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Pronounced ionic liquid effect in the synthesis of biologically active isatin-3-oxime derivatives under acid catalysis

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ABSTRACT

An efficient method was developed for the preparation of isatin-3-oxime derivatives with Bronsted and/or Lewis acids in imidazolium-based ionic liquids. Isatin-3-oxime bearing the electron donating methoxy group was equally obtained in good yields. The pronounced ionic liquid effect avoids the direct formation of isatin in the acidified media and the reaction leads exclusively to isatin-3-oxime derivatives.

Isatins are synthetically versatile substrates that display diverse biological and pharmacological properties.[1,2] These substances were found in urine and brain regions associated with hunger, but their endogenous role has not been fully clarified yet.[2] Moreover, isatins can be found in nature. Recently, 6-methoxy-1-methylisatin was isolated from the plant *Boronella koniambiensislies*.[3] Isatin-3-oximes are useful antiallergic agents with potent and prolonged action. Derivatives of these compounds are also potassium channel openers for treatment of respiratory diseases, convulsions, renal disorders, urinary incontinence and diarrhea.[4]

The most common route to prepare isatins is the Sandmeyer method that involves the reaction of anilines, chloral hydrate and hydroxylamine hydrochloride in the presence of sodium sulfate solution, followed by treatment of the formed isonitrosoacetanilides with concd sulfuric acid.[5] Several modifications have been introduced in the original methodology to prepare this class of biologically active compounds.[6] Nevertheless, the methodologies fail in the preparation of isonitrosoacetanilides bearing electro donating groups. Those cases require a five-step procedure and, in all cases, nitrone intermediates are involved.[7] Normally, isatin-3-oximes systems are prepared from respective isatins upon treating them with hydroxylamine hydrochloride in ethanol in the presence of a base.[8] The only procedure described in the literature not passing through isatin intermediates, consists of the hydrolyses reactions of 1-arylamine-1-methylthio-2-nitroethenes that allow the obtainment of 2-nitroacetanilides, which in turn afford isatin 3-oxime in the presence of strong acids.[9]

Ionic liquids (ILs), especially those based in 1-*n*-butyl-3-methylimidazolium cation (BMI, Fig. 1), are among the most studied and applied in catalysis.[10] ILs have been efficiently used in biphasic catalysis. Moreover, it was shown in several cases that ILs have a salutary effect on the reaction rate and selectivity. Besides, they can also promote reactions that are not easy to take place in classical organic solvents.[11] ILs are also very effective media for 'classic' acid catalysis and the acidity of acids normally increases when dissolved in ILs.[12] Furthermore, ILs are less solvating than water.[13]

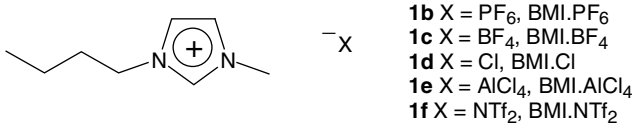

Figure 1. Structure of some imidazolium-based ILs.

Recently, we have successfully used ILs for the preparation of synthetic intermediates of biologically active molecules[14a] and explored their effect to promote reactions under catalytic acidic conditions.[15] Due to our interest in biologically active compounds[14] and the preparation of isatin-3-oximes derivatives,[2] we describe herein the use of ILs as great media to support different Lewis and Bronsted acids and to promote direct formation of isatin-3-oximes derivatives from substituted isonitrosoacetanilides (Scheme 1).

Isonitrosoacetanilides were prepared, in good yields, upon treatment of anilines with chloral hydrate and hydroxylamine hydrochloride, in a saturated aqueous sodium sulfate medium, according to a previous report.[5b] Preliminary studies with isonitrosoacetanilide were carried out using different acids and ILs. The results are summarized in Table 1.

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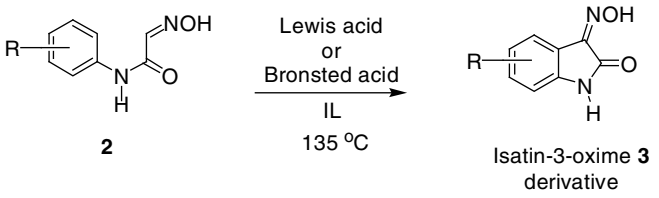
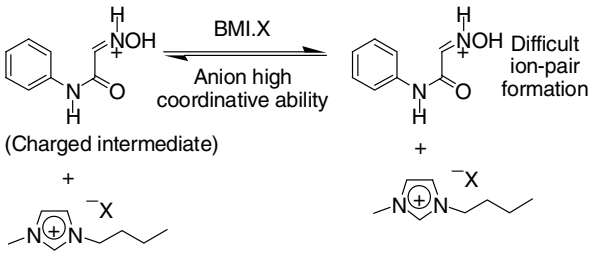


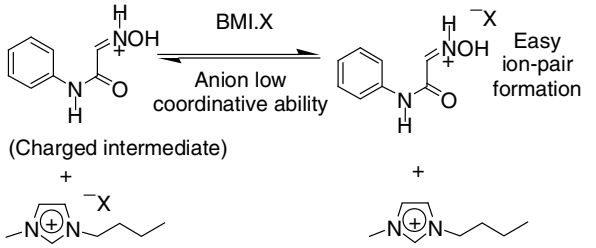
Scheme 1. Cyclization promoted in ILs under acid conditions.

Table 1
Conditions for the cyclization isonitrosoacetanilide (R = H, Scheme 1)[a]

Entry	IL	Acids (5 mol %)	Yield[b] (%)
1	BMI·NTf_2 **1f**	CF_3CO_2H	61
2	BMI·NTf_2 **1f**	CH_3SO_3H	88
3	BMI·NTf_2 **1f**	p-$TolSO_3H$	31
4	BMI·NTf_2 **1f**	$PhB(OH)_2$	0
5	BMI·NTf_2 **1f**	HBF_4	96
6	BMI·NTf_2 **1f**	$BF_3.OEt_2$	95
7	BMI·$InCl_4$ **1a**	—	15
8	BMI·$InCl_4$ **1**[a]	$InCl_3$	31
9	BMI·BF_4 **1c**	HBF_4	25

[a] See Ref. 19 for the best condition used.
[b] Isolated yield.





Scheme 2. Anion stabilizing effect of the charged intermediate.

It is possible to observe that the use of BMI·BF_4 **1c** and HBF_4 gave a low yield of the product (Table 1, entry 9). The inherent Lewis acid nature of BMI·$InCl_4$ **1a**[16] resulted in the formation of the desired compound in low yields (Table 1, entry 7), despite the fact that no additional Lewis or Bronsted acid was required to promote the reaction. When additional $InCl_3$ as Lewis acid was added, it was not effective enough to promote a high yield formation of the isatin-3-oxime (Table 1, entry 8). Once we had in mind that the coordinative ability of the anion has a major role in acid-catalyzed reactions in ILs,[15] we decided to test the use of BMI·NTf_2 **1f**, a poorly coordinating anion, as the medium to promote the reaction. In fact, the choice showed to be appropriate and we could test different acids to promote the reaction. Even in the case of choice of BMI·NTf_2 **1f** some acids gave poor results, for example, phenylboronic acid (Table 1, entry 4) and *p*-toluenesulfonic acid (Table 1, entry 3). Nevertheless, the use of CF_3CO_2H (Table 1, entry 1), CH_3SO_3H (Table 1, entry 2), HBF_4 (Table 1, entry 5) and $BF_3{\cdot}OEt_2$ (Table 1, entry 6) gave the respective isatin-3-oxime in good to excellent yields in short reaction time (90 min).

It is worth noting that the use of the same acid (HBF_4—Table 1, entries 5 and 9) gave very distinct results just switching the anion of the IL. The use of BMI·NTf_2 **1f** gave the product in 96% (Table 1, entry 5) while the use of BMI·BF_4 **1c** resulted in only 25% yield (Table 1, entry 9). The drastic difference in the yields clearly indicates the importance of the anion to ion pair formation of charged intermediates and their stabilization. The divergence in the observed behavior of both ILs **1c** and **1f** can be explained in terms of the coordinative ability of the anion. Upon increasing the anion coordinative ability ($OTf > PF_6 > BF_4 > InCl_4 > NTf_2$),[17] the probability of ion pair formation among the anion and the protonated substrate decreases (the charged intermediate) and, thereby, the reaction yield decreases too, as a consequence of lack of stabilization of the reaction intermediate, as seen in Scheme 2. If the anion has a low coordinative ability it will be more available to stabilize the charged intermediate, facilitating its formation/stabilization and increasing the reaction yield. In the opposite case, the anion will prefer to be stacked in the well-organized ionic channels of the three-dimensional structural arrangement of imidazolium-based ILs.[18]

Our results illustrate a case where the pronounced ionic liquid effect was essential to form and stabilize the charged intermediates. $InCl_4^-$ (low coordinative ability anion) was sufficient to promote the reaction by ion pair formation and stabilization of the charged intermediate. In this case, BMI·$InCl_4$ **1a** showed a dual function: Lewis acid property and ion pair formation. Upon increasing the reaction time using IL **1a**, it was possible to observe an increase in the yield. For instance, if the reaction was carried out over a period of 6 hours, the yield increased from 15% (Table 1,entry 7) to 41% without the addition of other Lewis or Bronsted acid.

Table 2
Cyclization reactions using BMI·NTf_2 and HBF_4 (5 mol %)[a]

Entry	R	Yield[b] (%)
1	7-CF_3	73
2	7-Cl	12
3	7-I	72
4	7-OMe	83
5	6-OMe	81
6	5-OMe	78

[a] See Ref. 19 for the best condition used.
[b] Isolated yield.

In order to gain insight as to the generality of this catalytic cyclization reaction, it was performed on several other derivatives using the established best reaction conditions (BMI·NTf_2, HBF_4). Other isatin-3-oximes derivatives were prepared varying the substituent in the aromatic ring (as seen in Scheme 1, Table 2).

Over a period of 90 min, we observed a poor result only when R = Cl (Table 2, entry 2). The high electronegativity of the element consistently decreased the charge density of the aromatic ring, turning its nucleophilic character lower than the other examples tested. Still, under the developed conditions, this effect was not very pronounced when the substituent is a CF_3 group and the isatin-3-oxime derivative was obtained in 73% (Table 2, entry 1). Interestingly, better results were obtained using OMe group as substituent in the aromatic ring. In all cases, (Table 2, entries 4–6) we observe good yields (78–83%) using the developed conditions. The donating effect of methoxy groups allows an easy nucleophilic attack on the electrophilic carbon of the oxime resulting in the desired isatin-3-oxime.

In conclusion, we developed a novel, efficient, and fast methodology for preparation of isatin-3-oximes under Lewis or Bronsted

acid catalysis in different imidazolium-based ILs.[19] Moreover, this approach also proved to be useful when the aromatic ring has an electron withdrawing group, except when the substituent is a chlorine. The results suggest that the ionic nature of BMI·NTf_2, associated with the low coordinative ability of the anion, is a powerful combination capable of co-promoting the formation and stabilization of different types of intermediates through supramolecular ion pairs formation. The pronounced ionic liquid effect was responsible for a fast, selective, and efficient synthesis of isatin-3-oximes derivatives.

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19. General procedure for the preparation of isatin-3-oximes derivatives: Isonitrosoacetanilide (1 mmol), BMI·NTf_2 (0.5 mL) and acid catalyst (0.050 mmol) were added to a sealed tube. The reaction was stirred for 90 min and the temperature maintained at 135 °C. After, Et_2O (2 × 10 mL) was used to extract organic compounds from the ionic liquid phase and the combined organic layers were concentrated under reduced pressure. Product purification was performed by column chromatography (silica gel, gradients of hexane/Et_2O). Overall yields were determined by a combination of isolated products.