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Synthesis of multi-substituted 4-aminopyridines *via* ring-opening and recyclization reactions of 2-iminopyridines†

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A novel synthesis of multi-substituted 4-aminopyridines from 2-iminopyridines by a two-step procedure is described. During this transformation, 4-amino-2-iminopyridines undergo a regioselective ring-opening reaction in the presence of KOH in *t*-butanol to afford 5-oxo-pent-3-enimidamides, which are then converted into 4-aminopyridines in toluene under reflux following a 6π-azaelectrocyclization and *N*-to-*N* 1,3-sulfonyl group migration mechanism.

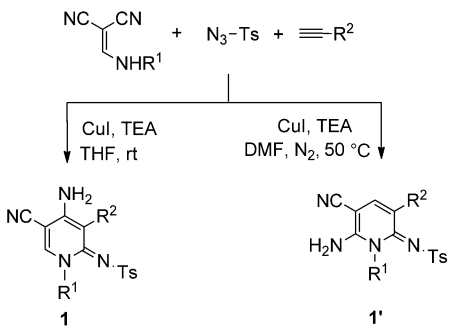
Introduction

The vast number of bioactive natural products and pharmaceutical drugs based on the pyridine ring system have become very important areas of research in natural product and medicinal chemistry.[1] In addition, functionalized pyridines are widely used as key intermediates in the preparation of natural products and related structures.[2] 4-Aminopyridines, as an important subset of pyridines, constitute the core structure of a number of active pharmaceutical ingredients, such as torsemide,[3] roflumilast,[4] pinacidil[5] and piclamilast.[6] The pharmaceutical and synthetic importance have directed great research activities to synthesize 4-aminopyridines with diverse substitution patterns. Thus, a number of efficient approaches have been developed based on either the modification of pyridines by reduction reactions of *p*-nitropyridines,[7] amination reactions of *p*-halopyridines[8] and denitrification reactions of *p*-azidopyridines,[9] or the construction of the skeleton from appropriately open-chain precursors *via* tandem amination/annulation reaction of ketoalkyne,[10] cascade cyclization/oxidation of arylmethylidene derivatives of malononitrile dimer,[11] three-component reaction of malononitrile, cycloketones and ammonium acetate,[12] transition metal mediated cyclotrimerization of malononitrile.[13]

Very recently, we achieved a facile synthesis of 2-iminopyridines *via* a copper-catalyzed three-component reaction of 2-[(amino)methylene]malononitriles, sulfonyl azides and alkynes.[14] To investigate the synthetic utilization of these aza-heterocycles, we examined the reaction behavior of 4-amino-2-iminopyridines under different conditions. As results of these studies, a novel and efficient protocol for the 4-aminopyridine synthesis by a two-step procedure was developed. Herein, we report the experimental results and the mechanism involved in the cascade reactions.

Results and discussion

In our previous work, we developed a facile and efficient solvent-controlled regioselective synthesis of multi-substituted 4-amino- and 6-amino-2-iminopyridines *via* the copper-catalyzed three-component reaction of sulfonyl azides, alkynes, and 2-[(amino)methylene]malononitriles based on the reaction conditions selection (Scheme 1).[14] Through the three component reaction, 4-amino-2-iminopyridines **1** were synthesized in moderate to good yield in THF at room temperature, whereas 6-amino-2-iminopyridines **1′** were dominantly obtained in DMF at 50 °C under N_2.



Scheme 1

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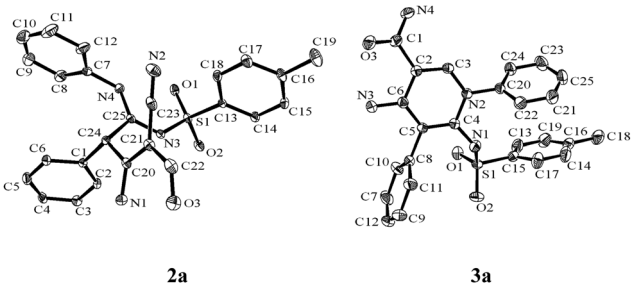
† Electronic supplementary information (ESI) available: Copies of NMR spectra for compounds **2–4**, and crystallographic data for compounds **2a**, **3a** and **4a**. CCDC 983980, 983981 and 983982. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4ra02428a

With these 4-amino-2-iminopyridines **1** in hand, we selected *N*-(4-amino-5-cyano-1,3-diphenylpyridin-2(1*H*)-ylidene)-4-methylbenzenesulfonamide **1a** as a model compound to examine its reaction behavior. Thus, the reaction of **1a** and KOH (4.0 equiv.) was first attempted in DMSO at 80 °C. As monitored by TLC, the reaction proceeded, but the conversion was rather low. After work-up and subsequent purification by column chromatography of the resulting mixture, the reaction furnished two products, which were characterized as 3-amino-4-cyano-5-oxo-*N*,2-diphenyl-*N*′-tosylpent-3-enimid-amide **2a** and 4-amino-1,5-diphenyl-6-(tosylimino)-1,6-dihydro pyridine-3-carboxamide **3a** on the basis of their spectral and analytical data (Table 1, entry 1). The structures of **2a** and **3a** were further elucidated by X-ray diffraction analysis (Fig. 1). Similar results were obtained when the reaction was performed in DMF and absolute ethanol (Table 1, entries 2 and 3). Subjecting **1a** and KOH (4.0 equiv.) to 95% ethanol, **3a** was exclusively obtained in 85% yield (Table 1, entry 4). The results revealed that **1a** preferred the hydrolysis of the nitrile to the ring-opening reaction of iminopyridine in the presence of KOH, providing there was adequate water within the reaction system.

To optimize the yield of **2a**, the reaction conditions, including solvents, bases, reaction temperature and time were investigated. When the reaction of **1a** with KOH (4.0 equiv.) in *t*-BuOH was conducted at 80 °C, **2a** could be obtained in 71% yield (Table 1, entry 5). With the increase of the amount of KOH to 6 equiv., the reaction could be significantly accelerated, as could be verified by the shortened reaction time and high yield of **2a** (Table 1, entry 6). With the addition of 2.0 equiv. of water to the reaction, the yield of **2a** decreased due to the formation of the hydrolyzed product **3a** (Table 1, entry 7). However, no reaction was observed when **1a** and KOH (6.0 equiv.) in *t*-BuOH was conducted at 30 °C (Table 1, entry 8). In the presence of other inorganic and organic bases, such as K_2CO_3, diazabicycloundecene (DBU) and triethylamine (TEA), the reaction of **1a** in *t*-BuOH could not take place (Table 1, entries 9–11).



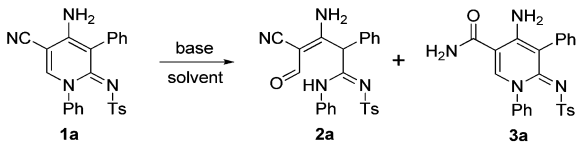
2a **3a**

Fig. 1 ORTEP drawings of **2a** and **3a**.

Under the reaction conditions as for **2a** in Table 1, entry 6, a series of reactions of **1b–i** were carried out in *t*-BuOH in the presence of KOH at 80 °C to determine the scope of the pyridine synthesis, and some of the results are summarized in Table 2. The ring-opening reaction proved to be suitable for **1a–i** bearing both electron-donating and electron-withdrawing substituents in the aromatic ring in R^1 and R^2 to give the corresponding **2b–i** in moderate to good yields. It should be mentioned that a complex mixture was formed when subjecting *N*-(6-amino-5-cyano-1,3-diphenylpyridin-2(1*H*)-ylidene)-4-methylbenzenesulfonamide **1a**′ to the identical conditions. The results suggested that the substituent pattern had significantly affected the ring-opening reaction of 2-iminopyridines.

It is well-known that pyridine derivatives tend to undergo ring-opening reactions in the presence of base to form a mixture of ring-opened isomers.[15] Thus, there are two possible cleavage modes for 2-iminopyridines **1**, as an important class of pyridine derivatives, mediated by base (Scheme 2).[16] Actually, in the

Table 1 Reactions of 4-amino-2-iminopyridines **1a** under different conditions[a]

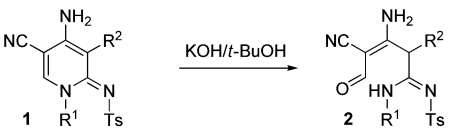


1a **2a** **3a**

Entry	Base (equiv.)	Solvent	Time (h)	Yield[d] (%) 2a	3a
1	KOH (4)	DMSO	12	13	8
2	KOH (4)	DMF	12	14	11
3	KOH (4)	EtOH	12	17	23
4	KOH (4)	EtOH (95%)	4	0	85
5	KOH (4)	*t*-BuOH	12	71	0
6	KOH (6)	*t*-BuOH	1	83	0
7	KOH (6)	*t*-BuOH[b]	1	65	16
8[c]	KOH (6)	*t*-BuOH	12	0	0
9	K_2CO_3 (6)	*t*-BuOH	12	0	0
10	DBU (6)	*t*-BuOH	12	0	0
11	TEA (6)	*t*-BuOH	12	0	0

[a] Reaction conditions: **1a** (1.0 mmol), base, solvent (10 mL), 80 °C. [b] H_2O (2.0 equiv.) was added. [c] Reaction temperature: 30 °C. [d] Isolated yields.

Table 2 Ring-opening reaction of 2-iminopyridines **1**[a]



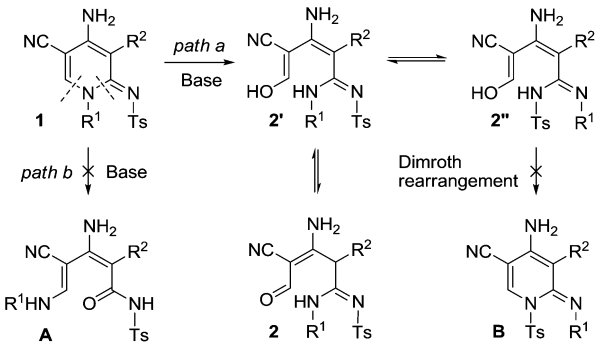
1 **2**

Entry	1	R^1	R^2	2	Yield[b] (%)
1	**1a**	Ph	Ph	**2a**	83
2	**1b**	Ph	*p*-MeC_6H_4	**2b**	85
3	**1c**	Ph	*p*-$MeOC_6H_4$	**2c**	87
4	**1d**	*o*-MeC_6H_4	Ph	**2d**	78
5	**1e**	*o*-MeC_6H_4	*p*-MeC_6H_4	**2e**	81
6	**1f**	*p*-MeC_6H_4	Ph	**2f**	80
7	**1g**	*m*-ClC_6H_4	Ph	**2g**	83
8	**1h**	*p*-ClC_6H_4	Ph	**2h**	82
9	**1i**	*p*-$MeOC_6H_4$	Ph	**2i**	72

[a] Reaction conditions: **1** (1.0 mmol), KOH (6.0 mmol), *t*-BuOH (10 mL), 80 °C, 1.0–2.0 h. [b] Isolated yields.

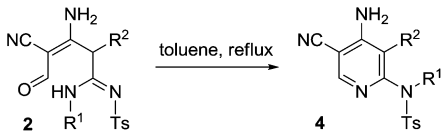
present work, 5-oxo-pent-3-enimidamide **2** was exclusively obtained *via* path a, and no isomer **A** of **2** (*via* path b) or Dimroth rearrangement product **B** was isolated from the reaction system. These results demonstrated that the reaction of 2-iminopyridines **1** with KOH in *t*-BuOH proceeded in a highly regioselective manner.

It should be noted that 5-oxo-pent-3-enimidamides **2** showed fascinating structural characteristics, especially their formyl, cyano, amino and imino patterns, and could be exploited in further organic transformations. In addition, its isomers **2′** and **2″** can be regarded as azatrienes that may undergo 6π-azaelectrocyclization under appropriate conditions to afford the corresponding heterocycles.[17] Thus, the azaelectrocyclization reaction was attempted by subjecting **2a** to toluene under reflux. As indicated by TLC results, the reaction proceeded smoothly. After work-up and subsequent purification by column chromatography of the resulting mixture, the reaction furnished a product, which was characterized as *N*-(4-amino-5-cyano-3-phenylpyridin-2-yl)-4-methyl-*N*-phenyl benzene sulfonamide **4a** on the basis of its spectral and analytical data (Table 3, entry 1).



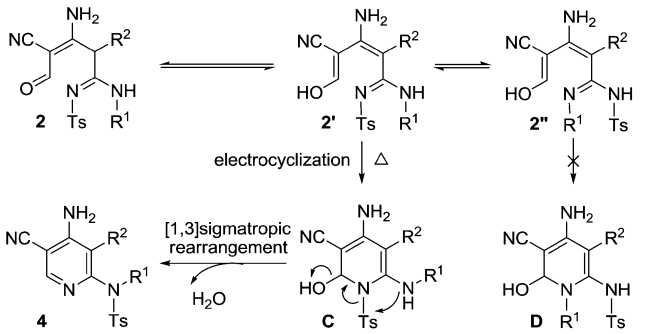
Scheme 2 Possible ring-opening reactions of 2-imino-pyridines **1**.

Table 3 Reactions of 5-oxo-pent-3-enimidamides **2**[a]



Entry	2	R^1	R^2	4	Yield[b] (%)
1	**2a**	Ph	Ph	**4a**	89
2	**2b**	Ph	*p*-MeC_6H_4	**4b**	87
3	**2c**	Ph	*p*-$MeOC_6H_4$	**4c**	88
4	**2d**	*o*-MeC_6H_4	Ph	**4d**	91
5	**2e**	*o*-MeC_6H_4	*p*-MeC_6H_4	**4e**	84
6	**2f**	*p*-MeC_6H_4	Ph	**4f**	81
7	**2g**	*m*-ClC_6H_4	Ph	**4g**	83
8	**2h**	*p*-ClC_6H_4	Ph	**4h**	92
9	**2i**	*p*-$MeOC_6H_4$	Ph	**4i**	86

[a] Reaction conditions: **2** (1.0 mmol), toluene (10 mL), reflux, 5.0–12.0 h. [b] Isolated yields.



Scheme 3 Proposed mechanism for the synthesis of 4-aminopyridines **4**.

In the same fashion, a range of reactions of 5-oxo-pent-3-enimidamides **2b–i** bearing different aromatic substituents were carried out, and some of the results are summarized in Table 3. It was found that all the reactions could proceed efficiently to afford the corresponding 4-aminopyridines **4b–i** in good to excellent yields. The structure of **4a** was further elucidated by the X-ray single crystal analysis (ESI). Therefore, we provide a novel and alternative synthetic protocol for multi-substituted 4-aminopyridines.

On the basis of all the results obtained and the literature, a plausible mechanism for the synthesis of 4-aminopyridines **4** from 5-oxo-pent-3-enimidamides **2** is proposed as depicted in Scheme 3. As a tautomer of 5-oxo-pent-3-enimidamides **2**, *N*-tosylpenta-2,4-dienimid amide **2′** is a multi-substituted azatriene, which undergoes a 6π-azaelectrocyclization at high temperature to give a 1,2-dihydropyridine intermediate **C**.[17] Upon a [1,3]sigmatropic sulfonyl group migration of **C**,[18] 4-aminopyridine **4** is finally formed with the elimination of water.

Conclusions

In summary, a novel synthesis of multi-substituted 4-aminopyridines from 2-iminopyridines has been developed by a two-step procedure. This protocol is associated with readily available starting materials, mild conditions, simple execution, high regioselectivity and a wide range of synthetic potential of products. Expanding the scope of the methodology and further exploration of the utility of the as-synthesized functionalized 4-aminopyridines in pharmacology are currently underway in our laboratory.

Experimental section

General

All reagents were purchased from commercial sources and used without treatment, unless otherwise indicated. ^{1}H NMR and ^{13}C NMR spectra were recorded at 25 °C at 400 MHz (or 300 MHz) and 100 MHz, respectively, with TMS as internal standard. IR spectra (KBr) were recorded on FTIR spectrophotometer in the range of 400–4000 cm^{-1}. Starting materials **1a–i** are known compounds and prepared according to the literature.[14]

Typical procedure for the synthesis of substituted 3-amino-4-cyano-5-oxo-*N*′-tosylpent-3-enimidamide 2 (2a as an example)

To a stirred mixture of *N*-(4-amino-5-cyano-1,3-diphenyl pyridin-2(1*H*)-ylidene)-4-methyl benzenesulfonamide **1a** (441 mg, 1.0 mmol) and *tert*-butanol (10 mL) was added KOH (336 mg, 6.0 mmol) at room temperature. The reaction mixture was stirred at 80 °C for 1 h. When the starting material was consumed completely (monitored by TLC), the mixture was cooled to room temperature and diethyl ether (30 mL) was added. The precipitates were filtered, washed with diethyl ether (10 mL), and was added into the mixture of saturated aqueous NH_4Cl solution (10 mL) and CH_2Cl_2 (20 mL) and stirred for a few minutes. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layer was washed with water (2 × 10 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated under vacuum and the resulting residue was purified by flash column chromatography to give **2a** (380 mg, 83%) as a colourless solid.

3-Amino-4-cyano-5-oxo-*N*,2-diphenyl-*N*′-tosylpent-3-enimidamide (2a). Colourless solid, mp: 135–137 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 10.69 (1H, s, NH_2), 10.07 (1H, s, NH_2), 9.07 (1H, s, CHO), 7.75 (2H, d, J = 8.1 Hz, Ar-H), 7.37–7.13 (9H, m, Ar-H, Ph-NH), 7.07 (2H, d, J = 7.2 Hz, Ar-H), 6.96 (2H, d, J = 6.0 Hz, Ar-H), 4.89 (1H, s, CH), 2.39 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 187.1, 168.8, 162.3, 143.8, 137.9, 134.7, 131.8, 130.1, 129.8, 129.6, 129.6, 129.3, 128.7, 128.2, 127.4, 126.4, 118.6, 117.6, 84.5, 50.9, 21.6; IR (KBr, cm^{-1}): 3353, 3240, 3168, 3064, 2921, 2833, 2759, 2202, 1645, 1608, 1581, 1496, 1460, 1394, 1271, 1251, 1184, 1134, 1085, 987, 811, 746; anal. calcd (%) for $C_{25}H_{22}N_4O_3S$: C, 65.48; H, 4.84; N, 12.22; S, 6.99; found: C, 65.26; H, 4.81; N, 12.17; S, 6.92.

3-Amino-4-cyano-5-oxo-*N*-phenyl-2-(*p*-tolyl)-*N*′-tosylpent-3-enimidamide (2b). Colourless solid, mp: 129–131 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 10.71 (1H, s, NH_2), 10.09 (1H, s, NH_2), 9.09 (1H, s, CHO), 7.79 (2H, d, J = 8.1 Hz, Ar-H), 7.32 (5H, m, Ar-H, Ph-NH), 7.23 (1H, s, Ar-H), 7.08 (2H, d, J = 8.1 Hz, Ar-H), 6.98 (4H, d, J = 7.8 Hz, Ar-H), 4.87 (1H, s, CH), 2.43 (3H, s, CH_3), 2.31 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 187.0, 169.1, 162.4, 143.7, 140.6, 139.7, 137.9, 134.7, 131.1, 130.2, 129.7, 129.4, 129.2, 128.5, 127.4, 126.3, 123.7, 118.6, 84.3, 50.6, 21.5, 21.0; IR (KBr, cm^{-1}): 3396, 3369, 3251, 3184, 3068, 3029, 2960, 2921, 2835, 2759, 2198, 1643, 1604, 1583, 1461, 1392, 1284, 1257, 1143, 1085, 987, 813, 750; anal. calcd (%) for $C_{26}H_{24}N_4O_3S$: C, 66.08; H, 5.12; N, 11.86; S, 6.79; found: C, 66.31; H, 5.06; N, 11.78; S, 6.71.

3-Amino-4-cyano-2-(4-methoxyphenyl)-5-oxo-*N*-phenyl-*N*′-tosylpent-3-enimidamide (2c). Colourless solid, mp: 137–139 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 10.72 (1H, s, NH_2), 10.07 (1H, s, NH_2), 9.09 (1H, s, CHO), 7.79 (2H, d, J = 8.1 Hz, Ar-H), 7.42–7.25 (5H, m, Ar-H, Ar-NH), 7.22 (1H, s, Ar-H), 7.02 (4H, d, J = 8.7 Hz, Ar-H), 6.79 (2H, d, J = 8.7 Hz, Ar-H), 4.84 (1H, s, CH), 3.77 (3H, s, CH_3O), 2.42 (3H, s, CH_3); ^{13}C NMR (1001 MHz, $CDCl_3$) δ = 187.0, 169.3, 162.5, 160.3, 143.7, 137.9, 134.7, 123.0, 129.7, 129.4, 129.2, 127.4, 126.3, 123.1, 118.6, 114.9, 84.2, 55.2, 50.2, 21.5; IR (KBr, cm^{-1}): 3340, 3244, 3151, 2962, 2840, 2198, 1639, 1604, 1585, 1450, 1409, 1384, 1261, 1178, 1128, 1078, 1037, 979, 869, 811, 802, 725; anal. calcd (%) for $C_{26}H_{24}N_4O_4S$: C, 63.92; H, 4.95; N, 11.47; S, 6.56; found: C, 63.78; H, 4.91; N, 11.41; S, 6.59.

3-Amino-4-cyano-5-oxo-2-phenyl-*N*-(*o*-tolyl)-*N*′-tosylpent-3-enimidamide (2d). Colourless solid, mp: 141–143 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 10.74 (1H, s, NH_2), 9.88 (1H, s, NH_2), 9.14 (1H, s, CHO), 8.01 (1H, s, Ar-NH), 7.78 (2H, d, J = 8.1 Hz, Ar-H), 7.37–7.17 (8H, m, Ar-H), 7.14 (1H, d, J = 7.2 Hz, Ar-H), 7.02 (2H, d, J = 7.5 Hz, Ar-H), 4.92 (1H, s, CH), 2.43 (3H, s, CH_3), 1.83 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 187.2, 168.4, 162.6, 143.9, 137.8, 135.4, 133.5, 131.8, 131.4, 129.7, 129.5, 129.4, 128.5, 127.7, 127.4, 126.3, 118.5, 84.3, 49.6, 21.5, 17.1; IR (KBr, cm^{-1}): 3421, 3247, 3232, 2962, 2925, 2852, 2202, 1645, 1610, 1591, 1579, 1467, 1400, 1272, 1135, 1085, 754; anal. calcd (%) for $C_{26}H_{24}N_4O_3S$: C, 66.08; H, 5.12; N, 11.86; S, 6.79; found: C, 66.31; H, 5.07; N, 11.78; S, 6.74.

3-Amino-4-cyano-5-oxo-*N*-(*o*-tolyl)-2-(*p*-tolyl)-*N*′-tosylpent-3-enimidamide (2e). Colourless solid, mp: 145–147 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 10.74 (1H, s, NH_2), 9.89 (1H, s, NH_2), 9.13 (1H, s, CHO), 7.94 (1H, s, Ar-NH), 7.80 (2H, d, J = 8.1 Hz, Ar-H), 7.38–7.18 (5H, m, Ar-H), 7.15 (1H, d, J = 7.5 Hz, Ar-H), 7.04 (2H, d, J = 8.1 Hz, Ar-H), 6.92 (2H, d, J = 8.1 Hz, Ar-H), 4.88 (1H, s, CH), 2.44 (3H, s, CH_3), 2.30 (3H, s, CH_3), 1.85 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 187.1, 168.7, 162.8, 143.8, 139.6, 137.9, 135.4, 133.5, 131.4, 130.0, 129.5, 128.6, 128.4, 127.7, 127.4, 126.3, 118.5, 84.2, 49.3, 21.5, 21.0, 17.2; IR (KBr, cm^{-1}): 3359, 3261, 3188, 3035, 2921, 2860, 2831, 2754, 2206, 1645, 1612, 1587, 1465, 1396, 1278, 1137, 1081, 981, 754, 663; anal. calcd (%) for $C_{27}H_{26}N_4O_3S$: C, 66.65; H, 5.39; N, 11.51; S, 6.59; found: C, 66.48; H, 5.43; N, 11.48; S, 6.55.

3-Amino-4-cyano-5-oxo-2-phenyl-*N*-(*p*-tolyl)-*N*′-tosylpent-3-enimidamide (2f). Colourless solid, mp: 163–165 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 10.75 (1H, s, NH_2), 10.04 (1H, s, NH_2), 9.13 (1H, s, CHO), 7.79 (2H, d, J = 8.2 Hz, Ar-H), 7.46–7.26 (5H, m, Ar-H, Ar-NH), 7.24 (1H, s, Ar-H), 7.19–7.08 (4H, m, Ar-H), 6.88 (2H, d, J = 8.1 Hz, Ar-H), 4.95 (1H, s, CH), 2.44 (3H, s, CH_3), 2.36 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 187.09, 168.86, 162.42, 143.71, 139.47, 132.00, 130.35, 129.50, 128.67, 127.06, 126.31, 118.53, 84.45, 50.62, 21.52, 21.08; IR (KBr, cm^{-1}): 3336, 3249, 3037, 3006, 2921, 2833, 2758, 2206, 1647, 1616, 1596, 1508, 1479, 1423, 1400, 1346, 1272, 1137, 1087, 987, 815; anal. calcd (%) for $C_{26}H_{24}N_4O_3S$: C, 66.08; H, 5.12; N, 11.86; S, 6.79; found: C, 66.35; H, 5.16; N, 11.88; S, 6.75.

3-Amino-*N*-(3-chlorophenyl)-4-cyano-5-oxo-2-phenyl-*N*′-tosylpent-3-enimidamide (2g). Colourless solid, mp: 160–162 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 10.76 (1H, s, NH_2), 10.11 (1H, s, NH_2), 9.14 (1H, s, CHO), 7.83 (2H, d, J = 8.1 Hz, Ar-H), 7.48–7.29 (7H, m, Ar-H, Ar-NH), 7.17 (2H, d, J = 7.2 Hz, Ar-H), 7.04 (1H, d, J = 7.5 Hz, Ar-H), 6.98 (1H, s, Ar-H), 6.90 (1H, s, Ar-H), 4.88 (1H, s, CH), 2.47 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 187.0, 168.8, 161.9, 143.9, 135.9, 135.3, 131.4, 130.7, 129.9, 129.6, 128.7, 128.0, 126.5, 125.8, 118.6, 84.6, 51.5, 21.6; IR (KBr, cm^{-1}): 3361, 3251, 3164, 3062, 2929, 2840, 2765, 2200, 1643, 1604, 1583, 1573, 1390, 1271, 1130, 1080; anal. calcd (%) for $C_{25}H_{21}ClN_4O_3S$: C, 60.91; H, 4.29; N, 11.36; S, 6.50; found: C, 61.25; H, 4.24; N, 11.29; S, 6.44.

3-Amino-*N*-(4-chlorophenyl)-4-cyano-5-oxo-2-phenyl-*N*′-tosylpent-3-enimidamide (2h). Colourless solid, mp: 142–145 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 10.77 (1H, s, NH_2), 10.06 (1H, s, NH_2), 9.13 (1H, s, CHO), 7.83 (2H, d, J = 8.1 Hz, Ar-H), 7.49–7.27 (7H, m, Ar-H), 7.17 (2H, d, J = 7.21 Hz, Ar-H), 6.95 (2H, d, J = 8.4 Hz, Ar-H), 6.82 (1H, s, Ar-H), 4.88 (1H, s, CH), 2.46 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 186.8, 168.9, 161.9, 143.8, 137.6, 135.3, 133.2, 132.0, 129.8, 129.5, 128.9, 128.7, 126.3, 118.7, 84.4, 51.6, 21.5; IR (KBr, cm^{-1}): 3423, 3315, 3271, 3244, 3166, 2210, 1639, 1610, 1583, 1400, 1085, 985; anal. calcd (%) for $C_{25}H_{21}ClN_4O_3S$: C, 60.91; H, 4.29; N, 11.36; S, 6.50; found: C, 60.66; H, 4.27; N, 11.29; S, 6.46.

3-Amino-4-cyano-*N*-(4-methoxyphenyl)-5-oxo-2-phenyl-*N*′-tosylpent-3-enimidamide (2i). Colourless solid, mp: 159–161 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 10.74 (1H, s, NH_2), 9.94 (1H, s, NH_2), 9.11 (1H, s, CHO), 7.78 (2H, d, J = 8.1 Hz, Ar-H), 7.41–7.25 (5H, m, Ar-H, Ar-NH), 7.23 (1H, s, Ar-H), 7.12 (2H, d, J = 7.2 Hz, Ar-H), 6.89 (2H, d, J = 9.0 Hz, Ar-H), 6.81 (2H, d, J = 9.0 Hz, Ar-H), 4.92 (1H, s, CH), 3.78 (3H, s, CH_3), 2.43 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 187.0, 169.0, 162.7, 159.9, 143.6, 137.9, 131.7, 129.5, 129.4, 128.7, 127.1, 126.3, 118.6, 114.7, 84.4, 55.4, 50.9, 21.5; IR (KBr, cm^{-1}): 3380, 3253, 3157, 2966, 2840, 2779, 2198, 1641, 1612, 1581, 1512, 1467, 1407, 1274, 1135, 1085, 985; anal. calcd (%) for $C_{26}H_{24}N_4O_4S$: C, 63.92; H, 4.95; N, 11.47; S, 6.56; found: C, 64.18; H, 4.91; N, 11.49; S, 6.60.

Typical procedure for the synthesis of substituted 4-amino-6-(tosylimino)-1,6-dihydro pyridine-3-carboxamide 3 (3a as an example)

To a stirred mixture of *N*-(4-amino-5-cyano-1,3-diphenylpyridin-2(1*H*)-ylidene)-4-methylbenzenesulfonamide **1a** (441 mg, 1.0 mmol), ethanol (10 mL 95%) was added KOH (224 mg, 6.0 mmol) at room temperature. The reaction mixture was stirred at 80 °C for 4 h. When the starting material was consumed completely (monitored by TLC), the mixture was concentrated under vacuum. The residue was poured into the mixture of saturated aqueous NH_4Cl solution (10 mL) and CH_2Cl_2 (20 mL) and stirred for a few minutes. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layer was washed with water (2 × 10 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated in vacuum and the resulting residue was purified by flash column chromatography to give **3a** (389 mg, 85%) as a colourless solid.

4-Amino-1,5-diphenyl-6-(tosylimino)-1,6-dihydropyridine-3-carboxamide (3a). Colourless solid, mp: 238–240 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ = 8.46 (1H, s, Py-NH_2), 8.32 (1H, s, Py-H), 8.12 (1H, s, $CONH_2$), 7.57 (1H, s, $CONH_2$), 7.49–7.28 (7H, m, Ar-H), 7.20 (3H, d, J = 7.5 Hz, Ar-H), 6.82 (4H, s, Ar-H), 5.89 (1H, s, Py-NH_2), 2.23 (3H, s, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 168.2, 156.6, 152.5, 145.3, 143.2, 142.6, 138.8, 133.5, 132.0, 129.0, 128.9, 128.7, 128.3, 127.9, 124.9, 113.5, 105.2, 21.1; IR (KBr, cm^{-1}): 3460, 3400, 3346, 3255, 3224, 3195, 3056, 3002, 2921, 2223, 1672, 1635, 1595, 1494, 1477, 1411, 1355, 1124, 1083, 750, 698; anal. calcd (%) for $C_{25}H_{22}N_4O_3S$: C, 65.48; H, 4.84; N, 12.22; S, 6.99; found: C, 65.11; H, 4.78; N, 12.18; S, 6.93.

Typical procedure for the synthesis of substituted *N*-(4-amino-5-cyanopyridin-2-yl)-4-methyl benzenesulfonamide 4 (4a as an example)

3-Amino-4-cyano-5-oxo-*N*,2-diphenyl-*N*′-tosylpent-3-enimidamide **2a** (450 mg, 1.0 mmol) was added into toluene (10 mL). The mixture was heated to reflux for 5 h. After the **2a** was consumed completely (monitored by TLC), the mixture was concentrated under vacuum. The residue was purified by flash column chromatography to give **4a** (392 mg, 89%) as a colourless solid.

***N*-(4-Amino-5-cyano-3-phenylpyridin-2-yl)-4-methyl-*N*-phenylbenzenesulfonamide (4a).** Colourless solid, mp: 176–178 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.39 (1H, s, Py-H), 7.61 (2H, d, J = 8.2 Hz, Ar-H), 7.47–7.38 (3H, m, Ar-H), 7.19 (2H, d, J = 8.1 Hz, Ar-H), 7.10 (3H, d, J = 6.0 Hz, Ar-H), 7.01 (2H, t, J = 7.5 Hz, Ar-H), 6.65 (2H, d, J = 7.5 Hz, Ar-H), 4.81 (2H, s, NH_2), 2.40 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.4, 154.7, 150.8, 143.3, 138.9, 136.4, 130.8, 129.7, 129.3, 128.9, 128.6, 128.3, 128.2, 127.3, 120.2, 115.3, 93.4, 21.5; IR (KBr, cm^{-1}): 3465, 3338, 3238, 3205, 3064, 3029, 2921, 2228, 1637, 1571, 1560, 1488, 1469, 1413, 1350, 1292, 1255, 1164, 1110, 1089, 1037; anal. calcd (%) for $C_{25}H_{20}N_4O_2S$: C, 68.16; H, 4.58; N, 12.72; S, 7.28; found: C, 68.28; H, 4.56; N, 12.68; S, 7.24.

***N*-(4-Amino-5-cyano-3-(*p*-tolyl)pyridin-2-yl)-4-methyl-*N*-phenylbenzenesulfonamide (4b).** Colourless solid, mp: 224–226 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.37 (1H, s, Py-H), 7.60 (2H, d, J = 8.1 Hz, Ar-H), 7.32–7.15 (4H, m, Ar-H), 7.14–7.06 (1H, m, Ar-H), 7.06–6.92 (4H, m, Ar-H), 6.67 (2H, d, J = 7.8 Hz, Ar-H), 4.81 (2H, s, NH_2), 2.43 (3H, s, CH_3), 2.41 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.4, 154.9, 150.7, 143.2, 139.0, 138.6, 136.4, 129.9, 129.5, 128.9, 128.6, 128.4, 128.2, 127.7, 127.3, 126.3, 120.4, 115.4, 93.2, 21.5, 21.2; IR (KBr, cm^{-1}): 3487, 3384, 3228, 3068, 2921, 2202, 1598, 1577, 1558, 1488, 1465, 1419, 1352, 1245, 1159, 1091, 1029, 1010; anal. calcd (%) for $C_{26}H_{22}N_4O_2S$: C, 68.70; H, 4.88; N, 12.33; S, 7.05; found: C, 68.65; H, 4.89; N, 12.30; S, 7.01.

***N*-(4-Amino-5-cyano-3-(4-methoxyphenyl)pyridin-2-yl)-4-methyl-*N*-phenylbenzenesulfonamide (4c).** Colourless solid, mp: 234–235 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.37 (1H, s, Py-H), 7.61 (2H, d, J = 8.2 Hz, Ar-H), 7.19 (2H, d, J = 8.1 Hz, Ar-H), 7.10 (1H, d, J = 7.1 Hz, Ar-H), 7.08–6.99 (4H, m, Ar-H), 6.95 (2H, d, J = 8.7 Hz, Ar-H), 6.69 (2H, d, J = 7.5 Hz, Ar-H), 4.82 (2H, s, NH_2), 3.88 (3H, s, CH_3O), 2.40 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.8, 155.6, 155.1, 150.6, 143.2, 139.0, 136.4, 131.0, 128.9, 128.6, 128.3, 128.2, 127.3, 122.7, 120.1, 115.4, 114.7, 93.3, 55.3, 21.5; IR (KBr, cm^{-1}): 3483, 3386, 3234, 3064, 2964, 2939, 2898, 2837, 2216, 1610, 1596, 1569, 1560, 1512, 1463, 1423, 1406, 1350, 1247, 1178, 1161, 1020, 1002, 962, 696, 676, 567, 522; anal. calcd (%) for $C_{26}H_{22}N_4O_3S$: C, 66.37; H, 4.71; N, 11.91; S, 6.81; found: C, 66.11; H, 4.68; N, 11.85; S, 6.78.

***N*-(4-Amino-5-cyano-3-phenylpyridin-2-yl)-4-methyl-*N*-(*o*-tolyl)benzenesulfonamide (4d).** Colourless solid, mp: 215–217 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.35 (1H, s, Py-H), 7.63 (2H, d, J = 8.1 Hz, Ar-H), 7.38 (3H, d, J = 3.3 Hz, Ar-H), 7.22 (2H, d, J = 8.1 Hz, Ar-H), 7.09–6.86 (4H, m, Ar-H), 6.75 (1H, t, J = 7.2 Hz, Ar-H), 6.62 (1H, d, J = 7.8 Hz, Ar-H), 4.66 (2H, s, Py-NH_2), 2.43 (3H, s, CH_3), 1.45 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.8,

154.8, 150.1, 143.3, 138.4, 137.5, 137.0, 131.5, 131.1, 130.9, 129.6, 129.5, 129.3, 128.6, 128.5, 127.8, 125.4, 118.2, 115.4, 92.3, 21.5, 17.8; IR (KBr, cm^{-1}): 3458, 3359, 3224, 3028, 2921, 2223, 1622, 1573, 1488, 1463, 1417, 1402, 1348, 1161, 1085, 676, 572; anal. calcd (%) for $C_{26}H_{22}N_4O_2S$: C, 68.70; H, 4.88; N, 12.33; S, 7.05; found: C, 68.55; H, 4.81; N, 12.28; S, 7.01.

***N*-(4-Amino-5-cyano-3-(*p*-tolyl)pyridin-2-yl)-4-methyl-*N*-(*o*-tolyl)-benzenesulfonamide (4e).** Colourless solid, mp: 213–214 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.32 (1H, s, Py-H), 7.61 (2H, d, J = 8.1 Hz, Ar-H), 7.24–7.09 (4H, m, Ar-H), 7.03 (1H, t, J = 7.2 Hz, Ar-H), 6.91 (1H, d, J = 7.2 Hz, Ar-H), 6.84 (2H, d, J = 7.8 Hz, Ar-H), 6.74 (1H, t, J = 7.2 Hz, Ar-H), 6.62 (1H, d, J = 7.8 Hz, Ar-H), 4.67 (2H, s, NH_2), 2.42 (3H, s, CH_3), 2.40 (3H, s, CH_3) 1.45 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.9, 155.0, 150.0, 143.2, 138.6, 138.4, 137.5, 137.1, 131.5, 130.8, 130.1, 129.5, 129.3, 128.4, 128.0, 127.8, 125.3, 118.4, 115.5, 92.2, 21.5, 21.1, 17.8; IR (KBr, cm^{-1}): 3458, 3359, 3226, 3028, 2921, 2223, 1622, 1573, 1417, 1402, 1350, 1161, 676, 572; anal. calcd (%) for $C_{27}H_{24}N_4O_2S$: C, 69.21; H, 5.16; N, 11.96; S, 6.84; found: C, 69.59; H, 5.11; N, 11.91; S, 6.82.

***N*-(4-Amino-5-cyano-3-phenylpyridin-2-yl)-*N*-(3-chlorophenyl)-4-methylbenzenesulfonamide (4f).** Colourless solid, mp: 240–241 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.37 (1H, s, Py-H), 7.61 (2H, d, J = 8.1 Hz, Ar-H), 7.26–7.15 (4H, m, Ar-H), 7.11 (1H, t, J = 7.2 Hz, Ar-H), 7.06–6.94 (4H, m, Ar-H), 6.67 (2H, d, J = 7.8 Hz, Ar-H), 4.81 (2H, s, Ar-H), 2.43 (3H, s, CH_3), 2.40 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.4, 154.9, 150.7, 143.2, 139.0, 138.6, 136.4, 129.9, 129.5, 128.9, 128.6, 128.4, 128.2, 127.7, 127.2, 120.5, 115.4, 93.3, 21.5, 21.2; IR (KBr, cm^{-1}): 3487, 3384, 3230, 3070, 3035, 2921, 2221, 1598, 1577, 1487, 1463, 1419, 1352, 1159, 1095, 825, 678, 565; anal. calcd (%) for $C_{26}H_{22}N_4O_2S$: C, 68.70; H, 4.88; N, 12.33; S, 7.05; found: C, 68.55; H, 4.81; N, 12.38; S, 7.01.

***N*-(4-Amino-5-cyano-3-phenylpyridin-2-yl)-4-methyl-*N*-(*p*-tolyl)-benzenesulfonamide (4g).** Colourless solid, mp: 201–203 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.39 (s, 1H), 7.63 (d, J = 8.1 Hz, 2H), 7.52–7.38 (m, 3H), 7.22 (d, J = 8.1 Hz, 2H), 7.15–7.03 (m, 3H), 6.94 (t, J = 8.1 Hz, 1H), 6.63 (s, 1H), 6.56 (d, J = 8.1 Hz, 1H), 4.84 (s, 2H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 154.9, 154.8, 151.0, 143.6, 140.0, 136.1, 133.7, 130.5, 129.6, 129.4, 129.0, 128.9, 128.8, 128.8, 128.4, 127.5, 126.2, 120.3, 115.2, 93.6, 21.5; IR (KBr, cm^{-1}): 3473, 3377, 3321, 3228, 3199, 3056, 2871, 2732, 2237, 1635, 1571, 1467, 1413, 1352, 1286, 1159, 1087, 1074, 1012, 973, 680, 576; anal. calcd (%) for $C_{25}H_{19}ClN_4O_2S$: C, 63.22; H, 4.03; N, 11.80; S, 6.75; found: C, 63.01; H, 4.08; N, 11.83; S, 6.71.

***N*-(4-Amino-5-cyano-3-phenylpyridin-2-yl)-*N*-(4-chlorophenyl)-4-methylbenzenesulfonamide (4h).** Colourless solid, mp: 236–237 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.38 (1H, s, Py-H), 7.61 (2H, d, J = 8.2 Hz, Ar-H), 7.51–7.36 (3H, m, Ar-H), 7.21 (2H, d, J = 8.1 Hz, Ar-H), 7.17–7.06 (2H, m, Ar-H), 6.98 (2H, d, J = 8.7 Hz, Ar-H), 6.58 (2H, d, J = 8.7 Hz, Ar-H), 4.84 (2H, s, Py-NH_2), 2.41 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.0, 154.8, 150.9, 143.6, 137.5, 136.0, 133.3, 130.7, 129.7, 129.5, 129.4, 128.9, 128.8, 128.4, 120.3, 115.2, 93.6, 21.5; IR (KBr, cm^{-1}): 3481, 3375, 3232, 3053, 2921, 2227, 1620, 1573, 1562, 1415, 1346, 1163, 1163, 1089, 1014, 678, 576; anal. calcd (%) for $C_{25}H_{19}ClN_4O_2S$ C, 63.22; H, 4.03; N, 11.80; S, 6.75; found: C, 63.48; H, 4.06; N, 11.85; S, 6.72.

***N*-(4-Amino-5-cyano-3-phenylpyridin-2-yl)-*N*-(4-methoxy-phenyl)-4-methylbenzenesulfonamide (4i).** Colourless solid, mp: 227–229 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.37 (1H, s, Py-H), 7.60 (2H, d, J = 8.1 Hz, Ar-H), 7.50–7.41 (3H, m, Ar-H), 7.23–7.07 (4H, m, Ar-H), 6.51 (4H, s, Ar-H), 4.80 (2H, s, NH_2), 3.71 (3H, s, CH_3O), 2.41 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.7, 155.5, 154.7, 150.8, 143.2, 136.3, 131.5, 131.0, 130.0, 129.8, 129.3, 129.0, 128.7, 128.6, 120.0, 115.4, 113.4, 93.3, 55.2, 21.5; IR (KBr, cm^{-1}): 3481, 3458, 3382, 3353, 3236, 3053, 2912, 2839, 2748, 2225, 1620, 1573, 1560, 1508, 1463, 1413, 1340, 1245, 1163, 1089, 1033, 678, 561; anal. calcd (%) for $C_{26}H_{22}N_4O_3S$ C, 66.37; H, 4.71; N, 11.91; S, 6.81; found: C, 66.21; H, 4.66; N, 11.88; S, 6.77.

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