Tetrahedron 72 (2016) 4938–4946

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Multicomponent reaction of pyridine, acetoacetamide/benzoylacetamides and sulfuryl chlorides: regioselective construction of 4-olefinated dihydropyridines

Xuna Zhao, Tong-Xin Liu *, Nana Ma, Zhiguo Zhang, Guisheng Zhang *

Collaborative Innovation Center of Henan Province for Green Manufacturing of Fine Chemicals, Key Laboratory of Green Chemical Media and Reactions, Ministry of Education, School of Chemistry and Chemical Engineering, Henan Normal University, Xinxiang, Henan 453007, PR China

ARTICLE INFO

Article history:
Received 21 March 2016
Received in revised form 24 June 2016
Accepted 27 June 2016
Available online 28 June 2016

Keywords:
Multicomponent reaction
N-activated pyridine
Catalyst-free
Olefination reaction
Dihydropyridines

ABSTRACT

A new, operationally simple one-pot method has been developed for the regioselective synthesis of a series of novel 4-olefinated dihydropyridines bearing various functional groups from the reaction of pyridine, acylacetamides, and sulfuryl chlorides under mild conditions. In this multicomponent process, subsequent the activation of pyridine by sulfuryl chloride/nucleophilic addition of acylacetonitrile formed in situ/enolization/sulfonylation leads to the formation of final products.

1. Introduction

Functionalization of nitrogen heterocycles represents a powerful tool for the synthesis of natural products and bioactive substances. Pyridines are an important class of structure motifs widely present in many bioactive compounds and functional materials.[1,2] The development of efficient methods for the functionalization and transformation of commercially available pyridine compounds is therefore highly desirable to provide facile access to numerous *N*-heterocyclic compounds with bioactive and photo-electronic functions. However, the chemistry to functionalize pyridines remains a significant challenge because of the electron-deficient nature of pyridine systems,[3] as well as their poor regioselectivity and strong coordination to transition metal centers. Considerable efforts have been directed towards addressing these challenges, and as a result a series of methods of functionalization of pyridines have been established. The most notable of these methods include traditional nucleophilic and electrophilic addition reactions to *N*-activated pyridines (pyridinium salts),[4] as well as the transition-metal-catalyzed direct transformation of activated and unactivated pyridines.[5] Despite transition-metal-catalyzed functionalization of pyridines has recently triggered widespread interest for synthetic flexibility and overall efficiency, the development of traditional metal-free organic transformation of pyridines is fundamental and important, given the particular purity requirements in the areas of biological and medicinal chemistry.

Reactive *N*-activated pyridinium species, which can be preformed or formed in situ from the corresponding pyridines, are usually indispensable for the success of these traditional metal-free transformations. Most of the reactions reported to date for the functionalization of pyridines through the corresponding *N*-activated pyridinium species involve the use of alkyl halides, acyl chlorides or chloroformates as activating agents to generate the required pyridinium salts.[4a,c,6] In contrast, there have been very few reports pertaining to the preparation of activated pyridinium salts by the N-sulfonylation of pyridines with triflic anhydrides or sulfonyl chlorides,[7] especially for the latter. Katritzky and co-workers investigated the nucleophilic addition of ketones to pyridine using triflic anhydride as activating agents, which provided regioselective access to a series of 4-(2-oxoalkyl) −1,4-dihydropyridines and -pyridines (Scheme 1a).[7c] Furthermore, Corey and Tian reported the regioselective 4-arylation of pyridines by the treatment of pyridines with electron-rich aromatic compounds in the presence of triflic anhydride (Scheme 1b).[7d] More recently, Clayden and Brice prepared various spirocyclic and doubly spirocyclic heterocycles using triflic anhydride to treat the pyridine containing a tethered latent nucleophile (Scheme 1c).[7e,f] Herein, we report a new,

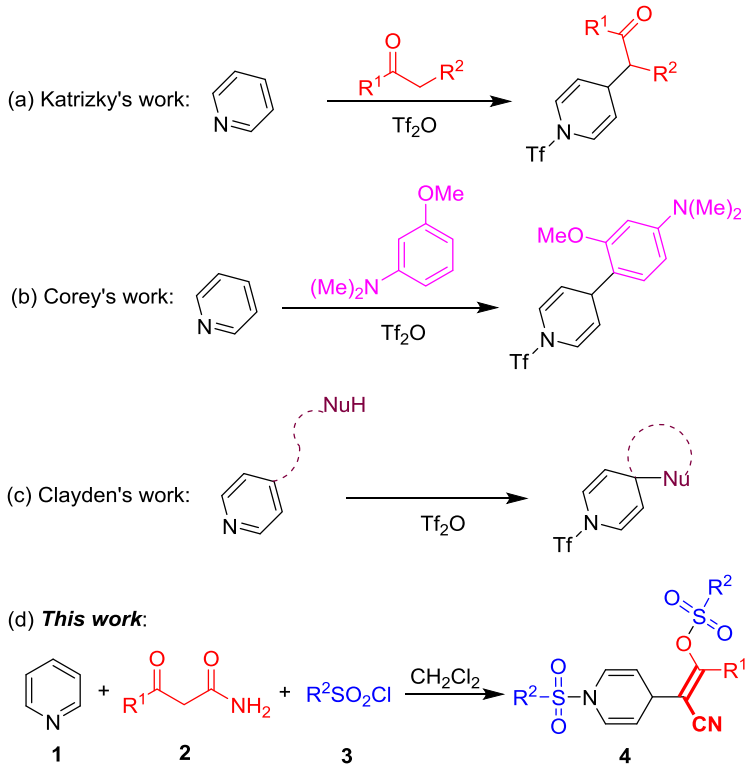
* Corresponding authors. E-mail addresses: liutongxin_0912@126.com (T.-X. Liu), zgs6668@yahoo.com (G. Zhang).

http://dx.doi.org/10.1016/j.tet.2016.06.068
0040-4020/

regioselective one-pot procedure for the synthesis of 4-olefinated dihydropyridine derivatives **4** bearing dihydropyridine, acrylonitrile, and enol ester moieties by the reaction of pyridine with an acetoacetamide/benzoylacetamide and a sulfonyl chloride (Scheme 1d). The dihydropyridine,[8] cyano and acrylonitrile[9] moieties present in these products are powerful functional groups for synthetic reactions. Furthermore, acrylonitrile moiety is the most common scaffold embedded in various dyes, agrochemicals, herbicides, and natural products.[10] These α,β-unsaturated nitriles also form a core motif of biologically important pharmaceuticals,[11] for example, entacapone[12] and rilpivirine,[13] which are used in the treatment of Parkinson's disease and HIV infections, respectively. Thus, this new method might be used in a wide range of synthetic applications to obtain complicated organic compounds, including pharmaceuticals and functional materials.

However, when 4-chlorobenzenesulfonyl chloride **3f** with an electron-withdrawing group was employed instead of tosyl chloride **3a**, the reaction only afforded the expected product **4af** in 12% yield (Table 1, entry 6). We then proceeded to investigate the effect of several different solvents. Pleasingly, the yield of the desired product **4af** was improved to 65% when CH_2Cl_2 was used as the solvent (Table 1, entry 7), while other solvents, such as DMF, DMSO, toluene, THF and CH_3CN were invalid or less effective (Table 1, entries 8–12). Attempting to increase or decrease the quantity of pyridine led to an obvious decrease in the yield of **4af** (Table 1, entries 13 and 14). We also found CH_2Cl_2 was compatible with tosyl chloride **3a**, giving the corresponding product **4aa** in 83% yield (Table 1, entry 15).

With the optimized conditions in hand, a variety of sulfonyl chlorides **3** were first evaluated in the reaction of pyridine and

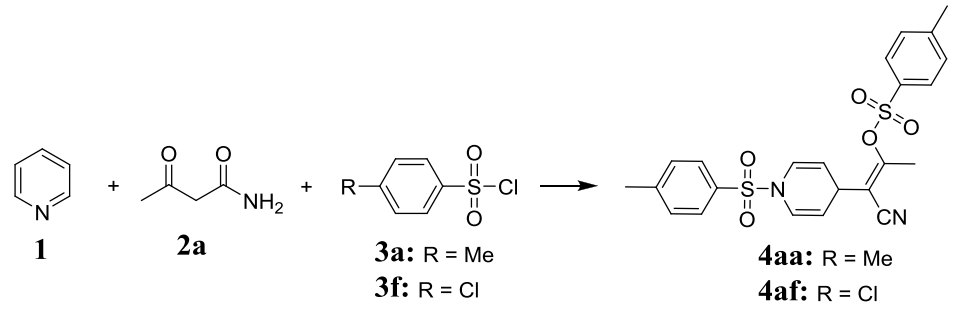


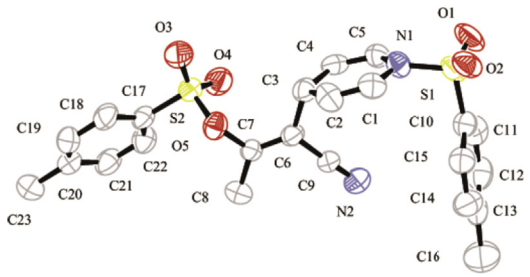
Scheme 1. Organic transformation of pyridine via N-sulfonylation intermediates.

2. Results and discussion

Initially, readily available acetoacetamide **2a** was treated with 2 equiv of tosyl chloride **3a** in pyridine as a solvent at 25 °C for 18 h. Surprisingly, this reaction afforded the highly functionalized dihydropyridine **4aa** as an unexpected product in 34% yield. The structure of **4aa** was unambiguously determined by X-ray analysis,[14] and the NOE spectrum revealed that the reaction occurred in a stereoselective manner to give the *E*-isomer exclusively. This interesting result promoted us to further optimize the reaction conditions, as shown in Table 1. Lowering the reaction temperature to 0 °C led to an increase in the yield to 52% (Table 1, entry 2). When the amount of tosyl chloride **3a** was increased to 3 equiv, the yield was improved drastically to 74% (Table 1, entry 3). Prolonging reaction time to 24 h could further enhance the yield to 81% (Table 1, entry 4). Further increasing the amount of tosyl chloride did not lead to a further improvement in the yield (Table 1, entry 5). acetoacetamide **2a**. As outlined in Table 2, various arylsulfonyl chlorides **3a**–**3h** with different substituents at different positions on the phenyl ring reacted smoothly with pyridine and acetoacetamide **2a** to give the corresponding 4-olefinated dihydropyridines **4aa**–**4ah** in moderate to good yields (35–83%). The position effect of the substituent group on the phenyl ring of arylsulfonyl chloride could be obviously observed, as exemplified for the *para*-, *meta*- and *ortho*-methyl substituted arylsulfonyl chloride **3a**–**3c**. The reaction with arylsulfonyl chlorides **3f**–**3h** bearing electron-withdrawing groups (Cl, CO_2Et and NO_2) gave the lower yield than the substrate with electron-rich groups, indicating that the electronic effect of substituent group had a significant influence on the reaction. β-Naphthalene sulfonylchloride gave a higher yield than the corresponding α-substituted substrate, which might be attributed to the steric hindrance. The use of 2-thiophenesulfonyl chloride and methylsufonyl chloride as activating agents only resulted in the formation of the desired products **4ak** and **4al** in 32%

Table 1
Screening of reaction conditions[a]





X-ray crystal structure of **4aa**

Entry	Molar ratio (1:2a:3)	Solvent	*R*	Time (h)	Yield (%)
1	Excess:1:2	Pyridine	Me	18	34[b]
2	Excess:1:2	Pyridine	Me	18	52
3	Excess:1:3	Pyridine	Me	18	74
4	Excess:1:3	Pyridine	Me	24	81
5	Excess:1:4	Pyridine	Me	24	82
6	Excess:1:3	Pyridine	Cl	24	12
7	10:1:3	CH_2Cl_2	Cl	24	65
8	10:1:3	DMF	Cl	24	0
9	10:1:3	DMSO	Cl	24	0
10	10:1:3	Toluene	Cl	24	32
11	10:1:3	THF	Cl	24	39
12	10:1:3	CH_3CN	Cl	24	35
13	20:1:3	CH_2Cl_2	Cl	24	35
14	5:1:3	CH_2Cl_2	Cl	24	24
15	10:1:3	CH_2Cl_2	Me	24	83

[a] All reactions were carried out at 0 °C unless specified otherwise.
[b] The reaction was performed at 25 °C.

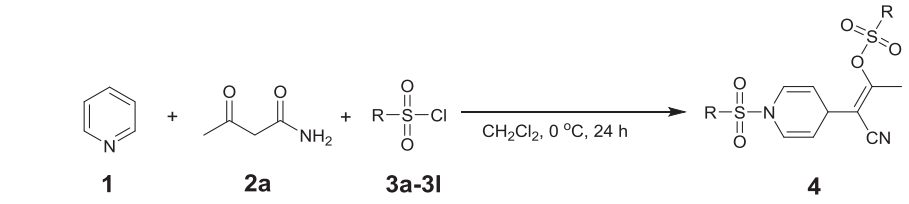
and 16%, respectively, and the exact reason are not clear at the present stage. It was envisaged that the use of triflic anhydride in this reaction would lead to nucleophilic attack predominantly at the 4-position. However, only a small quantity of 3-oxobutyronitrile was observed together with an unidentified black residue.

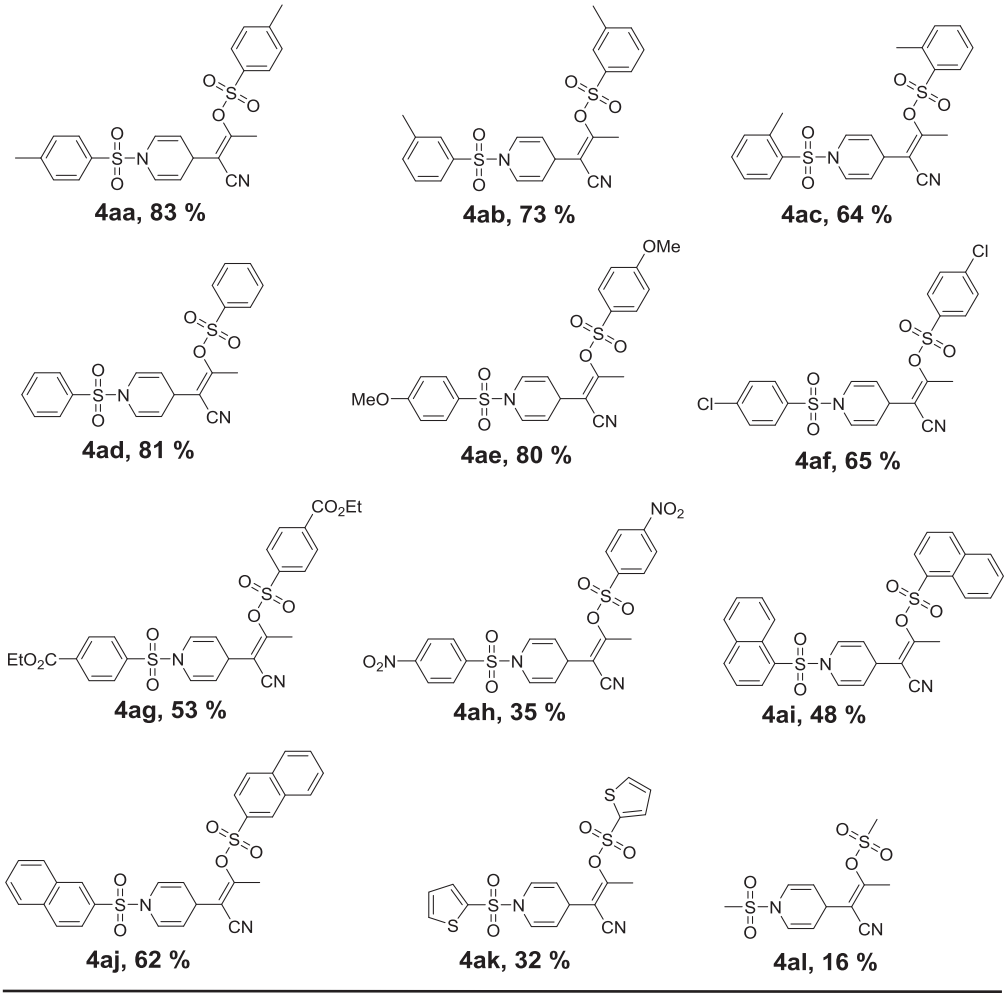
Next, different benzoylacetamides were investigated to expand the scope of this new method, as shown in Table 3. Interestingly, the treatment of pyridine and benzoylacetamide **2b** with tosyl chloride at 0 °C for 24 h, the reaction only afforded the expected product **4ba** in 32% yield, accompanied with the unwanted byproduct **5ba** in 62% yield. Raising reaction temperature to 25 °C, the yield of byproduct **5ba** was enhanced to 90%, with only a trace amount of **4ba** being observed. However, the desired product **4ba** was obtained in satisfactory yield of 79%, when the reaction temperature proceeded at −20 °C. Moreover, the reactions of benzenesulfonyl chloride and 4-nitrobenzenesulfonyl chloride with pyridine and benzoylacetamide gave the desired products **4bd** and **4bh** in 77% and 64% yield, respectively, under the same conditions. Based on these results, we also investigated the reaction of pyridine with 4-MeO-benzoylacetamide **2c** or 4-Cl-benzoylacetamide **2d** in the presence of several different arylsulfonyl chlorides at −20 °C. To our satisfactory, all of these reactions proceeded smoothly to afford the desired products in moderate to good yields (52–75%). In addition, other active methylene compounds, including acetylacetone **2e**, ethyl acetoacetate **2f**, pivaloylacetonitrile **2g** and 3-(1*H*-indol-3-yl)-3-oxopropanenitrile **2h** were also investigated. Only the reaction of pyridine, tosyl chloride and **2g** afforded the corresponding product **4ga** in 47% yield, while substrates **2e**, **2f** and **2h** did not provide any of the desired products **4ea**, **4fa** and **4ha** but resulting instead in the formation of a complex mixture.

To demonstrate the easy use of this method, the scale-up of the reaction of pyridine (16 mL, 200 mmol), acetoacetamide **2a** (2.022 g, 20 mmol), and tosyl chloride **3a** (11.44 g, 60 mmol) has been examined. The reaction afforded corresponding product **4aa** (8.0 g, 85% yield) as a yellow solid under identical conditions, indicating that the efficiency of the present method stays high at large scale.

During the course of our investigation on the reaction of pyridine, acetoacetamide **2a** and *p*-nitrobenzenesulfonyl chloride **3h**, the mixture of (*Z*)- and (*E*)-1-cyanoprop-1-en-2-yl 4-methylbenzenesulfonate **5ah** was obtained in 21% yield, besides the formation of desired product **4ah** (Scheme 2a). However, the compounds **5ah** and **5ba** could not be converted to the corresponding dihydropyridine compounds **4ah** and **4ba** under the standard conditions, indicating that they are not the intermediates

Table 2
Preparation of 4-olefinated dihydropyridines from pyridine, acetoacetamide and different sulfonyl chlorides





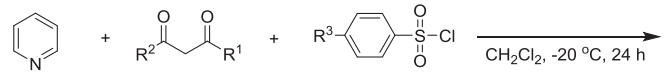
for the formation of 4-olefinated dihydropyridine derivatives (Scheme 2b and c). To pursue the reaction mechanism in more detail, the treatment of pyridine, 3-oxobutanenitrile **2i** and *p*-nitrobenzenesulfonyl chloride **3h** afforded the same product **4ah** in a comparable yield, thus indicating that the 3-oxobutanenitrile intermediate was generated during the transformation (Scheme 2d).

On the basis of the aforementioned experimental results, two possible reaction mechanisms are proposed for sequential formation of 4-olefinated dihydropyridine derivatives **4** (Scheme 3). Under the current reaction conditions, the pyridinium salt **I** and 3-oxobutanenitrile or 3-oxo-3-phenylpropanenitriles **II** were generated in situ via the activation or dehydration of sulfuryl chloride, respectively.[4b,c,6,7,15] The subsequent nuclear addition of intermediate **II** to pyridinium salt **I** occurred in the presence of pyridine as a base, which led to the formation of the key 4-(2-oxopentanenitrile)-1,4-dihydropyridine **III**. Intermediate **III** would then undergo sequential enolization and O-sulfonylation reactions in the presence of pyridine to give the final product **4**. Alternatively, the direct nucleophilic addition of the amide **2** to pyridinium salt **I** generated the corresponding intermediate **IV**, and then the intermediate **IV** undergo further dehydration and O-sulfonylation to afford the product **4**. The dual role of pyridine and the multiple role of sulfuryl chloride are clearly disclosed in this interesting transformation.

3. Conclusion

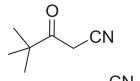
In summary, we have demonstrated a novel and operationally convenient method for the highly regioselective synthesis of 4-olefinated dihydropyridine derivatives bearing valuable reactive units of dihydropyridine, acrylonitrile, and enol ester groups from pyridine, acetoacetamide/benzoylacetamides and sulfuryl chlorides. This methodology might be used in constructing a variety of natural alkaloids, biologically active molecules, and functional materials. Investigations aimed at the further functionalization of

Table 3
Preparation of 4-olefinated dihydropyridines from pyridine, benzoylacetamides and arylsulfonyl chlorides

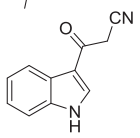


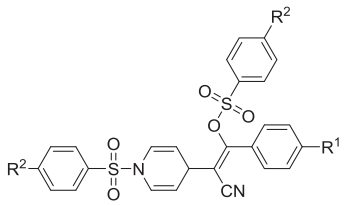
1 **2b-2d**: $R^1 = NH_2$, R^2 = Ar **3a**: R^3 = Me
2e: R^1 = Me, R^2 = Me **3d**: R^3 = H
2f: R^1 = OEt, R^2 = Me **3h**: $R^3 = NO_2$

2g:

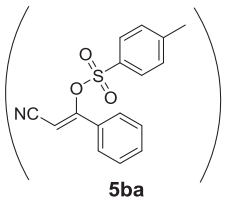


2h:

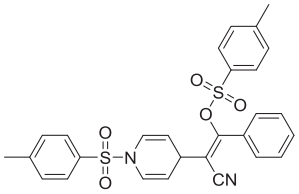




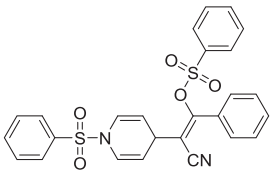
4



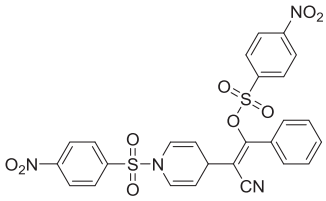
5ba



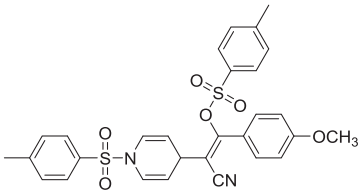
4ba,79 %



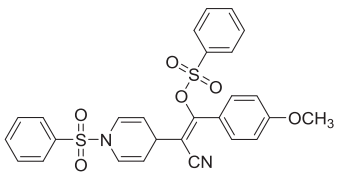
4bd, 77 %



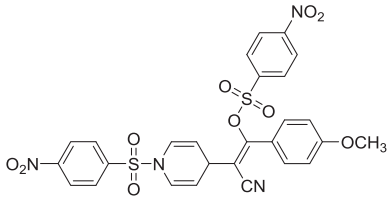
4bh, 64 %



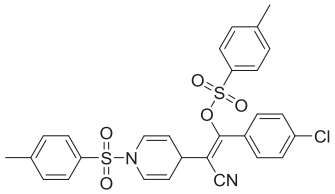
4ca, 75%



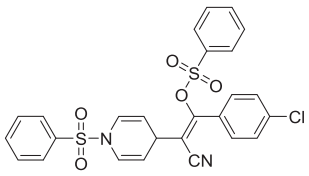
4cd, 72 %



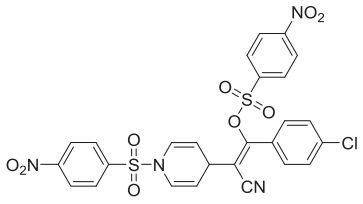
4ch, 67 %



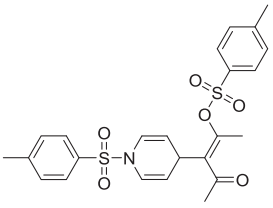
4da, 69 %



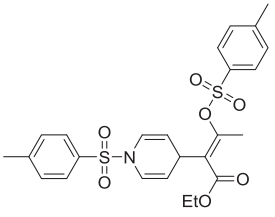
4dd, 63 %



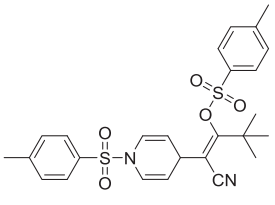
4dh, 52 %



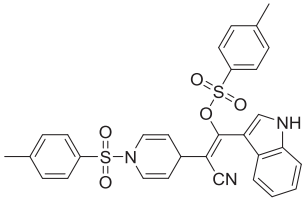
4ea, 0 %



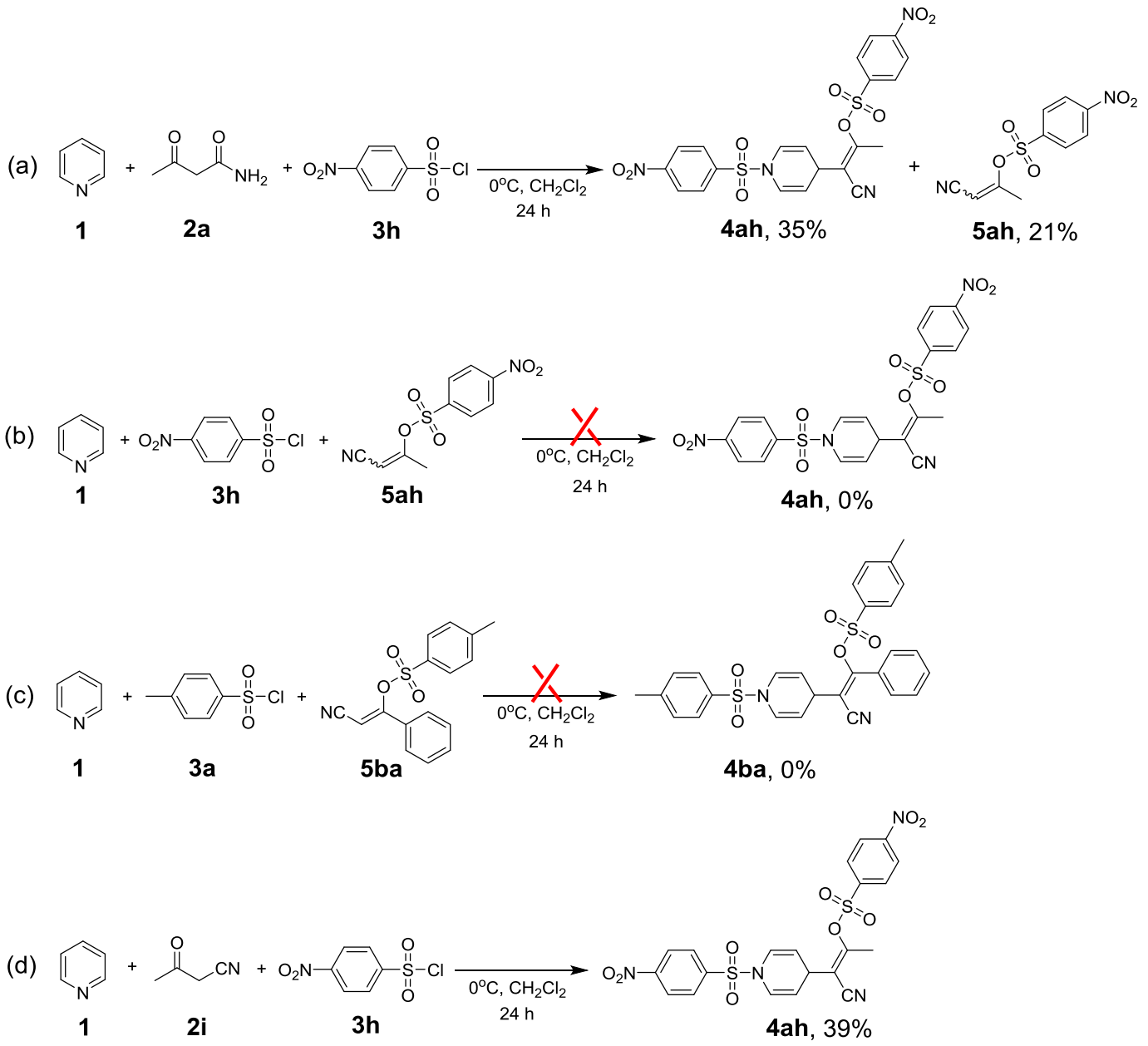
4fa, 0 %



4ga, 47 %



4ha, 0 %



Scheme 2. Probe reaction mechanism.

the dihydropyridine products resulting from this reaction, as well as the broadening of the scope of this transformation, are currently underway in our laboratory.

4. Experimental section

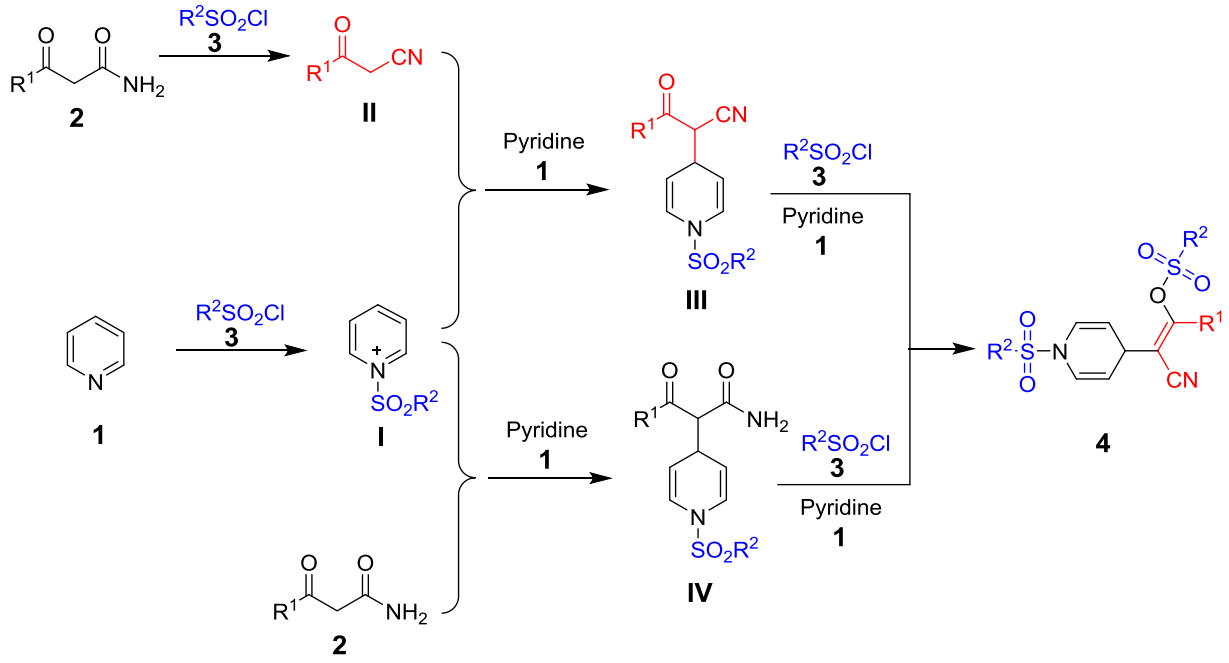
4.1. General

All chemicals, reagents, and solvents were purchased from commercial sources and used without further treatment. ^{1}H NMR and $^{13}C\{^{1}H\}$ NMR spectra were recorded on a 400 or 600 MHz NMR spectrometer. Data are represented as follows: chemical shift, integration, multiplicity (s=singlet, d=doublet, dd=double doublet, t=triplet, q=quartet, m=multiplet), coupling constants in Hertz (Hz). Chemical shifts are reported in δ units, parts per million (ppm) relative to the residual chloroform (^{1}H 7.26 ppm and ^{13}C 77.16 ppm) in the deuterated solvent. All high resolution mass spectra (HRMS) were performed on a mass spectrometer via electrospray ionization (ESI). Melting points were measured on a melting point apparatus equipped with a thermometer and were uncorrected. All reactions were monitored by TLC with GF254 silica gel pre-coated plates. Flash chromatography was carried out on SiO_2 (silica gel 200–300 mesh).

4.2. General Procedures for Preparing compounds 4aa–4al

To a conical flask (25 mL) were added a stir bar, pyridine (6 mmol, 0.5 mL), sulfonyl chlorides (1.8 mmol) and CH_2Cl_2 (1 mL). The flask was cooled to 0 °C and then acetoacetamide (0.6 mmol) was added. The resulting reaction mixture was stirred at 0 °C for 24 h and was directly purified by flash column chromatography on silica gel using petroleum ether and CH_2Cl_2 (v/v=1:3) as the eluent.

Compound **4aa**: 233.8 mg, 83%; yellow solid; mp 83–85 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J=8.0 Hz, 2H), 7.66 (d, J=8.0 Hz,



Scheme 3. Proposed reaction mechanism.

2H), 7.40 (d, *J*=8.0 Hz, 2H), 7.32 (d, *J*=8.0 Hz, 2H), 6.65 (dd, *J*=8.4 Hz, 1.2 Hz, 2H), 4.56–4.50 (m, 2H), 4.08–4.03 (m, 1H), 2.48 (s, 3H), 2.42 (s, 3H), 2.19 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 155.90, 146.69, 144.70, 134.77, 132.70, 130.47, 130.13, 128.13, 127.01, 124.86, 115.89, 111.87, 105.04, 31.84, 21.91, 21.73, 20.19. HRMS (ESI), *m/z* calcd for $C_{23}H_{23}N_2O_5S_2$ $[M+H]^+$ 471.1043, found 471.1050.

Compound **4ab**: 205.5 mg, 73%; yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J*=6.8 Hz, 2H), 7.60–7.46 (m, 4H), 7.41 (d, *J*=4.8 Hz, 2H), 6.67 (d, *J*=8.6 Hz, 0.8 Hz, 2H), 4.56–4.52 (m, 2H), 4.10–4.03 (m, 1H), 2.46 (s, 3H), 2.42 (s, 3H), 2.19 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 155.81, 140.44, 139.94, 137.52, 136.00, 135.57, 134.51, 129.71, 129.33, 128.29, 127.22, 125.23, 124.86, 124.16, 115.76, 111.99, 105.05, 31.86, 21.50, 21.46, 20.23. HRMS (ESI), *m/z* calcd for $C_{23}H_{23}N_2O_5S_2$ $[M+H]^+$ 471.1043, found 471.1055.

Compound **4ac**: 181.3 mg, 64%; yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J*=8.0 Hz, 1H), 7.92–7.87 (m, 1H), 7.60 (m, 1H), 7.50–7.38 (m, 3H), 7.36–7.29 (m, 2H), 6.69 (d, *J*=8.4 Hz, 0.8 Hz, 2H), 4.66–4.59 (m, 2H), 4.21 (t, *J*=3.6 Hz, 1H), 2.70 (s, 3H), 2.64 (s, 3H), 2.14 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 155.84, 138.75, 138.05, 137.06, 135.10, 134.98, 133.61, 133.24, 133.18, 129.70, 129.02, 126.94, 126.60, 125.13, 116.19, 112.26, 103.81, 32.11, 20.80, 20.63, 20.16. HRMS (ESI), *m/z* calcd for $C_{23}H_{23}N_2O_5S_2$ $[M+H]^+$ 471.1043, found 471.1051.

Compound **4ad**: 215.8 mg, 81%; yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J*=8.0 Hz, 2H), 7.82–7.72 (m, 3H), 7.62 (t, *J*=8.0 Hz, 3H), 7.54 (t, *J*=7.6 Hz, 2H), 6.67 (d, *J*=8.0 Hz, 2H), 4.59–4.50 (m, 2H), 4.05 (t, *J*=3.2 Hz, 1H), 2.19 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 155.80, 137.71, 135.76, 135.24, 133.69, 129.92, 129.57, 128.13, 127.03, 124.88, 115.70, 112.04, 105.20, 31.90, 20.25. HRMS (ESI), *m/z* calcd for $C_{21}H_{19}N_2O_5S_2$ $[M+H]^+$ 443.0730, found 443.0727.

Compound **4ae**: 240.7 mg, 80%; yellow solid; mp 44–46 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.85–7.81 (m, 2H), 7.73–7.68 (m, 2H), 7.06–7.02 (m, 2H), 7.00–6.96 (m, 2H), 6.65 (dd, *J*=8.4 Hz, 1.2 Hz, 2H), 4.58–4.52 (m, 2H), 4.08–4.04 (m, 1H), 3.90 (s, 3H), 3.85 (s, 3H), 2.18 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 164.86, 163.69, 155.94, 130.46, 129.20, 126.75, 124.87, 115.96, 115.02, 114.71, 111.74, 105.08, 56.05, 55.78, 31.83, 20.17. HRMS (ESI), *m/z* calcd for $C_{23}H_{23}N_2O_7S_2$ $[M+H]^+$ 503.0941, found 503.0962.

Compound **4af**: 199.1 mg, 65%; yellow solid; mp 110–112 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J*=8.8 Hz, 2H), 7.72 (d, *J*=8.8 Hz, 2H), 7.60 (d, *J*=8.8 Hz, 2H), 7.51 (d, *J*=8.8 Hz, 2H), 6.67 (d, *J*=8.0 Hz, 2H), 4.67–4.59 (m, 2H), 4.08 (t, *J*=3.6 Hz, 1H), 2.20 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 155.66, 142.24, 140.40, 135.99, 134.17, 130.29, 129.93, 129.50, 128.47, 124.80, 115.58, 112.17, 105.63, 31.99, 20.29. HRMS (ESI), *m/z* calcd for $C_{21}H_{17}Cl_2N_2O_5S_2$ $[M+H]^+$ 510.9950, found 510.9962.

Compound **4ag:** 186.1 mg, 53%; yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J*=8.4 Hz, 2H), 8.19 (d, *J*=8.4 Hz, 2H), 7.99 (d, *J*=8.4 Hz, 2H), 7.84 (d, *J*=8.4 Hz, 2H), 6.70 (dd, *J*=8.4 Hz, 0.8 Hz, 2H), 4.69–4.61 (m, 2H), 4.49–4.42 (q, *J*=7.2 Hz, 2H), 4.42–436 (q, *J*=7.2 Hz, 2H), 4.08 (t, *J*=3.6 Hz, 1H), 2.17 (s, 3H), 1.46–1.41 (t, *J*=7.2 Hz, 3H), 1.42–1.36 (t, *J*=7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.09, 164.56, 155.61, 141.15, 139.36, 136.55, 135.12, 130.91, 130.74, 128.12, 127.05, 124.76, 115.49, 112.24, 105.67, 62.33, 61.90, 31.99, 20.26, 14.37. HRMS (ESI), *m/z* calcd for $C_{27}H_{27}N_2O_9S_2$ $[M+H]^+$ 587.1152, found 587.1159.

Compound **4ah**: 111.0 mg, 35%; yellow solid; mp 121–123 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, *J*=8.8 Hz, 2H), 8.38 (d, *J*=8.8 Hz, 2H), 8.15 (d, *J*=8.8 Hz, 2H), 7.96 (d, *J*=8.8 Hz, 2H), 6.72 (d, *J*=7.6 Hz, 2H), 4.82–4.74 (m, 2H), 4.15 (t, *J*=4.0 Hz, 1H), 2.17 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 155.41, 150.76, 142.63, 141.26, 129.53, 128.41, 125.10, 124.95, 124.68, 115.10, 112.50, 106.49, 32.21, 20.36. HRMS (ESI), *m/z* calcd for $C_{21}H_{16}N_4O_9S_2Na$ $[M+Na]^+$ 555.0251, found 555.0264.

Compound **4ai**: 157.3 mg, 48%; yellow solid; mp 135–137 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.59 (t, *J*=10.0 Hz, 2H), 8.27 (d, *J*=7.2 Hz, 1H), 8.21 (d, *J*=8.4 Hz, 1H), 8.13 (d, *J*=7.2 Hz, 1H), 8.07 (d, *J*=8.4 Hz, 1H), 7.99 (d, *J*=8.4 Hz, 1H), 7.93 (d, *J*=8.4 Hz, 1H), 7.76–7.51 (m, 6H), 6.76 (d, *J*=8.4 Hz, 2H), 4.56–4.45 (m, 2H), 4.14 (t, *J*=3.2 Hz, 1H), 2.10 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 156.10, 136.73, 134.97, 134.56, 134.49, 134.34, 131.75, 130.56, 129.52, 129.41, 129.15, 128.76, 128.54, 128.42, 128.26, 127.92, 127.30, 125.04, 124.59, 124.42, 124.39, 124.31, 116.09, 111.78, 104.31, 31.91, 20.01. HRMS (ESI), *m/z* calcd for $C_{29}H_{23}N_2O_5S_2$ $[M+H]^+$ 543.1043, found 543.1042.

Compound **4aj**: 201.1 mg, 62%; yellow solid; mp 127–129 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, *J*=1.6 Hz, 1H), 8.36 (d, *J*=1.6 Hz,

1H), 8.05–7.89 (m, 6H), 7.83 (dd, *J*=8.8, 2.0 Hz, 1H), 7.68 (m, 5H), 6.71 (dd, *J*=8.4, 1.2 Hz, 2H), 4.56–4.48 (m, 2H), 4.09 (t, *J*=3.6 Hz, 1H), 2.18 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 155.88, 135.78, 135.33, 134.73, 132.41, 132.25, 131.93, 130.43, 130.38, 130.31, 130.04, 129.67, 129.56, 129.32, 128.60, 128.56, 128.27, 128.12, 127.82, 124.90, 122.07, 121.86, 115.80, 111.99, 105.14, 31.90, 20.30. HRMS (ESI), *m*/*z* calcd for $C_{29}H_{22}N_2O_5S_2Na$ $[M+Na]^+$ 565.0862, found 565.0860.

Compound **4ak**: 86.5 mg, 32%; yellow solid; mp 88–90 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (dd, *J*=15.2, 4.8 Hz, 2H), 7.62 (dd, *J*=13.4, 5.2 Hz, 2H), 7.21 (t, *J*=4.4 Hz, 1H), 7.13 (t, *J*=4.4 Hz, 1H), 6.69 (d, *J*=8.4 Hz, 2H), 4.68–4.61 (m, 2H), 4.12 (t, *J*=4.0 Hz, 1H), 2.26 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 156.00, 137.52, 135.87, 135.85, 135.07, 133.30, 133.05, 128.27, 127.93, 124.69, 115.56, 112.09, 105.98, 31.97, 20.09. HRMS (ESI), *m*/*z* calcd for $C_{17}H_{15}N_2O_5S_4$ $[M+H]^+$ 454.9858, found 454.9850.

Compound **4al**: 31.3 mg, 16%; yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 6.69 (d, *J*=8.4 Hz, 2H), 4.91–4.83 (m, 2H), 4.29 (t, *J*=4.4 Hz, 1H), 3.25 (s, 3H), 3.04 (s, 3H), 2.40 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 154.95, 125.15, 116.20, 112.47, 105.41, 40.01, 39.49, 32.39, 20.64. HRMS (ESI), *m*/*z* calcd for $C_{11}H_{15}N_2O_5S_2$ $[M+H]^+$ 319.0417, found 319.0416.

4.3. General Procedures for Preparing compounds 4ba–4ga

To a conical flask (25 mL) were added a stir bar, pyridine (3 mmol, 0.25 mL), sulfonyl chlorides (0.9 mmol) and CH_2Cl_2 (1 mL). The flask was cooled to −20 °C (for **4ga**: 0 °C) and then aroylacetamide (0.3 mmol) was added. The resulting reaction mixture was stirred at −20 °C for 24 h and was directly purified by flash column chromatography on silica gel using petroleum ether and CH_2Cl_2 (v/v=1:3) as the eluent.

Compound **4ba**: 126.7 mg, 79%; yellow solid; mp 122–124 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.73–7.67 (m, 2H), 7.46–7.40 (m, 2H), 7.37–7.32 (m, 3H), 7.32–7.28 (m, 2H), 7.21–7.15 (m, 2H), 7.12 (d, *J*=8.0 Hz, 2H), 6.76 (dd, *J*=8.8, 1.2 Hz, 2H), 4.83–4.76 (m, 2H), 4.44 (m, 1H), 2.41 (s, 3H), 2.37 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 155.40, 146.10, 144.66, 134.95, 132.62, 131.15, 130.87, 130.16, 129.87, 128.92, 128.37, 128.35, 127.09, 125.17, 116.35, 111.82, 105.06, 21.79, 21.75. HRMS (ESI), *m*/*z* calcd for $C_{28}H_{25}N_2O_5S_2$ $[M+H]^+$ 533.1199, found 533.1195.

Compound **4bd**: 116.2 mg, 77%; yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J*=8.0 Hz, 2H), 7.65–7.49 (m, 6H), 7.37–7.27 (m, 5H), 7.15 (t, *J*=7.6 Hz, 2H), 6.78 (d, *J*=8.0 Hz, 2H), 4.87–4.78 (m, 2H), 4.46 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 155.31, 137.69, 135.55, 134.68, 133.66, 131.30, 130.51, 129.54, 129.27, 128.81, 128.39, 128.24, 127.03, 125.07, 116.14, 111.80, 105.29, 33.34. HRMS (ESI), *m*/*z* calcd for $C_{26}H_{21}N_2O_5S_2$ $[M+H]^+$ 505.0886, found 505.0886.

Compound **4bh**: 114.8 mg, 64%; yellow solid; mp 133–135 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.35–8.25 (m, 2H), 8.10–7.98 (m, 2H), 7.96–7.87 (m, 2H), 7.68–7.57 (m, 2H), 7.30–7.19 (m, 1H), 7.16 (d, *J*=7.2 Hz, 2H), 7.07 (t, *J*=7.6 Hz, 2H), 6.74 (d, *J*=8.4 Hz, 2H), 5.01–4.89 (m, 2H), 4.46 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 154.76, 150.78, 150.51, 142.49, 140.80, 131.66, 129.66, 129.53, 128.69, 128.48, 128.28, 124.75, 124.66, 124.06, 115.31, 112.11, 106.36, 33.29. HRMS (ESI), *m*/*z* calcd for $C_{26}H_{18}N_4O_9S_2Na$ $[M+Na]^+$ 617.0407, found 617.0403.

Compound **4ca**: 126.1 mg, 75%; yellow solid; mp 113–115 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J*=8.4 Hz, 2H), 7.46 (d, *J*=8.4 Hz, 2H), 7.36–7.28 (m, 4H), 7.15 (d, *J*=8.0 Hz, 2H), 6.74 (dd, *J*=8.4 Hz, 1.2 Hz, 2H), 6.71–6.65 (m, 2H), 4.82–4.73 (m, 2H), 4.38 (m, 1H), 3.77 (s, 3H), 2.41 (s, 3H), 2.38 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.88, 155.40, 146.01, 144.62, 134.88, 132.68, 130.66, 130.13, 129.85, 128.34, 127.04, 124.94, 122.97, 116.79, 113.74, 109.85, 105.29, 55.51, 33.21, 21.77, 21.73. HRMS (ESI), *m*/*z* calcd for $C_{29}H_{26}N_2O_6S_2Na$ $[M+Na]^+$ 585.1124, found 585.1123.

Compound **4cd**: 115.7 mg, 72%; yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J*=8.0 Hz, 2H), 7.65–7.50 (m, 6H), 7.37 (t, *J*=7.6 Hz, 2H), 7.29 (d, *J*=8.4 Hz, 2H), 6.76 (d, *J*=8.4 Hz, 2H), 6.65 (d, *J*=8.8 Hz, 2H), 4.84–4.75 (m, 2H), 4.38 (t, *J*=3.2 Hz, 1H), 3.76 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.90, 155.33, 137.77, 135.77, 134.62, 133.64, 130.63, 129.54, 129.30, 128.30, 127.05, 124.93, 122.77, 116.61, 113.82, 109.97, 105.50, 55.53, 33.26. HRMS (ESI), *m*/*z* calcd for $C_{27}H_{23}N_2O_6S_2$ $[M+H]^+$ 535.0992, found 535.0992.

Compound **4ch**: 125.2 mg, 67%; yellow solid; mp 126–128 °C. 1H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J*=8.8 Hz, 2H), 8.13 (d, *J*=8.8 Hz, 2H), 7.99 (d, *J*=8.8 Hz, 2H), 7.71 (d, *J*=8.8 Hz, 2H), 7.17 (d, *J*=8.8 Hz, 2H), 6.80 (d, *J*=8.0 Hz, 2H), 6.62 (d, *J*=8.8 Hz, 2H), 5.03–4.93 (m, 2H), 4.48 (t, *J*=4.0 Hz, 1H), 3.73 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.36, 154.95, 150.97, 150.69, 142.72, 141.21, 130.66, 129.75, 128.45, 124.93, 124.72, 124.20, 121.86, 115.93, 114.00, 110.51, 106.73, 55.63, 33.43. . HRMS (ESI), *m*/*z* calcd for $C_{27}H_{20}N_4O_{10}S_2Na$ $[M+Na]^+$ 647.0513, found 647.0511.

Compound **4da**: 117.7 mg, 69%; yellow solid; mp 109–111 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J*=8.4 Hz, 2H), 7.45 (d, *J*=8.4 Hz, 2H), 7.35–7.25 (m, 4H), 7.21–7.11 (m, 4H), 6.76 (d, *J*=7.6 Hz, 2H), 4.82–4.70 (m, 2H), 4.41 (t, *J*=3.6 Hz, 1H), 2.41 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 154.06, 146.54, 144.72, 137.49, 134.82, 132.41, 130.20, 130.16, 129.99, 129.32, 128.70, 128.34, 127.07, 125.26, 116.11, 112.18, 104.80, 33.37, 21.81, 21.75. HRMS (ESI), *m*/*z* calcd for $C_{28}H_{24}ClN_2O_5S_2$ $[M+H]^+$ 567.0810, found 567.0809.

Compound **4dd**: 102.0 mg, 63%; yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J*=7.2 Hz, 2H), 7.64–7.51 (m, 6H), 7.39 (t, *J*=8.0 Hz, 2H), 7.28 (d, *J*=8.4 Hz, 2H), 7.14 (d, *J*=8.4 Hz, 2H), 6.78 (d, *J*=8.0 Hz, 2H), 4.83–4.75 (m, 2H), 4.42 (t, *J*=3.6 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 153.99, 137.71, 137.60, 135.52, 134.90, 133.71, 130.15, 129.57, 129.45, 129.17, 128.76, 128.28, 127.05, 125.24, 115.92, 112.27, 104.99, 33.42. HRMS (ESI), *m*/*z* calcd for $C_{26}H_{20}ClN_2O_5S_2$ $[M+H]^+$ 539.0497, found 539.0497.

Compound **4dh**: 98.7 mg, 52%; yellow solid; mp 130–132 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J*=8.8 Hz, 2H), 8.21 (d, *J*=8.8 Hz, 2H), 7.98 (d, *J*=8.8 Hz, 2H), 7.75 (d, *J*=8.8 Hz, 2H), 7.24–7.15 (m, 4H), 6.82 (d, *J*=8.0 Hz, 2H), 5.00–4.91 (m, 2H), 4.49 (t, *J*=4.0 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 153.44, 151.05, 150.63, 142.54, 140.83, 138.34, 129.97, 129.57, 128.96, 128.33, 124.92, 124.82, 124.33, 115.15, 112.62, 106.05, 33.50. HRMS (ESI), *m*/*z* calcd for $C_{26}H_{17}ClN_4O_9S_2Na$ $[M+Na]^+$ 651.0018, found 651.0019.

Compound **4ga**: 144.1 mg, 47%; yellow solid; mp 129–131 °C. ^1H NMR (600 MHz, $CDCl_3$) δ 7.80 (d, *J*=8.4 Hz, 2H), 7.69 (d, *J*=8.0 Hz, 2H), 7.38 (d, *J*=8.0 Hz, 2H), 7.33 (d, *J*=8.0 Hz, 2H), 6.73 (d, *J*=8.4 Hz, 2H), 4.78 (dd, *J*=8.4, 3.6 Hz, 2H), 4.26 (s, 1H), 2.47 (s, 3H), 2.42 (s, 3H), 1.26 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.25, 146.23, 144.60, 135.01, 133.36, 130.26, 130.13, 127.87, 127.12, 124.96, 115.94, 111.53, 105.25, 38.43, 35.03, 29.11, 26.26, 21.92, 21.78. HRMS (ESI), *m*/*z* calcd for $C_{26}H_{28}N_2O_5S_2$ $[M+Na]^+$ 535.1332, found 535.1332.

Compound **5ah$_1$** (*Z*-isomer): 19.2 mg, 12%; white solid; mp 84–86 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, *J*=8.8 Hz, 2H), 8.26 (d, *J*=8.8 Hz, 2H), 5.11 (s, 1H), 2.35 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 163.91, 151.62, 140.71, 130.12, 124.92, 112.88, 91.11, 21.57. HRMS (ESI), *m*/*z* calcd for $C_{10}H_9N_2O_5S$ $[M+H]^+$ 269.0227, found 269.0235.

Compound **5ah$_2$** (*E*-isomer): 14.7 mg, 9%; yellow solid; mp 72–74 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, *J*=8.8 Hz, 2H), 8.17 (d, *J*=8.8 Hz, 2H), 5.33 (s, 1H), 2.24 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.47, 151.60, 140.71, 129.81, 125.01, 114.32, 91.34, 20.12. HRMS (ESI), *m*/*z* calcd for $C_{10}H_9N_2O_5S$ $[M+H]^+$ 269.0227, found 269.0231.

Compound **5ba**:[16] 161.2 mg, 90%; white solid; mp 109–111 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.92–7.86 (m, 2H), 7.52–7.47 (m, 2H), 7.50 (s, 1H), 7.44–7.34 (m, 4H), 5.58 (s, 1H), 2.47 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.81, 146.55, 132.41, 132.28, 131.82, 130.20, 129.04, 128.91, 126.96, 114.07, 89.45, 21.95. HRMS

(ESI), *m*/*z* calcd for $C_{16}H_{13}NO_3SNa$ $[M+Na]^+$ 322.0508, found 322.0519.

Acknowledgements

We acknowledge the National Natural Science Foundation of China (NSFC) (No. 21272057, 21372065, 21302044 and U1304524), China Postdoctoral Science Foundation funded project (2015T80769 and 2013M530339) and Innovation Scientists and Technicians Troop Construction Projects of Henan Province (134200510016) for financial support.

Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2016.06.068.

References and notes

1. (a) Henry, G. D. *Tetrahedron* **2004**, *60*, 6043; (b) Michael, J. P. *Nat. Prod. Rep.* **2005**, *22*, 627; (c) Bagley, M. C.; Glover, C.; Merritt, E. A. *Synlett* **2007**, 2459; (d) Hill, M. D. *Chem.—Eur. J.* **2010**, *16*, 12052; (e) Hardin Narayan, A. R.; Sarpong, R. *Org. Biomol. Chem.* **2012**, *10*, 70; (f) Kiuru, P.; Yli-Kauhaluoma, J. In *Pyridine and its Derivatives in Heterocycles in Natural Product Synthesis*; Majumdar, K. C., Chattopadhyay, S. K., Eds.; Wiley-VCH, Weinheim: 2011; pp 267–297; Chap. 8.
2. (a) Yokoyama, A.; Nishiyama, I.; Yoshizawa, A. *Ferroelectrics* **1993**, *148*, 139; (b) Tsutsumi, H.; Okada, K.; Oishi, T. *Electrochim. Acta* **1996**, *41*, 2657; (c) Bangcuyo, C. G.; Rampey-Vaughn, M. E.; Quan, L. T.; Angel, S. M.; Smith, M. D.; Bunz, U. H. F. *Macromolecules* **2002**, *35*, 1563; (d) Vetrichelvan, M.; Valiyaveettil, S. *Chem.—Eur. J.* **2005**, *11*, 5889; (e) Sun, S.; Cheng, C.; Yang, J.; Taheri, A.; Jiang, D.; Zhang, B.; Gu, Y. *Org. Lett.* **2014**, *16*, 4520.
3. Katritzky, A. R.; Taylor, R. *Adv. Heterocycl. Chem.* **1990**, *47*, 1.
4. (a) Bull, J. A.; Mousseau, J. J.; Pelletier, G.; Charette, A. B. *Chem. Rev.* **2012**, *112*, 2642; (b) Chen, Q.; du Jourdin, X. M.; Knochel, P. *J. Am. Chem. Soc.* **2013**, *135*, 4958; (c) Mancheño, O. G.; Asmus, S.; Zurro, M.; Fischer, T. *Angew. Chem., Int. Ed.* **2015**, *54*, 8823.
5. For selected examples, see: (a) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 5332; (b) Godula, K.; Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 3648; (c) Kawashima, T.; Takao, T.; Suzuki, H. *J. Am. Chem. Soc.* **2007**, *129*, 11006; (d) Fischer, D. F.; Sarpong, R. *J. Am. Chem. Soc.* **2010**, *132*, 5926; (e) Nakao, Y.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2008**, *130*, 2448; (f) Tsai, C.-C.; Shih, W.-C.; Fang, C.-H.; Li, C.-Y.; Ong, T.-G.; Yap, G. P. A. *J. Am. Chem. Soc.* **2010**, *132*, 11887; (g) Nakao, Y.; Yamada, Y.; Kashihara, N.; Hiyama, T. *J. Am. Chem. Soc.* **2010**, *132*, 13666; (h) Ye, M.; Gao, G.-L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 6964; (i) Johnson, D. G.; Lynam, J. M.; Mistry, N. S.; Slattery, J. M.; Thatcher, R. J.; Whitwood, A. C. *J. Am. Chem. Soc.* **2013**, *135*, 2222; (j) Oshima, K.; Ohmura, T.; Suginome, M. *J. Am. Chem. Soc.* **2012**, *134*, 3699; (k) Gutsulyak, D. V.; van der Est, A.; Nikonov, G. I. *Angew. Chem., Int. Ed.* **2011**, *50*, 1384; (l) Osakada, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 3845; (m) Chau, S. T.; Lutz, J. P.; Wu, K.; Doyle, A. G. *Angew. Chem., Int. Ed.* **2013**, *52*, 9153.
6. (a) Comins, D. L.; Abdullah, A. H. *J. Org. Chem.* **1982**, *47*, 4315; (b) Akiba, K.; Iseki, Y.; Wada, M. *Tetrahedron Lett.* **1982**, *23*, 429; (c) Comins, D. L. *Tetrahedron Lett.* **1983**, *24*, 2807; (d) Shing, T.-L.; Chia, W.-L.; Shiao, M.-J.; Chau, T.-Y. *Synthesis* **1991**, 849; (e) Chia, W.-L.; Shiao, M.-J. *Tetrahedron Lett.* **1991**, *32*, 2033; (f) Mangeney, P.; Gosmini, R.; Raussou, S.; Commercon, M. *Tetrahedron Lett.* **1993**, *34*, 6399; (g) Krapcho, A. P.; Waterhouse, D. J.; Hammach, A.; Di Domenico, R.; Menta, E.; Oliva, A.; Spinelli, S. *Synth. Commun.* **1997**, *27*, 781; (h) Comins, D. L.; King, L. S.; Smith, E. D.; Février, F. C. *Org. Lett.* **2005**, *7*, 5059; (i) Loska, R.; Makosza, M. *J. Org. Chem.* **2007**, *72*, 1354.
7. (a) Toscano, R. A.; Hernadez-Galindo, M.; del, C.; Rosas, R.; Garcia-Mellado, O.; Portilla, F.; del, R.; Amabile-Cuevas, C.; Alvarez-Toledano, C. *Chem. Pharm. Bull.* **1997**, *45*, 957; (b) Toscano, R. A.; Rosas, R.; Hernadez-Galindo, M.; del, C.; Alvarez-Toledano, C.; Garcia-Mellado, O. *Transit. Met. Chem.* **1998**, *23*, 113; (c) Katritzky, A. R.; Zhang, S.; Kurz, T.; Wang, M. *Org. Lett.* **2001**, *3*, 2807; (d) Corey, E. J.; Tian, Y. *Org. Lett.* **2005**, *7*, 5535; (e) Arnott, G.; Brice, H.; Jonathan Clayden, J.; Blaney, E. *Org. Lett.* **2008**, *10*, 3089; (f) Brice, H.; Clayden, J. *Chem. Commun.* **2009**, 1964; (g) Rudler, H.; Parlier, A.; Sandoval-Chavez, C.; Herson, P.; Daran, J.-C. *Angew. Chem., Int. Ed.* **2008**, *47*, 6843; (h) Garduno-Alva, A.; Xu, Y.; Gualo-Soberanes, N.; Lopez-Cortes, J.; Rudler, H.; Parlier, A.; Ortega-Alfaro, M. C.; Alvarez-Toledano, C.; Toscano, R. A. *Eur. J. Org. Chem.* **2008**, 3714.
8. (a) Stout, D. M.; Meyers, A. I. *Chem. Rev.* **1982**, *82*, 223; (b) Sliwa, W. *Heterocycles* **1986**, *24*, 181; (c) Lavilla, R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1141; (d) Edraki, N.; Mehdipour, A. R.; Khoshneviszadeh, M.; Miri, R. *Drug Discov. Today* **2009**, *14*, 1058; (e) Wender, P. A.; Schaus, J. M.; White, A. W. *J. Am. Chem. Soc.* **1980**, *102*, 6157; (f) Marazano, C.; Goff, M. T. L.; Fourrey, J.-L.; Das, B. C. *J. Chem. Soc., Chem. Commun.* **1981**, 389; (g) Raucher, S.; Bray, B. L. *J. Org. Chem.* **1985**, *50*, 3236; (h) Sundberg, R. J.; Cherney, R. J. *J. Org. Chem.* **1990**, *55*, 6028; (i) Polniaszek, R. P.; Dillard, L. W. *J. Org. Chem.* **1992**, *57*, 4103; (j) Comins, D. L.; Brooks, C. A.; Al-awar, R. S.; Goehring, R. R. *Org. Lett.* **1999**, *1*, 229; (k) Zhao, G.; Deo, U. C.; Ganem, B. *Org. Lett.* **2001**, *3*, 201; (l) Satoh, N.; Akiba, T.; Yokoshima, S.; Fukuyama, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 5734; (m) Barbe, G.; Charette, A. B. *J. Am. Chem. Soc.* **2008**, *130*, 13873.
9. (a) Fatiadi, A. J. In *Preparation and Synthetic Applications of Cyano Compounds*; Patai, S., Rappaport, Z., Eds.; Wiley: New York, 1983; (b) Larock, R. C. *Comprehensive Organic Transformations*; VCH: New York, 1989; (c) Kleemann, A.; Engel, J.; Kutscher, B.; Reichert, D. *Pharmaceutical Substance: Synthesis, Patents, Applications*, 4th ed.; Georg Thieme: Stuttgart, 2001; (d) Miller, J. S.; Manson, J. L. *Acc. Chem. Res.* **2001**, *34*, 563; (e) Smith, M. B.; March, J. *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 6th ed.; Wiley: Hoboken, NJ, 2007; (f) Fleming, F. F.; Wang, Q. *Chem. Rev.* **2003**, *103*, 2035; (g) Magnus, P.; Scott, D. A.; Fielding, M. R. *Tetrahedron Lett.* **2001**, *42*, 4127; (h) Murdoch, D.; Keam, S. J. *Drugs* **2005**, *65*, 2379; (i) Njar, V. C. O.; Brodie, A. M. H. *Drugs* **1999**, *58*, 233.
10. (a) Haribal, M.; Yang, Z.; Attygalle, A. B.; Renwick, J. A. A.; Meinwald, J. *J. Nat. Prod.* **2001**, *64*, 440; (b) Van Boven, M.; Blaton, N.; Cokelaere, M.; Daenens, P. *J. Agric. Food Chem.* **1993**, *41*, 1605; (c) Kato, Y.; Fusetani, N.; Matsunaga, S.; Hashimoto, K.; Fujita, S.; Furuya, T. *J. Am. Chem. Soc.* **1986**, *108*, 2780; (d) Dalisay, D. S.; Molinski, T. F. *Org. Lett.* **2009**, *11*, 1967.
11. Fleming, F. F.; Yao, L.; Ravikumar, P. C.; Funk, L.; Shook, B. C. *J. Med. Chem.* **2010**, *53*, 7902.
12. Seeberger, L. C.; Hauser, R. A. *Expert Rev. Neurother.* **2009**, *9*, 929.
13. De Clercq, E. *Expert Opin. Emerg. Drugs* **2005**, *10*, 241.
14. CCDC 1436828 (**4aa**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
15. (a) Kashelikar, D. V.; Ressler, C. *J. Am. Chem. Soc.* **1964**, *86*, 2467; (b) Bose, D. S.; Goud, P. R. *Tetrahedron Lett.* **1999**, *40*, 747; (c) Stephense, C. R.; Bianco, E. J.; Pilgrim, F. J. *J. Am. Chem. Soc.* **1955**, *77*, 1701.
16. Chen, N.; Lu, Y.; Gadamasetti, K.; Hurt, C. R.; Norman, M. H.; Fotsch, C. *J. Org. Chem.* **2000**, *65*, 2603.