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Experimental and Theoretical Studies on the Tautomerism in 2-Aminopyridines and 2(1*H*)-Pyridinones: Synthesis of 2-Amino-4-aryl-3-cyano-6-(3,4-dimethoxyphenyl)pyridines and 4-Aryl-3-cyano-6-(3,4-dimethoxyphenyl)-2(1*H*)-pyridinones

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Under solvent-free conditions and in one-pot, a series of 2-amino-4-aryl-3-cyano-6-(3,4-dimethoxyphenyl)-pyridines and 4-aryl-3-cyano-6-(3,4-dimethoxyphenyl)-2(1*H*)-pyridinones were prepared using 3,4-dimethoxyacetophenone, an aldehyde, malononitrile (or ethyl cyanoacetate), and ammonium acetate in the presence of 3-methyl-1-(4-sulfonylbutyl)imidazolium hydrogen sulfate $[HO_3S(CH_2)_4MIM][HSO_4]$ (a Brønsted acidic ionic liquid) as the catalyst in very short reaction time. The preference for the formation of more stable tautomers was consistence with the theoretical calculation using the Gaussian 03 program at the B3LYP hybrid density functional level.

Key Words : Brønsted-acidic ionic liquids, 3-Cyanopyridines, 3-Cyanopyridinones, Multicomponent reactions, Tautomerism

Introduction

Pyridine derivatives have occupied an unique position in medicinal chemistry. Besides many naturally occurring pyridines, several synthetic derivatives show interesting biological activities. For examples, 2-amino-3-cyanopyridines have antibacterial,[1] antimicrobial,[2,3] antifungal,[4] and cardiotonic[5] activities. They are also found to be selective IKK-β serine-threonine protein kinase inhibitors.[6] On the other hand, 3-cyanopyridinone derivatives have antineoplastic,[7] PDE3 inhibitory,[8] cardiotonic,[5,9] and colon tumor cell growth inhibitory[10] effects. During past three decades, many synthetic methods have been used for the preparation of these 3-cyanopyridine,[1-6,11-14] and 3-cyanopyridinone derivatives.[5,7,9,10,15-18] As part of our efforts towards the development of synthetic methodologies,[19-27] here we report our investigation on the application of 3-methyl-1-(4-sulfonylbutyl)imidazolium hydrogen sulfate $[HO_3S(CH_2)_4MIM][HSO_4]$, a Brønsted acidic ionic liquid as a reusable catalyst,[28] for the synthesis of 3-cyanopyridines and 3-cyanopyridinones in high yields. For these syntheses, a mixture of 3,4-dimethoxyacetophenone, different aldehydes, malononitrile (or ethyl cyanoacetate), and ammonium acetate (a multicomponent reaction) was used in solvent-free conditions. Moreover, theoretical calculations were performed at the B3LYP hybrid density functional level using the Gaussian 03 program to predict the more stable tautomers. Geometries of tautomers were optimized at 6-31+G(d,p) basis sets. The calculated frequencies have no imaginary vibrational frequency, indicating that the optimized geometries are reasonable and reliable. These results are also presented here.

Experimental

All chemicals were commercially available and used as such. The Brønsted-acidic ionic liquid $[HO_3S(CH_2)_4MIM][HSO_4]$ was prepared using a literature method.[28] Melting points were recorded on an electrothermal type 9100 melting point apparatus. The IR spectra were obtained on a Shimadzu spectrophotometer as KBr disks. The ^{1}H-NMR (500 MHz) and ^{13}C-NMR spectra (125 MHz) were recorded on a Bruker DRX500 spectrometer. Mass spectrum was recorded on a Finnigan-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV.

General Procedure for the Synthesis of 2-Amino-4-aryl-3-cyano-6-(3,4-dimethoxyphenyl)pyridines B1-B5 and 4-Aryl (or alkyl)-3-cyano-6-(3,4-dimethoxyphenyl)-2(1*H*)-pyridinones D1-D5. A mixture of 3,4-dimethoxyacetophenone (2 mmol), an aldehyde (2 mmol), malononitrile (or ethyl cyanoacetate) (2 mmol), ammonium acetate (16 mmol), and $[HO_3S(CH_2)_4MIM][HSO_4]$ (10 mol % based on the aldehyde) was heated on the oil bath at 150 °C for a few minutes. After this time, the reaction mixture was cooled to room temperature, and cold ethanol was added. The crude product was collected and recrystallized from ethanol to give compounds **B1-B5** and **D1-D5** in high yields.

Computational Methodology. All calculations were performed at the B3LYP hybrid density functional level using the Gaussian 03 program. Geometries of tautomers were optimized at 6-31+G(d,p) basis sets. The calculation of quantum chemical energies is described as follows: all molecules were preoptimized using AM1 semiempirical method implemented in the Chemoffice 2004 program. The final geometries were obtained at B3LYP/6-31+G(d,p) level

using OPT keyword and then frequency calculations were done using FREQ keyword. Zero point energy corrections and thermal free energies have been obtained from frequency calculations. The total energy of molecule is the sum of electronic and zero point energy. All geometries have no imaginary vibrational frequency, indicating that they should be stable.

Spectral Data for New Compounds.

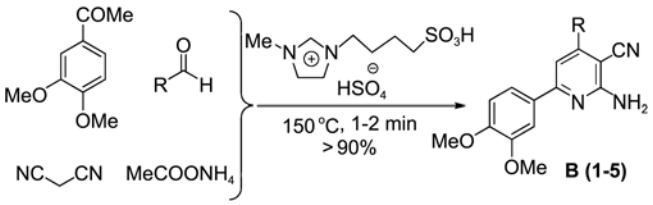
2-Amino-3-cyano-6-(3,4-dimethoxyphenyl)-4-phenylpyridine (B1): ^{1}H NMR (500 MHz, $CDCl_3$, δppm): 3.98 (s, 3H, OCH_3), 4.03 (s, 3H, OCH_3), 5.37 (s, 2H, NH_2), 6.98 (d, 1H, J = 8.5 Hz, arom-H), 7.20 (s, 1H, arom-H), 7.50-7.70 (m, 7H, arom-H); ^{13}C NMR ($CDCl_3$ & DMSO-d_6, δppm): 56.41, 56.46, 87.95, 110.68, 110.78, 111.40, 117.57, 120.86, 127.57, 128.54, 129.29, 130.17, 137.43, 149.61, 151.50, 155.49, 159.34, 160.53; IR (KBr disc): ν 3530, 3406 (NH_2), 2200 (CN) cm^{-1}; MS, *m/z* 331 (M^+).

2-Amino-4-(4-bromophenyl)-3-cyano-6-(3,4-dimethoxyphenyl)pyridine (B2). ^{1}H NMR (500 MHz, $CDCl_3$, δppm): 3.85 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 5.55 (s, 2H, NH_2), 6.86 (d, 1H, J = 8.4 Hz, arom-H), 7.01 (s, 1H, arom-H), 7.40-7.60 (m, 6H, arom-H); ^{13}C NMR ($CDCl_3$ & DMSO-d_6, dppm): 56.36, 56.39, 87.30, 110.27, 110.67, 111.37, 117.49, 120.82, 124.46, 130.15, 130.88, 132.43, 136.41, 149.53, 151.45, 153.92, 159.79, 160.73; IR (KBr disc): ν 3487, 3350 (NH_2), 2217 (CN) cm^{-1}; MS, *m/z* 409 (M^+), 411 (M^+ +2).

2-Amino-4-(4-chlorophenyl)-3-cyano-6-(3,4-dimethoxyphenyl)pyridine (B3). ^{1}H NMR (500 MHz, DMSO-d_6, δppm): 3.82 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 6.96 (s, 2H, NH_2), 7.05 (d, 1H, J = 8.5 Hz, arom-H), 7.27 (s, 1H, arom-H), 7.60-7.80 (m, 6H, arom-H); ^{13}C NMR (DMSO-d_6, δppm): 56.45, 56.52, 86.48, 109.47, 111.44, 112.34, 117.92, 121.43, 129.59, 130.88, 131.14, 135.26, 136.83, 149.62, 151.69, 154.24, 159.39, 161.54; IR (KBr disc): ν 3490, 3349 (NH_2), 2217 (CN) cm^{-1}; MS, *m/z* 365 (M^+), 367 (M^+ +2).

2-Amino-3-cyano-6-(3,4-dimethoxyphenyl)-4-(4-hydroxyphenyl)pyridine (B4). ^{1}H NMR (500 MHz, DMSO-d_6, δppm): 3.81 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 6.81 (s, 2H, NH_2), 6.91 (d, 2H, J = 7.7 Hz, arom-H), 7.04 (d, 1H, J = 8.5 Hz, arom-H), 7.20 (s, 1H, arom-H), 7.53 (d, 2H, J = 7.7 Hz, arom-H), 7.69 (s, 1H, arom-H), 7.72 (d, 1H, J = 8.2 Hz, arom-H), 9.90 (s br., 1H, OH); ^{13}C NMR (DMSO-d_6, δppm): 56.45, 56.51, 86.34, 109.25, 111.40, 112.34, 116.31, 118.47, 121.27, 128.49, 130.71, 131.16, 149.58, 151.51, 155.42, 158.99, 159.70, 161.70; IR (KBr disc): ν 3424, 3335 (NH_2), 2231 (CN) cm^{-1}; MS, *m/z* 347 (M^+).

2-Amino-3-cyano-6-(3,4-dimethoxyphenyl)-4-(4-methoxyphenyl)pyridine (B5). ^{1}H NMR (500 MHz, $CDCl_3$, δppm): 3.92 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 4.03 (s, 3H, OCH_3), 5.40 (s, 2H, NH_2), 6.98 (d, 1H, J = 8.4 Hz, arom-H), 7.08 (d, 2H, J = 8.7 Hz, arom-H), 7.17 (s, 1H, arom-H), 7.60 (dd, 1H, $^3J_1$ = 8.4 Hz, $^4J_2$ = 1.9 Hz, arom-H), 7.64 (d, 2H, J = 8.7 Hz, arom-H), 7.67 (d, 1H, ^4J = 1.9 Hz, arom-H); ^{13}C NMR ($CDCl_3$, δppm): 55.86, 56.44, 56.47, 87.78, 110.67, 110.78, 111.41, 114.80, 117.98, 120.77, 129.72, 130.03, 131.12, 149.67, 151.45, 155.01, 159.49, 160.63, 161.39; IR (KBr disc): ν 3494, 3348 (NH_2), 2214 (CN) cm^{-1}; MS, *m/z* 361 (M^+).



Scheme 1. Synthesis of 2-amino-4-aryl-3-cyano-6-(3,4-dimethoxyphenyl)pyridines.

Results and Discussion

2-Amino-4-aryl-3-cyano-6-(3,4-dimethoxyphenyl)pyridines were synthesized using the known method[11] (Scheme 1). The optimum conditions for using the catalyst [$HO_3S(CH_2)_4$-MIM][HSO_4], temperature, solvent, and time were investigated. A model compound (4-chlorophenyl derivative) was prepared using different conditions. As shown in Table 1 and 2, the best result was obtained in a solvent-free condition and 150 °C using 10 mol % of catalyst. Several compounds were synthesized using the optimized conditions. The results were presented in Table 3. In all cases, tautomers **B** were the only observed products.

In a similar manner, several 4-aryl(or alkyl)-3-cyano-6-(3,4-dimethoxyphenyl)-2(1*H*)-pyridinones are also prepar-

Table 1. Effect of the amounts of [$HO_3S(CH_2)_4MIM$][HSO_4] on the model reaction[a]

Entry	Catalyst (mol %)	Time (min)	Yield[b] (%)
1	None	5	trace
2	5	2	81
3	10	1.5	92
4	15	1.5	91
5	20	1.5	91
6	25	1.5	92

[a]2 mmol 3,4-dimethoxyacetophenone, 2 mmol 4-chlorobenzaldehyde, 2 mmol malononitrile, and 16 mmol ammonium acetate under solvent-free conditions at 150 °C. [b]The yields were calculated based on 4-chlorobenzaldehyde and refer to the pure isolated product.

Table 2. Synthesis of 2-amino-4-chlorophenyl-3-cyano-6-(3,4-dimethoxyphenyl)pyridine **B3** in the presence of [$HO_3S(CH_2)_4MIM$]-[HSO_4] (10 mol %) at different temperatures in solvent-free conditions[a]

Entry	Temperature (°C)	Time (min)	Yield[b] (%)
1	120	5	83
2	150	1.5	92
3	150	5	92
4	170	1.5	91
5	190	1.5	92

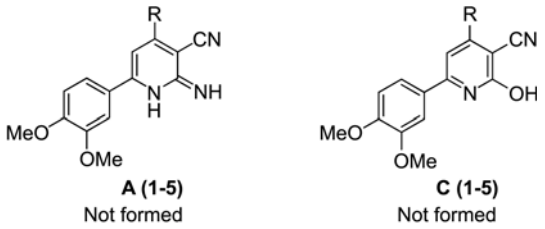
[a]2 mmol 3,4-dimethoxyacetophenone, 2 mmol 4-chlorobenzaldehyde, 2 mmol malononitrile, and 16 mmol ammonium acetate. [b]The yields were calculated based on 4-chlorobenzaldehyde and refer to the pure isolated product.

Table 3. Synthesis of 2-amino-4-aryl-3-cyano-6-(3,4-dimethoxyphenyl)pyridines **B1-B5** and 4-aryl(alkyl)-3-cyano-6-(3,4-dimethoxyphenyl)-2(*1H*)-pyridinones **D1-D5**[a]

Entry	R	Products	Time (min)	Yields (%)[b]	mp (°C)	
					Found	Reported
1	C_6H_5	**B1**	2	90	218-220	-
2	4-BrC_6H_4	**B2**	1	97	220-222	-
3	4-ClC_6H_4	**B3**	1.5	92	210-211	-
4	4-HOC_6H_4	**B4**	1.5	91	190-192	-
5	4-$CH_3OC_6H_4$	**B5**	1.5	97	175-178	-
6	C_6H_5	**D1**	1.5	92	290-291	285[17]
7	4-ClC_6H_4	**D2**	< 1	98	291-293	295[17]
8	4-HOC_6H_4	**D3**	< 1	98	298-299	311[17]
9	4-$CH_3OC_6H_4$	**D4**	< 1	97	262-264	266[17]
10	CH_3	**D5**	1.5	90	260-262	255[17]

[a]2 mmol 3,4-dimethoxyacetophenone, 2 mmol aryl (or alkyl) aldehyde, 2 mmol malononitrile (or ethyl cyanoacetate), and 16 mmol ammonium acetate in the presence of $[HO_3S(CH_2)_4MIM][HSO_4]$ (10 mol % based on aldehyde) under solvent-free conditions at 150 °C. [b]The yields were calculated based on aldehyde and refer to the pure isolated product.

Scheme 2. Synthesis of 4-aryl (or alkyl)-3-cyano-6-(3,4-dimethoxyphenyl)-2(1*H*)-pyridinones.



Scheme 3. Tautomers which have not formed in these syntheses.

Table 4. ΔE, ΔG (in kcal/mol) and equilibrium constants at B3LYP using the 6-31G(d,p) basis set

R	ΔE	B3LYP	ΔG	B3LYP
C_6H_5	E_{A1}-E_{B1}	16.12	G_{A1}-G_{B1}	16.24
4-BrC_6H_4	E_{A2}-E_{B2}	15.28	G_{A2}-G_{B2}	16.45
4-ClC_6H_4	E_{A3}-E_{B3}	17.80	G_{A3}-G_{B3}	17.60
4-HOC_6H_4	E_{A4}-E_{B4}	16.12	G_{A4}-G_{B4}	16.24
4-$CH_3OC_6H_4$	E_{A5}-E_{B5}	17.57	G_{A5}-G_{B5}	17.45
C_6H_5	E_{C1}-E_{D1}	2.40	G_{C1}-G_{D1}	1.26
4-ClC_6H_4	E_{C2}-E_{D2}	2.45	G_{C2}-G_{D2}	2.38
4-HOC_6H_4	E_{C3}-E_{D3}	2.54	G_{C3}-G_{D3}	2.24
4-$CH_3OC_6H_4$	E_{C4}-E_{D4}	2.51	G_{C4}-G_{D4}	2.15
CH_3	E_{C5}-E_{D5}	2.28	G_{C5}-G_{D5}	2.48

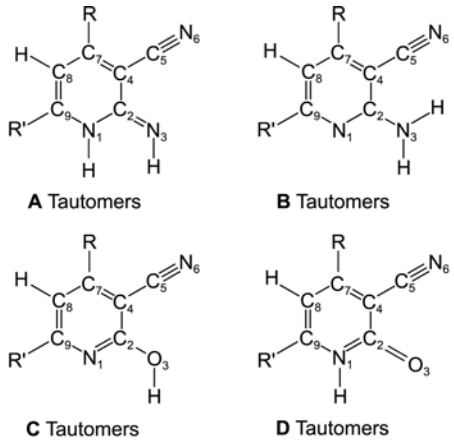


Figure 1. Structure of Tautomers **A**-**D**.

ed. In these cases, however, ethyl cyanoacetate was used instead of malononitrile (Scheme 2) and tautomers **D** are the predominant products (Table 3).

To compare the stability of the tautomers, theoretical calculations have been performed on each pair of compounds. These calculations showed that tautomers **B** and **D** are more stable than **A** and **C**, respectively (see Scheme 3).

Table 5. Some of the bond lengths (in Å) for **B** and **A** tautomers

Bond	**B** Tautomer					**A** Tautomer				
	B1	B2	B3	B4	B5	A1	A2	A3	A4	A5
r(N1)-r(H)						1.0133	1.01339	1.01335	1.01312	1.01309
r(N1)-r(C2)	1.33743	1.33775	1.33698	1.33703	1.33642	1.40520	1.40543	1.40546	1.40477	1.40466
r(C2)-r(N3)	1.36295	1.36026	1.36534	1.36314	1.36733	1.28586	1.28541	1.28542	1.28625	1.28643
r(N3)-r(H)	1.00793	1.00740	1.00831	1.00785	1.00847	1.01868	1.01868	1.01868	1.01867	1.01867
r(N3)-r(H)	1.0081	1.00755	1.00881	1.008	1.00899					
r(C2)-r(C4)	1.42868	1.42908	1.42766	1.42868	1.42751	1.47192	1.47179	1.47182	1.47141	1.47137
r(C4)-r(C5)	1.4245	1.42402	1.42419	1.42415	1.42429	1.42464	1.42437	1.42437	1.42421	1.42423
r(C5)-r(N6)	1.1668	1.16685	1.16684	1.16703	1.16706	1.16623	1.16619	1.16623	1.16649	1.16652
r(C4)-r(C7)	1.4116	1.41121	1.41221	1.41285	1.4135	1.39082	1.39045	1.39094	1.39268	1.39292
r(C7)-r(R)	1.48671	1.48574	1.48581	1.48359	1.48261	1.48745	1.48642	1.48686	1.48362	1.48298
r(C7)-r(C8)	1.39730	1.39661	1.39633	1.39851	1.39832	1.42558	1.42495	1.42521	1.42689	1.4273
r(C8)-r(H)	1.08204	1.08196	1.08192	1.08193	1.08532	1.08098	1.08109	1.08105	1.08094	1.08097
r(C8)-r(C9)	1.40487	1.40559	1.40626	1.40416	1.40444	1.37799	1.37857	1.37865	1.37746	1.37712
r(C9)-r(R')	1.48586	1.48571	1.48477	1.48637	1.48558	1.47844	1.47813	1.47827	1.47876	1.47893
r(C9)-r(N1)	1.34337	1.34316	1.34457	1.34393	1.34548	1.36098	1.36061	1.36053	1.36111	1.3613

Table 6. Some of the dihedral angels (in degrees) for **B** and **A** tautomers

Angel	**B** Tautomer					**A** Tautomer				
	B1	B2	B3	B4	B5	A1	A2	A3	A4	A5
<(H-N1-C2)						113.5571	113.564	113.544	113.6002	113.6169
<(N1-C2-N3)	116.4884	116.5608	116.5442	116.4758	116.4803	116.4891	116.5216	116.5077	116.4445	116.4431
<(H-N3-C2)	116.9717	118.2334	116.9717	117.5751	116.646	111.52	111.5845	111.5732	111.4955	111.4631
<(H-N3-C2)	117.5223	121.8932	120.492	121.2595	120.1653					
<(H-N3-H)	119.1408	119.8719	118.2977	119.2068	118.005					
<(N3-C2-C4)	121.0332	121.0235	120.9648	120.995	120.9387	130.0397	130.0591	130.0392	130.022	130.0155
<(N1-C2-C4)	122.4683	122.4157	122.4869	122.518	122.5768	113.4705	113.4183	113.4524	113.5333	113.5411
<(C2-C4-C5)	117.8142	117.8974	117.9541	117.6982	117.7288	115.4528	115.526	115.5151	115.3062	115.2584
<(C4-C5-N6)	174.308	174.3324	174.5307	174.3675	174.2845	175.9405	175.9479	176.1684	176.0375	175.9178
<(C5-C4-C7)	123.7906	123.7474	123.7502	123.8073	123.7954	122.9664	123.9587	122.9462	122.9884	123.0184
<(C2-C4-C7)	118.3602	118.3042	118.2617	118.4554	118.4342	121.5563	122.5861	121.5128	121.6746	121.6917
<(C4-C7-R)	122.3363	122.1643	122.1825	122.4601	122.4679	122.5414	122.3631	122.4472	122.7523	122.8074
<(R-C7-C8)	119.9253	119.9617	119.9652	120.0264	120.0532	118.1561	118.2169	118.1639	118.2228	118.2079
<(C4-C7-C8)	117.7369	117.871	117.8519	117.5115	117.4788	119.2977	119.4145	119.3843	119.0208	118.9811
<(C7-C8-H)	119.1047	119.122	119.0846	119.0499	118.9855	119.7813	119.8796	119.8814	119.803	119.7832
<(H-C8-C9)	120.6845	120.7279	120.5804	120.6041	120.4862	119.7081	119.7086	119.6714	119.5531	119.5601
<(C7-C8-C9)	120.2085	120.1485	120.2513	120.3414	120.4438	120.5096	120.4115	120.4468	120.6439	120.6568
<(C8-C9-R')	121.6657	121.7178	121.7237	121.7204	121.7044	123.5097	123.592	123.5564	123.5161	123.5497
<(R'-C9-N1)	116.3929	116.3853	116.5708	116.314	116.4877	117.5076	117.4211	117.4703	117.4512	117.403
<(C8-C9-N1)	121.9408	121.8967	121.6966	121.9654	121.7979	118.9804	118.9864	118.972	119.0314	119.0463
<(C9-N1-H)						120.1788	120.1262	120.1418	120.2235	120.224
<(C9-N1-C2)	119.2695	119.3548	119.4355	119.1969	119.2436	126.1714	126.6437	126.2181	126.0797	126.0638

Table 7. Some of the bond lengths (in Å) for **C** and **D** tautomers

Bond	**D** Tautomer					**C** Tautomer				
	D1	D2	D3	D4	D5	C1	C2	C3	C4	C5
r(H)-r(N1)	1.01386	1.01388	1.01366	1.01361	1.01356					
r(N1)-r(C2)	1.40686	1.40694	1.40645	1.40635	1.40905	1.31945	1.31959	1.31926	1.31925	1.31994
r(C2)-r(O3)	1.22646	1.22605	1.22691	1.22708	1.22725	1.34992	1.3493	1.35029	1.35038	1.35164
r(O3)-r(H)						0.97061	0.9706	0.97054	0.97057	0.97013
r(C2)-r(C4)	1.46372	1.46373	1.46299	1.46286	1.4583	1.42195	1.42208	1.42211	1.42214	1.41823
r(C4)-r(C5)	1.4278	1.42751	1.42751	1.42752	1.42658	1.42514	1.42492	1.42483	1.42486	1.42424
r(C5)-r(N6)	1.16451	1.16453	1.16474	1.16477	1.16494	1.16683	1.16683	1.16706	1.16708	1.16692
r(C4)-r(C7)	1.39469	1.39474	1.39669	1.39702	1.39271	1.41387	1.41411	1.41526	1.41549	1.41229
r(C7)-r(R)	1.48742	1.48687	1.48328	1.4826	1.50717	1.48565	1.48498	1.48224	1.48158	1.50554
r(C7)-r(C8)	1.42374	1.42348	1.42527	1.42568	1.41803	1.39612	1.39592	1.39753	1.39791	1.3908
r(C8)-r(H)	1.08137	1.08143	1.08131	1.08132	1.08229	1.08181	1.08193	1.08184	1.08184	1.0826
r(C8)-r(C9)	1.37706	1.37762	1.37643	1.37612	1.3802	1.40558	1.40599	1.40456	1.40423	1.40883
r(C9)-r(R')	1.47745	1.47726	1.47781	1.47792	1.47635	1.48422	1.48358	1.48432	1.48467	1.48297
r(C9)-r(N1)	1.3663	1.36598	1.36645	1.36661	1.36598	1.34696	1.34676	1.34746	1.34754	1.34738

This comparison has been made on the basis of the energy level of tautomers (Table 4) as well as the single and double bond lengths in the pyrimidine ring (Fig. 1 & Table 5-8). On the basis of this comparison, a more effective resonance seems to occur in the pyrimidine ring of tautomers **B** and **D** relative to **A** and **C**. The comparison between the energy of tautomers shows that **B** tautomers are much more stable than **A** tautomers. In the case of **D** and **C** tautomers, the energy differences decrease compared to **B** and **A** tautomers, but are still noticeable. The pyrimidine ring in **D** tautomers shows more effective resonance.

The equilibrium constants between **B** and **A** and also **D** and **C** using ΔG could be calculated using:

$$K = \exp\left(-\frac{\Delta G}{RT}\right)$$

The equilibrium constants related to **B**$\rightleftharpoons$**A** are about 10^{-12}, showing that tautomers **B** are dominant. Although the equilibrium constants related to **D**$\rightleftharpoons$**C** have increased to about 10^{-2}-10^{-1}, the tautomers **D** are still predominant (Table

Table 8. Some of the dihedral angels (in degrees) for **C** and **D** tautomers

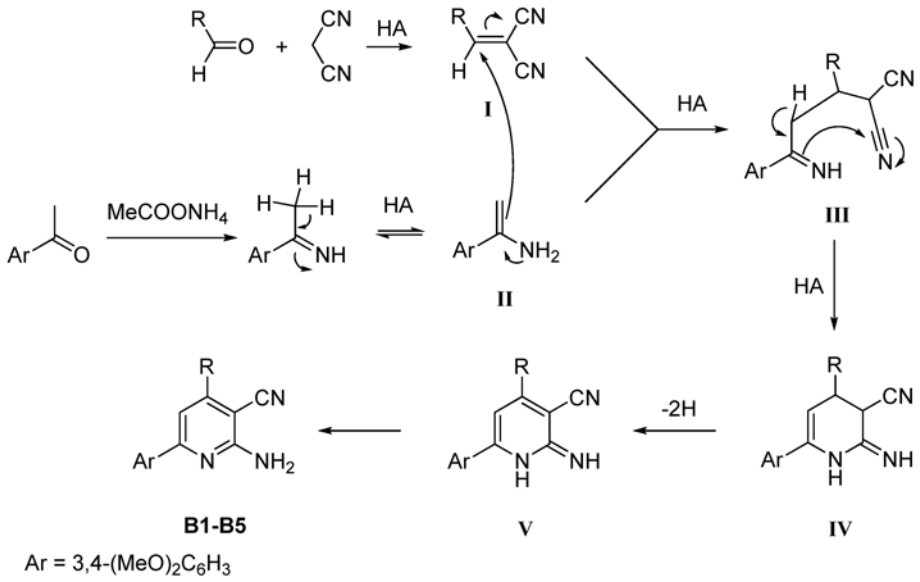
Angel	**D** Tautomer					**C** Tautomer				
	D1	D2	D3	D4	D5	C1	C2	C3	C4	C5
<(H-N1-C2)	113.6556	113.6503	113.7127	113.7245	113.566					
<(N1-C2-O3)	119.6569	119.706	119.6154	119.5915	119.5935	114.9166	114.8992	114.885	114.8768	114.9272
<(C2-O3-H)						110.7803	110.8928	110.7825	110.7794	110.7346
<(O3-C2-C4)	126.5589	126.5326	126.5324	126.5447	127.0979	121.6004	121.6343	121.5708	121.5665	121.808
<(N1-C2-C4)	113.7838	113.7608	113.852	113.8637	113.3059	123.4821	123.4656	123.543	123.5557	123.2648
<(C2-C4-C5)	115.7131	115.7609	115.521	115.4651	117.511	117.641	117.6807	117.5123	117.4362	119.1825
<(C4-C5-N6)	179.4065	179.608	179.4991	179.4113	177.4351	173.4512	173.6208	173.5576	173.4063	176.4447
<(C5-C4-C7)	122.918	122.9001	122.9584	122.9994	120.7817	124.308	124.2892	124.3016	124.3453	122.6108
<(C2-C4-C7)	121.3468	121.3175	121.4937	121.5071	121.7062	118.0037	117.98	118.133	118.1605	118.2055
<(C4-C7-R)	122.7033	122.6078	122.9245	122.9974	120.7624	122.3307	122.2969	122.4963	122.5487	120.6748
<(R-C7-C8)	118.0057	118.0304	118.1019	118.0694	119.6803	120.2979	120.2786	120.3957	120.4005	121.7994
<(C4-C7-C8)	119.287	119.3575	118.9697	118.9297	119.555	117.3704	117.4229	117.1054	117.0494	117.5255
<(C7-C8-H)	119.5417	119.6418	119.5713	119.5456	119.9123	118.6783	118.8377	118.7349	118.7428	118.9259
<(H-C8-C9)	119.4694	119.4296	119.2972	119.3075	119.3639	120.7782	120.669	120.6091	120.5803	120.6514
<(C7-C8-C9)	120.988	120.9282	121.1315	121.147	120.6773	120.536	120.487	120.6491	120.6696	120.4168
<(C8-C9-R')	123.8848	123.939	123.8794	123.9217	124.0164	122.3342	122.2766	122.2417	122.2343	122.3949
<(R'-C9-N1)	117.7918	117.7413	117.7286	117.6756	117.7448	116.2481	116.2901	116.2221	116.1978	116.3084
<(C8-C9-N1)	118.322	118.3189	118.3914	118.4022	118.2319	121.4173	121.4324	121.5357	121.5676	121.2939
<(C9-N1-H)	119.9854	119.9423	120.038	120.0372	119.771					
<(C9-N1-C2)	126.2604	126.3043	126.1451	126.1319	126.5202	119.182	119.2037	119.0277	118.9902	119.2878

Table 9. Equilibrium constants related to **B** $\rightleftharpoons$ **A** and **D** $\rightleftharpoons$ **C**

R	Equilibrium constants (K) for **B** $\rightleftharpoons$ **A**	Equilibrium constants (K) for **D** $\rightleftharpoons$ **C**
C_6H_5	1.26×10^{-12}	1.19×10^{-1}
4-BrC_6H_4	8.85×10^{-13}	-
4-ClC_6H_4	1.27×10^{-13}	1.80×10^{-2}
4-HOC_6H_4	1.26×10^{-12}	2.28×10^{-2}
4-$CH_3OC_6H_4$	1.64×10^{-13}	2.66×10^{-2}
CH_3	-	1.50×10^{-2}

9).

A plausible mechanism for the formation of compounds **B1-B5** is depicted in Scheme 4. We propose that the reactions occur *via* initial formation of the dicyano olefin **I** through the Knoevenagel condensation between aryl aldehydes and malononitrile, which then reacts with intermediate **II** produced from the reaction of 3,4-dimethoxyacetophenone with ammonium acetate, to give the intermediate **III**, which subsequently undergoes the cyclization followed by air oxidation to afford the desired compounds



Scheme 4. Plausible mechanism for the formation of 2-amino-4-aryl-3-cyano-6-(3,4-dimethoxyphenyl)pyridines in the presence of $[HO_3S(CH_2)_4MIM][HSO_4] \equiv$ HA as catalyst.

B1-B5 *via* the intermediate **IV** and **V**. The catalyst $[HO_3S(CH_2)_4MIM][HSO_4]$ HA facilitates the formation of the intermediates **I-IV**. Under these conditions, attempts to isolate the intermediates **I-V** by careful monitoring of reactions failed. Compounds **D1-D5** can also be formed by a similar route.

Conclusions

A series of 2-amino-4-aryl-3-cyano-6-(3,4-dimethoxyphenyl)pyridines and 4-aryl(or alkyl)-3-cyano-6-(3,4-dimethoxyphenyl)-2(1*H*)-pyridinones has been prepared through a facile one-pot solvent-free multicomponent reaction using $[HO_3S(CH_2)_4MIM][HSO_4]$ as the catalyst. The experimental results are consistent with the theoretical calculation regarding the formation of more stable tautomers.

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