	H	H	Cl	**3f**	75
7	**2g**	Cl	H	Cl	**3g**	65
8	**2h**	H	H	Br	**3h**	74
9	**2i**	H	H	F	**3i**	72

The cyclization is assumed to proceed through iminium cation which would be formed by Pummerer-type reaction of ethylmethylthioacetate (**1**) with *N*-benzenesulfonyl-β-phenethylamines (**2**) using PIFA.

Thus, our results herein that the modified Pictet-Spengler reaction of *N*-benzenesulfonyl-β-phenethylamines to the corresponding 1,2,3,4-tetrahydroisoquinolines can be achieved effectively using PIFA in the ionic liquid [bmim]PF_6 under mild conditions and gives significant rate accelerations of products. Separation of products from the ionic liquids is very straightforward, as is recycling of the ionic liquid.

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EXPERIMENTAL

All melting points are uncorrected. The IR spectra were recorded on a Shimadzu IR-27 G spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Unity Plus 400 MHz. Chemical shifts (δ) were measured in ppm with respect to TMS. MS were obtained on a JEOL JMS D-300 instrument.

Typical procedure for the preparation of 2-benzenesulfonyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid ethyl estetr (3a)

To a solution of the α-acyl sulfide (**1**) (0.13 g, 1.0 mmol) in [bmim]PF_6 (2 mL) was added PIFA (0.52 g, 1.2 mmol), and the mixture was stirred at rt for 1 h. Then *N*-benzenesulfony-β-phenethylamine (**2a**) (0.26 g, 1.0 mmol) was added and the mixture was heated at 50 ℃ for 1 h to complete the reaction. Subsequently, the reaction mixture was extracted with Et_2O. The remaining ionic liquid was reused after drying in vacuum. The combined ethereal solution was evaporated under reduced pressure. The residue was chromatographed on silica gel eluting with *n*-hexane: ethyl acetate (5:1) to give **3a**. Mp 60-61 ℃ (Lit.,[23] mp 61-62 ℃). IR (KBr) ν: 1738 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.15 (t, *J* = 7.2 Hz, 3H), 2.85-2.93 (m, 2H), 3.81-3.87 (m, 2H), 3.96-4.03 (m, 2H) 5.53 (s, 1H), 7.08-7.23 (m, 3H), 7.37-7.60 (m, 4H), 7.81-7.86 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.8, 28.2, 40.7, 57.7, 61.5, 126.4, 127.0, 127.3, 127.8, 128.9, 129.0, 129.7, 132.6, 133.8, 139.4, 170.1. MS (EI) m/z: 345 (M^+), 272, 77.

2-Benzenesulfonyl-7-methoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid ethyl estetr (3b)

Oily compound. IR (neat) ν: 1739 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ : 1.16 (t, *J* = 7.2 Hz, 3H), 2.74-2.86 (m, 2H), 3.76-3.86 (m, 2H), 3.77 (s, 3H), 3.98-4.01 (m, 2H), 5.49 (s, 1H), 6.79 (d, *J* = 8.8 Hz, 1H), 6.99 (dd, *J* = 2.4, 8.8 Hz, 1H), 6.92 (d, *J* = 2.4 Hz, 1H), 7.45-7.57 (m, 3H), 7.79-7.84 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.9, 27.4, 41.0, 55.3, 57.8, 61.5, 111.9, 114.4, 125.8, 126.9, 127.0, 128.9, 129.6, 130.0, 130.5, 132.6, 139.5, 157.9, 170.0. MS (EI) m/z: 375 (M^+), 302, 121, 77. HRMS (EI) Calcd for $C_{20}H_{21}NO_5$: 375.114. Found: 375.115.

2-Benzenesulfonyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid ethyl estetr (3c)

Mp 78-79 ℃ (Lit.,[23] mp 77-79 ℃). IR (KBr) ν: 1736 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.14 (t, *J* = 7.2 Hz, 3H),

2.75-2.83 (m, 2H), 3.77-3.86 (m, 2H), 3.84 (s, 3H), 3.85 (s, 3H), 3.96-4.01 (m, 2H), 5.44 (s, 1H), 6.55 (s, 1H), 6.88 (s, 1H), 7.45-7.49 (m, 2H), 7.53-7.55 (m, 1H), 7.81-7.84 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.8, 27.7, 40.6, 55.7, 55.8, 57.2, 61.4, 109.7, 111.2, 121.2, 126.0, 126.9, 128.8, 132.5, 139.5, 147.5, 148.6, 170.2. MS (EI) m/z: 405 (M^++1), 405 (M^+), 332.

2-Benzenesulfonyl-5-chloro-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid ethyl estetr (3d)

Oily compound. IR (neat) ν: 1738 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.14 (t, *J* = 7.2 Hz, 3H), 2.78-2.96 (m, 2H), 3.73-3.82 (m, 1H), 3.93-4.01 (m, 3H), 5.55 (s, 1H), 7.15 (t, *J* = 8.0 Hz,1H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.46-7.58 (m, 3H), 7.81-7.84 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.8, 26.0, 40.0, 57.3, 61.7, 125.9, 127.0, 127.1, 127.6, 128.6, 128.7, 131.8, 131.9, 132.7, 134.4, 139.3, 169.5. MS (EI) m/z: 382 (M^++2), 380 (M^+), 306, 77. HRMS (EI) Calcd for $C_{19}H_{18}NO_4Cl$: 379.064. Found: 379.063.

2-Benzenesulfonyl-6-chloro-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid ethyl estetr (3e)

Oily compound. IR (neat) ν: 1739 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.14 (t, *J* = 7.2 Hz, 3H), 2.77-2.93 (m, 2H), 3.74-3.91 (m, 2H), 3.95-4.02 (m, 2H), 5.52 (s, 1H), 7.11 (d, *J* = 2.4 Hz, 1H), 7.18 (dd, *J* = 2.4, 8.4 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 1H), 7.46-7.50 (m, 2H), 7.55-7.57 (m, 1H), 7.81-7.84 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.8, 28.1, 40.3, 57.2, 61.7, 126.7, 127.0, 128.2, 128.7, 128.9, 131.9, 132.7, 133.6, 135.7, 139.3, 169.7. MS (EI) m/z: 382 (M^++2), 380 (M^+), 306, 77. HRMS (EI) Calcd for $C_{19}H_{18}NO_4Cl$: 379.064. Found: 379.065.

2-Benzenesulfonyl-7-chloro-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid ethyl estetr (3f)

Oily compound. IR (neat) ν: 1739 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.17 (t, *J* = 7.2 Hz, 3H). 2.76-2.91 (m, 2H), 3.74-3.92 (m, 2H), 3.99-4.04 (m, 2H), 5.50 (s, 1H), 7.05 (d, *J* = 8.0 Hz, 1H), 7.18 (dd, *J* = 2.0, 8.0 Hz, 1H), 7.40 (d, *J* = 2.0 Hz, 1H), 7.47-7.59 (m, 3H), 7.81-7.84 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.8, 27.6, 40.4, 57.2, 61.8, 126.9, 127.2, 128.0, 128.9, 130.3, 131.3, 132.0, 132.3, 132.7, 139.3, 169.5. MS (EI) m/z: 382 (M^++2), 380 (M^+), 306. HRMS (EI) Calcd for $C_{19}H_{18}NO_4Cl$: 379.064. Found: 379.062.

2-Benzenesulfonyl-5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid ethyl estetr (3g)

Oily compound. IR (neat) ν: 1738 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.10 (t, *J* = 7.2 Hz, 3H), 3.11-3.26 (m, 2H), 3.46-3.48 (m, 2H), 3.93-3.99 (m, 2H), 5.70 (s, 1H), 7.18 (d, *J* = 2.0 Hz, 1H), 7.34 (dd, *J* = 0.8, 2.0 Hz, 1H), 7.48-7.52 (m, 2H), 7.57-7.61 (m, 1H), 7.86-7.88 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.8, 14.7, 34.4, 45.3, 62.1, 65.6, 127.2, 127.5, 128.9, 129.2, 132.0, 133.0, 134.8, 135.1, 139.1, 167.2. MS (EI) m/z: 417 (M^++4), 413 (M^+), 341, 306. HRMS (EI) Calcd for $C_{19}H_{17}NO_4Cl_2$: 413.025. Found: 413.026.

2-Benzenesulfonyl-7-bromo-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid ethyl estetr (3h)

Oily compound. IR (neat) ν: 1738 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.15 (t, *J* = 7.2 Hz, 3H), 2.73-2.87 (m, 2H), 3.71-3.79 (m, 1H), 3.85-3.93 (m, 1H), 3.99-4.02 (m, 2H), 5.49 (s, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 7.29 (dd, *J* = 2.0, 8.4 Hz, 1H), 7.45-7.49 (m, 2H), 7.52-7.57 (m, 2H), 7.80-7.83 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.8, 27.7, 40.4, 57.1, 61.8, 119.8, 126.9, 128.9, 130.1, 130.6, 130.9, 131.7, 132.7, 132.8, 139.4, 169.4. MS (EI) m/z: 426 (M^++2), 424 (M^+), 352, 350. HRMS (EI) Calcd for $C_{19}H_{18}NO_4Br$: 423.013. Found: 423.012.

2-Benzenesulfonyl-7-fluoro-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid ethyl estetr (3i)

Mp 90-92 ℃ (Lit.,[23] mp 92-93 ℃). IR (KBr) ν: 1741 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.17 (t, *J* = 7.2 Hz, 3H), 2.73-2.91 (m, 2H), 3.74-3.81 (m, 1H), 3.86-4.14 (m, 3H), 5.52 (s, 1H), 6.91-6.95 (m, 1H), 7.02-7.08 (m, 1H), 7.12 (dd, *J* = 2.4, 9.4 Hz, 1H), 7.46-7.52 (m, 2H), 7.54-7.58 (m, 1H), 7.79-7.85 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.8, 27.5, 40.7, 57.5, 61.7, 113.8, 114.1, 115.5, 127.0, 128.9, 129.5, 130.5, 131.3, 132.7, 139.4, 159.7, 169.5. MS (EI) m/z: 363 (M^+), 290, 148.

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