Organic & Biomolecular Chemistry

PAPER

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2014, **12**, 8036

An experimental and theoretical study of reaction mechanisms between nitriles and hydroxylamine†

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Received 25th April 2014,
Accepted 1st August 2014

DOI: 10.1039/c4ob00854e

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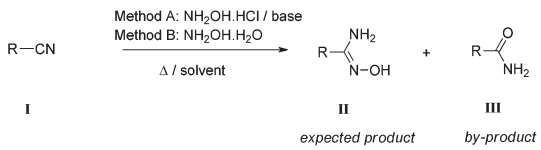
The industrially relevant reaction between nitriles and hydroxylamine yielding amidoximes was studied in different molecular solvents and in ionic liquids. In industry, this procedure is carried out on the ton scale in alcohol solutions and the above transformation produces a significant amount of unexpected amide by-product, depending on the nature of the nitrile, which can cause further analytical and purification issues. Although there were earlier attempts to propose mechanisms for this transformation, the real reaction pathway is still under discussion. A new detailed reaction mechanistic explanation, based on theoretical and experimental proof, is given to augment the former mechanisms, which allowed us to find a more efficient, side-product free procedure. Interpreting the theoretical results obtained, it was shown that the application of specific imidazolium, phosphonium and quaternary ammonium based ionic liquids could decrease simultaneously the reaction time while eliminating the amide side-product, leading to the targeted product selectively. This robust and economic procedure now affords a fast, selective amide free synthesis of amidoximes.

Introduction

Amidoximes (**I**, Scheme 1) are typical key intermediates for the synthesis of numerous heterocycles and are used to introduce selected important functional groups (Scheme S1†). Such building blocks can be found in many organic and biologically active molecules. For example, oxadiazole and oxadiazolone five membered heterocycles are generally prepared from amidoximes by ring closure with carbonyl derivatives. These are frequent substructures of drug substances, and some of the relevant examples are listed in Scheme S2 in the ESI.†[1–4] Besides, amidoximes proved to be a good final intermediate for the preparation of amidines[5] (Scheme S1 in the ESI†), among which numerous examples are known as biologically active molecules such as antimicrobial agents,[6] nitric oxide inhibitors[7] and tyrosine kinase inhibitors[8,9] (Scheme S2 in the ESI†), whose functional group can be prepared *via* Pinner reaction of amidoximes. Note that in this paper, general structures are labeled with roman numerals, while specific structures are characterized by Arabic numerals.



Scheme 1 Reaction of arylnitrile (**1**) with hydroxylamine to yield the expected amidoxime (**II**) and unexpected amide byproduct (**III**) by two methods.

Since, most of the time, these amidoxime intermediates (**II**) are among the last isolated compounds in the synthesis of active pharmaceutical ingredients, the selectivity of the amidoxime formation, as well as the purity of the prepared amidoxime, is crucial. The most common synthetic route to amidoximes (**II**) is based on the reaction of a nitrile (**I**) with hydroxylamine. Hydroxylamine is mainly used as a hydrate (Method B in Scheme 1) or *in situ* released from its salt in a typical protic solvent[10] (Method A in Scheme 1). However, whilst a good yield of the expected amidoxime product (**II**) exists, typically a significant amount of amide side product (**III**) is formed ranging from a few percent up to 20–30%. Due to the analogous physical/chemical properties, this amide side-product (**III**) is usually the main and critical impurity of the last isolated intermediate, which has the potential to be a toxic or genotoxic ingredient, giving enormous workload for the analytical and synthetic departments during the process of

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†Electronic supplementary information (ESI) available: Table S1 contains the experimental conditions of the HPLC methods, applied. Tables S2–S5 show the row and calculated kinetic data, measured by HPLC. Table S7 contains the computed energies (E), zero-point energies (E_{ZPE}), internal energies (U) and enthalpies (H) in hartree at various levels of theories for compounds involved. See DOI: 10.1039/c4ob00854e

drug development. From that point of view, an amide free synthesis could be a more economical and shorter process, thus improving the efficacy.

In this study, we aimed to understand the mechanism of formation of the amide side product (**III**) and develop a selective amidoxime (**II**) synthesis from nitriles (**I**) by means of hydroxylamine. Finally, the novel reaction mechanism is checked and proved by experimental means. According to the earlier proposed mechanism,[11] hydroxylamine may acts as an ambient nucleophile by its N or O sides in the course of the reaction and we aimed to differentiate this dual reactivity by the quality of the solvent applied. A marked influence was expected from ionic liquids.[12,13] Ionic liquids have melting points below 100 °C, low vapor pressure and inflammability contrary to conventional volatile organic molecular solvents.[14–19] Their physical properties, such as melting point, viscosity, and density, are limited generally by the organic anion, controlling the chemical reactivity of the solute substantially.[20,21]

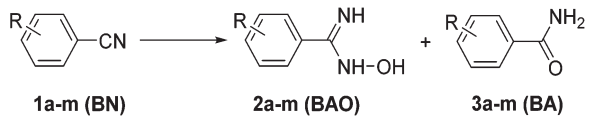
Results

Amidoxime type molecules (**II**) can be prepared on a large scale under various conditions, in most of the cases in heterogeneous reaction mixture; however, recently, concentrated aqueous hydroxylamine (50%) was applied successfully under homogeneous conditions in a continuous micro reactor.[22]

Here, we aimed to study the heterogeneous reaction of nitrile derivatives with hydroxylamine hydrochloride in different molecular and ionic solvents. The reaction mechanism was investigated and compared to proposals of Stephenson *et al.* and Srivastava *et al.*[11,23]

Experimental findings and conversion obtained in molecular solvents

The preparation of benzamidoxime (**BAO**, **2**) was investigated from benzonitrile (**BN**, **1**) in the presence of two equivalents of hydroxylamine hydrochloride in various molecular solvents (Scheme 2) such as aprotic *N*-methyl-pyrrolidone (NMP; entries 1–4) and 2-methyltetrahydrofuran (Me-THF; entries 5–8) as well as different types of alcohols (entries 9–20) and water (entries 1–4). The reaction temperature was set to 50 °C and 80 °C. In the course of the reactions, one or two equivalents of Na_2CO_3 or Et_3N were used as the base (Table 1). The conversions observed were typically high and reaction rates were nearly the same in dipolar aprotic NMP (ε = 32.2) and in protic solvents, such as propanol (ε = 20.33) or ethanol (ε = 24.55) in the presence of Et_3N as the base.



Scheme 2 Reaction of aromatic nitrile derivatives (**1a–m**; **BN**) with hydroxylamine hydrochloride providing aromatic amidoxime (**2a–m**; **BAO**) and aromatic amide (**3a–m**; **BA**).

Comparing the two aprotic solvents Me-THF and NMP applied, a significant increase can be observed in NMP having a larger relative permittivity, and a low conversion in apolar Me-THF (ε = 6.97). The combination of a protic solvent (EtOH, *n*-PrOH and H_2O) and an organic base, such as Et_3N, provided generally a better conversion than the combination of a protic solvent and Na_2CO_3. Due to the enhanced solubility of Na_2CO_3 in water (ε = 80.1), similarly improved conversion was achieved by inorganic bases analogously to Et_3N in alcohols. The amount of base was found to be a crucial parameter from the selectivity point of view. In general, a slightly decreased conversion and an increased amount of amide by-product were observed with increasing the base from one to two eq. (Table 1).

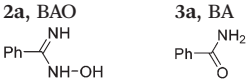
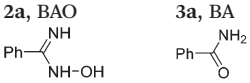
An interesting solvent effect can be observed on the conversion (30 min at 50 °C) and amide formation for different types of alcohols, such as *n*-PrOH or EtOH (primary; entries 11 and 18), i-PrOH (secondary; entry 13) and *t*-BuOH (tertiary; entry 14), in the presence of 1 eq. TEA. In that series, the largest conversions were detected for primary alcohols (81% in *n*-PrOH, 76% in EtOH), while the conversion in secondary alcohol proved to be moderate under the same conditions (44% in i-PrOH). Tertiary alcohol exhibited only low conversion at 30 min (22% in *t*-BuOH), which is close to the value observed in the aprotic Me-THF (4%). As is known, the HB donor and acceptor ability of the alcohols is strongly influenced by their orders, the OH group of primary alcohols is exposed, while the OH groups of tertiary alcohols are sterically hindered. This series of values shows that HB ability plays an important role in the mechanism, due to the fact that the sterically more hindered the OH group in the alcohol, the less the conversion that occurs.

2,2,2-Trifluoroethanol (TFE, entry 20 in Table 1) and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP, entry 15 in Table 1), two extremely strong hydrogen bonding (HB) solvents, somewhat decreased the conversion; however, the percentage of the amide by-product remained. This effect can be explained by the much stronger HB effect between the OH group of the solvent molecule and the nitrogen of NH_2OH, decreasing its nucleophilicity. In the light of the results of the different alcohols, it can be concluded that mostly the HB acceptor ability influences the reaction in the beneficial direction, instead of the HB donor ability. This observation is confirmed by other HB donor solvents, such as NMP, which gave good conversion, and the sterically hindered ether type MeTHF providing poor conversion. Water represents a compromise between the good HB acceptor and donor abilities, providing moderate conversion. Temperature has also a significant effect on the conversion; at higher temperatures larger conversions were observed than at lower temperatures for the same reaction time.

Experimental findings and conversion obtained in ionic liquid solvents

In our study, as shown in Table 2, two different types of ionic liquids (ILs) were applied, depending on the type of the anion. Ionic liquids, ranked in the first group (entries 25–26 in

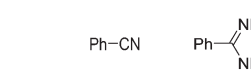
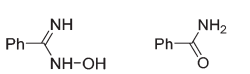
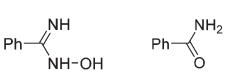
Table 1 Reaction composition (%) of unsubstituted benzonitrile (**BN**; R = H; **1a**) to benzamidoxime (**BAO**, **2a**) and benzamide (**BN**, **3a**) by $NH_2OH{\cdot}HCl$ in different organic solutions in the presence of inorganic (Na_2CO_3) or organic bases (Et_3N), in 1 or 2 eq., using 30 min reaction time at 80 °C as well as 50 °C reaction temperature

				80 °C			50 °C		
				1a, BN	**2a**, BAO	**3a**, BA	**1a**, BN	**2a**, BAO	**3a**, BA
	Entry	Base	Base eq.	Ph–CN			Ph–CN		
1	NMP[a]	Na_2CO_3	1	80	16	4	87	12	1
2	NMP[a]	Na_2CO_3	2	71	24	5	—	—	—
3	NMP[a]	Et_3N	1	0	96	4	11	87	2
4	NMP[a]	Et_3N	2	0	96	4	—	—	—
5	Me-THF[b]	Na_2CO_3	1	98	1	1	100	0	0
6	Me-THF[b]	Na_2CO_3	2	98	1	1	—	—	—
7	Me-THF[b]	Et_3N	1	90	8	2	95	4	1
8	Me-THF[b]	Et_3N	2	80	17	3	—	—	—
9	*n*-PrOH	Na_2CO_3	1	74	23	3	94	5	1
10	*n*-PrOH	Na_2CO_3	2	60	36	4	—	—	—
11	*n*-PrOH	Et_3N	1	1	96	3	16	81	3
12	*n*-PrOH	Et_3N	2	0	95	5	—	—	—
13	i-PrOH	Et_3N	1	—	—	—	54	44	2
14	*t*-BuOH	Et_3N	1	—	—	—	76	22	2
15	HFIPA[c]	Et_3N	1	—	—	—	66	33	1
16	EtOH	Na_2CO_3	1	22	75	3	70	29	1
17	EtOH	Na_2CO_3	2	27	70	3	—	—	—
18	EtOH	Et_3N	1	3	94	3	23	76	1
19	EtOH	Et_3N	2	4	90	6	—	—	—
20	TFE[d]	Et_3N	1	—	—	—	38	60	2
21	H_2O	Na_2CO_3	1	15	82	3	42	56	2
22	H_2O	Na_2CO_3	2	13	82	5	—	—	—
23	H_2O	Et_3N	1	3	95	2	42	56	2
24	H_2O	Et_3N	2	7	88	5	—	—	—

[a] *N*-Methyl-pyrrolidone. [b] 2-Methyl-tetrahydrofuran. [c] 1,1,1,3,3,3-Hexafluoro-2-propanol. [d] 2,2,2-Trifluoroethanol.

Table 2), possess anions, where their conjugate acids are strong ($pK_a < 2$); consequently these anions are weak bases, such as trifluoromethanesulfonate (TFMSI), Cl^-, $AlCl_4^-$, BF_4^-, PF_6^-, $alkylSO_4^-$, OTs^-, and trifluoroacetate (TFA). The second group (entries 27–29 in Table 2) contains ILs, where the conjugate acids are weak ($pK_a > 2$); therefore the anion is a stronger base, such as carboxylates (OAc^-, OBz^-, lactate). In these cases, a real equilibrium exists between the cation–anion pair and their neutral counterparts. Many different cations were involved as the positively charged counterpart of the IL,[24] such as imidazolium, phosphonium and ammonium. In general, independently from the cations applied, low conversion was achieved (0–20%) in ionic liquids belonging to the first group; only TFA (entry 18 in Table S2 in the ESI†) showed a moderate transformation (40%). This inactivity remained in the course of the variation of various reaction parameters, such as reaction time, temperature, excess and type of base. However, the second group of ILs provided high conversion rates (99–100%)

Table 2 Conversion to unsubstituted benzamidoxime (BAO, **2a**) in different ionic liquid solutions from benzonitrile (**1a**) by $NH_2OH{\cdot}HCl$ in the presence of inorganic (Na_2CO_3) or organic bases (Et_3N) in 1 or 2 eq. with 30 min reaction time at 80 °C as well as 50 °C reaction temperature. 30 min reaction time in different ionic liquids with 1 eq. Na_2CO_3 at 80 °C

		80 °C						50 °C		
		1. eq.			2. eq.			1. eq.		
Entry	Ionic liquids (IL)[a]	**1a**, BN	**2a**, BAO	**3a**, BA	**1a**, BN	**2a**, BAO	**3a**, BA	**1a**, BN	**2a**, BAO	**3a**, BA
		Ph–CN			Ph–CN			Ph–CN		
25	[BMIM][Cl]	81	13	6	—	—	—	—	—	—
26	[MOIM][BF_4]	96	2	2	—	—	—	—	—	—
27	[BMIM][OAc][b]	0	99	1	0	99	1	1	98	1
28	[EMIM][OAc]	0	100	0	0	99	1	3	96	1
29	[Ch][OAc]	0	100	0	0	98	2	2	97	1

[a] Abbreviations listed in the Experimental section. [b] The reaction took place with 0 eq. of the base (99%, BAO).

of the expected major product, within a short reaction time at 80 °C. More importantly, the formation of the amide by-product was very limited in all these cases.

Both the organic (TEA) and inorganic (Na_2CO_3) bases exhibited the same high yields and fast reaction rates. An excess of base had also no impact on the results observed. It is important to highlight that the reaction took place in the absence of external bases using [BMIM][OAc][24] as the solvent, which can be explained by the presence of anions that behave as a strong base. Papers of Nyulászi *et al.* and R. D. Rogers *et al.* proved that,[25,26] when an imidazolium IL has a carboxylate counterion, the reaction mixture is in equilibrium with the corresponding N-heterocyclic carbene (NHC), which can act as a base or nucleophile, releasing the NH_2OH base from its salt.

The influence of temperature was also investigated at two points (80 and 50 °C) and no significant effect was found either on conversion or yield. From this result, it can be seen that the cation has also no influence on the outcome of the reaction; in all the cases we observed high selectivity toward the amidoxime and a fast reaction rate. Contrary to molecular solvents, ILs always showed a higher reaction rate and better selectivity, independent of the amount of base, reaction temperature and concentration applied. This highly robust procedure offers a new possibility of amide free amidoxime synthesis.

Reaction kinetics

Up to this point, only the 30 min conversion was studied in various solvents. However, it is worth examining the kinetics of the reaction in different media (Fig. 1). In this experiment the same reaction conditions were applied (50 °C; 2 eq. of $NH_2OH{\cdot}HCl$; 2 eq. of TEA) as those used previously in solvent screening. The relative concentrations of the reaction components were measured by HPLC (at 210 nm) using small but precisely added toluene as an internal standard. Due to the excess of the hydroxylamine reactant, the quasi first order assumption can be a good approximation to compare the initial reaction rates of the product BAO [k'(initial)], which were estimated from the very beginning of the reaction (Table 3). In agreement with the earlier results, the aprotic MeTHF shows the lowest reaction rate, in contrast to the protic alcohols and [BMIM][OAc]. The highest and nearly the same reaction rates are exhibited by *n*-PrOH and [BMIM][OAc], a lower rate was calculated for i-PrOH, while almost the quarter value for the *t*-BuOH. The earlier conclusion also confirmed that the HB donor ability of the solvent applied influenced significantly the reaction rates. It was determined quantitatively that the formation of BA side-product is also more preferred in fewer HB donor solvents. In secondary and tertiary alcohols (*e.g.* *t*-BuOH) and MeTHF, 10.4% and 21.6% of BA/BAO product ratios were observed, respectively, in percentages (Fig. 1C, upper line). IL proved to be the best choice, with the fastest reaction rate and the lowest BA concentration.

Table 3 The calculated initial quasi first order reaction rates of the product BAO formation in various solvents at 50 °C

Solvent	k'(initial) [1/s]	Error [1/s]	R^2
MeTHF	0.0066	0.0026	0.756
n-PrOH	0.2028	0.0170	0.966
i-PrOH	0.1126	0.0190	0.895
t-BuOH	0.0502	0.0123	0.796
[BMIM][OAc]	0.1993	0.0298	0.768

Substituent effect

In the next part, the influence of various *ortho* and *para*-phenyl substituents of **1** was studied on the reaction rate and the amide concentration, in a protic solvent (ethanol) alongside the best IL [BMIM][OAc], with Et_3N base at 50 °C reaction temperature (Table S2, in the ESI†). The electron withdrawing (EW) and electron donating (ED) properties of the phenyl substituents were observed to modify the reaction rate and the product distribution to a large extent. In the case of a *para* EW group, such as halogens (4-Cl **1b**; 4-F **1c**) and nitro groups (4-NO_2 **1d**), increased yields were observed compared to

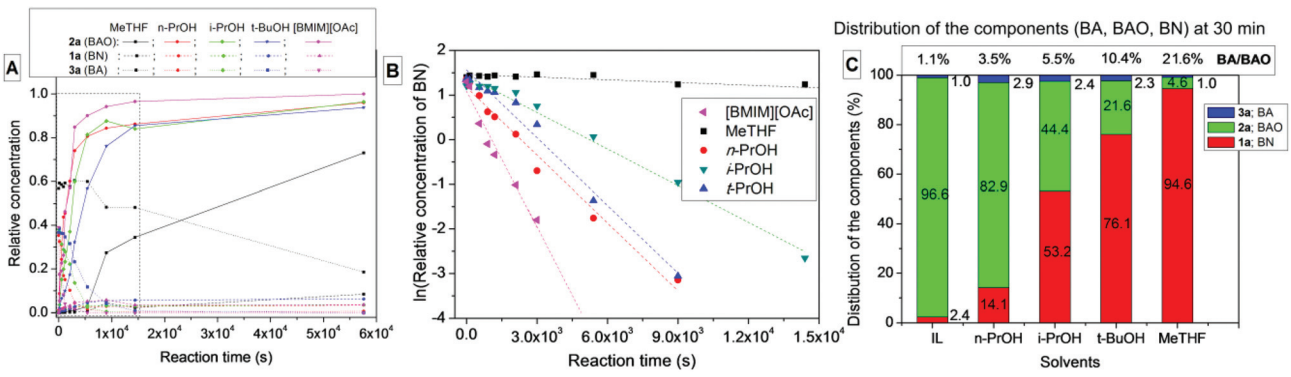


Fig. 1 (A) The reaction kinetics for the transformation of BN to the BAO product and BA side-product in five selected solvents at 50 °C in the presence of 2 eq. of $NH_2OH{\cdot}HCl$; 2 eq. of TEA, given in relative concentration. (B) Determination of the relative reaction rate by the linear fitting on the relating data points. (C) The segment of the reaction in the light of the distribution of components at 30 min reaction time. The upper line shows the BA/BAO ratio in percentage for the solvents studied.

unsubstituted benzonitrile, while ED groups slowed down the reaction, thus decreasing the conversion to the product. The product rate is also slightly varied by the quality of the *para* substituent; in the case of the EW group the amide rate is lower, while for the ED group it is higher (entries 2–6; Table S2†). In the case of ED groups, ILs could increase the yield of the reaction significantly compared to ethanol as the solvent, whilst keeping the amide concentration low.

Lower conversions were reached by the use of *ortho* substituted derivatives (entries 7–12 in Table S2†) in both solvent systems, presumably due to the steric hindrance. This steric effect can be verified by 2-pyridinecarbonitrile (entry 14 in Table S2;† **1l**), whereas the reaction behaves similarly to the *para*-substituted derivatives (**1b–d**), giving fast and selectively the amidoxime derivative. However, for all these *ortho* substituted compounds, ILs were able to provide better conversions and a lower amide formation rate.

The most extreme example proved to be 2-nitrobenzamidoxime (entry 8 in Table S2;† **2h**), which provided very poor conversion (51%) with the highest amide product rate (17 : 51) in ethanol, but it could be prepared effectively (conv. = 99%) and selectively (1 : 99) within an IL. ED groups in the *ortho* position decreased further the reaction rate.

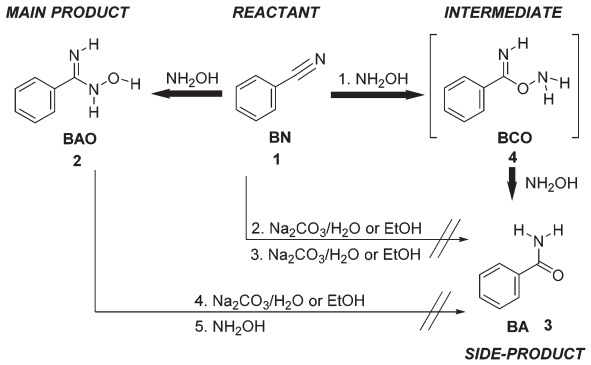
One of the lowest conversions could be observed for the 2,6-disubstituted derivative (entry 15 in Table S2;† **1m**), where the accumulated influences of the unbeneficial steric and electronic effects inhibit the product formation, which also doubled by using an IL. In all the cases, when conversion was low in IL, somewhat better conversion and selectivity was reached with an increased amount of base (2. eq. Et_3N; Table S2†); however, it was not a crucial parameter in the case of high yields. In two cases, where the conversions were quite low (entries 10 and 12, Table S2;† **1i** and **1j**) in both solvents, a longer reaction time increased the yields somewhat.

Variation of reaction conditions

We examined most combinations of the reaction conditions applied in order to find a way of forming BA. BA can form directly from BN under basic or aqueous conditions by the attraction of the OH^- anion. Theoretically, BAO can be hydrolyzed analogously by a strong base. Finally, NH_2OH can react with the BN in two ways due to its ambient nucleophilic character on the N as well as O atoms, which can lead to the expected BAO and a new *N*-amino benzenecarboximidate (BCO; **4**) intermediate. This unstable BCO intermediate was supposed earlier to be able to react with a new NH_2OH, furnishing the BA side-product.[11]

In the first part, the starting compound (BN) was treated under various conditions. The standard reaction conditions (entry 1 in Table S5 in the ESI†) provide the expected product distribution. When $NH_2OH{\cdot}H_2O$ was applied in excess (entry 2 in Table S5†), besides the fast reaction rate, the amide ratio was significantly higher than that for the salt form.

Secondly, the simple reflux of the BN in ethanol in the absence or in the presence of Na_2CO_3 (entries 3 and 4 in Table S5†) did not yield BA (Scheme 3).



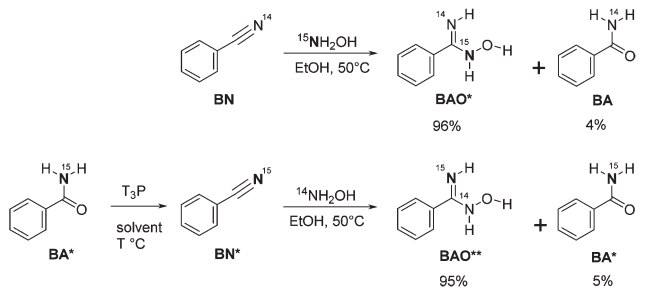
Scheme 3 Schematic reaction mechanism for (**ROUTE A–D**) the formation of benzamidoxime (**BAO**, **2**) and benzamide (**BA**, **3**) formation from benzonitrile (**BN**, **1**) and NH_2OH.

The addition of water was not able to initiate the amide formation, even in trace amounts (entry 5 in Table S5†). This created a non-reactive, or in other words, apparent stability of the nitrile proving that the hydrolysis of the BN does not provide the amide by-product. An interesting experiment was carried out between BN and NH_2OH in the presence of one equivalent of NaH. In that case, the OH side of the hydroxylamine deprotonated exclusively, due to its larger acidity and was expected to produce the reactive intermediate, BCO. However, when the H_2NO^- species reacts with BN (**1**), it resulted that only BA and not BAO or BCO was detected, strongly confirming the hypothesis that the origin of BA is coming from the O attack of the hydroxylamine yielding BCO and the consequent reaction with an additional hydroxylamine. In the second series (entries 7–10 in Table S5†), the possible transformation of the BAO product was examined under several conditions.

In the third part, the simple refluxing of BAO in the absence or in the presence of Na_2CO_3 (entries 7 and 8 in Table S5†) did not result any BA even in trace amounts and the addition of water did not initiate it (entry 9 in Table S5†). Finally, applying the standard reaction conditions with BAO (entry 10 in Table S5†), no transformation of any kind was observed within hours. These simple experiments undoubtedly exclude any alternative source of BA; consequently, it can be concluded that BA can form exclusively from the reaction of BN and NH_2OH.

^{15}N Isotope experiment

Two isotope experiments were planned to clarify the origin of the N atom in BA. In the first experiment, BN was treated with isotope labeled $^{15}NH_2OH{\cdot}HCl$ under standard reaction conditions in EtOH and in the presence of TEA (Scheme 4), and the reaction was followed by HPLC-MS. As expected, the isotope labeled BAO* formed including one ^{15}N atom ($M + H^+$ = 137.1 Da); however, the BA formed also contained only ^{14}N ($M + H^+$ = 121.1 Da). For the reverse experiment, isotope labeled BN* was prepared from a commercially available isotope labeled BA* by propylphosphonic anhydride (T3P) in



Scheme 4 Experimental ^{15}N isotope labeling to prove the origin of the N atom in the reaction of **BN** with hydroxylamine to **BAO** and **BA**. The stars show the ^{15}N isotope labeled compounds.

EtOAc at RT and purified carefully from the remaining starting material. In the next step, it was reacted with $NH_2OH{\cdot}HCl$ under standard reaction conditions, resulting in the alternatively isotope labeled BAO** (M + H^+ = 137.1 Da) and also ^{15}N labeled BA* (M + H^+ = 122.1 Da). According to these two experiments, one can conclude undoubtedly that the origin of the N atom of the BA is the N atom of the BN and not the NH_2OH, supporting the mechanism proposed previously (Scheme 4).

Reaction with Me_2NOH

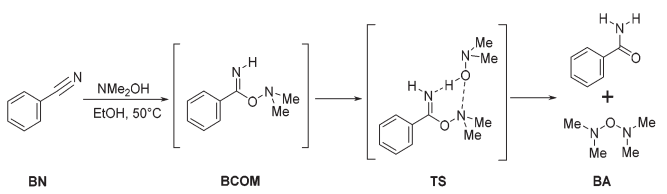
Finally, the mechanism of the amide by-product was checked experimentally; therefore **BN** was reacted with the Me_2NOH reagent, which is able to react only by the O side of the molecule, forcing the formation exclusively of the dimethyl derivative of **BCO** (**BCOM**), as shown in Scheme 5. In that experiment, the formation of **BA** was observed exclusively, but with much lower conversion (9% for **BA** and 91% for **BN** after 2 h) and consequently slower reaction rates, compared to the NH_2OH reagent. This significant difference in reaction rates can be explained by the suggested mechanism (see Theoretical results, Scheme 11), where the **BCOM** intermediate is able to react with only the O side of the Me_2NOH, yielding **BA** and Me_2NONMe_2. However, as computational results show later, the O-side attack of the hydroxylamine exhibits a much higher activation enthalpy than the N-side attack, supporting the much slower reaction rate observed.

Theoretical results

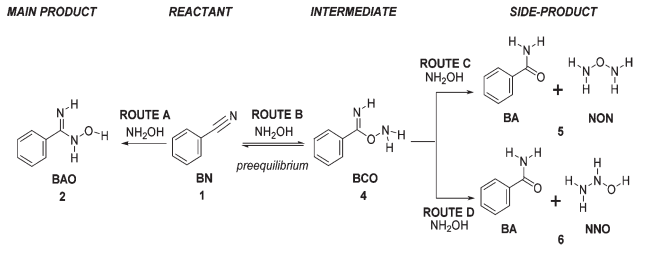
It is a typical situation, in most of the cases the real mechanism of an experimentally simple chemical reaction is very complex, involving many species in each elementary step, like reactants, reagents, solvent molecules, catalysts, as well as acids or bases.[27–32] All these components have to be involved in the calculation in order not only to find the real mechanism, but to access the correct and accurate energy values taking place in a real medium. Furthermore, an inappropriate chemical model provides not only inaccurate energy values, but typically could lead to completely wrong or opposite results.[27] Reactions, taking place in solution, usually require the consideration of a catalyst together with many solvent molecules in an appropriate 3D arrangement.[27,31,32] For the sake of simplicity and easier understanding in the discussion, numbers indicate the molecular complexes (reagent, reactant, solvent, additives) in different arrangements and combinations, while to identify the chemical species we introduced some letter codes.

Thermodynamical aspects. The benzonitrile (**BN**; **1**) can react with the NH_2OH in two ways. When the N-side attacks the nitrile carbon (**ROUTE A**), the expected benzamidoxime (**BAO**; **2**) forms, but the O-side attack (**ROUTE B**) results in the *N*-amino benzenecarboximidate (**BCO**; **4**) intermediate (Scheme 6). From a purely thermodynamic aspect, neglecting the explicit solvent effect, both routes show significant exothermicity and the formation of **BAO** (**3**) is preferred to **BCO** (**4**). According to earlier assumptions[11,23] and our experimental findings, the origin of **BA** can be attributed to the reaction of the formed **BAO** with an additional NH_2OH and may result in two product states (**5** and **6**) involving two possible side products H_2N–NH–OH (**NNO**) *via* **ROUTE C** or H_2N–O–NH_2 (**NON**) *via* **ROUTE D**. In both cases, the formation of **BA** from **BN** exhibits large exothermicity (Table 4), which means a strong preference toward this product. The significant difference between the two end states is attributed exclusively to the different heats of formation of the **NNO** and **NON**.

Reaction mechanism in a molecular solvent (alcohol). To model the real mechanism, the combined explicit–implicit solvent model was applied in order to obtain accurate values. However, different solvents require various solvent models. The protic media with an organic base (Et_3N) was modeled by one EtOH solvent molecule, one Et_3N and one Et_3NH^+, in the arrangement shown in Scheme 7. The best solvent model for acetate counterion containing ionic liquids was represented by an acetate anion (AcO^-) and one acetic acid (AcOH) molecule, shown in Scheme 10 in the next paragraph. In both cases, the relative permittivity (ε_{rel}) was set to 30.0 to consider the



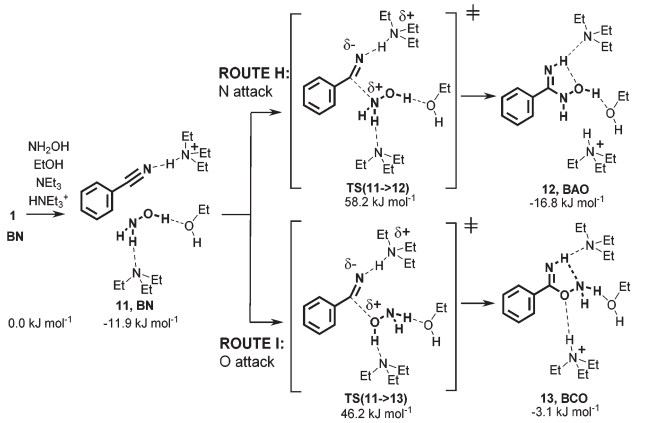
Scheme 5 Formation of benzamide (**BA**) from benzonitrile (**BN**) by means of *N*,*N*-dimethylhydroxylamine through the **BCOM** intermediate.



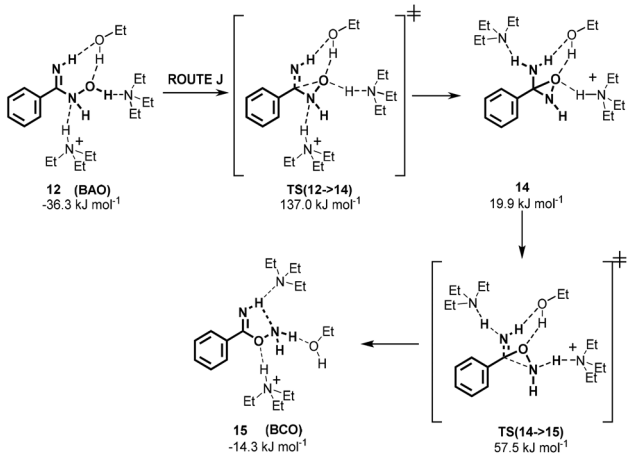
Scheme 6 Schematic reaction mechanism for (**ROUTES A–D**) the formation of benzamidoxime (**BAO**, **2**) and benzamide (**BA**, **3**) formation from benzonitrile (**BN**, **1**) and NH_2OH.

Table 4 Computed thermodynamic parameters for reaction ROUTES A, B, C and D, shown in Scheme 6

Process	Reactions	Computed parameters $\Delta_r H°$	$\Delta_r G°$	$\Delta_r S°$
1 → 2 (ROUTE A)	**BN** + NH_2OH → **BAO**	**−78.6**	**−25.8**	−177.3
1 → 4 (ROUTE B)	**BN** + NH_2OH → **BCO**	**−44.9**	**6.0**	−170.8
1 → 5 (ROUTE C)	**BN** + 2 NH_2OH → **BA** + **NON**	**−130.5**	**−79.7**	−170.3
1 → 6 (ROUTE D)	**BN** + 2 NH_2OH → **BA** + **NNO**	**−203.3**	**−150.6**	−176.8



Scheme 7 Novel, direct solvation mechanism for the reaction of benzonitrile (**BN**, **1**) to produce the expected benzamidoxime product (**BAO**; **12**) and the key intermediate (**BCO**, **13**) for the benzamide by-product in protic media (**ROUTES H** and **I**), including their enthalpy values in kJ mol^{-1}.



Scheme 8 Possible interconversion (**ROUTE J**) of the solvated benzamidoxime (**BAO**; **12**) and **BCO** (**15**) *via* the formation of an oxaziridine ring (**14**), including their enthalpy values in kJ mol^{-1}.

continuum media as an implicit solvent model. The necessity of the hydrogen bond solvent network was proved experimentally as well; when the aprotic Me-THF was used as a solvent only marginal conversion of **BN** (**1**) was observed (*ca.* 7%) in the presence of NH_2OH, irrespective of the base applied.

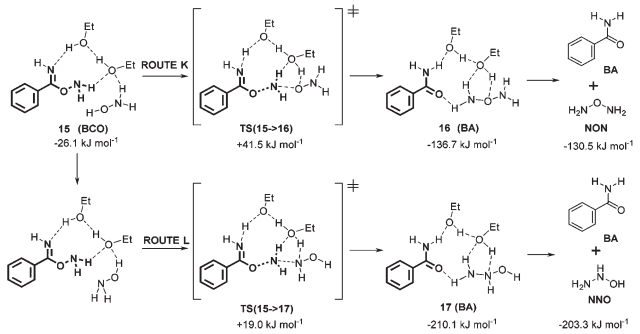
Using the defined solvent model to model the protic media (Scheme 7; **11**), we could obtain both products (**12** and **13**) smoothly in one elementary step, without any fraction of the potential energy surface, through reaction coordinates. In contrast with the thermodynamic data, the transition state [**TS(11→12)** and **TS(11→13)**] toward **BAO** (**12**) is larger by 12.2 kJ mol^{-1} than that for **BCO** (**13**) [**TS(11→13)**], which shows an unquestioned kinetic preference of the side product.

Earlier, the literature supposed a possible direct equilibrium reaction between **BAO** and **BCO**, which can be an alternative possibility for the formation of the side product **BCO**. This process involves one low energy cyclic intermediate (**14**) and two TSs [**TS(12→14)**; **TS(14→13)**], which could be modeled using the same solvent network. However, the first activation energy was found to be too high to be considered a real transformation of **BCO**; consequently it was skipped from the mechanistic study (Scheme 8).

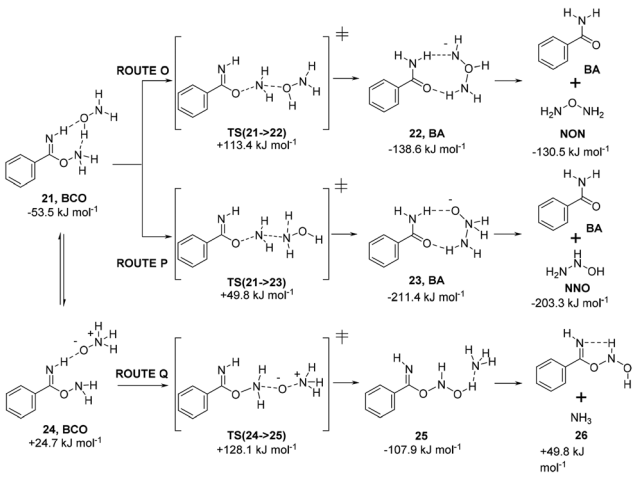
Earlier and our recent experimental studies supposed that the amide side product **BA** forms by the reaction between **BCO** and an additional NH_2OH; however, it was not confirmed by any computational or experimental study. In a recent paper, this hypothesis was checked by theoretical methods. For the modeling of the situation occurring in the protic solvent, an implicit–explicit solvent model was applied; however, a new solvent network should be introduced involving **BCO**, two EtOH and one NH_2OH in a proper arrangement (**13**). It was a debate in the literature which side of the NH_2OH attacks the NH_2 group of **BCO** (**ROUTE L**). Stephenson and colleagues proposed[11] the attack of the nitrogen atom of NH_2OH on the NH_2 group of **BCO** with the formation of **BA** and **NNO** as side products (**ROUTE K**). In contrast, a novel paper assumed[23] an opposite attack of the NH_2OH by its O side, resulting in **BA** and **NON**; however, they did not study and prove this process by any calculation of the corresponding TSs.

Consequently, both possible **ROUTE K** and **L** were considered in our theoretical study. In the first case, the attacking NH_2OH approaches by its O side (**ROUTE K**) the NH_2 group of **BCO** in an appropriate solvent complex (**15**), resulting directly in the lower energy complex of **BA** and **NON** as the product state (**16**) through one well defined TS [**TS(15→16)**], exhibiting a low 86.3 kJ mol^{-1} activation enthalpy calculated from the **BCO** level. When NH_2OH attacks by its N side (**ROUTE L**), an analogue TS [**TS(15→17)**] leads to another product state (**17**) involving **NNO** and **BA** in one elementary step; however, the enthalpy of the TS was found to be lower (63.9 kJ mol^{-1}). In both cases, the two EtOH molecules, forming a solvent network, mediate the proton transfer in the course of the reaction from NH_2OH to the product. According to these activation gaps, obtained in protic media, we confirm Stephenson's theory, namely the N attack *via* **ROUTE L** (Scheme 9).

Reaction mechanism in an ionic liquid (IL). From the experimental results, we concluded that irrespective of the cation, only the carboxylate-type ionic solvent could provide the amidoxime product (**BAO**); consequently only this type of ionic solvent was selected for theoretical study. In order to



Scheme 9 Details of finishing reaction steps for two alternative mechanisms (**ROUTES K** and **L**) of **BA** from **BCO** in EtOH solvents, including their enthalpy values in kJ mol^{-1}.



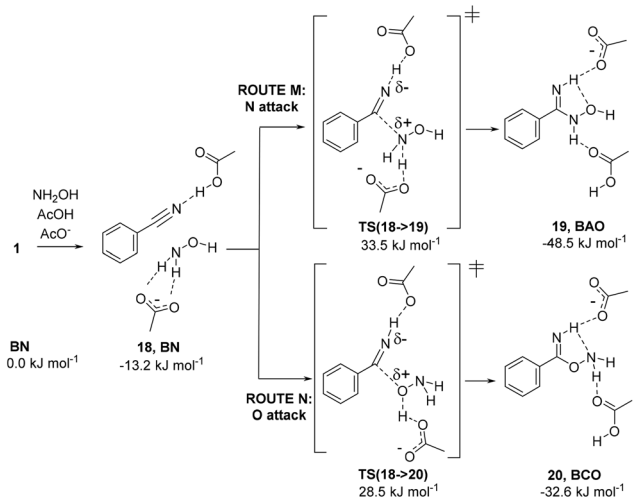
Scheme 11 Three possible mechanisms (**ROUTES O–Q**) of the transformation of **BCO** to **BA** *via* O and N attack of hydroxylamine, including their enthalpy values in kJ mol^{-1}.

model properly the environment of a carboxylic-type ionic liquid, one acetate and one acetic acid were considered, supposing that the acid–base equilibrium between the cation or water and the acetate anion can provide a low concentration of acetic acid. Using the solvent–reagent–reactant structure in the arrangement (**18**) as shown in Scheme 10, the two known reaction routes toward **BAO** [**18→TS(18→19)→19; ROUTE M**] and **BCO** [**18→TS(18→20)→20; ROUTE N**] were modeled successfully.

In the ionic solvent model, also the activation barrier of the **ROUTE N** proved to be lower by 5 kJ mol^{-1}, preferring the formation of **BCO** in contrast to **BAO**, showing analogy to the result obtained in protic media. As was concluded in the previous section, the formation of **BA** starts from the **BCO** intermediate by an additional NH_2OH attack.

Three possible attacks (Scheme 11) of the hydroxylamine were considered (**ROUTE O–Q**) toward **BCO** and computed by a theoretical method. In these cases, no explicit solvent was considered; only the implicit shell was included. **ROUTE O** and **P** model the O and N attack of hydroxylamine, respectively, toward the N atom of the **BCO**.

Analogously to the mechanism in molecular solvents, the N-side attack of the hydroxylamine is more preferred from both the kinetic and thermodynamic aspects than the O-side attack (Scheme 11), due to the lower TS [**TS(21→22)** *vs.* **TS(21→23)**] and the product state (**22** *vs.* **23**). An alternative route (**ROUTE Q**) was also considered and computed, where the zwitterionic form of NH_2OH attacks by its O atom the **BCO** intermediate. However, here, not the usual **BA** forms in the course of the reaction, but a very unusual "dead-end" product **27**, by the elimination of NH_3 (**ROUTE Q**). The activation enthalpy of the process **TS(24→25)** is higher than the previous two, making it more unlikely (Fig. 2).



Scheme 10 Direct solvation mechanism (**ROUTES M** and **N**) for the reaction of benzonitrile (**BN**, **1**) to produce the expected benzamidoxime product (**BAO**; **19**) and the key intermediate (**BCO**, **20**) for the benzamide by-product in carboxylic-type ionic liquid (IL), including their enthalpy values in kJ mol^{-1}.

Discussion

In this section the theoretical and experimental results obtained for the two types of solvents are analyzed and compared with each other. Fig. 3 shows the simplified mechanisms, where only the allowed routes are summarized. In both types of solvents, the expected product, **BAO** (**2**), forms in one elementary step from **BN** (**1**) and NH_2OH with one TS, while the mechanism toward the by-product, **BA** (**3**), involves one intermediate **BCO** between two TSs. In a molecular solvent (such as EtOH), the rate determining step for **BA** is the reaction of **BA** with NH_2OH [**TS(11→13)**], which is somewhat lower by 12.0 kJ mol^{-1} (orange arrow) than that of the competitive route of **BAO** [**TS(11→12)**]. The TS of the step of **BCO** to **BA** [**TS(15→17)**] is significantly lower. These data undoubtedly show that the formation of **BA** is preferred a little bit against **BAO**, which means parallel formation of both products. This slight

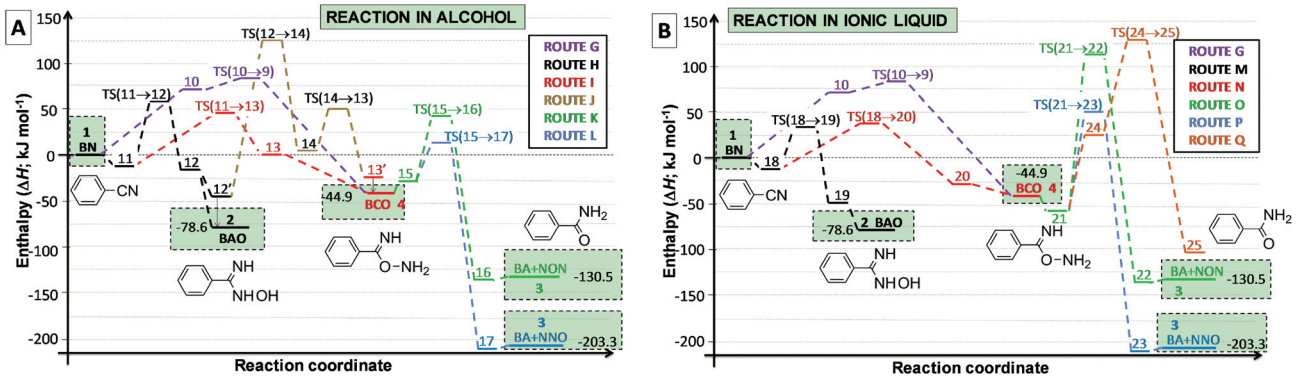


Fig. 2 (A) Direct solvation mechanism enthalpy levels for the various **ROUTES G–L** along the reaction coordinates in molecular solvent (EtOH) from benzonitrile (**BN**, **1**) to benzamidoxime (**BAO**, **2**), benzamide (**BA**, **3**) *via* **BCO** (**4**), including their enthalpy values in kJ mol^{-1}. (B) Enthalpy levels in kJ mol^{-1} for the various transformations of benzonitrile (**BN**, **2**) to benzamidoxime (**BAO**, **2**) and benzamide (**BA**, **3**) *via* **BCO** (**3**) along the reaction coordinates in acetate containing ionic liquid (**ROUTES G**; **M–Q**).

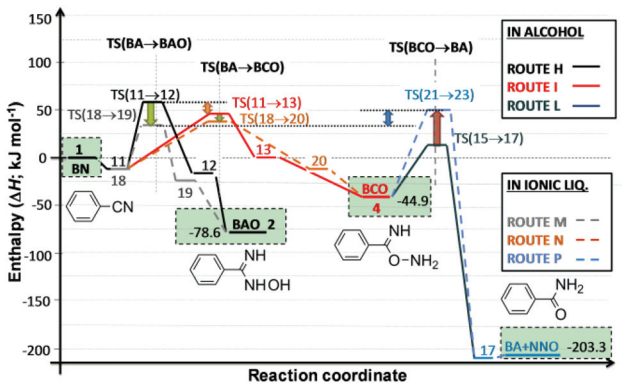


Fig. 3 Comparison of the enthalpy levels for the various transformations of benzonitrile (**BN**, **1**) to benzamideoxime (**BAO**, **2**) and benzamide (**BA**, **3**) *via* **BCO** along the reaction coordinates **ROUTES G**; **M–R** in acetate containing ionic liquid.

preference towards **BA**, which is in contrast with the experimental results, may be attributed to the small error of the calculation.

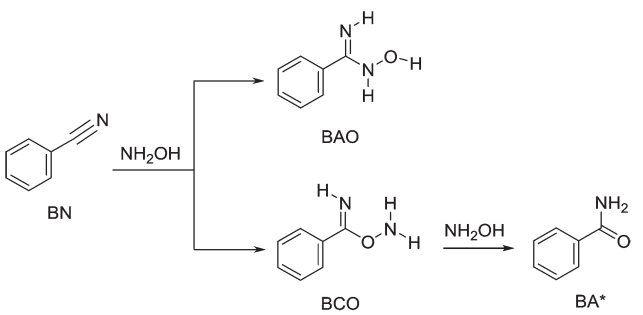
In IL, the situation differs significantly. In this case, the rate determining step for the **BA** is the last **BCO→BA** transformation [**TS(21→23)**], which controls the rate of formation of **BA**, and this value is higher by 16.3 kJ mol^{-1} compared to the TS of the transformation of **BN→BAO** [**TS(18→19)**, blue arrow]. It means that the preferred product in IL is the **BAO**, and the formation of **BA** is hindered, due to the last step. It means that the formed **BCO** *via* **TS(18→20)** is unable to transform forward to **BA** and the process turns back from this intermediate due to the high **TS(21→23)** and goes back to **BN**.

Comparing the two solvents applied, it can be concluded that the TS of **BN→BAO** is significantly lower in IL than in molecular solvent (green arrow), while the TS of **BN→BCO** exhibits very similar values (green arrow). In contrast with that, the TS of **BCO→BA** is higher in IL than in molecular solvent (red arrow).

Conclusions

For several decades the reaction of hydroxylamine with electrophiles appeared to be rather confusing due to the O and N atoms possessing sharply different nucleophilicities. This dual activity of the reagent was attributed to the significant formation of the unexpected benzamide (**BA**) side-product in the course of the reaction of hydroxylamine and benzonitrile (**BN**), producing benzamideoxime (**BAO**) as the expected product. In this paper the detailed mechanism was explored and proved by experimental and theoretical means. As a consequence of the results of the new reaction mechanism, it was shown that an ionic liquid, composed of a carboxylic type anion, like [BMIM][OAc], is able to eliminate the **BA** side-product completely, in contrast with the frequently used protic-type solvent, where the concentration of the **BA** can be up to 40%, depending on the circumstances (Scheme 12).

Theoretical computations predicted that the two heteroatoms in hydroxylamine, exhibiting different characters, can react with benzonitrile resulting in two different products benzamidoxime (**BAO**) and *O*-(imino(phenyl)methyl)hydroxylamine (**BCO**). The latter proved to be a reactive intermediate that was never isolated even though numerous attempts were made. Due to the reactivity of **BCO**, it reacted readily with a



Scheme 12 Summary of the transformation of benzonitrile (**BN**) to benzamideoxime (**BAO**) and its side-product benzamide (**BA**).

further hydroxylamine by its O side, resulting at the first sight the strange benzamide side-product. According to computations in protic media, the transformation of **BCO** exhibits lower TS than the TS of the formation of the **BAO** product; however, the order of TSs reverses in ionic liquids; consequently the amide formation is hindered. ^{15}N isotope labeling experiments were designed to prove the validity of the computer modeling mechanism.

Experimental section

All chemicals were purchased from Sigma-Aldrich except for 2,6-dimethylbenzonitrile, which was bought from Alfa Aesar and 4-chlorobenzonitrile which was bought from Merck.

Ionic liquids were purchased from Fluka except for [EMIM][OAc], [Ch][OAc], and [BMIM][TFA], which were bought from Sigma-Aldrich and Ammoeng 100 and [BMIM][BF_4], which were bought from Solvent Innovation.

All the reactions were tracked using appropriate HPLC methods on Agilent 1100 equipment, the column temperature was 30 °C, and the flow rate was 1.0 ml min^{-1} in each of the five methods (see ESI†).

High-resolution MS spectra were measured using an Agilent 6230 TOF LC/MS spectrometer.

^{1}H and ^{13}C NMR spectra were obtained at room temperature as solutions in DMSO using tetramethylsilane as an internal standard. The spectra were recorded using a Bruker Avance 500 MHz spectrometer.

General procedure for the preparation of benzamidoxime derivatives (2a–m)

0.5 mmol **1a** (1 eq.) and 1 or 2 eq. Na_2CO_3 (0.5 mmol, 0.053 g, 1.0 mmol, 0.106 g) or Et_3N (1.0 mmol, 140 μl; 2.0 mmol, 280 μl) were heated in 0.5 ml of solvent at 50 or 80 °C and 0.0695 g (1 mmol) HA·HCl was added. The reaction was stirred and checked by HPLC (method no. 1–4, 225 nm, RT). The reaction mixture was added to ice water, and the product was filtered off, washed with water (2 × 0.5 ml) and dried for analysis. Analytical data of **2a–2m** were identical to those described in the literature.[22,24,32–36]

Experiments to reaction mechanism investigations

51 μl **1a** benzonitrile (51.56 mg, 0.5 mmol) was heated in 0.5 ml EtOH at 80 °C, and 61 μl (0.0661 g; 1.0 mmol) 50% water solution of HA was added dropwise. The reaction was stirred and checked by HPLC (method no. 3, 225 nm, RT: **1a**: 10.6, **2a**: 8.12, **3a**: 8.31).

51 μl **1a** benzonitrile (51.56 mg, 0.5 mmol) was heated in 0.5 ml EtOH at 50 °C. The reaction was stirred and checked by HPLC (method no. 3, 225 nm, RT: **1a**: 10.6, **2a**: 8.12, **3a**: 8.31).

51 μl **1a** benzonitrile (51.56 mg, 0.5 mmol) and 1 eq. Na_2CO_3 (0.5 mmol, 0.053 g) were heated in 0.5 ml EtOH at 50 °C. The reaction was stirred and checked by HPLC (method no. 3, 225 nm, RT: **1a**: 10.6, **2a**: 8.12, **3a**: 8.31).

51 μl **1a** benzonitrile (51.56 mg, 0.5 mmol) and 1 eq. Na_2CO_3 (0.5 mmol, 0.053 g) were heated in 0.5 ml EtOH and 0.25 ml H_2O at 50 °C. The reaction was stirred and checked by HPLC (method no. 3, 225 nm, RT: **1a**: 10.6, **2a**: 8.12, **3a**: 8.31).

51 μl **1a** benzonitrile (51.56 mg, 0.5 mmol) was heated in 0.5 ml H_2O at 50 °C. The reaction was stirred and checked by HPLC (method no. 3, 225 nm, RT: **1a**: 10.6, **2a**: 8.12, **3a**: 8.31).

51 μl **1a** benzonitrile (51.56 mg, 0.5 mmol) and 1 eq. Na_2CO_3 (0.5 mmol, 0.053 g) were heated in 0.5 ml H_2O at 50 °C. The reaction was stirred and checked by HPLC (method no. 3, 225 nm, RT: **1a**: 10.6, **2a**: 8.12, **3a**: 8.31).

0.0695 g (1 mmol) HA·HCl was stirred in 10 ml ACN at RT and 8 eq. NaH 60% dispersion of mineral oil (4.0 mmol, 0.16 g) was added to the mixture. After half an hour 51 μl **1a** benzonitrile (51.56 mg, 0.5 mmol) was added to the solution. The reaction was checked by HPLC (method no. 3, 225 nm, RT: **1a**: 10.6, **2a**: 8.12, **3a**: 8.31).

68 mg **2a** benzamidoxime (0.5 mmol) was heated in 0.5 ml EtOH at 50 °C. The reaction was stirred and checked by HPLC (method no. 3, 225 nm, RT: **1a**: 10.6, **2a**: 8.12, **3a**: 8.31).

68 mg **2a** benzamidoxime (0.5 mmol) and 1 eq. Na_2CO_3 (0.5 mmol, 0.053 g) was heated in 0.5 ml EtOH at 50 °C. The reaction was stirred and checked by HPLC (method no. 3, 225 nm, RT: **1a**: 10.6, **2a**: 8.12, **3a**: 8.31).

68 mg **2a** benzamidoxime (0.5 mmol) was heated in 0.5 ml EtOH and 0.25 ml H_2O at 50 °C. The reaction was stirred and checked by HPLC (method no. 3, 225 nm, RT: **1a**: 10.6, **2a**: 8.12, **3a**: 8.31).

68 mg **2a** benzamidoxime (0.5 mmol) and 1 eq. Na_2CO_3 (0.5 mmol, 0.053 g) were heated in 0.5 ml EtOH and 0.25 ml H_2O at 50 °C. The reaction was stirred and checked by HPLC (method no. 3, 225 nm, RT: **1a**: 10.6, **2a**: 8.12, **3a**: 8.31).

68 mg **2a** benzamidoxime (0.5 mmol) and 1 eq. Et_3N (1.0 mmol, 140 μl) were heated in 0.5 ml EtOH at 50 °C and 0.0695 g (1 mmol) HA·HCl was added. The reaction was stirred and checked by HPLC (method no. 3, 225 nm, RT: **1a**: 10.6, **2a**: 8.12, **3a**: 8.31).

68 mg **2a** benzamidoxime (0.5 mmol) was heated in 0.5 ml EtOH and 0.25 ml H_2O at 50 °C. The reaction was stirred and checked by HPLC (method no. 3, 225 nm, RT: **1a**: 10.6, **2a**: 8.12, **3a**: 8.31).

51 μl **1a** benzonitrile (51.56 mg, 0.5 mmol) and 1 eq. Et_3N (1.0 mmol, 140 μl) were heated in 0.5 ml EtOH at 50 °C and 0.0976 g (1 mmol) DMHA·HCl (99%) was added. The reaction was stirred and checked by HPLC (method no. 3, 225 nm, RT: **1a**: 10.6, **3a**: 8.31) and HPLC-MS.

51 μl **1a** benzonitrile (51.56 mg, 0.5 mmol) and 1 eq. Et_3N (1.0 mmol, 140 μl) were heated in 0.5 ml NMP at 50 °C and 0.0742 g (1 mmol) ^{15}HA·HCl (95%) was added. The reaction was stirred and checked by HPLC-MS.

0.201 g benzamide (**BA***) (1.65 mmol) was stirred in 248 μl EtOAc at 45 °C and 1.18 ml (1.98 mmol, 1.68 M) T3P was added to the mixture. The reaction was checked by HPLC-MS.

52 μl (**BN***) (52.1 mg, 0.5 mmol) and 1 eq. Et_3N (1.0 mmol, 140 μl) were heated in 0.5 ml EtOH at 50 °C and 0.0695 g

(1 mmol) HA·HCl was added. The reaction was stirred and checked by HPLC-MS.

Kinetic measurements

510 μl of **1a** (516 mg, 5 mmol) and 1 eq. Et_3N (5 mmol, 700 μl) were heated in 55 ml of solvent at 50 °C, and 695 mg (10 mmol) HA·HCl and 100 μl of toluene as the internal standard were added. The reaction was stirred and followed by HPLC (method no. 3) at different reaction times for 16 h. Kinetic data are listed in Tables S2–S6.†

Computational methods

All computations were carried out with the Gaussian09 program package (G09),[37] using standard convergence criteria. Computations were carried out at the B3LYP/6-31G(d,p) level of theory,[38,39] using the IEF-PCM solvent method;[40] CH_2Cl_2 does not require consideration of the solvent effect during the modelling process. The method and basis sets were chosen for their reliability in agreement with the studies established earlier.[27,31,41,42] The vibrational frequencies were computed at the same levels of theory as those used for geometry optimization in order to properly confirm all structures as residing at minima on their potential energy hypersurfaces (PESs). Thermodynamic functions *U*, *H*, *G* and *S* were computed at 298.15 K, using the quantum chemical, rather than the conventional, thermodynamic reference state.

Ionic liquid abbreviations

[BMIM][TFMSI]	1-Butyl-3-methylimidazolium bis(trifluoromethyl-sulfonyl)imide
[EMIM][Cl]	1-Ethyl-3-methylimidazolium chloride
[BMIM][Cl]	1-Butyl-3-methylimidazolium chloride
[THTDP][Cl]	Trihexyltetradecylphosphonium chloride
[BMIM][$AlCl_4$]	1-Butyl-3-methylimidazolium tetrachloroaluminate
[BMIM][BF_4]	1-Butyl-3-methylimidazolium tetrafluoroborate
[HMIM][BF_4]	1-Hexyl-3-methylimidazolium tetrafluoroborate
[MOIM][BF_4]	1-Methyl-3-octylimidazolium tetrafluoroborate
[THTDP][BF_4]	Trihexyltetradecylphosphonium tetrafluoroborate
[TBP][BF_4]	Tetrabutylphosphonium tetrafluoroborate
[THTDP][PF_6]	Trihexyltetradecylphosphonium hexafluorophosphate
[EMIM][$EtSO_4$]	1-Ethyl-3-methylimidazolium ethylsulfate
[EMIM][$HeSO_4$]	1-Ethyl-3-methylimidazolium hexylsulfate
[EMIM][$BuSO_4$]	1-Ethyl-3-methylimidazolium butylsulfate
Ammoeng 100	Tetraalkylammonium methylsulfate
[TIBMP][OTs]	Triisobutylmethylphosphonium tosylate
[BMIM][TFA]	1-Butyl-3-methylimidazolium trifluoroacetate
[BMIM][OAc]	1-Butyl-3-methylimidazolium acetate
[EMIM][OAc]	1-Ethyl-3-methylimidazolium acetate
[Ch][OAc]	Choline acetate
[Ch][L]	2-Hydroxyethyl-trimethylammonium L-(+)-lactate
[TBAB][OBz]	Tetrabutylammonium benzoate

Acknowledgements

This paper is dedicated to the memory of István Hermecz (1944–2011). Special acknowledgement goes to: Edit Alattyáni, Csilla Busa, Péter Hudáky, Attila Németh and Charlotte Wiles. The author expresses his gratitude to Sanofi for contributing to his Ph.D. scholarship and is grateful to Pro Progressio and József Varga Foundations for their financial support.

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