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Ionic liquids-assisted synthesis of 3,4-dihydroisoquinolines by the Bishler–Napieralski reaction

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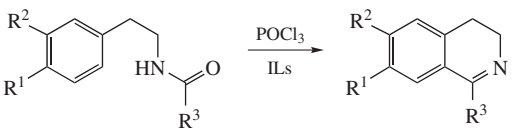
The Bishler–Napieralski cyclodehydration of *N*-acyl-2-arylethylamines into the corresponding 3,4-dihydroisoquinolines with $POCl_3$ as a dehydration reagent proceeds in ionic liquids under milder conditions and in higher yields.

Over a few recent years our research[1] has been focused on the use of ionic liquids (ILs) as reaction media and/or catalysts. ILs are known to have considerable advantages against commercial organic solvents – they are fire-resistant and recyclable, and have limited vapor pressure thus allowing efficient recovery of organic products. We studied a possibility of implementing 1,3-dipolar cycloaddition reactions in ILs, dealing with syntheses of triazoles,[2] tetrazoles[3] and fused systems,[4,5] Henry and Mannich reactions,[6] synthesis of aminothiadiazoles,[7] Schmidt rearrangement,[8] *etc*. These reactions in ILs required milder conditions and provided higher yields. If acidic catalysis was necessary (*e.g.*, in case of Henry and Mannich reactions) so-called acidic ILs (1,3-dialkylimidazolium hydrogen sulfate or triflate) played a part both of a catalyst and reaction medium.

This paper discusses the Bishler–Napieralski reaction – cyclodehydration of *N*-acyl-2-arylethylamines **1** to 3,4-dihydroisoquinolines **2** in ILs in the presence of $POCl_3$ as a dehydration reagent (Scheme 1). The isoquinoline ring is a common structural motif found in a variety of natural products and biologically active compounds.[9,10] 1,2,3,4-Tetrahydroisoquinoline derivatives are constituents of D_1-dopamine antagonists[11] and have a potential for the treatment of Parkinson's disease.[12]

The synthesis of 3,4-dihydroisoquinolines **2** by the Bishler–Napieralski reaction is usually carried out by refluxing of *N*-acyl-2-arylethylamines **1** in high-boiling solvents (xylene, toluene, chlorobenzene) in the presence of dehydration reagents such as P_2O_5,[11] $POCl_3$ or $POCl_3 + P_2O_5$,[10,13] PPA + $POCl_3$.[14] Typically a significant molar excess of dehydration reagent is required, electron-donating groups (*e.g.*, MeO) in aromatic rings facilitating the cyclization. Non-substituted amides **1** and especially those containing electron-withdrawing groups in the aromatic ring undergo the Bishler–Napieralski cyclization under very drastic conditions providing low yields of the products. In the previous years various modifications of the Bishler–Napieralski reaction have been proposed, *e.g.*, use of $(CO)_2Cl_2/FeCl_3$[15] and Tf_2O/2-ClPy[16] as dehydration systems. 1-Butyl-3-methylimidazolium hexafluorophosphate IL [bmim][PF_6] was tested as a reaction medium for for this purpose, too.[17] In this paper the cyclization of non-substituted *N*-acetyl-2-phenylethylamine **1c** and *N*-acetyl-2-arylethylamines **1a**,**b** containing one or two MeO groups under the action of $POCl_3$ as a dehydration reagent (the molar ratio **1a–c**:$POCl_3$ of 1:9) at 95–100 °C within 1 h was studied. The corresponding 3,4-dihydroisoquinolines **2a**,**b** were obtained in 74–80% yields. *N*-Acetyl-2-phenylethylamine **1c** did not react under these conditions.



1a–h **2a–c**,**e–h**

a $R^1 = R^2 = MeO$, $R^3 = Me$
b $R^1 = MeO$, $R^2 = H$, $R^3 = Me$
c $R^1 = R^2 = H$, $R^3 = Me$
d $R^1 = Cl$, $R^2 = H$, $R^3 = Me$
e $R^1 = R^2 = MeO$, $R^3 = Ph$
f $R^1 = MeO$, $R^2 = H$, $R^3 = Ph$
g $R^1 = R^2 = H$, $R^3 = Ph$
h $R^1 = Cl$, $R^2 = H$, $R^3 = Ph$

Scheme 1

Since the Bishler–Napieralski reaction is carried out in the presence of dehydration reagents having acidic nature one can expect that acidic ILs used either as a reaction medium or as a catalyst would be effective for cyclization of deactivated of *N*-acyl-2-arylethylamines **1**. In the current study we have synthesized various *N*-acyl-2-arylethylamines **1a–h** and tested them in the Bishler–Napieralski reaction in the presence of $POCl_3$ in different ILs, namely, in 1-butyl-3-methylimidazolium hydrogen sulfate ([bmim][HSO_4]), 1-ethyl-3-methylimidazolium and 1-butyl-3-methylpyrrolidinium triflates ([emim][CF_3SO_3], [bmpyrr][CF_3SO_3]) and for comparison with published data[17] in [bmim][PF_6] (Scheme 1).†

The reaction time was monitored by TLC until the full consumption of the starting amides **1**. First, we applied the described procedure[17] to substrates using [bmim][PF_6] as a medium and found that for cyclization of amides **1a**,**b** molar ratio $POCl_3$:amide can be reduced to 2.5:1 (Table 1, entries 1, 4). Amides **1c**,**d** did not yield corresponding 3,4-dihydroisoquinolines **2c**,**d** under these conditions.

† All starting (**1a–h**) and final (**2a–c**,**e–h**) compounds were previously reported. Their structures were confirmed by comparison of mp or bp and spectral characteristics (IR, MS, ^1H and ^{13}C NMR) with literature data. If the ^1H and ^{13}C NMR spectra of the prepared 3,4-dihydroisoquinolines **2** had not been published these data were determined in this work (see below). The IR spectra were measured on an UR-20 spectrometer. The ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer (300 MHz for ^1H and 75.5 MHz for ^{13}C). The MS spectra were measured on a Finnigan MAT INCOS-50 instrument. Melting points were determined on a Gallenkamp instrument (Sanyo). TLC was carried out on Silufol plates (UV_{254}).

None of the amides **1a–h** reacted properly in [bmim][HSO_4] as the IL. Luckily, triflate ILs such as [emim][CF_3SO_3] and [bmpyrr][CF_3SO_3] proved to be efficient reaction media for the preparation of 3,4-dihydroisoquinoline **2c** (2.5 molar excess of $POCl_3$, entries 7, 8). These ILs were also good to prepare 3,4-dihydroisoquinolines **2a**,**b** (entries 2, 3, 5, 6). Amide **1d** did not produce 3,4-dihydroisoquinoline **2d** in any tested ILs even by heating at 95–100 °C for 40 h. Raising the temperature to 130 °C resulted in the splitting of the amide bond.

Similar results were obtained for the Bishler–Napieralski reaction of *N*-benzoyl-2-arylethylamines **1e–h**. Amides **1e** and **1f** with MeO activating groups were converted into 3,4-dihydroisoquinolines **2e** and **2f** in [bmim][PF_6] in high yields. However, $POCl_3$: amide molar ratio of 9 : 1 (Table 1, entries 9, 11) and a longer reaction time for **1f** were required. Close results were obtained in case of [emim][CF_3SO_3] (entries 10, 12). Conversion of **1f** to **2f** proceeds faster in triflate ILs than in [bmim][PF_6]. Triflate ILs, [emim][CF_3SO_3] and [bmpyrr][CF_3SO_3], also favoured preparation of 3,4-dihydroisoquinolines **2g** from amide **1g** (reaction time 1–2.5 h, entries 13, 14). The cyclization of *N*-benzoyl-2-(4-chlorophenyl)ethylamine **1h** in triflate ILs was never complete even within 44 h. However, raising the temperature to 130 °C and $POCl_3$: amide molar ratio to 9 : 1 in [bmim][PF_6] afforded the target **2h** in 65% yield (entry 15). The IL [bmim][PF_6] was regenerated and reused in the same reactions without a remarkable drop in the yield of the product (see entries 1*, 15*).

The anion of IL has a significant effect on its catalytic activity.[18,19] However, such studies were carried out only for an optimization of scarce reactions. Both reported data[20,21] and our previous results[4] confirm that ILs are substrate-specific solvents.

Table 1 Synthesis of 3,4-dihydroisoquinolines **2a–c**,**e–h** by the Bishler–Napieralski reaction of *N*-acyl-2-arylethylamines **1a–c**,**e–h** (1 mmol) with $POCl_3$ in ILs at 95–100 °C.

Entry	Initial amide	$POCl_3$/ mmol	IL	*t*/h	Yield of **2** (%)	Yield with $POCl_3$ (%)
1	**1a**	2.5	[bmim][PF_6]	1	**2a** (85)	74–80[23,24,*b*]
1*	**1a**	2.5	[bmim][PF_6] (regen.)	1	**2a** (84)	
2	**1a**	2.5	[emim][CF_3SO_3]	3	**2a** (90)	
3	**1a**	2.5	[bmpyrr][CF_3SO_3]	3	**2a** (88)	
4	**1b**	2.5	[bmim][PF_6]	5	**2b** (86)	36[12,*c*]
5	**1b**	2.5	[emim][CF_3SO_3]	6	**2b** (90)	
6	**1b**	2.5	[bmpyrr][CF_3SO_3]	18	**2b** (82)	
7	**1c**	2.5	[emim][CF_3SO_3]	1	**2c** (93)	35[12,*c*], 75[25,*d*]
8	**1c**	2.5	[bmpyrr][CF_3SO_3]	1	**2c** (94)	
9	**1e**	9.0	[bmim][PF_6]	1	**2e** (83)	>90[27,*e*]
10	**1e**	9.0	[emim][CF_3SO_3]	12	**2e** (85)	
11	**1f**	9.0	[bmim][PF_6]	18	**2f** (80)	65[28,*f*]
12	**1f**	9.0	[emim][CF_3SO_3]	8	**2f** (78)	
13	**1g**	9.0	[emim][CF_3SO_3]	2.5	**2g** (75)	90[28,*f*]
14	**1g**	9.0	[bmpyrr][CF_3SO_3]	1	**2g** (81)	
15	**1h**	9.0	[bmim][PF_6]	10[*a*]	**2h** (65)	54[29,*g*]
15*	**1h**	9.0	[bmim][PF_6] (regen.)	10[*a*]	**2h** (63)	

[*a*] Temperature 130 °C. [*b*] $POCl_3$, refluxing in toluene for 3 h. [*c*] $POCl_3 + P_2O_5$, refluxing in toluene for 3 h. [*d*] $POCl_3 + P_2O_5$ in toluene, microwave irradiation for 6 min. [*e*] $POCl_3$, refluxing in MeCN for 2 h. [*f*] $POCl_3 + P_2O_5$, refluxing in xylene for 4 h. [*g*] $POCl_3 + P_2O_5$, refluxing in xylene for 6 h.

The general principles for selection of ILs for different reactions are absent. Nevertheless, a high acidic-catalytic activity of triflate ILs was indicated earlier. A series of pyridinium ILs with different anions was investigated for acid-catalysed transesterification of Jatropha oil,[22] when triflate IL showed the best catalytic activity. Evidently, our success in the synthesis of 3,4-dihydroisoquinolines **2c**,**g** with non-activated aromatic ring can be rationalized in view of acid-catalytic activity of triflates used.

According to literature data[12,23–28] preparation of 3,4-dihydroisoquinolines **2** from the corresponding *N*-acyl-2-arylethylamines **1** in conventional organic solvent with $POCl_3$ as dehydrating reagent required higher temperature and application of P_2O_5 additive, whereas the yields of products were usually lower.

In summary, the results obtained in this work exemplifying the Bishler–Napieralski synthesis of 3,4-dihydroisoquinolines **2** demonstrate the preparative and environmental advantages of ILs as reaction media and catalysts as compared to conventional organic solvents.

General procedure for the preparation of 3,4-dihydroisoquinolines **2** *in ILs*. A mixture of *N*-acyl-2-arylethylamine **1** (1 mmol), $POCl_3$ (2.5 or 9 mmol) and 2 g of the corresponding IL (Table 1) was heated with a backflow condenser and protection from moisture at 95–100 °C at stirring until the full consumption of **1** (TLC control). Then the reaction mixture was cooled to 20 °C, diluted with water (3 ml) and NaOH aqueous solution was added dropwise to pH 10. The liberated 3,4-dihydroisoquinoline was extracted with diethyl ether (5 × 3 ml), the ether solution was washed with water (2 × 3 ml), dried with $MgSO_4$ and the solvent was evaporated. The residue was purified by flash chromatography through a short column with SiO_2 or by crystallization.

General procedure for the preparation of 3,4-dihydroisoquinolines **2** *with [bmim][PF_6] regeneration*. To regenerate IL [bmim][PF_6] after the reaction completion, a $POCl_3$ excess was pumped off, 3 ml water was added, an IL layer was separated, washed with 2 ml water, dried in a vacuum dessicator over P_2O_5 and reused in a similar reaction. NaOH aqueous solution was added to the combined aqueous fraction to achieve pH 10 and corresponding 3,4-dihydroisoquinoline was isolated as described above.

6,7-Dimethoxy-1-methyl-3,4-dihydroisoquinoline **2a**: mp 100–102 °C (lit.,[29] mp 101–103 °C).

7-Methoxy-1-methyl-3,4-dihydroisoquinoline **2b**: yellow oil. IR (ν/cm^{-1}): 997, 2938, 2837, 1630, 1609, 1573, 1513, 1496, 1462, 1431, 1372, 1312, 1295, 1245, 1218, 1180, 1082, 1063, 873, 821, 751, 699, 635. ^{1}H NMR ($CDCl_3$) δ: 2.35 (s, 3H, MeC=N), 2.62 (t, 2H, NCH_2CH_2, ^3J 7.3 Hz), 3.65 (t, 2H, NCH_2CH_2, ^3J 7.3 Hz), 3.84 (s, 3H, MeO), 6.70 (s, 1H, H_{Ar}), 6.85, 7.28 (2d, 2×1H, H_{Ar}). ^{13}C NMR ($CDCl_3$) δ: 23.00 (*Me*C=N), 24.99 (NCH_2CH_2), 47.01 (NCH_2CH_2), 111.36, 113.84, 115.62, 128.06, 129.28, 129.63, 164.25 (Me*C*=N). MS, *m*/*z*: 175 [M$^+$] (100), 160 [M$^+$ – Me] (12), 144 [M$^+$ – MeO] (29), 131 (24), 121 (24).

1-Methyl-3,4-dihydroisoquinoline **2c**: bp 104–107 °C (11 Torr) [lit.,[30] 110–116 °C (12 Torr)]. Spectral data are identical to reported in refs. 30,31.

6,7-Dimethoxy-1-phenyl-3,4-dihydroisoquinoline **2e**: mp 121–122 °C (lit.,[32] 120–121 °C). Spectral data are identical to reported in ref. 26.

7-Methoxy-1-phenyl-3,4-dihydroisoquinoline **2f**: crystallized oil, spectral data are identical to reported in ref. 33.

1-Phenyl-3,4-dihydroisoquinoline **2g**: bp 165–170 °C (4 Torr) [lit.,[29] 150–160 °C (2–3 Torr)], spectral data are identical to reported in ref. 34.

7-Chloro-1-phenyl-3,4-dihydroisoquinoline **2h**: mp 145–146 °C, spectral data are identical to reported in ref. 28.

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