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Facile One-pot Protocol of Derivatization Nitropyridines: Access to 3-Acetamidopyridin-2-yl 4-methylbenzenesulfonate Derivatives

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Abstract: This paper discloses an efficient one-pot protocol to convert easily accessible 3-nitropyridines to 3-acetamidopyridin-2-yl 4-methylbenzenesulfonate derivatives which are core structures of many pharmaceutical molecules. The strategy successfully combined a three-step reaction in one pot via progressively adding different reactants at rt. The reaction displays good functional group tolerance and regioselectivity. Structurally diversified 3-nitropyridine could be time-efficiently (3.5 h) derivatized to various functional 2-*O*,3-*N*-pyridines which are apt for further elaborations. The transformation was amenable to gram-scale synthesis.

Keywords: One-pot, [3,3]-sigmatropic rearrangement, heteroarene, pyridine derivatives, late-stage functionalization.

Introduction

Pyridine derivatives are among the most significant structural motifs with tremendous biological application [1]. Numerous reports revealed that, by changing the substituents on pyridine nucleus, the derivatives usually showed different activities toward the biological targets, varying from microbial disease to viral problems and varieties of cancerous cells, and therefore syntheses of versatile pyridine derivatives are an attractive area in organic synthesis [2,3]. Pyridine derivatives, with C-O and C-N substituents at 2 and 3 positions respectively, were often presented as one of the important building blocks in numerous pharmaceuticals with a wide range of promising biological properties (Figure 1) [4]. For instance, GSK2126458 (A1), a small-molecule pyridylsulfonamide inhibitor, has been identified as a highly potent, orally bioavailable inhibitor of phosphatidylinositol 3-kinase (PI3K) and mammalian target of rapamycin (mTOR) with in vivo activity in both pharmacodynamic and tumor growth efficacy models [5]; BMS-488043 (A2) was found to be a special small molecule in treatment of HIV infection [4g]; pyrido[3,4*d*]pyrimidine (A3) displayed highly selective activities against breast cancer and renal cancer cell lines [4e].

Despite of their high pharmaceutical importance, general and practical strategies that allow rapid access to 2-*O*,3-*N*-pyridines for bioactivity studies are really limited [6]. The most known way to synthesize these molecules is via S_NAr-type reactions between alcohols and electron deficient halogenated pyridines [4e,4f,7]. Transition metal catalyzed amination/oxylation of halogenated pyridines provided a powerful method to gain these pyridine derivatives, while prefunctionalization of starting material was usually needed for achieving the transformation, along with limited functional group tolerance [8,9]. 2-*O*,3-*N*-Pyridines could also be readily prepared from 3-nitropyridine 1-oxide with acetic anhydride or tosyl chloride through a thermally induced rearrangement [10]. However, an efficient way to get 3-nitropyridine 1-oxide derivatives is still under development, which hinders further application of the strategy [11]. [3,3]-Sigmatropic rearrangement of *N*-pyridine-*O*-acyl(tosyl)hydroxylamine derivatives should be an alternative way to gain access to these molecules [12]. Similar strategies have been well applied to transform *N*-phenyl-*O*-protected hydroxylamine derivatives

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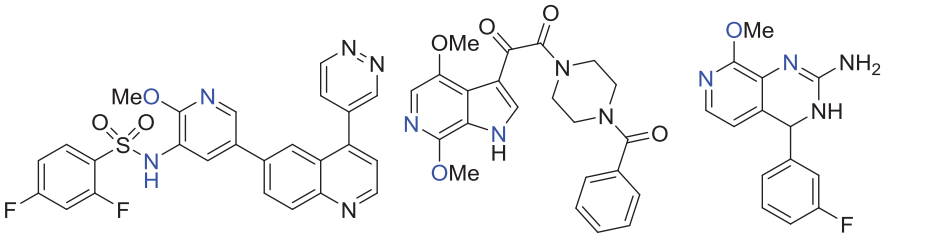
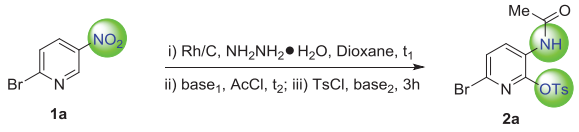


Figure 1 Selected bioactive molecules bearing the 3-amino-2-oxylpyridine core structure.

to related 2-aminophenols [13]. Although it seems a shortcut to deliver 2-*O*,3-*N*-Pyridines, several challenging issues make this route less attractive to chemists, such as less efficient generation of *N*-pyridine hydroxylamine, which is unstable under air [14], and multi-step transformation to obtain the rearrangement precursor, including reduction/purification, protection/purification [15]. As part of our ongoing interest in the synthesis of heteroarenes [16], we have disclosed a one-pot, three-step reaction sequence procedure for efficient formation of 2-*O*,3-*N*-Pyridine derivatives from 3-nitropyridines. Notable features of our general strategy include 1) structurally diversified 3-nitropyridine can be successfully converted to product in a short time period; 2) the transformation has good function group tolerance and could be amenable to a gram-scale synthesis; 3) the product could be further elaborated.

Table 1 Optimization of the one pot protocol.[a]



Entry[b]	t_1	$Base_1$	t_2	$Base_2$	Yield[c]
1	2 h	$NaHCO_3$	2 h	$NaHCO_3$	11%
2	2 h	$NaHCO_3$	2 h	Et_3N	25%
3	2 h	Et_3N	2 h	Et_3N	trace
4	0.25 h	$NaHCO_3$	2 h	Et_3N	56%
5	0.25 h	$NaHCO_3$	0.25 h	Et_3N	79%
6	0.25 h	$NaHCO_3$	0.25 h	Et_3N	71%[d]

[a](All reactions were run on a 0.5 mmol scale of **1a** with its concentration of 0.2 M in 1,4-dioxane, along with 5% Rh/C, Hydrazine hydrate (1.20 eq.), $base_1$ (1.20 eq.), $base_2$ (1.20 eq.), TsCl (1.20 eq.) at rt. Otherwise noted.).
[b]each entry was run 3 times and the deviation of yield was around 3%.
[c](isolated yield.)
[d](The reaction was run in THF as solvent.)

Results and Discussion

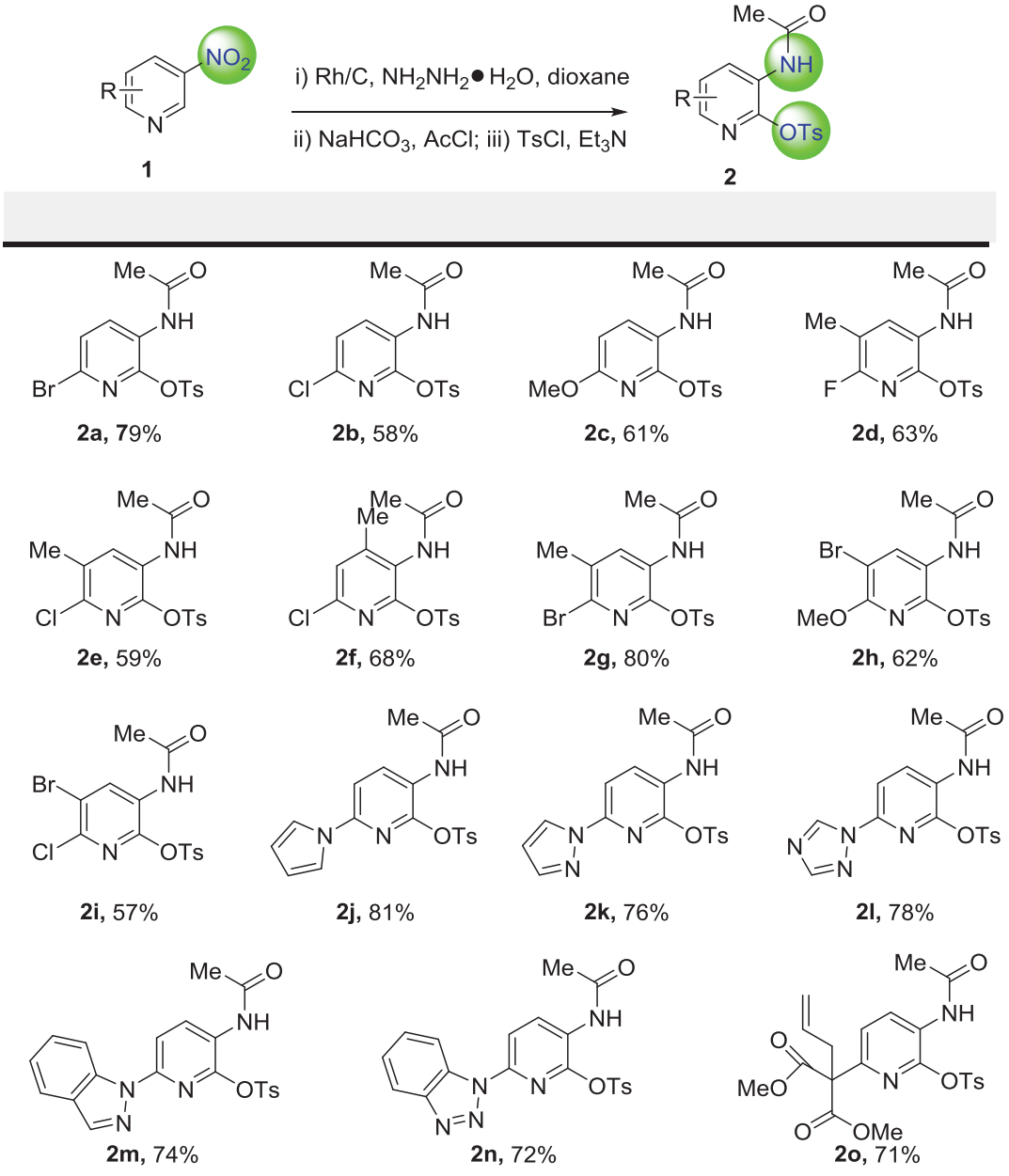
The reaction optimization was outset by using 2-bromo-5-nitropyridine as model substrate which was mixed with 5% Rh/C and hydrazine monohydrate in 1,4-dioxane at rt for 2h to selectively form a hydroxylamine intermediate. This was subsequently protected by acetyl chloride in the presence of $NaHCO_3$. Two hour later, tosyl chloride and another batch of $NaHCO_3$ were added to the reaction mixture which was stirred for 3 hours. Subsequent workup furnished the desired rearrangement product (**2a**) in 11% yield (Table 1, entry 1). Encouraged by this, various bases, solvents and reaction time of each sequence were screened to get the optimal yield of product **2a** (for detail reaction optimization, see supporting information). It was found that $NaHCO_3$ was crucial for the success of the acetyl protection step and Et_3N was beneficial for improving the efficiency of the tosyl protection step (Table 1, entries 2–3). The efficiency of this transformation was highly influenced by the reaction time of each step in the sequence. The yield of **2a** was dramatically increased when the reduction step and acetyl protection step were conducted in a short reaction period (Table 1, entries 4–5). Other solvents, such as THF, were found to be less efficient than 1,4-dioxane.

With the optimized conditions in hand, the generality of this transformation utilizing structurally diverse nitropyridine was explored. Notably, 3-nitropyridines with various functional groups and substitution patterns are well tolerated and the reaction shows good efficiency and high regioselectivity. Particularly, halogen functionalities (**2a**–**2b**, **2d**–**2i**) remained intact during the transformation, providing useful synthetic handles for further structural elaborations. Substrates with heteroaryl substituents, such as pyrrole, pyrazole, triazole, indazole, benzotrizale, smoothly underwent this one-pot strategy and delivered product in relatively high yield (**2j**–**2n**). Moreover, complex nitropyridine with multi functional groups (alkene, ester) was also successfully converted to the desired product in good yield (**2o**, 71%), which indicates a late-stage functionalization inherence of our strategy.

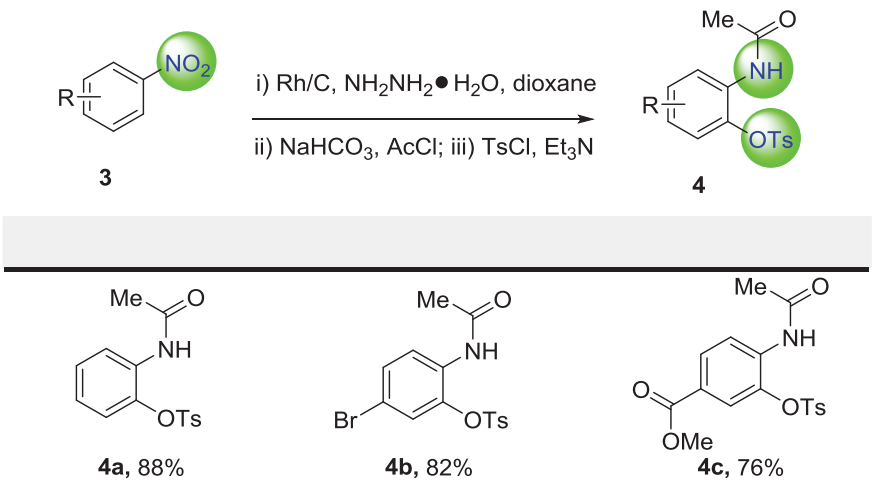
Gratifyingly, the reaction was successfully applied to nitrobenzene derivatives. Selected examples were summarized in Scheme 2. Nitrobenzene efficiently underwent the one-pot transformation, providing product **4a** in 88% yield. A substrate with a bromo substituent had a similar high reaction efficiency (**4b**, 82% yield). An electron withdrawing group, such as ester, was well tolerated by the protocol leading to a slightly lower yield of **4c** in comparison with **4a** and **4b.**

To highlight both the practicality and effectiveness of our protocol for large-scale synthesis, the one-pot transformation was conducted on a gram scale (Scheme 3). Promisingly, 2.70 g of the desired product **2j** was achieved in 73% yield, only slightly lower than the small-scale reaction.

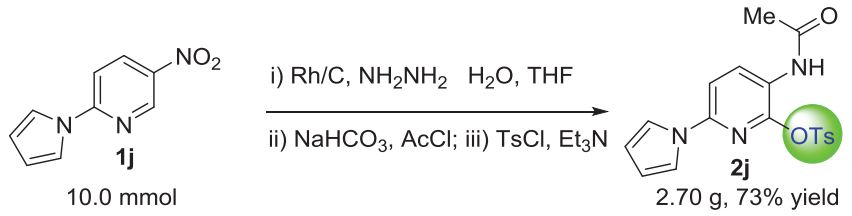
The functional group, which was introduced onto the pyridine ring via the one-pot protocol, offers possibility for further manipulation (Scheme 4). The tosyl group could be easily removed in the presence of Cs_2CO_3 at rt to uncover a hydroxyl group, which is viable for more synthetically useful transformations [17,18]. The pyridine substrate is well compatible with traditional cross-coupling methodologies, such as Suzuki coupling to afford **6** in 91% yield, thus providing the chance to access diverse substituted 3-aminopyridines [19,20].



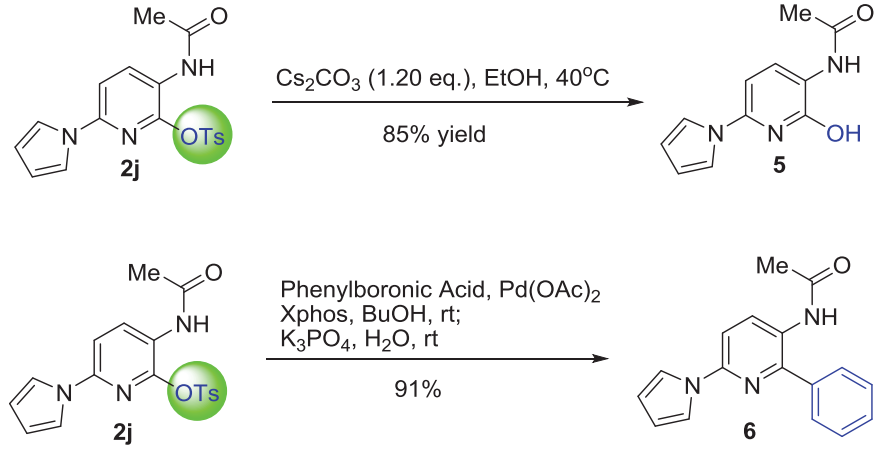
Scheme 1 Reaction scoe for synthesis of 3-acetamidopyridin-2-yl 4-methylbenzenesulfonate derivatives.



Scheme 2 Selected examples for synthesis of 2-acetamidophenyl 4-methylbenzenesulfonate under optimized conditions.



Scheme 3 Gram-Scale Synthesis of Compound **2j**.



Scheme 4 Manipulation of the product.

The resulting one-pot protocol allowed the efficient gain of 3-acetamidopyridin-2-yl 4-methylbenzenesulfonate derivatives from easily accessible 3-nitropyridines. Our strategy successfully combined a three-step reaction in one pot via progressively adding different reactants at rt. The reaction displays good function group tolerance and regioselectivity. Structurally diversified 3-nitropyridine can be time-efficiently converted to the desired product (3.5 h). The transformation could be amenable to a 10 mmol-scale synthesis with slightly lower reaction efficiency in comparison to the small scale reaction. The introduced functional groups (OTs, NHAc) are synthetic handles for further elaborations.

Experimental

All commercially available reagents were used without further purification. Analytical grade solvents were bought from Beijing ouhe technology Co., LTD and used

after bubbling with N_2 for 5 min. The reactions were carried out under an ambient atmosphere whilst being magnetically stirred. They were monitored by thin layer chromatography (TLC) and visualized by fluorescence quenching under UV light. Flash chromatography was performed on silica gel (200–300 mesh). All deuterated solvents were purchased from Meryer (Shanghai) chemical technology Co., LTD. Melting points were determined on a Mel-Temp (Laboratory Devices) apparatus and are uncorrected. NMR spectra were recorded on a Bruker Ascend 300 spectrometer operating at 300 MHz for ^{1}H acquisitions, 75 MHz for ^{13}C acquisitions. Chemical shifts were referenced to the residual proton solvent peaks (^{1}H: $CDCl_3$, 7.26; $(CD_3)_2SO$, 2.50), solvent ^{13}C signals ($CDCl_3$, 77.16; $(CD_3)_2SO$, 39.52). Signals are listed in ppm, and multiplicity identified as s = singlet, br = broad, d = doublet, t = triplet, q = quartet, m = multiplet; coupling constants in Hz; integration. High-resolution mass spectra were obtained using Agilent LC-UV-TOF mass spectrometer. Yields refer to purified and spectroscopically pure compounds.

General procedure of the one-pot protocol

Under N_2 atmosphere, hydrazine monohydrate (30.0 mg, 0.60 mmol, 1.20 equiv) was added dropwise to a suspension of 3-nitropyridine (0.50 mmol, 1.00 equiv) and 5% Rh/C (3.3 mg, 0.30 mol% Rh) in 1,4-dioxane (5.0 mL, 0.100 M), After the reaction mixture was stirred at rt for 0.25 h. $NaHCO_3$ (51 mg, 0.60 mmol, 1.20 equiv) was directly added, followed by a solution of acetyl chloride (50.0 mg, 0.60 mmol, 1.20 equiv) in 1,4-dioxane (1.0 mL, 0.600 M). The reaction mixture was stirred at rt for another 0.25 h. Tosyl chloride (190 mg, 1.00 mmol, 2.00 equiv) and Et3N (101.0 mg, 1.00 mmol, 2.00 equiv) were added to the reaction mixture which was allowed to stir at rt for 3h. The reaction was quenched by adding distilled water (2.0 mL), extracted with EtOAc (10 mL X 3), dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by chromatography on silica gel, eluting with EtOAc: petroleum ether (v/v), to afford the desired product.

3-Acetamido-6-bromopyridin-2-yl 4-methylbenzenesulfonate (2a) Light yellow solid (152 mg, 79 % yield, R_f = 0.41 (petroleum ether/ethyl acetate = 5 : 1 (v/v)); m.p. 147.1–149.0 °C; NMR Spectroscopy: ^{1}H NMR (300 MHz, $(CD_3)_2SO$, 25 °C, δ): 9.83 (s, 1H), 8.23 (d, J = 8.4 Hz, 1H), 7.86 (d, J = 8.1 Hz, 2H), 7.58 (d, J = 8.4 Hz, 1H), 7.49 (d, J = 8.1 Hz, 2H), 2.42 (s, 3H), 2.00 (s, 3H). ^{13}C NMR (75 MHz, $(CD_3)_2SO$, 25 °C, δ): 169.1, 146.4, 146.0, 136.3, 132.8, 130.4, 129.9, 128.6, 127.2, 125.2, 23.4, 21.2. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{14}H_{14}BrN_2O_4S^+$ ([M +H]$^+$), 384.9852, found, 384.9859.

3-Acetamido-6-chloropyridin-2-yl 4-methylbenzenesulfonate (2b) White solid (99 mg, 58 % yield, R_f = 0.35 (petroleum ether/ethyl acetate = 5 : 1 (v/v)); m.p. 151.4–152.3 °C; NMR Spectroscopy: ^{1}H NMR (300 MHz, $(CD_3)_2SO$, 25 °C, δ): 9.83 (s, 1H), 8.30 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 8.4 Hz, 2H), 7.51–7.45 (m, 3H), 2.42 (s, 3H), 1.99 (s, 3H). ^{13}C NMR (75 MHz, $(CD_3)_2SO$, 25 °C, δ): 169.0, 146.0, 140.7, 136.7, 132.9, 130.0, 128.6, 125.0, 123.4, 23.3, 21.2. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{14}H_{14}ClN_2O_4S^+$ ([M +H]$^+$), 341.0357, found, 341.0351.

3-Acetamido-6-methoxypyridin-2-yl 4-methylbenzenesulfonate (2c) White yellow solid (102 mg, 61 % yield, R_f = 0.35 (petroleum ether/ethyl acetate = 5 : 1 (v/v)); m.p. 135.3–136.9 °C; NMR Spectroscopy: ^{1}H NMR (300 MHz, $(CD_3)_2SO$, 25 °C, δ): 9.61 (s, 1H), 7.98 (d, J = 8.6 Hz, 1H), 7.87 (d, J = 8.3 Hz, 2H), 7.48 (d, J = 8.0 Hz, 2H), 6.76 (d, J = 8.6 Hz, 1H), 3.52 (s, 3H), 2.42 (s, 3H), 1.98 (s, 3H). ^{13}C NMR (75 MHz, $(CD_3)_2SO$, 25 °C, δ): 168.6, 158.4, 146.4, 145.4, 139.2, 134.0, 129.9, 128.2, 118.2, 108.9, 53.7, 23.0, 21.1. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{15}H_{17}N_2O_5S^+$ ([M +H]$^+$), 337.0853, found, 337.0851.

3-Acetamido-6-fluoro-5-methylpyridin-2-yl 4-methylbenzenesulfonate (2d) Light yellow solid (107 mg, 63 % yield, R_f = 0.32 (petroleum ether/ethyl acetate = 5 : 1 (v/v)); m.p. 132.1–134.1 °C; NMR Spectroscopy: ^{1}H NMR (300 MHz, $(CD_3)_2SO$, 25 °C, δ): 9.72 (s, 1H), 8.18 (d, J = 9.1 Hz, 1H), 7.83 (d, J = 8.3 Hz, 2H), 7.49 (d, J = 8.1 Hz, 2H), 2.42 (s, 3H), 2.20 (s, 3H), 1.93 (s, 3H). ^{13}C NMR (75 MHz, $(CD_3)_2SO$, 25 °C, δ): 168.6, 145.9, 140.4 (d, J = 12.9 Hz), 132.9, 130.0, 128.3, 126.8 (d, J = 185.2 Hz), 123.4 (d, J = 5.3 Hz), 118.4 (d, J = 31.7 Hz), 23.0, 21.2, 13.4 (d, J = 1.6 Hz). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{15}H_{16}FN_2O_4S^+$ ([M +H]$^+$), 339.0809, found, 339.0812.

3-Acetamido-6-chloro-5-methylpyridin-2-yl 4-methylbenzenesulfonate (2e) White solid (105 mg, 59 % yield, R_f = 0.28 (petroleum ether/ethyl acetate = 5 : 1 (v/v)); m.p. 155.6–157.2 °C; NMR Spectroscopy: ^{1}H NMR (300 MHz, $(CD_3)_2SO$, 25 °C, δ): 9.77 (s, 1H), 8.25 (s, 1H), 7.58 (d, J = 8.3 Hz, 2H), 7.49 (d, J = 8.2 Hz, 2H), 2.42 (s, 3H), 2.28 (s, 3H), 1.96 (s, 3H). ^{13}C NMR (75 MHz, $(CD_3)_2SO$, 25 °C, d): 168.9, 145.9, 144.4, 140.7, 137.1, 132.9, 131.7, 129.9, 128.5, 124.9, 23.3, 21.2, 18.4. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{15}H_{16}ClN_2O_4S^+$ ([M +H]$^+$), 355.0514, found, 355.0514.

3-Acetamido-6-chloro-4-methylpyridin-2-yl 4-methylbenzenesulfonate (2f) White solid (121 mg, 68 % yield, R_f = 0.31 (petroleum ether/ethyl acetate = 5 : 1 (v/v)); m.p. 120.8–121.9 °C; NMR Spectroscopy: ^{1}H NMR (300 MHz, $(CD_3)_2SO$, 25 °C, δ): 9.68 (s, 1H), 7.89 (d, J = 8.4 Hz, 2H), 7.52

(d, *J* = 8.0 Hz, 2H), 7.49 (s, 1H), 2.44 (s, 3H), 2.20 (s, 3H), 1.96 (s, 3H). ^{13}C NMR (75 MHz, $(CD_3)_2SO$, 25 °C, d): 168.2, 152.7, 151.3, 145.8, 143.8, 133.3, 130.0, 128.3, 124.6, 123.6, 22.4, 21.2, 17.6. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{15}H_{16}ClN_2O_4S^+$ ([M +H]$^+$), 355.0514, found, 355.0520.

3-Acetamido-6-bromo-5-methylpyridin-2-yl 4-methylbenzenesulfonate (2g) Light yellow solid (160 mg, 80 % yield, R_f = 0.35 (petroleum ether/ethyl acetate = 5 : 1 (v/v)); m.p. 160.9–162.3 °C; NMR Spectroscopy: ^{1}H NMR (300 MHz, $(CD_3)_2SO$, 25 °C, δ): 9.77 (s, 1H), 8.22 (s, 1H), 7.85 (d, *J* = 8.2 Hz, 2H), 7.48 (d, *J* = 8.2 Hz, 2H), 2.42 (s, 3H), 2.27 (s, 3H), 1.97 (s, 3H). ^{13}C NMR (75 MHz, $(CD_3)_2SO$, 25 °C, d): 168.9, 145.9, 144.4, 136.3, 134.2, 132.9, 129.9, 128.6, 125.0, 23.3, 21.2, 20.5. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{15}H_{16}BrN_2O_4S^+$ ([M +H]$^+$), 399.0009, found, 399.0013.

3-Acetamido-5-bromo-6-methoxypyridin-2-yl 4-methylbenzenesulfonate (2h) Brown solid (129 mg, 62 % yield, R_f = 0.41 (petroleum ether/ethyl acetate = 5 : 1 (v/v)); m.p. 145.1–146.7 °C; NMR Spectroscopy: ^{1}H NMR (300 MHz, $(CD_3)_2SO$, 25 °C, δ): 9.78 (s, 1H), 8.36 (s, 1H), 7.87 (d, *J* = 8.3 Hz, 2H), 7.49 (d, *J* = 8.1 Hz, 2H), 3.57 (s, 3H), 2.42 (s, 3H), 1.98 (s, 3H). ^{13}C NMR (75 MHz, $(CD_3)_2SO$, 25 °C, d): 168.9, 154.0, 145.7, 144.9, 140.7, 133.5, 130.0, 128.3, 119.6, 102.5, 54.8, 23.0, 21.2. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{15}H_{16}BrN_2O_5S^+$ ([M +H]$^+$), 414.9958, found, 414.9951.

3-Acetamido-5-bromo-6-chloropyridin-2-yl 4-methylbenzenesulfonate (2i) Light yellow solid (120 mg, 57 % yield, R_f = 0.35 (petroleum ether/ethyl acetate = 5 : 1 (v/v)); m.p. 138.6–140.3 °C; NMR Spectroscopy: ^{1}H NMR (300 MHz, $(CD_3)_2SO$, 25 °C, δ): 10.00 (s, 1H), 8.70 (s, 1H), 7.87 (d, *J* = 8.3 Hz, 2H), 7.50 (d, *J* = 8.3 Hz, 2H), 2.43 (s, 3H), 2.00 (s, 3H). ^{13}C NMR (75 MHz, $(CD_3)_2SO$, 25 °C, δ): 169.4, 146.2, 144.8, 139.5, 138.2, 132.5, 130.0, 128.7, 125.9, 117.0, 23.4, 21.2. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{14}H_{13}BrClN_2O_4S^+$ ([M +H]$^+$), 418.9462, found, 418.9460.

3-Acetamido-6-(1H-pyrrol-1-yl)pyridin-2-yl 4-methylbenzenesulfonate (2j) White solid (150 mg, 81 % yield, R_f = 0.21 (petroleum ether/ethyl acetate = 5 : 1 (v/v)); m.p. 119.2–121.1 °C; NMR Spectroscopy: ^{1}H NMR (300 MHz, $(CD_3)_2SO$, 25 °C, δ): 9.82 (s, 1H), 8.29 (d, *J* = 8.6 Hz, 1H), 7.89 (d, *J* = 8.3 Hz, 2H), 7.62 (d, *J* = 8.6 Hz, 1H), 7.51 (d, *J* = 8.3 Hz, 2H), 7.23 (t, *J* = 2.2 Hz, 2H), 6.24 (t, *J* = 2.2 Hz, 2H), 2.44 (s, 3H), 2.04 (s, 3H). ^{13}C NMR (75 MHz, $(CD_3)_2SO$, 25 °C, δ): 169.0, 146.5, 145.7, 144.3, 137.6, 133.9, 130.2, 128.2, 121.9, 118.1, 111.5, 110.0, 23.3, 21.2. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{18}H_{18}N_3O_4S^+$ ([M +H]$^+$), 372.1013, found, 372.1013.

3-Acetamido-6-(1H-pyrazol-1-yl)pyridin-2-yl 4-methylbenzenesulfonate (2k) Light yellow solid (124 mg, 76 % yield, R_f = 0.15 (petroleum ether/ethyl acetate = 5 : 1 (v/v)); m.p. 151.6–152.8 °C; NMR Spectroscopy: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, δ): 8.78 (d, *J* = 8.7 Hz, 1H), 7.90–7.86 (m, 3H), 7.76 (d, *J* = 8.7 Hz, 2H), 7.69 (s, 1H), 7.61 (s, 1H), 7.34 (d, *J* = 7.9 Hz, 2H), 6.31 (s, 1H), 2.42 (s, 3H), 2.20 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, δ): 168.9, 146.2, 144.14, 144.07, 142.3, 133.9, 133.5, 130.0, 128.9, 126.7, 123.8, 111.2, 107.9, 24.7, 21.9. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{17}H_{17}N_4O_4S^+$ ([M +H]$^+$), 373.0965, found, 373.0968.

3-Acetamido-6-(1H-1,2,4-triazol-1-yl)pyridin-2-yl 4-methylbenzenesulfonate (2l) White solid (146 mg, 78 % yield, R_f = 0.18 (petroleum ether/ethyl acetate = 5 : 1 (v/v)); m.p. 160.6–161.5 °C; NMR Spectroscopy: ^{1}H NMR (300 MHz, $(CD_3)_2SO$, 25 °C, δ): 10.01 (s, 1H), 8.55 (s, 1H), 8.52 (d, *J* = 3.3 Hz, 1H), 8.29 (s, 1H), 7.94 (d, *J* = 8.3 Hz, 2H), 7.78 (d, *J* = 8.6 Hz, 1H), 7.51 (d, *J* = 8.3 Hz, 2H), 2.42 (s, 3H), 2.07 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, δ): 169.2, 153.2, 146.0, 145.8, 141.4, 137.2, 133.4, 130.2, 128.5, 125.2, 112.0, 23.5, 21.2. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{16}H_{16}N_5O_4S^+$ ([M +H]$^+$), 374.0918, found, 374.0913.

3-Acetamido-6-(1H-indazol-1-yl)pyridin-2-yl 4-methylbenzenesulfonate (2m) Yellow solid (156 mg, 74 % yield, R_f = 0.22 (petroleum ether/ethyl acetate = 5 : 1 (v/v)); m.p. 149.2–151.0 °C; NMR Spectroscopy: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, δ): 9.41 (s, 1H), 8.61 (d, *J* = 8.5 Hz, 1H), 8.44 (d, *J* = 8.9 Hz, 1H), 7.80–7.40 (m, 3H), 7.55 (d, *J* = 8.9 Hz, 1H), 7.47 (d, *J* = 8.9 Hz, 1H), 7.29–7.24 m, 3H), 6.77 (s, 1H), 1.60 (s, 3H), 1.28 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, δ): 189.8, 145.6, 134.1, 127.9, 127.4, 126.2, 125.3, 124.1, 118.5, 116.7, 112.9, 112.2, 108.4, 25.8, 18.3. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{21}H_{19}N_4O_4S^+$ ([M +H]$^+$), 423.1122, found, 423.1128.

3-Acetamido-6-(1H-benzo[d][1,2,3]triazol-1-yl) pyridin-2-yl 4-methylbenzenesulfonate (2n) Light yellow solid (152 mg, 72 % yield, R_f = 0.12 (petroleum ether/ethyl acetate = 5 : 1 (v/v)); m.p. 133.6–134.7 °C; NMR Spectroscopy: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, δ): 9.00 (d, *J* = 8.8 Hz, 1H), 8.20 (d, *J* = 8.8 Hz, 1H), 8.08 (d, *J* = 7.4 Hz, 1H), 7.89 (d, *J* = 8.2 Hz, 2H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.76 (s, 1H), 7.46-7.37 (m, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 2.38 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, δ): 169.0, 146.6, 146.5, 143.7, 134.0, 132.8, 131.0, 130.3, 128.9, 128.7, 125.1, 120.0, 114.0, 113.8, 24.9, 21.9. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{20}H_{18}N_5O_4S^+$ ([M +H]$^+$), 424.1074, found, 424.1081.

Dimethyl-2-(5-acetamido-6-(tosyloxy)pyridin-2-yl)-2-allylmalonate (2o) White solid (169 mg, 71 % yield, R_f = 0.35 (petroleum ether/ethyl acetate = 5 : 1 (v/v)); m.p. 105.8–106.9 °C; NMR Spectroscopy: ^{1}H NMR (300 MHz, $(CD_3)_2SO$, 25 °C, δ): 9.87 (s, 1H), 8.30 (d, *J* = 8.4 Hz, 3H), 7.83 (d, *J* = 8.2 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 1H), 7.45

(d, *J* = 8.2 Hz, 2H), 5.63–5.52 (m, 1H), 4.93–4.85 (m, 2H), 3.65 (s, 6H), 2.72 (d, *J* = 6.0 Hz, 2H), 2.39 (s, 3H), 2.07 (s, 3H). ^{13}C NMR (75 MHz, $(CD_3)_2SO$, 25 °C, δ): 169.3, 169.0, 148.6, 146.5, 145.5, 134.1, 133.6, 133.0, 130.0, 128.2, 124.6, 123.2, 119.0, 64.1, 52.9, 39.2, 23.5, 21.2. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{22}H_{25}N_2O_8S^+$ ([M +H]$^+$), 477.1326, found, 477.1326.

2-Acetamidophenyl 4-methylbenzenesulfonate (4a) Brown solid (134 mg, 88 % yield, R_f = 0.30 (petroleum ether/ethyl acetate = 5 : 1 (v/v)); m.p. 132.2–133.7 °C; NMR Spectroscopy: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, δ): 8.22 (d, *J* = 8.2 Hz, 1H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.57 (s, 1H), 7.38 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.02 (d, *J* = 8.0 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 2.52 (s, 3H), 2.05 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, δ): 168.9, 146.3, 139.1, 131.8, 131.4, 130.2, 128.7, 127.9, 124.5, 123.0, 122.9, 24.8, 22.0. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{15}H_{16}NO_4S^+$ ([M +H]$^+$), 306.0795, found, 306.0793.

2-Acetamido-5-bromophenyl 4-methylbenzenesulfonate (4b) White solid (158 mg, 82 % yield, R_f = 0.35 (petroleum ether/ethyl acetate = 5 : 1 (v/v)); m.p. 125.6–126.8 °C; NMR Spectroscopy: ^{1}H NMR (300 MHz, $(CD_3)_2SO$, 25 °C, δ): 9.42 (s, 1H), 7.73 (d, *J* = 8.9 Hz, 1H), 7.69 (d, *J* = 8.3 Hz, 2H), 7.47 (d, *J* = 8.3 Hz, 1H), 7.44-7.41 (m, 3H), 2.38 (s, 3H), 1.80 (s, 3H). ^{13}C NMR (75 MHz, $(CD_3)_2SO$, 25 °C, d): 168.1, 146.1, 140.0, 131.2, 130.7, 130.4, 130.0, 128.3, 126.1, 125.5, 114.9, 23.3, 21.1. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{15}H_{15}BrNO_4S^+$ ([M +H]$^+$), 383.9900, found, 383.9906.

Methyl 4-acetamido-3-(tosyloxy)benzoate (4c) White solid (138 mg, 76 % yield, R_f = 0.40 (petroleum ether/ethyl acetate = 5 : 1 (v/v)); m.p. 117.5–118.9 °C; NMR Spectroscopy: ^{1}H NMR (300 MHz, $(CD_3)_2SO$, 25 °C, δ): 9.60 (s, 1H), 8.02 (d, *J* = 8.6 Hz, 1H), 7.83 (dd, *J* = 8.6, 3.5 Hz, 1H), 7.79 (d, *J* = 1.8 Hz, 1H), 7.68 (d, *J* = 8.3 Hz, 1H), 7.42 (d, *J* = 8.2 Hz, 1H), 3.84 (s, 3H),2.38 (s, 3H), 1.87 (s, 3H). ^{13}C NMR (75 MHz, $(CD_3)_2SO$, 25 °C, δ): 168.5, 164.8, 146.2, 138.5, 135.7, 131.1, 130.0, 128.5, 128.4, 124.9, 124.0, 122.9, 52.3, 23.5, 21.1. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{17}H_{18}NO_6S^+$ ([M +H]$^+$), 364.0849, found, 364.0857.

Gram-scale synthesis of compound 2j. Under N_2 atmosphere, hydrazine monohydrate (600.0 mg, 12.0 mmol, 1.20 equiv) was added dropwise to a suspension of 5-nitro-2-(1*H*-pyrrol-1-yl)pyridine (10.0 mmol, 1.00 equiv) and 5% Rh/C (66.0 mg, 0.30 mol% Rh) in 1,4-dioxane (100.0 mL, 0.100 M). The reaction mixture was then stirred at rt for 20 min. $NaHCO_3$ (1.00 g, 12.0 mmol, 1.20 equiv) was directly added, followed by a solution of acetyl chloride (1.0 g, 12.0 mmol, 1.20 equiv) in 1,4-dioxane (10.0 mL, 1.20 M). The reaction mixture was stirred at rt for another 20 min. Tosyl chloride (3.80 g, 20.0 mmol, 2.00 equiv) and Et_3N (2.0 g, 20.0 mmol, 2.00 equiv) were added to the reaction mixture which was allowed to stir at rt for 5h. The reaction was quenched by adding distilled water (30 mL), extracted with EtOAc (40 mL X 3), dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by chromatography on silica gel, eluting with EtOAc: petroleum ether (10:1 to 5:1 (v/v)), to afford the compound **2j** as a light yellow solid (2.70 g, 73% yield).

Synthesis of compound 5. Under N_2 atmosphere, Compound **2j** (371 mg, 1.0 mmol) was dissolved in MeOH (20 mL, 0.05 M). Cs_2CO_3 (650 mg, 2.0 mmol) was added to the reaction mixture which was stirred at rt for 24 h. The reaction mixture was concentrated under vacuum, diluted with distilled water (20 mL), extracted with EtOAc (40 mL X 3), dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by chromatography on silica gel, eluting with EtOAc: petroleum ether (1:1 (v/v)), to afford the compound **5** as a light yellow solid (184 mg, 85% yield, R_f = 0.11 (petroleum ether/ethyl acetate = 2 : 1 (v/v)); m.p. 197.5–198.9 °C; NMR Spectroscopy: ^{1}H NMR (300 MHz, $(CD_3)_2SO$, 25 °C, δ): 11.82 (brs, 1H), 9.33 (s, 1H), 8.27 (d, *J* = 8.3 Hz, 1H), 7.50 (s, 2H), 6.99 (brs, 1H), 6.24 (t, *J* = 2.2 Hz, 2H), 2.09 (s, 3H). ^{13}C NMR (75 MHz, $(CD_3)_2SO$, 25 °C, δ): 169.0, 154.3, 131.6, 118.3, 118.2, 118.0, 111.7, 110.7, 23.7. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{11}H_{10}N_3O_2^-$ ([M - H]$^-$), 216.0779, found, 216.0781.

Synthesis of compound 6. Under N_2 atmosphere, to an oven-dried 100 mL flask was added **2j** (371 mg, 1.0 mmol), $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), Xphos (54.8 mg, 0.12 mmol), phenylboronic acid (146 mg, 1.2 mmol) and degassed n-butanol (10.0 mL, 0.1 M). The mixture was stirred at rt for 15 min, and then a solution of K_3PO_4 (300.0 mg, 1.5 mmol) in degassed H_2O (2.0 mL) was added in one portion. After stirring at rt for 24 h, the reaction was quenched by adding distilled water (20 mL), extracted with EtOAc (30 mL X 3), dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by chromatography on silica gel, eluting with EtOAc: petroleum ether (10:1 to 5:1 (v/v)), to afford the compound **6** as a white solid (252 mg, 91 % yield, R_f = 0.25 (petroleum ether/ethyl acetate = 5 : 1 (v/v)); m.p. 132.7–133.5 °C; NMR Spectroscopy: ^{1}H NMR (300 MHz, $(CD_3)_2SO$, 25 °C, d): 8.58 (d, *J* = 8.8 Hz, 1H), 7.70–7.64 (m, 2H), 7.60–7.40 (m, 5H), 7.32 (brs, 1H), 7.28 (d, *J* = 8.8 Hz, 1H), 6.33 (t, *J* = 2.1 Hz, 1H), 2.08 (s, 3H). ^{13}C NMR (75 MHz, $(CD_3)_2SO$, 25 °C, δ): 151.9, 146.3, 122.6, 122.1, 118.8, 117.6, 116.5, 113.0, 55.8. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{17}H_{16}N_3O^+$ ([M +H]$^+$), 278.1288, found, 278.1280.

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