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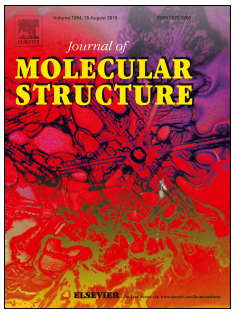

A convenient method for preparation of 2-amino-4,6-diphenylnicotinonitrile using HBF_4 as an efficient catalyst *via* an anomeric based oxidation: A joint experimental and theoretical study

Mohammad Ali Zolfigol, Mahya Kiafar, Meysam Yarie, Avat(Arman) Taherpour, Thomas Fellowes, Amber Nicole Hancok, Ako Yari

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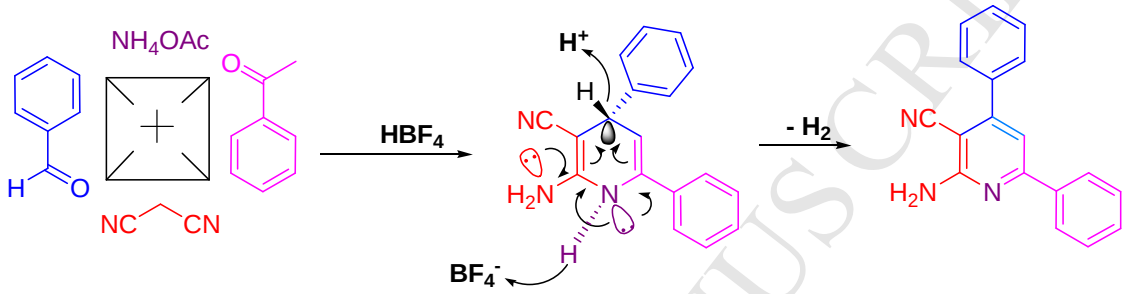
Mohammad Ali Zolfigol,[*a] Mahya Kiafar,[a] Meysam Yarie,[a] Avat(Arman) Taherpour[*b,c] ,Thomas Fellowes[d], Amber Nicole Hancok[e], Ako Yari[b]



2-Amino-4,6-diphenylnicotinonitriles were synthesized by using HBF_4 as oxidizing promoter catalyst. The suggested anomeric based oxidation mechanism was supported by experimental and theoretical evidences.

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A convenient method for preparation of 2-amino-4,6-diphenylnicotinonitrile using HBF_4 as an efficient catalyst *via* an anomeric based oxidation: A joint experimental and theoretical study

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Abstract

Experimental and computational studies in the synthesis of 2-amino-4,6-diphenylnicotinonitrile using HBF_4 as an oxidizing promoter catalyst under mild and solvent free conditions were carried out. The suggested anomeric based oxidation (ABO) mechanism is supported by experimental and theoretical evidence. The theoretical study shows that the intermediate isomers with 5R- and 5S- chiral positions have suitable structures for the aromatization through an anomeric based oxidation in the final step of the mechanistic pathway.

Keywords: HBF_4**,** 2-amino-4,6-diphenylnicotinonitrile**,** anomeric based oxidation**,** experimental and theoretical study , solvent free conditions**.**

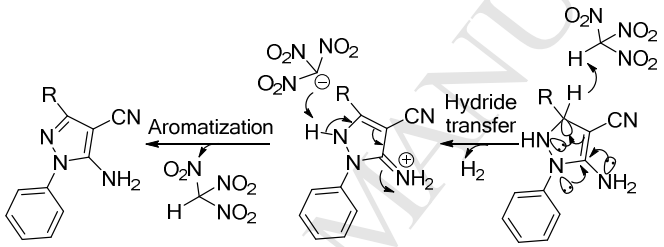
Introduction

After the discovery of the anomeric effect (The Edward-Lemieux effect) by J.T. Edward in 1955, it attracted the attention of a generation of chemists, leading to a great deal of research in this area [1]. It was found that despite unfavorable steric and solvation effects, the axial conformer of 2-methoxy-tetrahydro-2*H*-pyran is more stable than the equatorial conformer. An explanation for this unusual preference is based on stereoelectronic effects involving the oxygen's lone pair [2]. The obtained data from the study on the anomerization equilibria of the fully acetylated derivatives of the aldohexopyranoses confirmed the stereoelectronic effect for these equilibria [3].

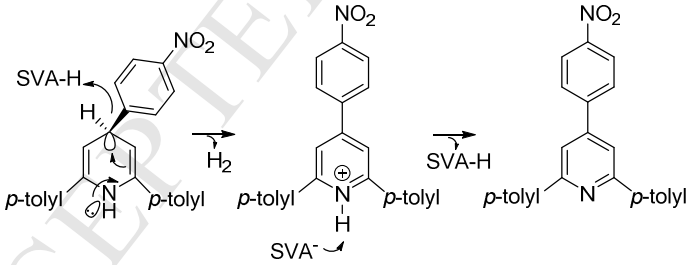
The anomeric effect is a stabilizing phenomenon and refers to the tendency of an electronegative substituent in the structure of the pyranoid ring at C1 position to prefer the axial rather than equatorial orientation [1]. Since the original definition, it has become clear that the anomeric effect is not restricted to the aforementioned interpretation in the context of carbohydrate chemistry and could be an explanation for the preference of the gauche- over the anti-orientation in Newman projections of other compounds [1]. Anomeric interactions can also explain the stereochemical selectivity in radical reactions [4] and conformational preferences in *N*-alkoxy

cyclic hydroxylamines, bisoxo-substituted amines, *ONO* systems and *N*-alkoxy-*N*-chloroureas [5-8].
A striking example of the anomeric effect can be observed in the activation and fixation of some small molecules like H_2, CO, NO, N_2O and CO_2 at *N*-heterocyclic carbene centers [9]. The interaction of lone-pair electrons of the nitrogen atoms with the carbene center, stabilize this intermediate in the activation and the fixation process.

In some cases, like the Cannizzaro reaction and tricyclic orthoamide, the anomeric effect can cause the generation of hydrogen gas through a hydride transfer. These examples show that the anomeric effect can contribute to the mechanistic aspects of certain reactions [10,11]. In light of this, we have recently introduced a new term, "anomeric based oxidation (ABO)" for the mechanistic interpretation of the aromatization of some nitrogen-containing heterocyclic compounds. As depicted in Scheme 1 and 2, in the final steps of the presented mechanisms for the synthesis of the 1,4-dihydropyrano-[2,3-*c*]-pyrazole derivatives and 2,4,6-triarylpyridines, the lone pair of the nitrogen atom can promote the hydride transfer leading to the liberation of H_2 from substrate molecules [12,13].



Scheme 1. The anomeric based oxidation effect in the aromatization of 1,4-dihydropyrano-[2,3-*c*]-pyrazole derivatives[12]

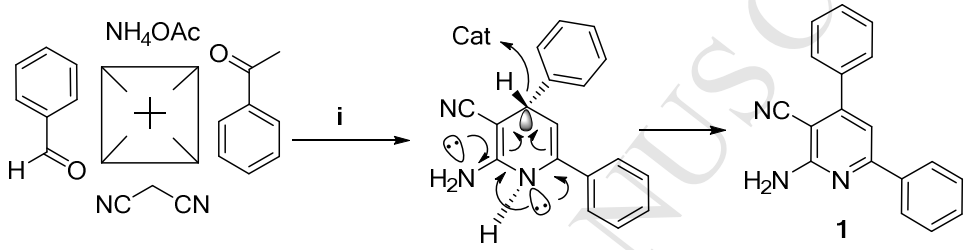


Scheme 2. The anomeric based oxidation effect in the aromatization of 1,4-dihydropyrano-[2,3-*c*]-pyrazole derivatives[13]

In order to develop our concept of "anomeric based oxidation" (ABO) in the aromatization of heterocyclic molecules, we have looked for suitable compounds that possess the necessary structural properties. In addition to the above compounds (Schemes 1 and 2), we found that the 2-amino-4,6-diphenylnicotinonitrile 1 is a suitable target molecule for this purpose. The 2-amino-4,6-diphenylnicotinonitrile derivatives contain pyridine ring systems which possess wide chemotherapeutic and pharmaceutical applications such as IKK-b inhibitors [14], A_{2A}adenosine receptor antagonists [15], and potent inhibitors of HIV-1 integrase [16]. As a consequence of the biological and therapeutic significance of these heterocyclic molecules, a number of methods have been developed for their preparation [17-25].

Results and Discussion

Recently, we have introduced a new concept entitled "Anomeric Based Oxidation" (ABO).[12,13] In an ABO reaction, the major driving force is aromatization supported by stereoelectronic effects. In order to demonstrate this, we synthesized 2-amino-4,6-diphenylnicotinonitrile 1, via one-pot four component reaction of benzaldehyde, acetophenone, malononitrile and ammonium acetate using HBF_4 as an oxidizing promoter catalyst under mild and solvent free conditions (Scheme 3). To verify that ABO was occurring in the synthesis of 2-amino-4,6-diphenylnicotinonitrile 1, the reaction was carried out under N_2 atmosphere. The obtained results show no change in the yields and the reaction times. The related intermediate **7** has two nitrogen atoms that can contribute to the resonance through their unshared electrons and interact with the anti-bonding orbital of C-H ($\sigma^*_{C\text{-}H}$ orbital). The delocalization of the electrons through the ring leads to the weakening of the C-H bond, promoting hydride transfer and the generation of molecular hydrogen (H_2).



i: HBF_4, 0.1 gr, Solvent free, 100 ^oC, under air or nitrogen atmosphere, 150 min, 60 %

Scheme 3. The preparation of the 2-amino-4,6-diphenylnicotinonitrile in the presence of catalytic amount of HBF_4 as oxidizing promoter catalyst

Modeling of the reactions of HBF_4 (as its hydrated form $[BF_4^-]_2[H_3O^+]_2$) as an oxidizing catalyst with the R- and S- isomers of intermediate **7** was performed using the *Spartan '10* package [26]. The calculations on the structures of the R- and S- isomers of intermediate 7, the different positions of the transition states (TS) of the reactions, intermediates and the product were undertaken using a DFT-B3LYP/6-31G* method [26]. The transition states were obtained by reaction coordinate methods. The HF/6-31G* was applied for initial optimization of the precisely transition states and then DFT-B3LYP/6-31G** performed for final optimization of the transition states as well as the reactants and the intermediates. The vibration frequencies were checked for optimized TS structures. The supplementary data (S1), shows selected structural data (bond length (Å), bond angle (°) and torsional angle (°)) of the precursors (intermediate **7**; R- and S- isomers), the transition states with different orientations of the $[BF_4^-]_2[H_3O^+]_2$ as oxidizing agent with respect to the R- and S- isomers of the precursors, intermediates and the product. In Figure 1 we show the optimized structures of $[BF_4^-]_2[H_3O^+]_2$ as an oxidizing agent.

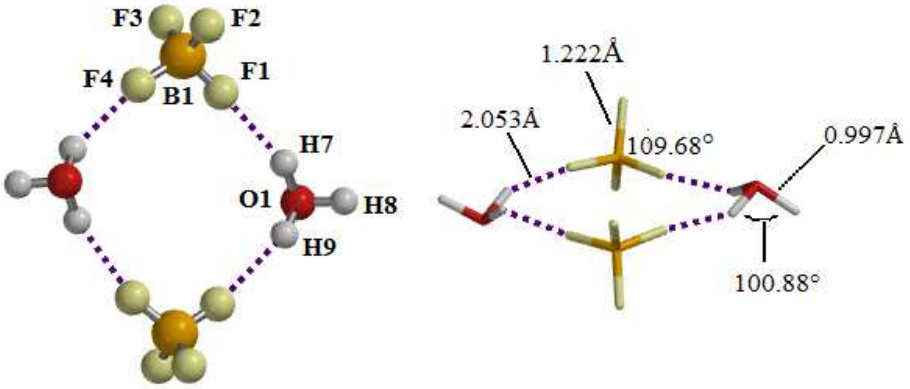


Figure 1: Structure of the oxidizing promoter catalyst: $[BF_4^-]_2[H_3O^+]_2$

Figure 2 shows the optimized structures of the "R" and "S" enantiomers of intermediate 7. Table 1 shows the calculated Mulliken bond orders (MBO) in intermediate **7**. The data show that the MBO of C5-H6 bond for the isomers with 5R- and 5S- chiral positions of intermediate **7** are 0.93 and 0.91, respectively. It seems that the S-isomer is more likely than the R-isomer to take part in the ABO reaction in the first step of the reaction, as the MBO is smaller by 0.02. The DFT calculations show that in the R- and S- isomers of intermediate **7** the MBO of C5-C7 due to the anomeric effect were calculated at 0.95 for both isomers. It seems that the N2-C3-C4-C5-H6 pathway for electron transfer facilitates electron ring currents and satisfies the Hückel requirement for aromaticity in the heterocyclic ring. There appears to be an anomeric effect via outside electron transfer (N10-C9-C8-C5-H6), but there are no electron ring currents or sextet for the heterocyclic ring in comparison to the inside electron transfer. The MBO of C9-N10 was calculated to be 1.03, which is much smaller than 2.00 as the simple B.O. of a double bond. The DFT calculation has shown pyramidality for the NH_2 group in intermediate **7**. The lower MBO for C8-C9 (1.57) than C3-C4 (1.77) demonstrated another pathway (N2-C9-C8-C5-H6) for electron transfer. In this pathway, the MBO of N2-C9 and C9-C8 were calculated to be 0.99 and 1.57, respectively. This pathway is not only better suited for electron ring currents and the aromatic electronic sextet for the heterocyclic ring, but also allows the NH and NH_2 groups to better participate in the anomeric effect on C5-H6 bond. The inside (N2-C3-C4-C5-H6) pathway of electron transfer (red pathway in figure of Table 1) includes: $n_{N2} \rightarrow \pi^*_{C3-C4}$ and $\pi_{C3-C4} \rightarrow \sigma^*_{C5-C6}$. The other inside electron transfer pathway (N2-C9-C8-C5-H6) includes: $n_{N2} \rightarrow \pi^*_{C9-C8}$ and $\pi_{C9-C8} \rightarrow \sigma^*_{C5-C6}$ electron conjugations. The outside (N10-C9-C8-C5-H6) pathway of electron conjugation (blue pathway in figure of Table 1) includes: $n_{N10} \rightarrow \pi^*_{C9-C8}$ and $\pi_{C9-C8} \rightarrow \sigma^*_{C5-C6}$.

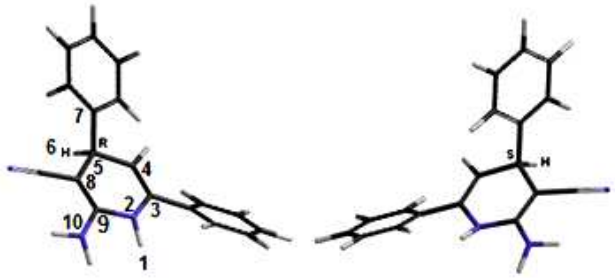
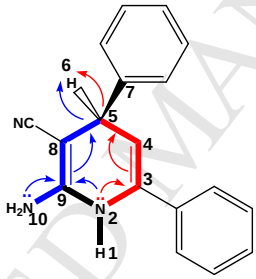


Figure 2: The structures of the "5R" and "5S" epimers of intermediate **7**. The energy level differences of the epimers (2.9 kcal mol^{-1}) and the barrier energy of inversion on N2-atom for the interconversion of the two isomers (about 1 kcal mol^{-1}) have obtained very low. So, the energies have approximately considered with equal energy levels.

Table 1: The bond orders of the resonance process in intermediate **7** for the anomeric effect on C5-H6 bond in the different pathways.



Structures and pathways	Bond Orders									
	C9-N10	C8-C9	C5-C8	C5-C7	C5-H6	C4-C5	C3-C4	N2-C3	N2-C9	H1-N2
R-Isomer	1.04	1.57	0.97	0.95	0.91	0.97	1.77	0.91	0.99	0.87
S-Isomer	1.04	1.56	0.98	0.95	0.93	0.97	1.77	0.97	0.99	0.88
R-NH	1.03	1.55	0.97	0.94	0.93	0.97	1.76	0.97	0.99	0.89
S-NH	1.03	1.55	0.98	0.94	1.10	0.97	1.77	0.97	0.99	0.89
R-NH2	1.03	1.55	0.97	0.94	1.10	0.97	1.77	0.97	0.99	0.89
S-NH2	1.04	1.56	0.98	0.95	1.10	0.97	1.77	0.97	0.99	0.88

The isomers with 5R- and 5S- chiral positions have *trans*- and *cis*- structures respect to N2-atom, respectively. The energy level differences of the epimers (2.9 kcal mol^{-1}) and the barrier energy of inversion on N2-atom for the interconversion of the two isomers (about 1 kcal mol^{-1}) have obtained very low. So, the energies have approximately considered with equal energy levels. This point could be important when the isomers react with the structure of HBF_4 (as its hydrated form $[BF_4^-]_2[H_3O^+]_2$). The interactions like electrostatic attractions and H-bonding between the

isomer structures and specially the endo orientation (A) of $[BF_4^-]_2[H_3O^+]_2$ has made the condition for different rate of the isomer reactions. The calculated structures of the transition states ($[TS]_R$ and $[TS]_S$) for the first step of the ABO reaction in the R- and S- isomers of intermediate 7 with $[BF_4^-]_2[H_3O^+]_2$ are presented in Figure 4. In the reactions, the isomers with 5R- and 5S- chiral positions of intermediate **7** with $[BF_4^-]_2[H_3O^+]_2$ the bond lengths of C5-H6 and H6…H8 in the more stable transition state (TS(A); the isomers with 5R chiral positions) were obtained as 1.889 and 0.784Å, respectively. These bond lengths in the less stable transition state (TS(B); the isomers with 5S chiral positions) were obtained as: 1.611 and 0.849Å, respectively. See supplementary data (**S1**), (**S2**) and Figure 3. The DFT calculations shows that the endo-orientation is more stable than the exo-orientation for $[TS]_R$ and $[TS]_S$. The hydrogen bonds and dipole-dipole interactions between the reactants in the endo-orientation is stronger than in the exo-orientation. The supplementary data (**S3**) shows the structures of the H^+ attractions step from intermediate 8 by $[BF_4^-]_2[H_3O^+]_2$.

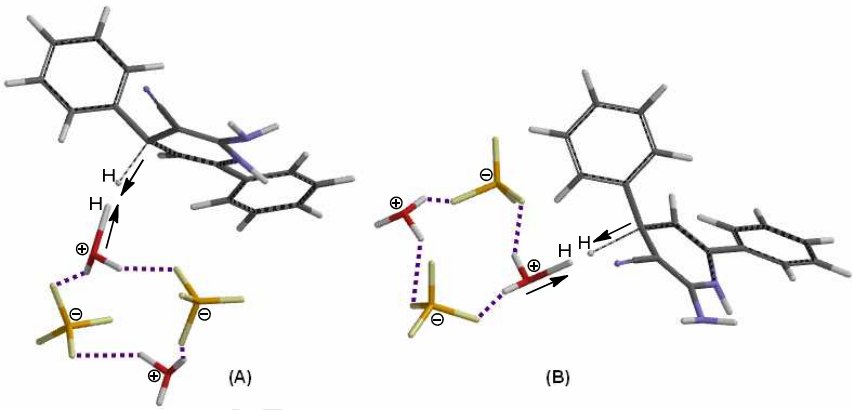
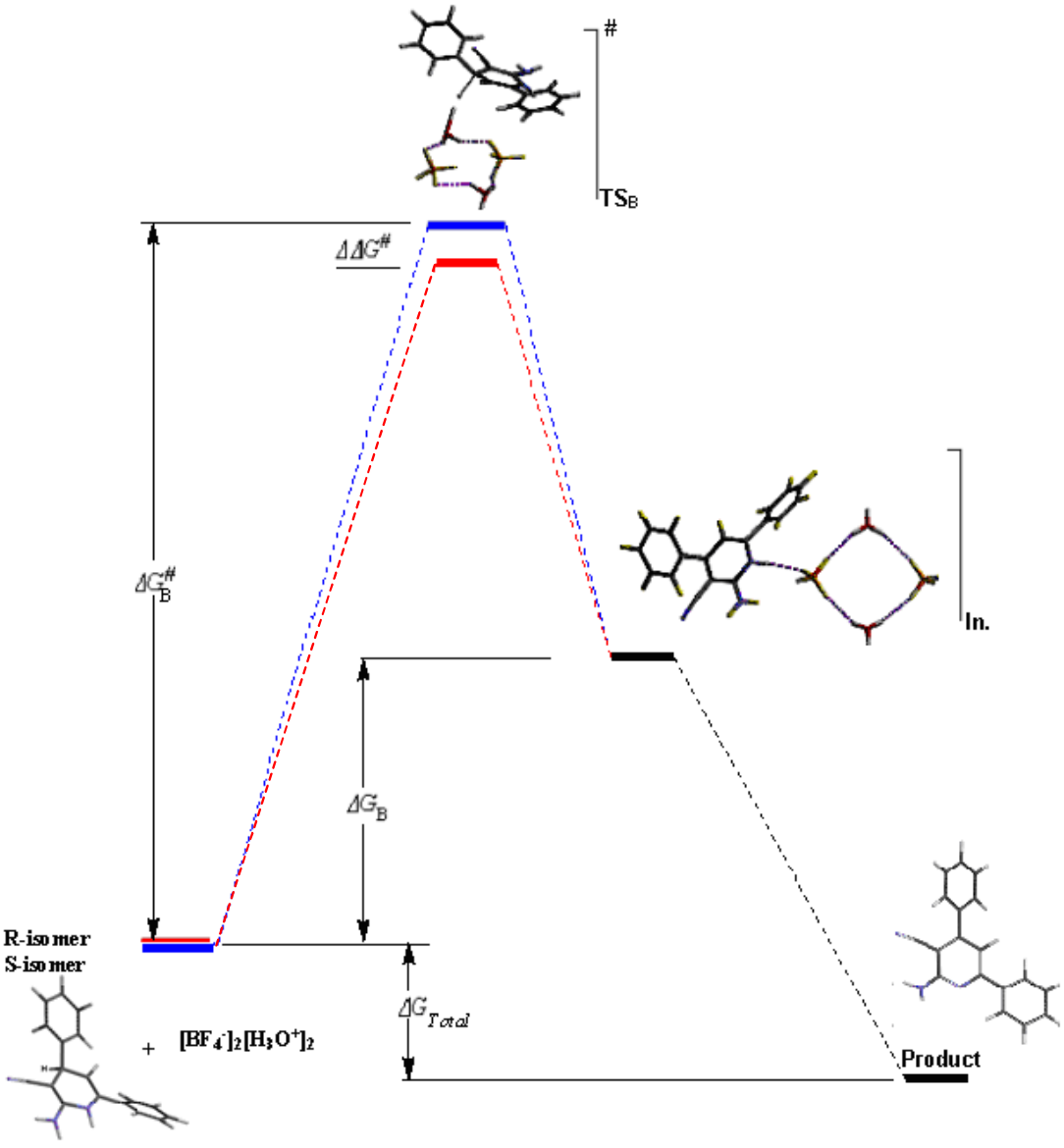


Figure 3: Two structures of the transition states ([TS] of endo orientation (A) and of exo orientation (B)) for the first step of the intermediate **7** oxidation reactions with $[BF_4^-]_2[H_3O^+]_2$. The structure (A) is more stable than (B).

The reaction diagram and free energies (in kcal mol^{-1}) of the anomeric based oxidation of intermediate 7 by $[BF_4^-]_2[H_3O^+]_2$ is shown in Figure 6. The DFT results demonstrated that the $\Delta G^{\#}$ of R- and S- isomers of intermediate 7 with $[BF_4^-]_2[H_3O^+]_2$ in the endo-orientation are 31.7 and 43.8 kcal mol^{-1}, respectively. The DFT calculations show that the endo-orientation is more stable than exo-orientation for $[TS]_R$ and $[TS]_S$. The results have shown that the $\Delta G^{\#}$ of the isomers with 5R- and 5S- chiral positions of intermediate **7** with $[BF_4^-]_2[H_3O^+]_2$ in the exo-orientation are 39.1 and 45.1 kcal mol^{-1}, respectively. The differences between the free activation energies ($\Delta\Delta G^{\#}$) for the endo- and exo-orientations reactions were obtained 12.4 and 6.8 kcal mol^{-1}, respectively. See Figure 4.

The oxidation reactions by $[BF_4^-]_2[H_3O^+]_2$ for the exo-orientation (with $\Delta G^{\#}$ =39.1 (5R) and 45.1 (5S) kcal mol^{-1}) has the highest reaction rate among the different calculated situations. As mentioned before, the calculated Mulliken bond order (MBO) of C5-H6 for 5R-isomer is 0.02 less that 5S-isomer and it could be the reason of the higher reactivity of the 5R-isomer compared

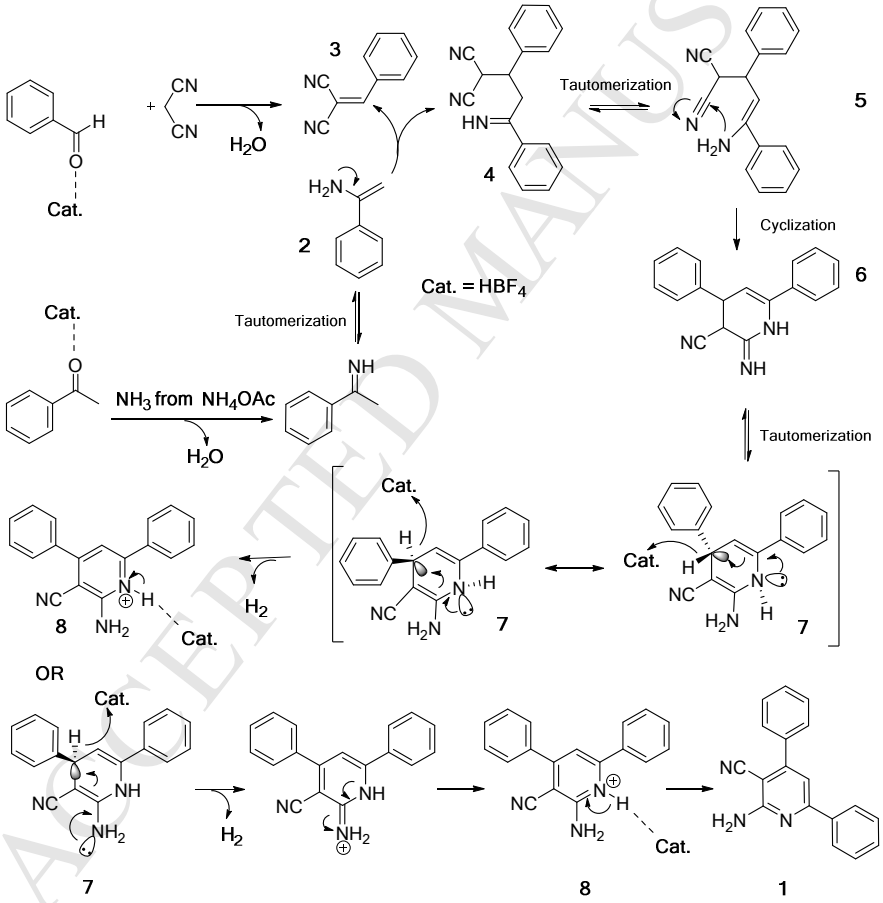
to the 5S-isomer on the basis of the anomeric effect in intermediate **7** structure. The DFT calculated free energies of the reactant and the product (ΔG_{Total}) of the oxidation reactions for the isomers with 5R- and 5S- chiral positions of intermediate **7** were calculated to be -20.6 and -20.3 kcal mol^{-1}, respectively. See the free energies table of Figure 4. The DFT-B3LYP/6-31G* show that the 5S-isomer is more stable than 5R-isomer of intermediate **7**, but the reaction of the R-isomer is faster because of the lower Mulliken bond order of C5-H6 due to the anomeric effect.



Energy Data *(kcal mol^{-1})*	$\Delta G^{\#}$		$\Delta\Delta G^{\#}$	ΔG_B	
	R-7	S-7		R-7	S-7
$[BF_4^-]_2[H_3O^+]_2$ (Out)	39.1	45.1	6.8	-18.7	-18.4
$[BF_4^-]_2[H_3O^+]_2$ (In)	31.7*	43.8	12.4	-18.7	-18.4

Figure 4: The reaction diagram of intermediate 7 oxidation reaction on the basis of anomeric effect by $[BF_4^-]_2[H_3O^+]_2$ agent. For exo (A) and endo (B) orientation. The calculated values of ΔG_{Total} (S and R isomers) are: -20.6 and -20.3 kcal mol^{-1}, respectively. *The highest rate of the oxidation reaction.

The suggested mechanistic pathway, as described in Scheme 4, shows that $[BF_4^-]_2[H_3O^+]_2$ can act as oxidizing promoter catalyst and activate acetophenone and benzaldehyde as electrophilic species to yield the related intermediate **2** and **3**, respectively by the reaction with *in-situ* generated NH_3 (from ammonium acetate) and malononitrile. The reaction between these two intermediates afford intermediate 4 that can convert to the intermediate 7 through a sequence of tautomerization, cyclization and again tautomerization. As depicted in Scheme 4, the intermediate **7** has an appropriate structure with two active nitrogen atoms that can release their unpaired electrons in resonance and interact with the anti-bonding orbital of C-H ($\sigma^*_{C\text{-}H}$ orbital). Finally, the intermediate **7** undergoes anomeric based oxidation to yields the desired aromatized product **1**.



Scheme 4. A plausible mechanistic pathway for the synthesis of 2-amino-4,6 diphenylnicotinonitrile in the presence $[BF_4^-]_2[H_3O^+]_2$ as oxidizing promoter catalyst

Conclusion

In summary, the synthesis of 2-amino-4,6-diphenylnicotinonitrile **1** using HBF_4 as oxidizing promoter catalyst under mild and solvent free conditions was investigated. Also, in addition to the experimental efforts, the theoretical study has demonstrated that the isomers with 5R- and 5S- chiral positions of intermediate have suitable structures for the aromatization through an anomeric based oxidation (ABO) in the final step of the mechanistic pathway. The theoretical aspects of the preparation of 2-amino-4,6-diphenylnicotinonitrile using HBF_4 as an efficient catalyst via the anomeric based oxidation (ABO) mechanism have investigated. We think that the proposed mechanism has potential for entering into the graduate text book in the future.

Experimental

General

All chemicals were purchased from Merck chemical company. The structural confirmation of known products was done by comparison of their physical properties and spectral data with their reported authentic samples in the literature. The progress of the reaction and the purity of the product were monitored using TLC using silica gel SIL G/UV 254 plates. The ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker spectrometer in DMSO*d*6, using TMS as internal standard and the chemical shifts are expressed in δ ppm. Melting points were determined by Buchi B-545 apparatus in open capillary tubes and are uncorrected. An aqueous solution of HBF_4 (40% W/W) was used.

General procedure for the synthesis of 2-amino-4,6-diphenylnicotinonitrile

To a round bottom flask containing a mixture of benzaldehyde (1 mmol, 0.106 g), acetophenone (1 mmol, 0.120 g), malononitrile (1 mmol, 0.066 g), and ammonium acetate (3 mmol, 0.23 g), a catalytic amount of $[BF_4^-]_2[H_3O^+]_2$ (0.46 mmol of HBF_4, 0.1 g of solution) as oxidizing promoter catalyst was added. Then, the resulting mixture was stirred under solvent free condition at 90 ^{o}C for appropriate times under air or nitrogen atmosphere. The progress of the reaction was monitored using TLC with a mixture of *n*-hexane and ethyl acetate as the eluent. Upon completion of the reaction, the mixture was cooled to room temperature. 5 mL of distillated water was added to the reaction mixture and decanted after few minutes in order to remove excess ammonium acetate. The desired product was obtained by recrystallization from ethanol with good yield.

Spectral data

2-amino-4,6-diphenylnicotinonitrile (1)

Melting point: 187-188 ^{o}C, [186-187][29]
FT-IR (KBr): υ(cm^{-1}) = 3466, 3305, 3180, 2206, 1638, 1573, 1423, 1370, 1259, 755, 698.
^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) = 7.06 (s, 2H,NH_2), 7.29 (s, 1H, aromatic), 7.52 (m, 8H, aromatic), 8.14 (s, 2H, aromatic).
^{13}C NMR (DMSO-d_6, 100 MHz): δ (ppm) = 86.6, 109.2, 117.0, 127.2, 128.3, 128.6, 128.7, 129.6, 130.1, 137.0, 137.5, 154.9, 128.6, 160.9.

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- The synthesis of 2-amino-4,6-diphenylnicotinonitrile using HBF_4 as oxidizing promoter catalyst under mild and solvent free conditions was investigated.
- HBF_4 is a commercially available low cost reagent.
- Our recently new introduced concept entitled "anomeric based oxidation" (ABO) was developed for the final step of the described synthesis and it was also approved using theoretical studies.
- We think that the proposed mechanism have potential for entering into the graduate text book in the future.