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DMAP-promoted in situ activation of bromoacetic acid as a 2-carbon synthon for facile synthesis of pyridines and fused pyridin-2-ones

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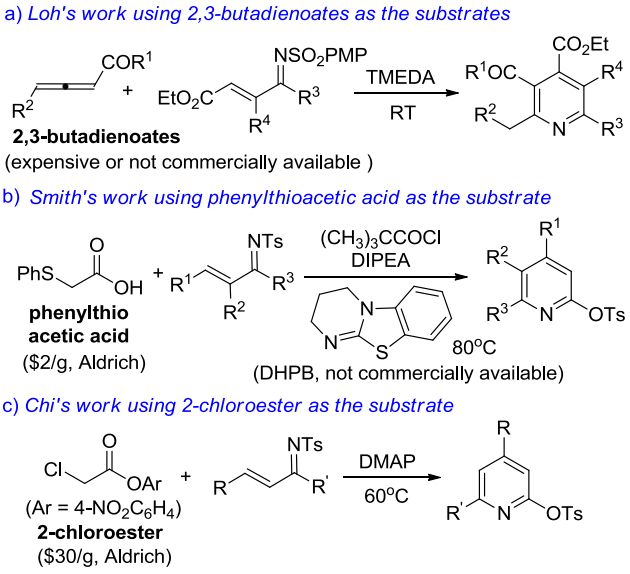
ABSTRACT

A general and simple synthesis of 2,4,6-trisubstituted pyridines and fused pyridine-2-ones from bromoacetic acid is developed via a DMAP-promoted in situ activation strategy. In this protocol, readily accessible bromoacetic acid has been effectively employed as a 2C synthon to undergo formal [2+4] cycloadditions with diverse acyclic and cyclic 1-azadienes. Low costs of the reagents and materials, mild reaction conditions and broad functional-group tolerance make this protocol applicable for practical and scalable synthesis.

1. Introduction

Functionalized pyridines are recognized as attractive privileged structures and important building blocks due to their prevalence in numerous natural products, pharmaceuticals and functional materials.[1] Thus, they have become common synthetic targets among organic community.[2] However, among exisiting synthetic methods,[3] relatively high reaction temperature is usually required or toxic transition-metals are used as the catalysts. Besides, the substrates applied for pyridine synthesis are sometimes not readily accessible. Therefore, the development of more general and environmentally benign (metal-free) methods that allow rapid access to the pyridine motif from readily accessible starting materials is highly desirable.

Recently, organocatalysis has been established as a powerful tool for the synthesis of substituted pyridines owing to the non-toxic nature and unique reactivity of organocatalysts. Loh and co-workers[4] reported a synthetic approach to functionalized pyridines via an amine-catalyzed aza-Rauhut–Currier/cyclization/desulfonation cascade reaction of 2,3-butadienoates with *N*-sulfonyl-1-azadienes (Scheme 1, eq a). Smith and co-workers[5] developed an isothiourea-catalyzed one-pot synthesis of polysubstituted pyridines bearing a readily derivatived 2-sulfonate functionality by the reaction of (phenylthio)acetic acid with *N*-sulfonyl-1-azadienes (Scheme 1, eq b). Chi and co-workers[6] reported DMAP-catalyzed facile synthesis of similar 2-sulfonate functionalized trisubstituted pyridines from α-chloro acetic ester



Scheme 1. Previous organocatalytic synthesis of pyridines from 1-azadienes.

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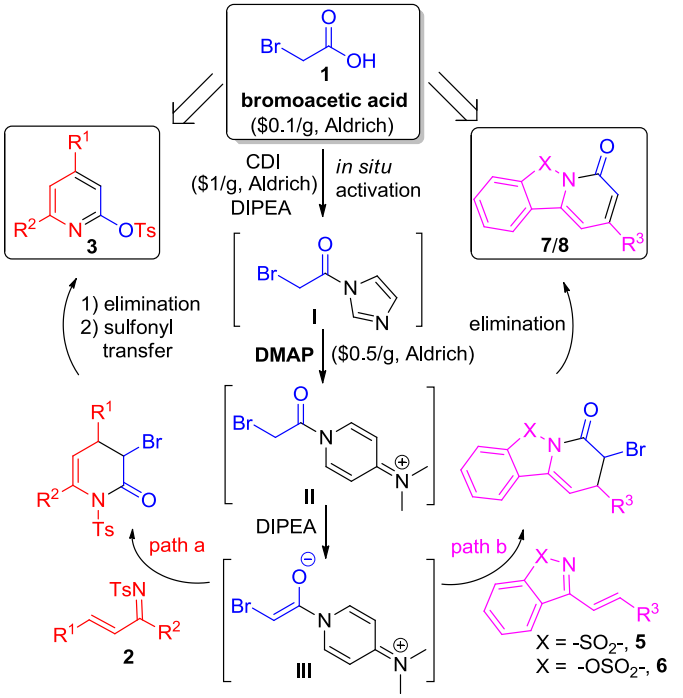
and *N*-sulfonyl-1-azadienes (Scheme 1, eq c). For these methods, *N*-sulfonyl-1-azadienes are used as the nitrogen source[3b,3f,7] to combine with diverse 2-carbon synthon precursors for the construction of the pyridine motif under different organocatalytic conditions. However, there are still some limitations for these methods, such as expensive or not commercially available substrates or catalysts.

In order to develop simple and practical synthetic protocols from readily accessible starting materials and catalysts for rapid access to pyridines, we reason that bromoacetic acid, a low-cost commercially available reagent ($0.1/g, Aldrich), may be used as the potential 2-carbon synthon precursor to combine with *N*-sulfonyl-1-azadienes via an organocatalyst-promoted in situ activation strategy. Herein, we reported 4-dimethylaminopyridine (DMAP)-promoted in situ activation of bromoacetic acid **1** for facile synthesis of 2,4,6-trisubstituted pyridines **3** from 1-azadienes **2**, which can be easily prepared through the condensation of α,β-unsaturated enones with 4-methylbenzenesulfonamide[8] (Scheme 2, path a). In addition, this protocol proved to be equally applicable for the synthesis of fused pyridin-2-ones **7**/**8** from cyclic 1-azadienes **5**/**6**[9] (Scheme 2, path b). For these reactions, imidazole-bound acyl intermediate **I** derived from in situ activation of bromoacetic acid by CDI/DIPEA is unreactive. So, the more reactive DMAP-bound acyl intermediate **II** is formed by nucleophilic substitution of **I** with DMAP to facilitate the reaction. The subsequent deprotonation of **II** with DIPEA affords the key DMAP-bound enolate **III**, which undergoes formal [4+2] cycloaddition with acyclic 1-azadienes **2** or cyclic azadienes **5**/**6** to afford the corresponding (fused) 2-bromo pyridin-2-one intermediates. For acyclic 1-azadiene substrates, the 2-bromo pyridin-2-one intermediates undergo a tandem HBr elimination/*N*- to *O*- sulfonyl transfer process to afford 2,4,6-trisubstituted pyridines **3**. For cyclic 1-azadiene substrates, the fused 2-bromo pyridin-2-one intermediates only undergo HBr elimination to give fused pyridin-2-ones **7**/**8**.

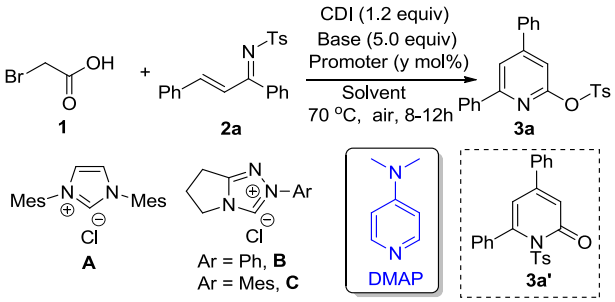


Scheme 2. Our pyridine and fused pyridine-2-one synthesis starting from bromoacetic acid.

2. Results and discussion

Our recent research focuses on the development of novel synthetic methodologies for quick construction of diverse heterocyclic frameworks with *N*-heterocyclic carbene (NHC) catalysis.[10] Since NHCs[11] have been successfully applied to generate NHC-bound enolates via in situ activation of carboxylic acids,[12] several NHC precursors were first employed to examine the reaction of bromoacetic acid **1** with 1-azadiene **2a** in the presence of CDI ($1/g, Aldrich), a low-cost commonly used peptide coupling reagent. As result, precursor triazolium salt **C** was found effective for the synthesis of pyridine **3a** in 37% yield (Table 1, entry 2). As DMAP is

Table 1
Optimization of the reaction conditions[a]



Entry	Promoter (y mol %)	Base	Solvent	Yield (%)[b]
1[c]	**A**/**B** (15)	NEt_3	1,2-DCE	Trace
2[c]	**C** (15)	NEt_3	1,2-DCE	37
3	DMAP (120)	NEt_3	1,2-DCE	64
4	DMAP (120)	Cs_2CO_3	1,2-DCE	28
5	DMAP (120)	NaH	1,2-DCE	43
6	***DMAP (120)***	***DIPEA***	***1,2-DCE***	***82***
7	DMAP (120)	DBU	1,2-DCE	78
8	DMAP (120)	DIPEA	toluene	49
9	DMAP (120)	DIPEA	CH_3CN	24
10	DMAP (120)	DIPEA	1,4-dioxane	14
11	DMAP (120)	DIPEA	DME	18
12	DMAP (80)	DIPEA	1,2-DCE	62
13	DMAP (40)	DIPEA	1,2-DCE	41

Bold entry aims to highlight that this is the optimal reaction condition.

[a] All reactions were performed in a 25 mL round-bottom flask on a 0.3 mmol scale with 1.2 equiv of **1**, 1.0 equiv of **2a**, 1.2 equiv of CDI, 5.0 equiv of a base, in an anhydrous solvent (3 mL) at 70 °C for 8–12 h in air.

[b] Isolated yields based on **2a**.

[c] The reactions were carried out under N_2. CDI=*N*,*N*′-Carbonyldiimidazole; DBU=1,8-diazabicyclo[5.4.0]-undec-7-ene; Mes=2,4,6-$(CH_3)_3C_6H_2$; DIPEA=*N*,*N*-diisopropylethylamine.

frequently used for facilitating the peptide coupling reactions, we then used stoichiometric amount of DMAP to promote this reaction. It was found that product **3a** was obtained in 64% yield when the reaction was heated at 70 °C in the presence of 1.2 equiv of DMAP (entry 3). Notably, unlike the NHC-catalyzed reaction usually carried out under inert gas shielding, this reaction is not air-sensitive which makes it more simple and practical. Then, an array of bases and solvents were used to further optimize the reaction conditions using DMAP as the promoter. DIPEA and 1,2-DCE were finally established as the optimal base and solvent, respectively (entry 6). Unfortunately, lowering DMAP loading resulted in significantly decreased yield (entries 12 and 13). Considering the low cost of DMAP ($0.5/g, Aldrich), the optimal reaction conditions were established as that in entry 6 affording **3a** in 82% yield. Notably, *N*-Ts pyridin-2-one intermediate **3a**′ was observed under lower temperature (40 °C), and it was converted to products **3a** under higher temperature with prolonged reaction time.

With the optimized conditions established, the substrate scope and generality of the reaction were probed (Scheme 3). Generally,

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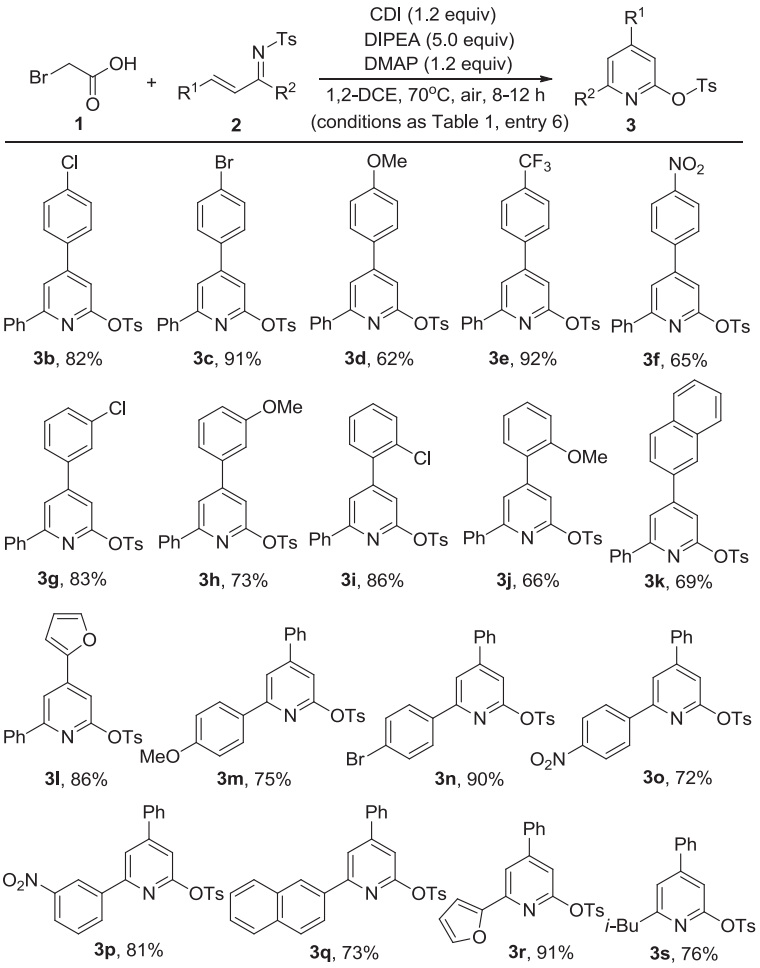
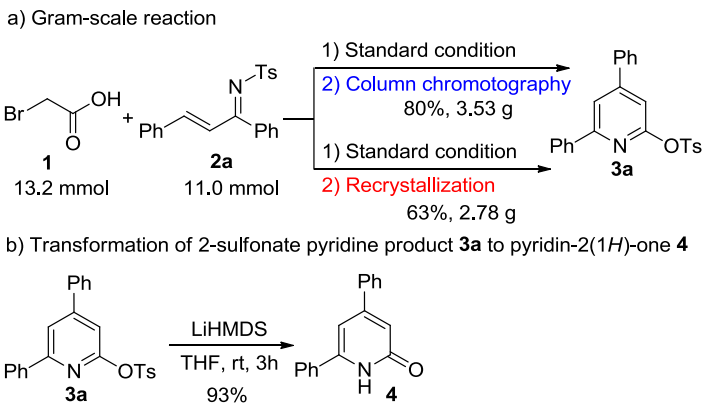


Scheme 3. The substrate scope of the reaction between bromoacetic acid and 1-azadienes.

substituted 1-azadienes worked well under the optimized reaction conditions. When R^1 groups of 1-azadienes were substituted phenyls, a wide range of functional groups at diverse positions on the benzene ring like halos (**3b**–**c**, **3g** and **3i**), methoxy (**3d**, **3h** and **3j**), trifluoromethyl (**3e**) and nitro (**3f**) groups were well tolerated, affording the corresponding products **3b**–**j** in good to high yields. More steric hindered 2-naphthyl 1-azadiene and 2-furyl substituted 1-azadiene also furnished the desired product **3k** and **3l** in good yields. On the other hand, 1-azadienes whose R^2 groups are substituted phenyls, 2-naphthyl or 2-furyl reacted smoothly to give the pyridine products **3m**–**r** in good to high yields. It is noteworthy that aliphatic 1-azadiene was also suitable for this protocol; product **3s** was obtained in 76% yield.

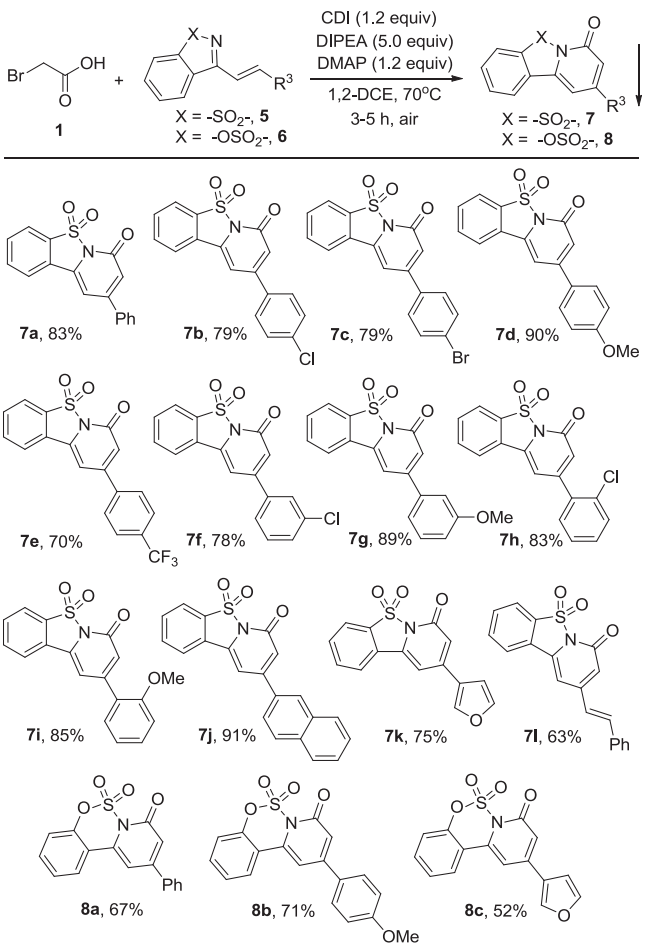
Given the low costs of reagents and materials used as well as the tolerance of air, this protocol is expected to be practical for larger scales. Therefore, a gram-scale preparation of **3a** was demonstrated under the standard conditions with two different purification methods (Scheme 4a). Column chromatography purification



Scheme 4. Synthetic applications.

afforded **3a** in comparable yield to the small scale, while purification by recrystallization afforded **3a** in 63% yield. Although the latter method resulted in decreased isolated yield, it is more superior to the former one in terms of application in organic process research and development. The utility of products **3** has been well illustrated by the chemical transformations of the tosylate unit, which is widely applied in cross-coupling reactions for diverse C–C or C–N bond formations.[2b,5–6,13] Another useful application is demonstrated in the synthesis of 4,6-diphenylpyridin-2(1*H*)-one **4** from **3a** in high yield by treatment with LiHMDS (Scheme 4b).[14]

We next turn our attention to investigate the reaction of cyclic 1-azadienes **5** or **6** containing a 1,2-benzoisothiazole-1,1-dioxide or 1,2,3-benzoxathiazine-2,2-dioxide motif with bromoacetic acid in the presence of DMAP (Scheme 5). Gratifyingly, the conditions used in above pyridine synthesis were also applicable to this reaction. The desired fused pyridin-2-ones **7a-l** and **8a-c** were obtained in moderate to high yields. This reaction could tolerate a broad array of R^3 groups including substituted phenyls, 2-naphthyl, styryl and heteroaromatic groups. Notably, there are several other advantages for this reaction. The reaction of cyclic 1-azadienes is faster than the reaction of acyclic 1-azadienes. On the other hand, products **7** and **8** can precipitate from the solution owing to their low solubility in the solvent. The precipitate was filtered and subsequently washed with DCM to get the pure products. So, the separation and purification of products **7** and **8** are simpler and practical, and thus matches the GAP (Group-Assisted Purification) chemistry/technology concept which avoids traditional chromatography to substantially minimize the use of silica gels and solvents.[15]



Scheme 5. The reaction between bromoacetic acid and cyclic 1-azadienes.

3. Conclusion

In conclusion, we have described a DMAP-promoted facile synthesis of 2,4,6-trisubstituted pyridines and fused pyridine-2-ones from bromoacetic acid via a in situ activation strategy. The advantages of this protocol include: a) easily accessible and low costs of the reagents and materials; b) mild reaction conditions; c) wide reaction scope; d) simple separation and purification of the products; e) practical and scalable synthesis. In addition, the synthesized 2-sulfonate pyridines are amenable to diverse chemical transformations to access other pyridine derivatives. In this protocol, bromoacetic acid has been effectively employed as a 2C synthon to undergo formal [2+4] cycloadditions with both acyclic and cyclic 1-azadienes. Further investigation of bromoacetic acid as a 2C synthon for other formal [2+m] cycloadditions is currently underway in our laboratory.

4. Experimental

4.1. General information

All reactions were carried out in dry glassware, and were monitored by analytical thin-layer chromatography (TLC), which was visualized by ultraviolet light (254 nm). All solvents were obtained from commercial sources and were purified according to standard procedures. Bromoacetic acid is obtained from commercial source without further purification prior to use. Substrates **2**[8] and **5**/**6**[9] can be prepared according to known procedures. Purification of the products **3** was accomplished by flash chromatography using silica gel (200–300 mesh). Purification of the products **7** and **8** was accomplished by filtration followed by azeotrope from DCM. All NMR spectra were recorded on Bruker spectrometers, running at 300 MHz or 500 MHz for ^{1}H and 75 MHz or 125 MHz for ^{13}C, respectively. Chemical shifts (δ) and coupling constants (J) are reported in ppm and Hz, respectively. The solvent signals were used as references (residual $CHCl_3$ in $CDCl_3$: δ_H=7.26 ppm, δ_c=77.0 ppm; residual DMSO in DMSO-d_6: δ_H=2.50 ppm, δ_c=39.5 ppm). The following abbreviations are used to indicate the multiplicity in NMR spectra: s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet). High resolution mass spectrometry (HRMS) was recorded on TOF perimer for ESI$^+$.

4.2. General procedure for the synthesis of pyridines 3 via DMAP-promoted reaction of bromoacetic acid 1 with 1-azadienes 2

To an oven-dried 25 mL round-bottom flask was charged with bromoacetic acid **1** (50 mg, 0.36 mmol), 1-azadienes **2** (0.3 mmol), CDI (58 mg, 0.36 mmol) and DIPEA (194 mg, 1.5 mmol). Then anhydrous 1,2-DCE (3 mL) was added to the flask and the resulting mixture was heated at 70 °C in air for a period time until the completion of the reaction as monitored by TLC. The mixture was cooled to room temperature. 20 mL of 1,2-DCE was added to the solution which was washed with saturated aqueous $NaHCO_3$ (15 mL×2). The organic phase was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by chromatography on silica gel to using hexane/EtOAc (10:1) as the eluent afford products **3**.

*4.2.1. 4,6-Diphenylpyridin-2-yl 4-methylbenzenesulfonate (**3a**).* Known compound,[2b,6] white solid, mp: 121–123 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.98 (d, J=8.2 Hz, 2H), 7.83 (s, 1H), 7.79–7.72 (m, 2H), 7.65 (d, J=6.0 Hz, 2H), 7.52–7.49 (m, 3H), 7.44–7.33 (m, 5H), 7.25 (s, 1H), 2.48 (s, 3H).

*4.2.2. 4-(4-Chlorophenyl)-6-phenylpyridin-2-yl 4-methylbenzenesulfonate (**3b**).* White solid, mp: 141–143 °C. ^{1}H

NMR (300 MHz, $CDCl_3$): δ 7.97 (d, *J*=8.3 Hz, 2H), 7.78 (d, *J*=0.8 Hz, 1H), 7.74 (dd, *J*=6.6, 2.9 Hz, 2H), 7.59 (d, *J*=8.5 Hz, 2H), 7.48 (d, *J*=8.5 Hz, 2H), 7.44–7.34 (m, 5H), 7.21 (d, *J*=0.8 Hz, 1H), 2.48 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.69, 156.70, 152.37, 145.04, 137.27, 135.84, 135.68, 134.38, 129.64, 129.54, 129.36, 128.73, 128.56, 128.33, 126.90, 116.58, 111.30, 21.59. HRMS (ESI) calcd for $C_{24}H_{19}ClNO_3S$ $(M+H)^+$: 436.0769, found 436.0763.

*4.2.3. 4-(4-Bromophenyl)-6-phenylpyridin-2-yl 4-methylbenzenesulfonate (**3c**).* Known compound,[6] white solid, mp: 157–159 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.97 (d, *J*=8.1 Hz, 2H), 7.78 (s, 1H), 7.77–7.70 (m, 2H), 7.63 (d, *J*=8.4 Hz, 2H), 7.51 (d, *J*=8.4 Hz, 2H), 7.45–7.33 (m, 5H), 7.20 (s, 1H), 2.48 (s, 3H).

*4.2.4. 4-(4-Methoxyphenyl)-6-phenylpyridin-2-yl 4-methylbenzenesulfonate (**3d**).* Known compound,[6] white solid, mp: 153–155 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.98 (d, *J*=8.2 Hz, 2H), 7.80 (s, 1H), 7.74 (dd, *J*=6.4, 2.9 Hz, 2H), 7.62 (d, *J*=8.7 Hz, 2H), 7.40 (dd, *J*=6.0, 2.6 Hz, 4H), 7.36 (s, 1H), 7.21 (s, 1H), 7.02 (d, *J*=8.7 Hz, 2H), 3.88 (s, 3H), 2.48 (s, 3H).

*4.2.5. 6-Phenyl-4-(4-(trifluoromethyl)phenyl)pyridin-2-yl 4-methylbenzenesulfonate (**3e**).* White solid, mp: 163–165 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.98 (d, *J*=8.3 Hz, 2H), 7.82 (d, *J*=0.7 Hz, 1H), 7.80–7.73 (m, 6H), 7.46–7.34 (m, 5H), 7.25 (d, *J*=0.7 Hz, 1H), 2.49 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.78, 156.99, 152.27, 145.15, 140.93, 137.23, 134.43, 131.58 (q, J_{C-F}=32.6 Hz, 1C), 129.82, 129.61, 128.81, 128.67, 127.60, 126.99, 126.16, 123.86 (q, J_{C-F}=271.0 Hz, 1C), 116.98, 111.80, 21.65. HRMS (ESI) calcd for $C_{25}H_{19}F_3NO_3S$ $(M+H)^+$: 470.1032, found 470.1037.

*4.2.6. 4-(4-Nitrophenyl)-6-phenylpyridin-2-yl 4-methylbenzenesulfonate (**3f**).* White solid, mp: 172–174 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.26 (d, *J*=8.8 Hz, 2H), 7.99–7.91 (m, 5H), 7.68–7.65 (m, 2H), 7.57–7.52 (m, 3H), 7.40 (d, *J*=8.1 Hz, 2H), 7.34 (s, 1H), 2.50 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.96, 154.50, 153.91, 148.48, 145.35, 143.43, 136.85, 134.45, 130.04, 129.68, 129.39, 128.75, 127.79, 127.14, 123.87, 117.85, 113.18, 21.73. HRMS (ESI) calcd for $C_{24}H_{19}N_2O_5S$ $(M+H)^+$: 447.1009, found 447.1002.

*4.2.7. 4-(3-Chlorophenyl)-6-phenylpyridin-2-yl 4-methylbenzenesulfonate (**3g**).* White solid, mp: 96–98 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.97 (d, *J*=8.3 Hz, 2H), 7.79 (d, *J*=0.9 Hz, 1H), 7.76 (dd, *J*=6.6, 2.9 Hz, 2H), 7.62 (s, 1H), 7.56–7.50 (m, 1H), 7.47–7.35 (m, 7H), 7.20 (d, *J*=0.9 Hz, 1H), 2.49 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.74, 156.89, 152.33, 145.11, 139.24, 137.33, 135.27, 134.43, 130.50, 129.75, 129.61, 128.84, 128.65, 127.29, 127.00, 125.33, 116.86, 111.66, 21.68. HRMS (ESI) calcd for $C_{24}H_{19}ClNO_3S$ $(M+H)^+$: 436.0769, found 436.0769.

*4.2.8. 4-(3-Methoxyphenyl)-6-phenylpyridin-2-yl 4-methylbenzenesulfonate (**3h**).* White solid, mp: 100–102 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82 (d, *J*=8.3 Hz, 2H), 7.65 (s, 1H), 7.63–7.55 (m, 2H), 7.25–7.18 (m, 6H), 7.04 (d, *J*=6.1 Hz, 2H), 6.98 (s, 1H), 6.83 (dd, *J*=8.2, 2.0 Hz, 1H), 3.69 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.03, 157.49, 156.32, 153.43, 144.90, 138.46, 137.26, 134.31, 130.74, 130.10, 129.43, 128.58, 128.41, 126.78, 119.26, 116.75, 114.73, 112.73, 111.36, 55.19, 21.43. HRMS (ESI) calcd for $C_{25}H_{22}NO_4S$ $(M+H)^+$: 432.1264, found 432.1269.

*4.2.9. 4-(2-Chlorophenyl)-6-phenylpyridin-2-yl 4-methylbenzenesulfonate (**3i**).* White solid, mp: 113–115 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.99 (d, *J*=8.3 Hz, 2H), 7.77–7.73 (m, 3H), 7.54–7.49 (m, 1H), 7.46–7.33 (m, 8H), 7.13 (s, 1H), 2.48 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.00, 156.00, 152.03, 145.03, 137.38, 136.96, 134.46, 132.08, 130.76, 130.37, 130.19, 129.58, 128.80, 128.59, 127.26, 126.99, 119.60, 114.16, 21.65. HRMS (ESI) calcd for $C_{24}H_{19}ClNO_3S$ $(M+H)^+$: 436.0769, found 436.0768.

*4.2.10. 4-(2-Methoxyphenyl)-6-phenylpyridin-2-yl 4-methylbenzenesulfonate (**3j**).* White solid, mp: 129–131 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.99 (d, *J*=8.3 Hz, 2H), 7.82 (s, 1H), 7.73 (dd, *J*=6.5, 3.0 Hz, 2H), 7.46–7.36 (m, 7H), 7.28 (d, *J*=0.6 Hz, 1H), 7.10–7.02 (m, 2H), 3.86 (s, 3H), 2.48 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.08, 156.55, 155.64, 151.48, 144.84, 137.86, 134.68, 130.66, 130.35, 129.50, 129.28, 128.82, 128.50, 126.94, 126.82, 121.09, 119.59, 114.23, 111.54, 55.60, 21.64. HRMS (ESI) calcd for $C_{25}H_{22}NO_4S$ $(M+H)^+$: 432.1264, found 432.1264.

*4.2.11. 4-(Naphthalen-2-yl)-6-phenylpyridin-2-yl 4-methylbenzenesulfonate (**3k**).* Known compound,[6] white solid, mp: 106–108 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.23 (s, 1H), 8.03–7.98 (m, 3H), 7.91–7.83 (m, 4H), 7.70 (dd, *J*=7.8, 1.6 Hz, 2H), 7.58–7.49 (m, 5H), 7.40 (d, *J*=8.1 Hz, 2H), 7.29 (d, *J*=0.9 Hz, 1H), 2.51 (s, 3H).

*4.2.12. 4-(Furan-2-yl)-6-phenylpyridin-2-yl 4-methylbenzenesulfonate (**3l**).* Known compound,[2b,6] white solid, mp: 118–120 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.96 (d, *J*=8.3 Hz, 2H), 7.86 (s, 1H), 7.73 (dd, *J*=6.6, 2.9 Hz, 2H), 7.57 (d, *J*=1.1 Hz, 1H), 7.44–7.32 (m, 5H), 7.26 (s, 1H), 6.95 (d, *J*=3.4 Hz, 1H), 6.56 (dd, *J*=3.3, 1.7 Hz, 1H), 2.47 (s, 3H).

*4.2.13. 6-(4-Methoxyphenyl)-4-phenylpyridin-2-yl 4-methylbenzenesulfonate (**3m**).* Known compound,[6] white solid, mp: 119–121 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.97 (d, *J*=8.3 Hz, 2H), 7.70–7.75 (m, 3H), 7.62–7.65 (m, 2H), 7.46–7.53 (m, 3H), 7.37 (d, *J*=8.1 Hz, 2H), 7.17 (d, *J*=1.0 Hz, 1H), 6.91 (d, *J*=8.9 Hz, 2H), 3.86 (s, 3H), 2.47 (s, 3H).

*4.2.14. 6-(4-Bromophenyl)-4-phenylpyridin-2-yl 4-methylbenzenesulfonate (**3n**).* Known compound,[6] white solid, mp: 112–114 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.96 (d, *J*=8.2 Hz, 2H), 7.79 (s, 1H), 7.69–7.58 (m, 4H), 7.57–7.44 (m, 5H), 7.38 (d, *J*=8.1 Hz, 2H), 7.25 (s, 1H), 2.49 (s, 3H).

*4.2.15. 6-(4-Nitrophenyl)-4-phenylpyridin-2-yl 4-methylbenzenesulfonate (**3o**).* White solid, mp: 169–171 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.26 (d, *J*=8.8 Hz, 2H), 7.91–7.99 (m, 5H), 7.65–7.68 (m, 2H), 7.52–7.54 (m, 3H), 7.41 (d, *J*=8.1 Hz, 2H), 7.34 (s, 1H), 2.51 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.92, 154.45, 153.87, 148.44, 145.35, 143.38, 136.78, 134.40, 130.02, 129.67, 129.36, 128.71, 127.76, 127.12, 123.83, 117.82, 113.1, 21.71. HRMS (ESI) calcd for $C_{24}H_{19}N_2O_5S$ $(M+H)^+$: 447.1009, found 447.1014.

*4.2.16. 6-(3-Nitrophenyl)-4-phenylpyridin-2-yl 4-methylbenzenesulfonate (**3p**).* Known compound,[6] white solid, mp: 140–142 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.59 (t, *J*=1.8 Hz, 1H), 8.26 (dd, *J*=8.1, 1.4 Hz, 1H), 8.13 (d, *J*=7.8 Hz, 1H), 7.99 (d, *J*=8.3 Hz, 2H), 7.89 (d, *J*=0.9 Hz, 1H), 7.67 (dd, *J*=7.5, 2.0 Hz, 2H), 7.60 (t, *J*=8.0 Hz, 1H), 7.56–7.51 (m, 3H), 7.43 (d, *J*=8.1 Hz, 2H), 7.34 (d, *J*=0.9 Hz, 1H), 2.49 (s, 3H).

*4.2.17. 6-(Naphthalen-2-yl)-4-phenylpyridin-2-yl 4-methylbenzenesulfonate (**3q**).* Known compound,[6] white solid, mp: 152–154 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.24 (s, 1H), 8.02 (d, *J*=8.3 Hz, 2H), 7.98 (d, *J*=1.0 Hz, 1H), 7.90–7.85 (m, 4H), 7.70 (dd, *J*=7.8, 1.6 Hz, 2H), 7.57–7.49 (m, 5H), 7.40 (d, *J*=8.1 Hz, 2H), 7.29 (d, *J*=0.9 Hz, 1H), 2.51 (s, 3H).

*4.2.18. 6-(Furan-2-yl)-4-phenylpyridin-2-yl 4-methylbenzenesulfonate (**3r**).* Known compound,[6] white solid, mp: 143–145 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00 (s, 1H), 7.97 (s, 1H),

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7.78 (d, *J*=1.1 Hz, 1H), 7.63–7.66 (m, 2H), 7.46–7.52 (m, 4H), 7.39 (s, 1H), 7.36 (s, 1H), 7.15 (d, *J*=1.1 Hz, 1H), 6.77 (d, *J*=3.3 Hz, 1H), 6.50 (dd, *J*=3.3 Hz, *J*=1.7 Hz, 1H), 2.47 (s, 3H).

*4.2.19. 6-Isobutyl-4-phenylpyridin-2-yl 4-methylbenzenesulfonate (**3s**).* Colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89 (d, *J*=8.3 Hz, 2H), 7.58 (dd, *J*=7.7, 1.8 Hz, 2H), 7.51–7.42 (m, 3H), 7.32 (d, *J*=8.1 Hz, 2H), 7.21 (s, 1H), 7.17 (s, 1H), 2.52 (d, *J*=7.2 Hz, 2H), 2.43 (s, 3H), 1.86 (sep, 1H), 0.82 (d, *J*=6.6 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.39, 157.19, 152.78, 144.94, 137.30, 134.03, 129.44, 129.09, 128.76, 127.05, 120.31, 110.51, 46.75, 28.69, 22.27, 21.59. HRMS (ESI) calcd for $C_{22}H_{24}NO_3S$ $(M+H)^+$: 382.1471, found 382.1474.

4.3. Procedure for the scalable synthesis of pyridine 3a from 1 and 2a

To an oven-dried 250 mL round-bottom flask was charged with bromoacetic acid **1** (1.82 g, 13.2 mmol), 1-azadiene **2a** (3.97 g, 11.0 mmol), CDI (2.13 g, 13.2 mmol) and DIPEA (7.10 g, 55 mmol). Then anhydrous 1,2-DCE (80 mL) was added to the flask and the resulting mixture was heated at 70 °C in air for a period time until the completion of the reaction as monitored by TLC. The mixture was cooled to room temperature. Then, the solution was washed with water (50 mL×2) and saturated aqueous $NaHCO_3$ (50 mL×2). The organic phase was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The residue was recrystallized from hexane/EtOAc to afford 2.78 g of product **3a**.

4.4. Procedure for the transformation of 3a to pyridin-2-one 4

To an oven-dried 25 mL round-bottom flask was charged with **3a** (120 mg, 0.3 mmol) and anhydrous THF (3 mL). Then LiHMDS (1 M in THF, 0.9 mL, 0.9 mmol) was added to the flask and the resulting mixture was stirred at rt for 3 h. The reaction was quenched with water (10 mL) and the resulting mixture was extracted with EtOAc (15 mL×3). The organic phase was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by chromatography on silica gel to using hexane/EtOAc (5:1) as the eluent afford 69 mg of compound **4**.

*4.4.1. 4,6-Diphenylpyridin-2(1H)-one (**4**).* Known compound,[2b] brown solid, mp: 209–211 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.83 (br s, 1H), 7.93 (d, *J*=5.9 Hz, 2H), 7.83 (d, *J*=6.3 Hz, 2H), 7.52–7.50 (m, 6H), 7.02 (s, 1H), 6.70 (s, 1H).

4.5. General procedure for the synthesis of fused pyridine-2-ones 7 or 8 via DMAP-promoted reaction of bromoacetic acid 1 with cyclic 1-azadienes 5 or 6

To an oven-dried 25 mL round-bottom flask was charged with bromoacetic acid **1** (50 mg, 0.36 mmol), cyclic 1-azadienes **5** or **6** (0.3 mmol), CDI (58 mg, 0.36 mmol) and DIPEA (194 mg, 1.5 mmol). Then anhydrous 1,2-DCE (3 mL) was added to the flask and the resulting mixture was heated at 70 °C in air for 3–5 h. The mixture was cooled to room temperature and the products will precipitate from the solution due to their low solubility in 1,2-DCE. The precipitate was filtered and washed with DCM to give the pure products.

*4.5.1. 9-Phenyl-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-7-one 5,5-dioxide (**7a**).* White solid, mp: >300 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.49 (d, *J*=7.8 Hz, 1H), 8.28 (d, *J*=7.8 Hz, 1H), 8.00 (t, *J*=7.4 Hz, 1H), 7.95–7.83 (m, 3H), 7.76 (s, 1H), 7.61–7.53 (m, 3H), 6.93 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.35, 153.21, 135.30, 135.43, 135.38, 132.91, 131.79, 130.64, 129.10, 127.23, 125.09, 123.38, 122.20, 118.10, 101.71. HRMS (ESI) calcd for $C_{17}H_{12}NO_3S$ $(M+H)^+$: 310.0532, found 310.0533.

*4.5.2. 9-(4-Chlorophenyl)-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-7-one 5,5-dioxide (**7b**).* White solid, mp: >300 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.47 (d, *J*=7.9 Hz, 1H), 8.28 (d, *J*=7.8 Hz, 1H), 8.06–7.91 (m, 3H), 7.87 (t, *J*=7.6 Hz, 1H), 7.76 (s, 1H), 7.63 (d, *J*=8.5 Hz, 2H), 6.97 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.23, 151.82, 135.56, 135.42, 134.14, 132.94, 131.69, 129.06, 124.99, 123.79, 122.20, 118.33, 101.42. HRMS (ESI) calcd for $C_{17}H_{11}ClNO_3S$ $(M+H)^+$: 344.0143, found 344.0140.

*4.5.3. 9-(4-Bromophenyl)-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-7-one 5,5-dioxide (**7c**).* White solid, mp: >300 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.47 (d, *J*=7.7 Hz, 1H), 8.29 (d, *J*=7.7 Hz, 1H), 8.01 (t, *J*=7.5 Hz, 1H), 7.92–7.84 (m, 3H), 7.80–7.74 (m, 3H), 6.97 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.25, 151.94, 135.61, 135.44, 134.55, 132.97, 132.03, 131.76, 129.30, 125.02, 124.39, 123.83, 122.23, 118.35, 101.38. HRMS (ESI) calcd for $C_{17}H_{11}BrNO_3S$ $(M+H)^+$: 387.9638, found 387.9636.

*4.5.4. 9-(4-Methoxyphenyl)-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-7-one 5,5-dioxide (**7d**).* White solid, mp: >300 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.48 (d, *J*=7.8 Hz, 1H), 8.26 (d, *J*=7.8 Hz, 1H), 7.99 (t, *J*=7.5 Hz, 1H), 7.91 (d, *J*=8.8 Hz, 2H), 7.85 (t, *J*=7.6 Hz, 1H), 7.74 (s, 1H), 7.09 (d, *J*=8.8 Hz, 2H), 6.87 (s, 1H), 3.84 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.44, 158.43, 152.49, 135.33, 135.29, 132.80, 131.83, 128.89, 127.25, 125.17, 123.77, 122.14, 116.15, 114.53, 101.35, 55.45. HRMS (ESI) calcd for $C_{18}H_{14}NO_4S$ $(M+H)^+$: 340.0638, found 340.0638.

*4.5.5. 9-(4-(Trifluoromethyl)phenyl)-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-7-one 5,5-dioxide (**7e**).* White solid, mp: >300 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.48 (d, *J*=7.7 Hz, 1H), 8.30 (d, *J*=7.8 Hz, 1H), 8.12 (d, *J*=8.0 Hz, 2H), 8.02 (t, *J*=7.6 Hz, 1H), 7.94–7.85 (m, 3H), 7.80 (s, 1H), 7.04 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.17, 151.74, 139.50, 135.76, 135.49, 133.04, 131.74, 128.19, 125.90, 125.85, 124.97, 123.86, 122.27, 119.63, 101.60. HRMS (ESI) calcd for $C_{18}H_{11}F_3NO_3S$ $(M+H)^+$: 378.0406, found 378.0401.

*4.5.6. 9-(3-Chlorophenyl)-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-7-one 5,5-dioxide (**7f**).* White solid, mp: >300 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.50 (d, *J*=7.8 Hz, 1H), 8.30 (d, *J*=7.8 Hz, 1H), 8.04–7.99 (m, 2H), 7.91–7.86 (m, 2H), 7.79 (d, *J*=1.4 Hz, 1H), 7.64–7.56 (m, 2H), 7.02 (d, *J*=1.4 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.15, 151.55, 137.42, 135.55, 135.37, 133.95, 132.91, 131.68, 130.82, 130.28, 127.00, 125.88, 124.97, 123.83, 122.16, 118.88, 101.47. HRMS (ESI) calcd for $C_{17}H_{11}ClNO_3S$ $(M+H)^+$: 344.0143, found 344.0138.

*4.5.7. 9-(3-Methoxyphenyl)-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-7-one 5,5-dioxide (**7g**).* White solid, mp: >300 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.51 (d, *J*=7.8 Hz, 1H), 8.29 (d, *J*=7.7 Hz, 1H), 8.01 (t, *J*=7.5 Hz, 1H), 7.87 (t, *J*=7.7 Hz, 1H), 7.76 (s, 1H), 7.49–7.45 (m, 3H), 7.15–7.13 (m, 1H), 6.98 (s, 1H), 3.87 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.73, 158.29, 153.00, 136.75, 135.36, 132.84, 131.73, 130.14, 126.53, 125.04, 123.82, 122.14, 119.45, 118.26, 116.30, 112.59, 101.75, 55.35. HRMS (ESI) calcd for $C_{18}H_{14}NO_4S$ $(M+H)^+$: 340.0638, found 340.0633.

*4.5.8. 9-(2-Chlorophenyl)-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-7-one 5,5-dioxide (**7h**).* White solid, mp: >300 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.39 (d, *J*=7.7 Hz, 1H), 8.32 (d, *J*=7.7 Hz, 1H), 7.98 (t, *J*=7.4 Hz, 1H), 7.88 (t, *J*=7.4 Hz, 1H), 7.68–7.65 (m, 1H), 7.60–7.52 (m, 3H), 7.49 (s, 1H), 6.67 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.80, 152.73, 135.93, 135.49, 134.79, 132.95, 131.60, 131.05, 130.72, 130.39, 129.94, 127.66, 124.73, 123.68, 122.27, 122.24, 104.11.

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HRMS (ESI) calcd for $C_{17}H_{11}ClNO_3S$ $(M+H)^+$: 344.0143, found 344.0140.

*4.5.9. 9-(2-Methoxyphenyl)-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-7-one 5,5-dioxide (**7i**).* White solid, mp: >300 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.39 (d, *J*=7.8 Hz, 1H), 8.29 (d, *J*=7.7 Hz, 1H), 7.97 (t, *J*=7.6 Hz, 1H), 7.86 (t, *J*=7.7 Hz, 1H), 7.53–7.48 (m, 3H), 7.22–7.20 (m, 1H), 7.11 (t, *J*=7.6 Hz, 1H), 6.70 (d, *J*=1.2 Hz, 1H), 3.86 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.11, 156.43, 152.23, 135.37, 134.18, 132.71, 131.62, 131.47, 129.72, 125.30, 125.00, 123.54, 122.15, 121.20, 120.78, 112.04, 104.38, 55.77. HRMS (ESI) calcd for $C_{18}H_{14}NO_4S$ $(M+H)^+$: 340.0638, found 340.0633.

*4.5.10. 9-(Naphthalen-2-yl)-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-7-one 5,5-dioxide (**7j**).* White solid, mp: >300 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.64–8.46 (m, 2H), 8.30 (d, *J*=7.0 Hz, 1H), 8.10–7.97 (m, 5H), 7.95–7.83 (m, 2H), 7.63 (s, 2H), 7.09 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.38, 152.89, 135.50, 135.40, 133.70, 132.91, 132.75, 132.55, 131.82, 128.74, 127.62, 127.38, 126.94, 125.15, 124.15, 123.82, 122.23, 118.28, 101.67. HRMS (ESI) calcd for $C_{21}H_{14}NO_3S$ $(M+H)^+$: 360.0689, found 360.0687.

*4.5.11. 9-(Furan-2-yl)-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-7-one 5,5-dioxide (**7k**).* White solid, mp: >300 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.40 (d, *J*=7.8 Hz, 1H), 8.27 (d, *J*=7.8 Hz, 1H), 8.12–7.95 (m, 2H), 7.86 (t, *J*=7.6 Hz, 1H), 7.70 (s, 1H), 7.51 (d, *J*=3.2 Hz, 1H), 6.80 (s, 1H), 6.72 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.29, 149.06, 146.88, 141.64, 135.85, 135.38, 132.97, 131.78, 124.88, 123.61, 122.16, 114.31, 113.20, 112.29, 98.75. HRMS (ESI) calcd for $C_{15}H_{10}NO_4S$ $(M+H)^+$: 300.0325, found 300.0326.

*4.5.12. (E)-9-Styryl-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-7-one 5,5-dioxide (**7l**).* White solid, mp: >300 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.41 (d, *J*=7.8 Hz, 1H), 8.28 (d, *J*=7.8 Hz, 1H), 8.02 (t, *J*=7.5 Hz, 1H), 7.87 (t, *J*=7.6 Hz, 1H), 7.79 (s, 1H), 7.75–7.67 (m, 3H), 7.38–7.50 (m, 3H), 7.27 (d, *J*=16.5 Hz, 1H), 6.63 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 158.52, 150.44, 136.79, 135.57, 135.28, 134.96, 132.73, 131.80, 129.39, 128.93, 127.40, 125.14, 125.05, 123.39, 122.10, 119.23, 99.21. HRMS (ESI) calcd for $C_{19}H_{14}NO_3S$ $(M+H)^+$: 336.0689, found 336.0684.

*4.5.13. 10-Phenyl-8H-benzo[e]pyrido[1,2-c][1,2,3]oxathiazin-8-one 6,6-dioxide (**8a**).* White solid, mp: >300 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.38 (d, *J*=6.9 Hz, 1H), 8.02–7.91 (m, 2H), 7.73–7.71 (m, 1H), 7.65–7.61 (m, 2H), 7.59–7.51 (m, 4H), 7.00 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 159.79, 152.42, 146.89, 138.57, 135.51, 133.94, 131.16, 129.51, 128.76, 128.16, 127.82, 119.67, 118.91, 116.93, 105.15. HRMS (ESI) calcd for $C_{17}H_{12}NO_4S$ $(M+H)^+$: 326.0482, found 326.0472.

*4.5.14. 10-(4-Methoxyphenyl)-8H-benzo[e]pyrido[1,2-c][1,2,3]oxathiazin-8-one 6,6-dioxide (**8b**).* White solid, mp: >300 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.49 (d, *J*=7.8 Hz, 1H), 8.27 (d, *J*=7.8 Hz, 1H), 7.98–8.03 (m, 1H), 7.84–7.94 (m, 3H), 7.75 (s, 1H), 7.10 (d, *J*=8.8 Hz, 2H), 6.88 (s, 1H), 3.85 (s, 3H)· ^{13}C NMR (125 MHz, DMSO-d_6): δ 161.49, 159.37, 151.28, 146.42, 137.85, 133.36, 129.04, 128.22, 127.64, 126.91, 119.17, 118.49, 114.57, 114.47, 104.33, 55.41. HRMS (ESI) calcd for $C_{18}H_{14}NO_5S$ $(M+H)^+$: 356.0587, found 356.0581.

*4.5.15. 10-(Furan-2-yl)-8H-benzo[e]pyrido[1,2-c][1,2,3]oxathiazin-8-one 6,6-dioxide (**8c**).* White solid, mp: >300 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.33–8.24 (m, 1H), 8.04 (d, *J*=1.2 Hz, 1H), 7.77–7.70 (m, 1H), 7.68 (d, *J*=3.5 Hz, 1H), 7.66–7.58 (m, 2H), 7.51 (d, *J*=1.4 Hz, 1H), 6.81 (dd, *J*=3.5, 1.7 Hz, 1H), 6.76 (d, *J*=1.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.24, 148.65, 147.14, 146.50, 140.51, 138.66, 133.59, 128.29, 127.51, 119.28, 118.31, 114.98, 113.26, 110.64, 101.66. HRMS (ESI) calcd for $C_{15}H_{10}NO_5S$ $(M+H)^+$: 316.0274, found 316.0269.

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Supplementary data

Supplementary data (The copies of ^{1}H NMR, ^{13}NMR charts of all products) associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2016.08.062.

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