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ORIGINAL PAPER

Synthesis, mechanism of formation, and molecular orbital calculations of arylamidoximes

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Abstract A simple and easy synthesis of ten arylamidoximes from arylnitriles and hydroxylamine is described. The formation of the arylamides has been observed to a much lesser extent in the present work. A new mechanism for the formation of arylamidoximes, as well as arylamides, from arylnitriles and hydroxylamine is suggested. Quantum mechanical calculations have been carried out to support this mechanism. The enthalpy of formation in conjunction with atomic charges of the reactants and intermediates helped to understand more about the generation of the products.

Keywords Arylamidoximes · Amides · Quantum chemical calculations · Density functional calculations · Reaction mechanisms

Introduction

Amidoximes are an interesting class of compounds. They can serve as starting materials for the synthesis of valuable heterocyclic and other useful compounds [1–7]. Besides their chemical usefulness, this class of compounds possesses pronounced biological activities. Two reviews treating this subject provide the details of such activities [1, 2]. In fact, amidoximes are mainly used as NO generators in vivo, having neuromodulatory and neurotransmittory actions [8]. Another interesting feature concerning amidoximes is that they can be used as prodrugs for amidines, once endogenous cellular reductases reduce amidoximes to amidines [9–11]. Amidoximes are less basic than amidines and are not protonated under physiological conditions, enhancing intestinal absorption by diffusion [12]. In addition, two antithrombotic drugs, sibrafibran and ximelagatran, were developed using this principle of latentiation [13].

For a long time, our group has been involved in synthesizing 1,2,4-oxadiazole derivatives from arylamidoximes [6, 14]. Their synthesis always produced varying quantities of arylamides as well. However, the quantity of amide increases when there is an electron-withdrawing group at the phenyl ring. We therefore decided to investigate the reaction of arylnitriles and hydroxylamine with a view to clarify the mechanism of formation of the principal product as well as to reduce the formation of the undesired amide. Although all amidoximes described in this paper are known, we have developed a simpler procedure for synthesizing arylamidoximes, using hydroxylamine hydrochloride and arylnitriles at room temperature in the presence of sodium bicarbonate. Therefore, we describe herein the synthesis of ten benzamidoximes **6a-6j** (Scheme 1) under relatively mild conditions that we have standardized in our laboratory. A more appropriate mechanism of formation of arylamidoximes and arylamides is suggested. In order to support this mechanism, quantum mechanical calculations were performed, which indeed gave some insight about the reaction mechanism.

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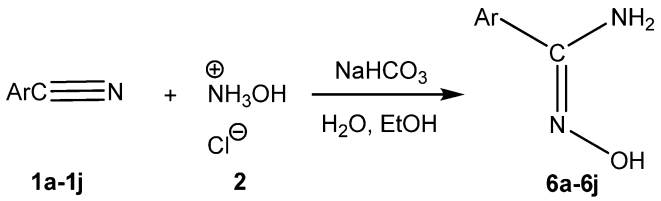
Scheme 1



Ar	Yield	Ar	Yield
a: Ph	80%	**f:** *m*-ClPh	80%
b: *o*-Tolyl	31%	**g:** *p*-ClPh	73%
c: *m*-Tolyl	89%	**h:** *p*-BrPh	79%
d: *p*-Tolyl	89%	**i:** *p*-HC≡CPh	93%
e: *p*-CH_3OPh	86%	**j:** *p*-AcPh	75%

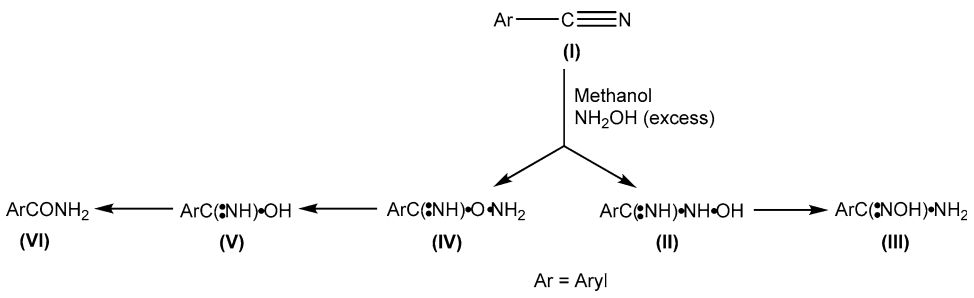
Results and discussion

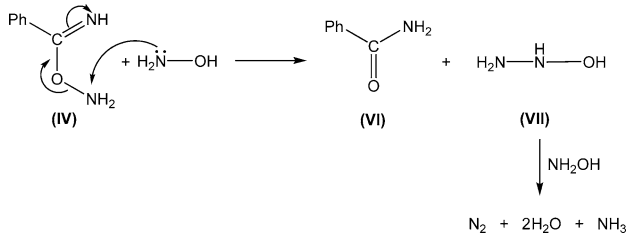
Stephenson et al. [15] found that treatment of 4-cyanopyridine or nitriles of the type X-C_6H_4CN (X = *o*-NO_2, *p*-CN, *p*-Cl, or *p*-CF_3) with excess of hydroxylamine in methanol yielded amidoximes (III), but contaminated with varying amounts (17–55%) of the corresponding amides (VI) as shown in Scheme 2. The above authors also proposed the mechanism of amide (VI) formation as given in Scheme 3.

Our suggestion concerning the mechanism is the following: The hard and soft acid base principle (the HSAB principle) [16–18] can be applied in the reaction between arylnitriles and hydroxylamine. Hydroxylamine is an ambident nucleophile, so either the oxygen or nitrogen atom of this molecule may attack the carbon atom of the nitrile, which behaves as a moderately hard acid. Since a strong base would prefer to bind a strong acid, we convincingly feel that the oxygen atom attacks the carbon atom of the nitrile group preferentially and this reaction is kinetically controlled. There are examples where *O*-acylhydroxylamine derivatives have been isolated as major initial products from the reaction of hydroxylamine with a number of acylating agents at neutral pH [19]. Ambident nucleophilic behavior of hydroxylamine has been demonstrated earlier [20]. Alkyloxylation of α, β-unsaturated esters and nitriles at β-carbon has also been reported [21]. Once the oxygen atom of hydroxylamine attacks the carbon atom of the nitrile, the carbon atom of the intermediate **3** becomes still a harder acid, and now the nitrogen atom of the $-O-NH_2$ moiety can attach to this carbon, forming an oxaziridine ring **4** as an unstable intermediate. Once a three-membered ring is formed, its opening in a normal way should occur through O_1–C_3 bond cleavage, which will have thermodynamic control. At higher temperature, ring opening may take place either through O_1–C_3 or N_2–C_3 bond cleavage, thus providing more amide. Scheme 4 provides a complete picture of the mechanism of formation of the products.

Also, it is important to comment on the mechanism of formation of the amides. Stephenson and colleagues [15] considered the attack of the nitrogen atom of hydroxylamine on the nitrogen atom of (IV) with the formation of (VI) and (VII) (see Scheme 3). Compound (VII) further reacts with a molecule of hydroxylamine to afford a molecule of nitrogen, two molecules of water and a molecule of ammonia. We feel that the initial attack of the hydroxylamine nitrogen at the nitrogen atom of (IV) in a S_N2 manner is very difficult because both nitrogen atoms involved in the reaction are electron deficient. Therefore, this kind of reaction is less favorable. Alternatively, the imine part of the nitrogen atom, which has higher electron density, picks up a proton from the –OH of NH_2OH and leaves the oxygen atom of hydroxylamine negatively

Scheme 2





Scheme 3

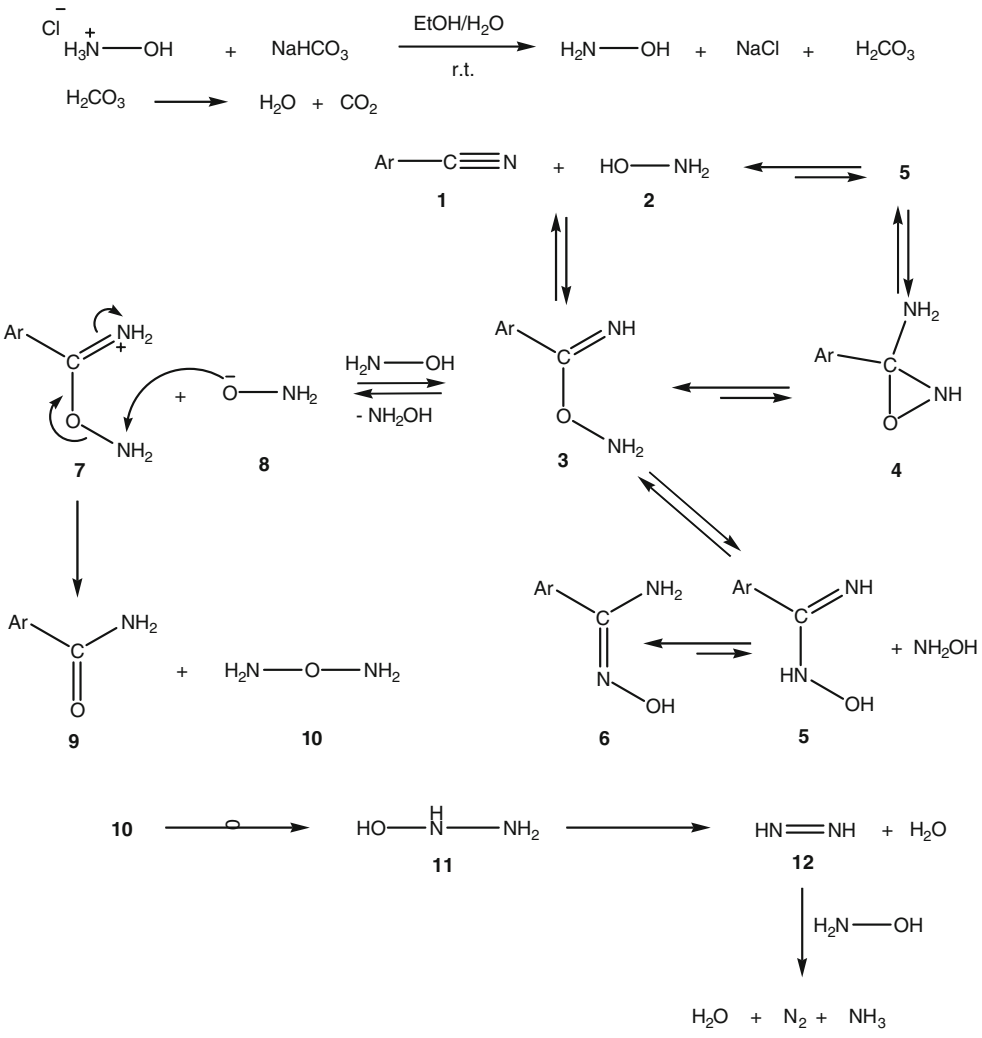
charged, which would easily attack the NH_2 group of **7** to provide **8** (Scheme 4).

In Fig. 1 the optimized geometries and the atomic charges for the most important atoms involved in the reaction mechanism are shown. We performed geometry optimization calculations to analyze which of the hydroxylamine atoms (nitrogen or oxygen) would first attack the nitrile carbon. This way, we analyzed a cluster containing one molecule of each reactant, arylnitrile, and hydroxylamine. Only one stable geometry was found, which is shown in Fig. 1a. In this cluster, the binding energy of the molecules is 21.4 kJ mol^{-1}, and they form a hydrogen bond between the hydroxyl group of hydroxylamine and the nitrile nitrogen. It can also be seen that the hydroxylamine oxygen atom ($Q_O = -0.563$) plays a stronger role as a base than the nitrogen atom ($Q_N = -0.331$). This supports our idea that the oxygen atom attacks the nitrile carbon.

In addition to these findings, it can also be noticed that:

- The atomic charges obtained from quantum mechanical calculations show that the oxygen atom of hydroxylamine has a higher charge compared with the nitrogen atom (see Fig. 1a). This clearly indicates that the electronic charges, as well as electron density, are higher either at the neutral or negatively charged (H_2NO^-) oxygen atom of hydroxylamine.

Scheme 4



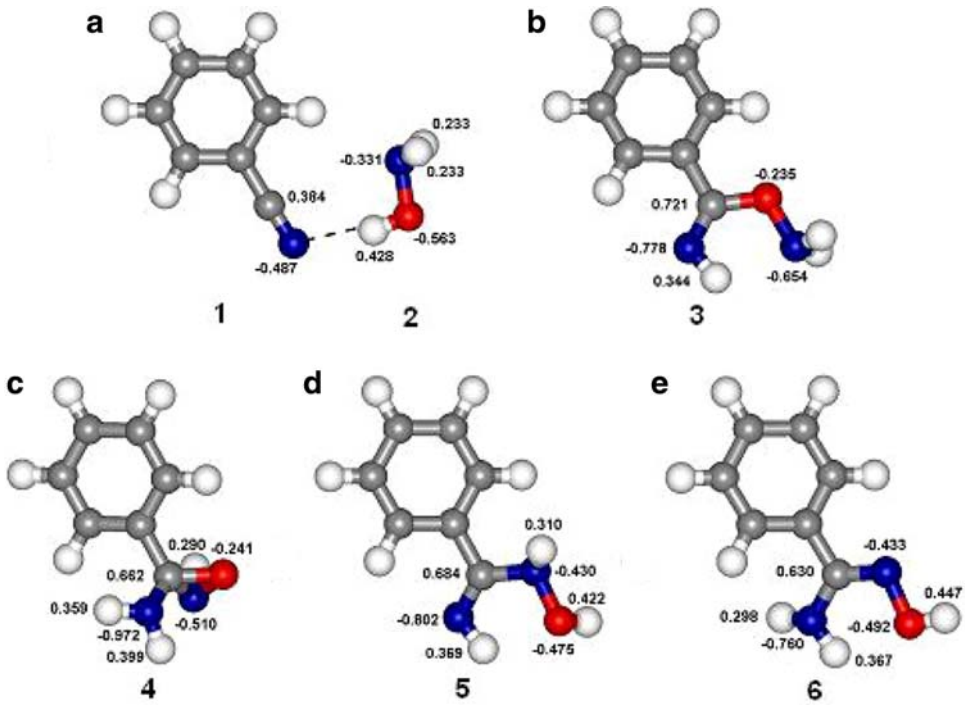


Fig. 1 Optimized geometries for reagents **1** and **2** (**a**), intermediates **3** (**b**), **4** (**c**), and **5** (**d**), and for product **6** (**e**). The atomic charges are shown in the structures, and they reproduce the electrostatic potential obtained in quantum calculations

- Since there is a lot of water in the reaction medium, the following equilibrium is also expected:

$$H_2N-OH + H_2O \leftrightarrows H_2N-O^- + H_3O^+$$

- Two molecules of hydroxylamine should give the equilibrium given below:

$$H_2N-OH + H_2N-OH \leftrightarrows H_3\overset{+}{N}-OH + {}^-O-NH_2$$

- Protonation of the oxygen atom from the second molecule of hydroxylamine should also take place to provide the following:

$$H_2N-OH + H_2N-OH \leftrightarrows {}^-O-NH_2 + H_2\overset{+}{O}-NH_2$$

Once the hydroxylamine oxygen atom attacks the nitrile carbon, the intermediate **3** is formed (see Fig. 1b), and it is 23.4 kJ mol^{-1} more stable than the reagents cluster (see Fig. 1a). Analyzing the calculated atomic charges at the imine carbon atom ($Q_C = 0.721$) and the hydroxylamine nitrogen atom in intermediate **3** ($Q_N = -0.654$), we can see that there is a strong and attractive electrostatic interaction between the amine nitrogen atom and imine carbon atom. This favors the formation of the oxaziridine ring **4**. The optimized geometry for intermediate **4** is shown in Fig. 1c. In this three-membered ring, the calculated atomic charges show a stronger bonding between the carbon ($Q_C = 0.662$) and the nitrogen ($Q_N = -0.510$), rather than between the carbon and the oxygen ($Q_O = -0.241$) atoms. Although the oxaziridine ring is of high energy, this attraction justifies the formation of a three-membered ring. Thus, the C–O bond cleavage should be favored, and intermediate **5** (see Fig. 1d) can be formed. Next, the tautomerization process may occur easily, and product **6** (see Fig. 1e) is generated.

The enthalpy of formation calculations for **3**, **4**, **5**, and **6** were performed in order to analyze their energies (Fig. 2). These energies were calculated as a function of the hydrogen-bonded cluster formed by the reagents (**1** and **2**). These calculations indicate that **6** is more stable than **3** by 38.1 kJ mol^{-1}. Our calculations also disclose that tautomer **5** is 47.7 kJ mol^{-1} less stable than **6**.

Also, our efforts to calculate the transition state between **8** and **7** did not work out, but the mechanism of amide formation, as depicted in Scheme 4, seems reasonable. Once this happens, the negatively charged oxygen atom of hydroxylamine **8** should attack the nitrogen atom of **7**, giving arylamide **9** and an unstable *O*-aminohydroxylamine **10**. This latter product must rearrange to **11**, which disproportionates to diimide **12** and water. It is this diimide that is the source of hydrogen and should cause the hydrogenolysis of hydroxylamine to give H_2O, N_2, and NH_3.

In conclusion, we achieved an easy synthesis of ten arylamidoximes under relatively mild conditions. The formation of unwanted arylamides under these conditions is very little. Geometry optimizations and charge densities obtained by quantum mechanical calculations employing the B3LYP/6-311 + G(d) method helped us to propose new mechanisms for the formation of arylamidoximes and arylamides. These calculations also furnished the enthalpy

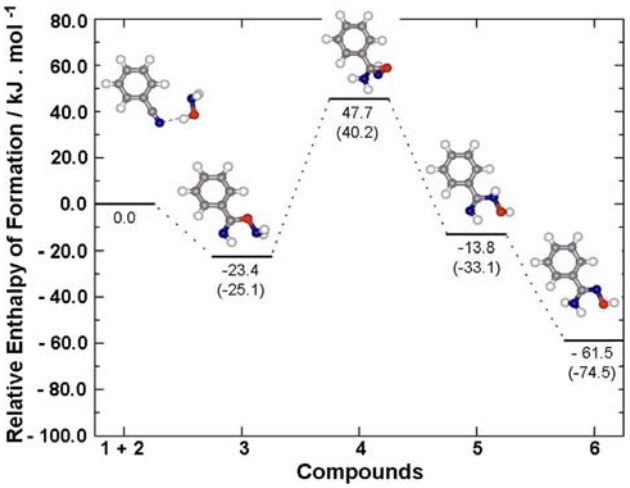


Fig. 2 Enthalpy of formation of compounds **3**, **4**, **5**, and **6** as a function of hydrogen-bonded cluster generated by the reagents **1** and **2**. The solvent effect was considered as a continuum model (*parenthesis*)

of formation of compounds **3**, **4**, **5**, and **6**, which gave more information about the mechanism of formation of the products.

Experimental

Synthesis of arylamidoximes

Hydroxylamine hydrochloride (2.0 g, 29.1 mmol), 2.4 g sodium bicarbonate (29.1 mmol) and 25.0 cm^3 water were stirred for about 10 min at room temperature followed by the addition of 3.0 g benzonitrile (29.1 mmol) in 25.0 cm^3 ethanol, and the stirring was continued at 25°C for 20 h. More hydroxylamine hydrochloride (1.0 g, 14.5 mmol) was added at room temperature, and the agitation was maintained for an additional 50 h. Filtration and solvent removal left crude amidoxime, which was dissolved in dichloromethane, dried (Na_2SO_4), filtered, and the solvent removed under reduced pressure. The crude product was recrystallized from chloroform–cyclohexane to give pure benzamidoxime. Other nitriles were transformed to arylamidoximes in a similar manner. Although we generally let the reaction run for 3 days, it is possible to complete the reaction in 20–24 h, except for compounds **6b** and **6c**, which require 3 days. The yields ranged between 72 and 93% of the pure material, except for **6b**, which yielded only 31%. The melting points of arylamidoximes **6a-6e**, **6 g**, **6 h** [14], **6f** [22], **6i** [23], and **6j** [24] agreed with the literature data. We tried to determine the percentage of amide formed in each reaction by ^1H NMR spectra of the crude material. In general, the percentage of amide in the crude mixture was $\leq$5.0%, except in **6b**, where it was 8.3%.

Computational methods

Ab initio quantum mechanical calculations were performed to determine geometries, energy and atomic charges for reagents **1** and **2**, intermediates **3**, **4**, and **5**, and product **6**. The atomic charges were obtained from an electrostatic fit using the CHELPG procedure [25, 26]. All calculations were performed using the Gaussian 03 program [26, 27] and the density-functional method, with the hybrid functional B3LYP [28] and the 6-311 + G(d) basis set. The solvent effects were included in the calculations using the continuum approach with a polarizable continuum model (PCM) [29–31], where all geometries were re-optimized. Atomic charges and enthalpy of formation of the intermediates were also calculated.

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