Tetrahedron 69 (2013) 8250–8254

Contents lists available at SciVerse ScienceDirect

Tetrahedron

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

# A novel kind of dimmer (excimer)-induced-AIE compound 2-phenylisothiazolo[5,4-*b*]pyridin-3(2*H*)-one as high selective bisulfite anion probe

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ARTICLE INFO

*Article history:*
Received 11 March 2013
Received in revised form 4 July 2013
Accepted 8 July 2013
Available online 17 July 2013

*Keywords:*
2-Phenylisothiazolo[5,4-*b*]pyridin-3(2*H*)-one
AIE
Bisulfite anion
Probe
X-ray crystallographic analysis

ABSTRACT

An interesting dimmer (excimer)-induced-AIE characteristic of 2-phenylisothiazolo[5,4-*b*]pyridin-3(2*H*)-one was observed. By using a ring-opening reaction, we developed a novel fluorescent probe based on sub-micron particles of 2-phenylisothiazolo[5,4-*b*]pyridin-3(2*H*)-one in water.



## 1. Introduction

Since 2001, a series of aggregation-induced emission (AIE) materials were found, such as Hexaphenylsilole (HPS),[1] 1,1,2,2-Tetraphenylethene (TPE),[2] 1-methyl-pentaphenyl silole (MPPS)[3] and so on. Unlike normal fluorescence materials, these compounds have higher emission intensity in high concentration solution and solid state compared with that in the dilute solution. After formation of aggregation, the fluorescence emission is intensified instead of quenched. These special materials show the new synthetic direction of fluorescence materials. And by using their aggregation-induced emission characteristics, new kinds of biological sensors have been designed, such as BSA probe, DNA probe,[4] and $CO_2$ probe.[5]

Isothiazolidin-3-one is a common bioactive skeleton. It is an inhibitor for cartilage breakdown[6] and HATs (histone acetyltransferase).[7] A lot of research about the bioactivity of isothiazolidin-3-one has been done, but its photometric characteristics remain unexplored. Recently, during the synthesis of benzothiazepine compounds, we unexpectedly found that one of our intermediate products 2-phenylisothiazolo[5,4-*b*]pyridin-3(2*H*)-ones had potential Aggregation-Induce Emission Enhancement (AIEE)[8] characteristic. It was non-emissive in good solvent (THF), but in poor solvent (water/THF) its emission gradually became intensified. Based on this unique characteristic and a ring-opening reaction, we developed a novel fast fluorescent sensor for bisulfite anion.

Bisulfite is usually used as preservative for foods, beverages, and pharmaceutical products. It acts like antioxidant, antimicrobial agent and enzyme inhibitor during production and storage.[9–12] But recent research discovered that certain concentration levels of bisulfite can cause asthmatic attacks, oculonasal symptoms, and allergic reaction in some sulfite-sensitive individuals.[13] So the levels of bisulfite and sulfur dioxide in food and medicine are rigorously limited in many countries. In China, the levels of bisulfite in wine and beer are confined to 0.05 mg $kg^{-1}$ (calculated as $SO_2$).[14] Therefore, it is very important to develop a quick, low cost, sensitive and selective method for bisulfite determination.

To detect sulfite in foods, the Monier-Williams method[15] is still the official method. Although many other analytical techniques are available for the determination of bisulfite, such as spectrofluorometry,[16] electro chemical methods,[17] chromatography,[18] enzymatic techniques,[19] sulfite biosensors,[20] and ion chromatography[21] with indirect UV detection method, most of which either are not selective enough, or need tedious pretreatment and complicated instruments. So it is still a challenge to find an easy and quick determination method. Herein, we reported the design and synthesis

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http://dx.doi.org/10.1016/j.tet.2013.07.038

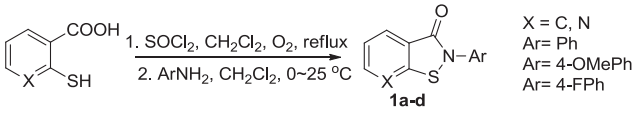
of 2-phenylisothiazolo[5,4-*b*]pyridin-3(2*H*)-one, which can act as a high sensitive and selective sensor for rapid and efficient detection of bisulfite in water.

## 2. Results and discussion

### 2.1. Synthesis of isothiazolidin-3-one derivatives and photophysical studies

The synthesis has been published by Monge,[22] but we changed it into a one-pot reaction. To investigate the compound's AIE characteristic formation mechanism,[23–25] two important electronic effects of the compound **1a** were tested. First, we tested the Intramolecular Charge Transfer (ICT) effect of the compound **1a**.[26] Second, the assembling structure of the molecule in poor solvent (THF/water) was investigated.

Compounds (**1a**–**d**) were synthesized to identify the ICT effect in the molecule (Scheme 1). The fluorescence microscope images (ISO 200) of these compounds are shown in Fig. 1. The configuration of **1a** was determined by X-ray crystallographic analysis (Fig. 2). After electron-donating group was introduced to the molecule, the emission was bathochromic-shifted. When electron-withdrawing group was added, the emission was hypsochromic-shifted. When we changed the ring from pyridine to benzene, the push–pull intramolecular electron effect was ruined, and the luminescence apparently reduced (Fig. 3).




**1a**: X = N, Ar = Ph $\Phi_F$ = 28% **1b**: X = N, Ar = 4-OMePh $\Phi_F \approx 1\%$

**1c**: X = N, Ar = 4-FPh $\Phi_F \approx$ 1% **1d**: X = C, Ar = Ph $\Phi_F$ < 1%

**Scheme 1.** Synthesis and absolute quantum yields determined by a calibrated integrating sphere system of fused isothiazolidin-3-ones **1**.

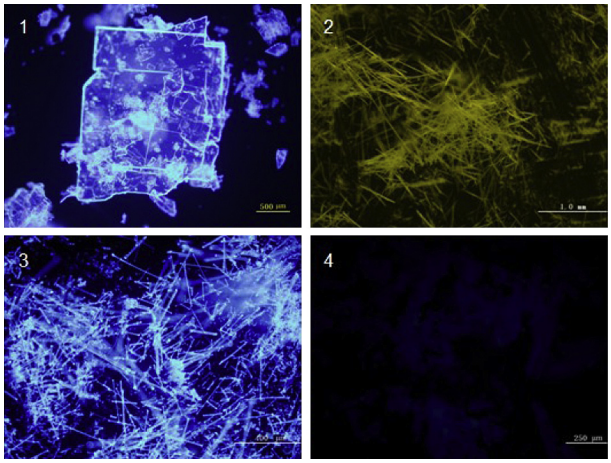



**Fig. 1.** Fluorescence microscope images (ISO 200) of compounds **1a**–**d**.

Meanwhile, after molecule's ring changed from pyridine to benzene, the formation of the dimmer became more difficult. There was another important reason that **1a** showed better fluorescence than **1d**. As we can see in Fig. 4, two molecules formed a dimmer via intermolecular N···S and N···N bonds in the crystal. When the dimmers were excited, they would turn into excimers without arrangement changes, and when the excimers returned to ground state, no repulsive interactions generated either. As a result, no

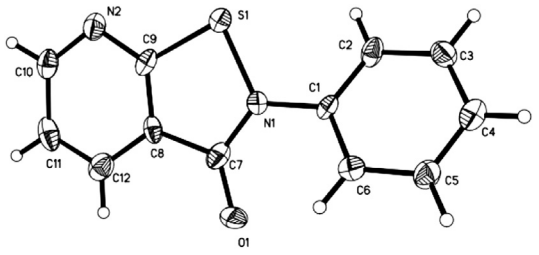



**Fig. 2.** X-ray structure of compound **1a**.

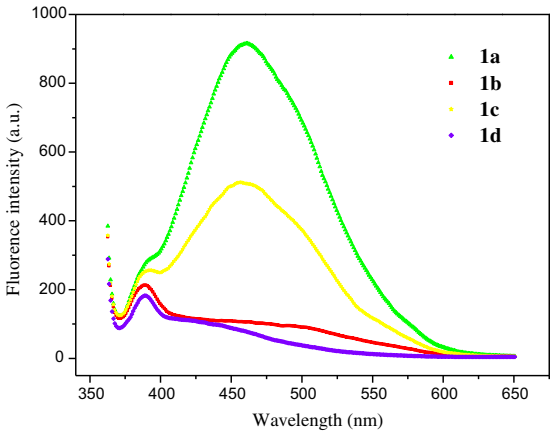



**Fig. 3.** Fluorescence emission spectra of **1a**–**d** (10 μM) in THF/water (1/99, v/v).

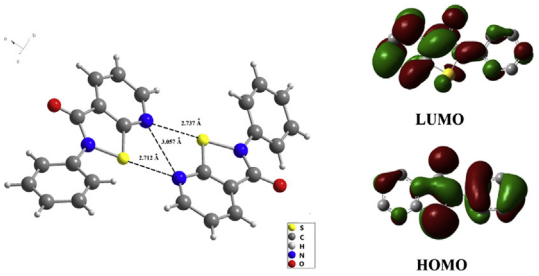



**Fig. 4.** Ball-and-Stick model of **1a** and HOMO/LUMO imagines of **1a** calculated by Gaussian 03 program using the B3LYP method with the 6-31G (d) basis set.

energy was wasted in energy-consuming and non-radiative decay pathways were suppressed, so luminescence became stronger.

The AIE characteristics of compound **1a** were investigated in THF/water (from 100/0 to 1/99, v/v) shown in Figs. 5 and 6. In pure THF, the luminescence was so weak that it was even undetected by the naked eyes. However as the water fraction rose to 99%, the fluorescence emission became very strong. The fluorescence intensity increased by 225 times compared with that in pure THF.

It was because that high percentage of poor solvent in the solution made the molecules aggregate into sub-micron particles. After sub-micron particles were formed, the emission progressively intensified.

The sub-micron particles of compound **1a** in THF/water solution (1/99, v/v) were graphed by polarized light microscope and tested by non-invasive back-scatter (NIBS, Fig. 7). The size of sub-micron particles was measured as about 266.7 nm, and crystal anisotropy was observed significantly, the colour of sub-micron particles changed from red to green. This proved that molecules formed dimmer and then grew into microcrystal after aggregation. It is just the same as what happened in the solid.

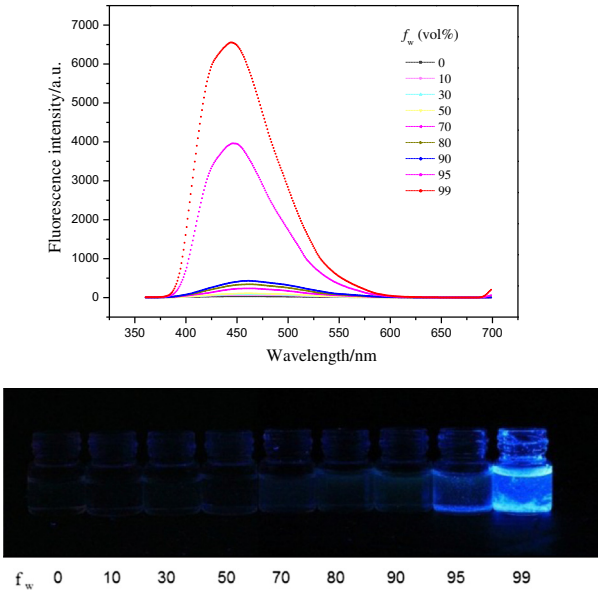



**Fig. 5.** Emission spectra (excitation at 350 nm) and fluorescent images of **1a** in THF/water mixtures with different water fractions ($f_w$).

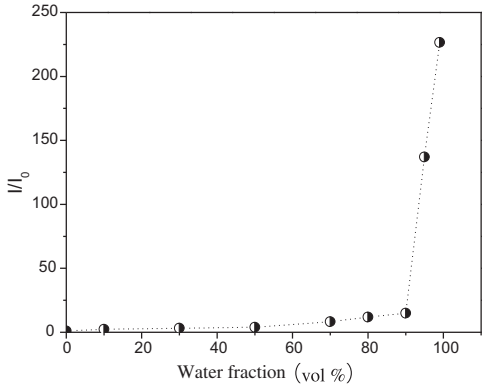



**Fig. 6.** $I/I_0$ of **1a** in THF/water mixtures with different water fractions ($f_w$).

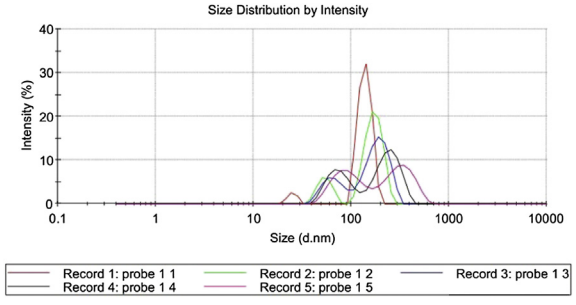



**Fig. 7.** Non-Invasive Back-scatter (NIBS) result of **1a** (10 μM) in THF/water (1/99, v/v) buffered by 20 mM HEPES at pH 7.0.

## 2.2. Mechanism study

After the test of AIE characteristics, we moved on to explore the uses of this type of molecules as $HSO_3^-$ probe based on the ring-opening reaction utilizing **1a** as a representative compound. The reaction was verified by $^1H$ NMR in $CDCl_3$ with tetramethylsilane (TMS) as internal standard. The chemical shift changes of hydrogens marked by squares were shown in Fig. 8.

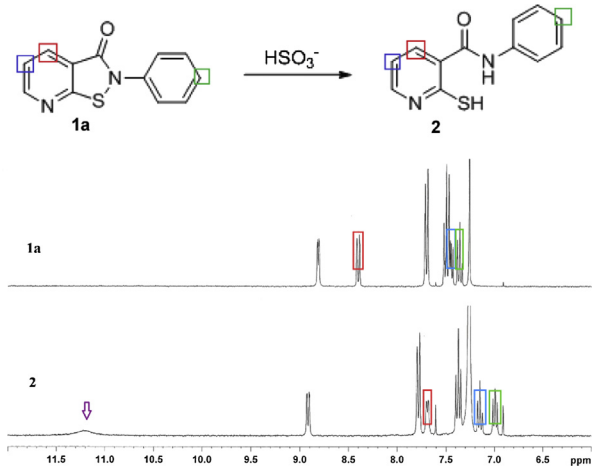



**Fig. 8.** $^1H$ NMR spectral change of probe **1a** and the product of **1a** with bisulfate.

After the conjugated π-system was destroyed, significant chemical shifts of the benzene protons were observed. The pyridine and benzene protons at around δ 8.40, 7.44, 7.36 were dramatically shifted to δ 7.72, 7.15, 7.00 (Fig. 8) and the active hydrogen signal was also observed at δ 11.20. The intermediate was also tested by mass spectrometry. The intermediate has a $[(M+H)^+]$ of 231.0605 *m/z* (Fig. S26) while the probe has a $[(M+H)^+]$ of 229.0425 *m/z* (Fig. S16). According to the experimental data above, the possible reaction mechanism is a ring-opening reaction of **1a** with bisulfite anion.

## 2.3. pH dependence

Firstly, the effect of pH on the probe was tested from 0.17 to 9.08 in THF/water (1/99, v/v). Different pH was obtained by mixing 1 M hydrochloric acid and 0.1 M NaOH solution at specific volume ratios buffered by 20 mM HEPES. As we can see from Fig. 9, the fluorescence was relatively stable when pH was between 7.00 and 9.08, and the emission raised slightly after solution became acidic. When pH was less than 2.27, the emission decreased quickly, and the emission at pH 2.27 was about five times stronger than that of at pH 0.17. At last we chose a relatively stable pH 7.20 for our analytical system.

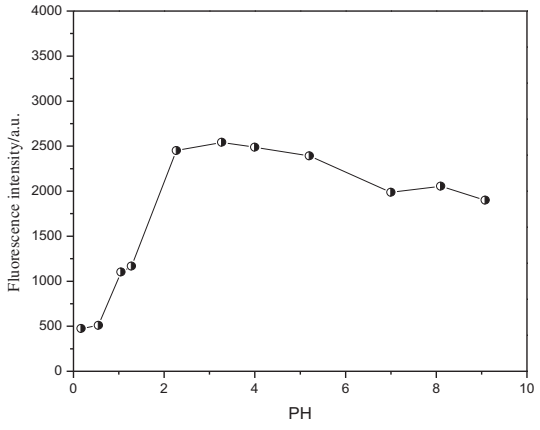



**Fig. 9.** Effect of pH on the fluorescent intensity of the probe.

## 2.4. Selective detection over other anions

Secondly, the selectivity of the analytical system for $HSO_3^-$ was compared to other anions, such as $F^-$, $Cl^-$, $Br^-$, $I^-$, $ClO_3^-$, $ClO_4^-$,

$NO_3^-$, $SO_4^{2-}$, $CO_3^{2-}$, $PO_4^{3-}$, $Ac^-$, $HCO_3^-$, $HSO_4^-$ shown in Fig. 10. We can see that only $HSO_3^-$ can cause the decrease of probe's emission. All the tests were investigated in THF/water (1/99, v/v) solution with $1\times10^{-4}$ M probe and 20 equiv of anions. The analytical system showed highly selectivity for $HSO_3^-$.

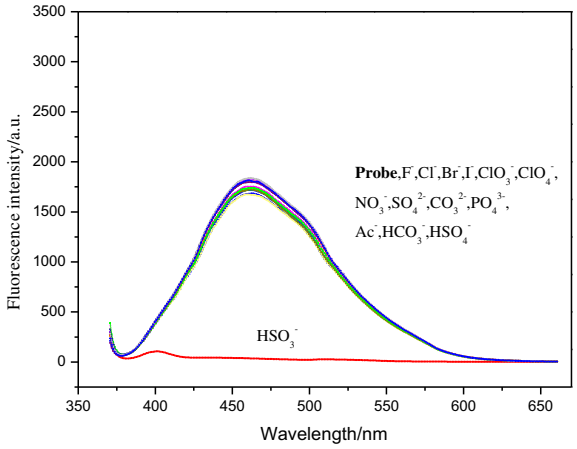



**Fig. 10.** Fluorescence emission spectra (excitation at 350 nm) of 100 μM **1a** in THF/water (v/v, 1/99) mixtures buffered by 20 mM HEPES at pH 7.20 with 20 equiv $HSO_3^-$, $F^-$, $Cl^-$, $Br^-$, $I^-$, $ClO_3^-$, $ClO_4^-$, $NO_3^-$, $SO_4^{2-}$, $CO_3^{2-}$, $PO_4^{3-}$, $Ac^-$, $HCO_3^-$, $HSO_4^-$.

## 2.5. Kinetics characteristic

Thirdly, the fluorescence kinetics characteristic was studied and the results are shown in Fig. 11. After adding the $HSO_3^-$ into the solution, the fluorescence of the solution quenched in 10 s. Compared to the other determination systems for bisulfite anion, the response speed is excellent.

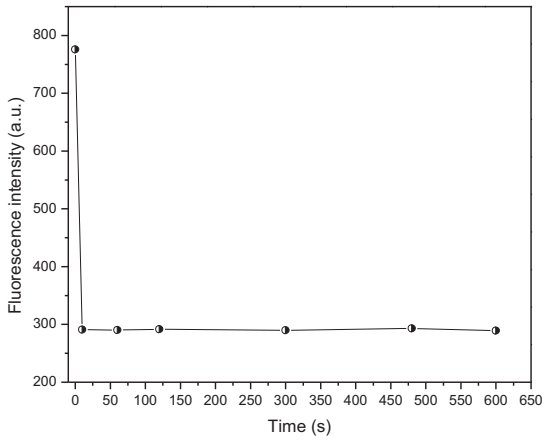



**Fig. 11.** Fluorescence kinetics graph (excitation at 350 nm) of **1a** (10 μM) titrated with $HSO_3^-$ (1 equiv) in THF/water solution (1/999, v/v) buffered by 20 mM HEPES at pH 7.2.

## 2.6. Work curve

Figs 12 and 13 show titration curve and linear correlation for $HSO_3^-$ at the concentration between 0.5 and 6.0 μM, $R$=0.99573 ($n$=12). According to IUPAC, the detection limit was calculated as 0.39 μM and a relative standard deviation of 0.9% was measured for 5.0 μM of bisulfite (Fig. 13).

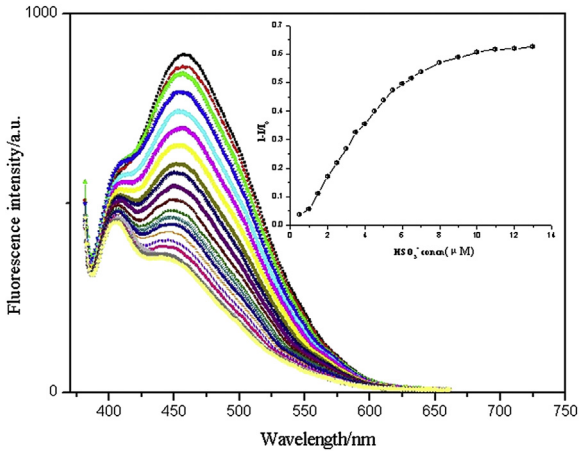



**Fig. 12.** Fluorescence emission (excitation at 350 nm) of **1a** (10 μM) titrated with $HSO_3^-$ (0–1.3 equiv) in THF/water solution (1/999, v/v) buffered by 20 mM HEPES at pH 7.2.

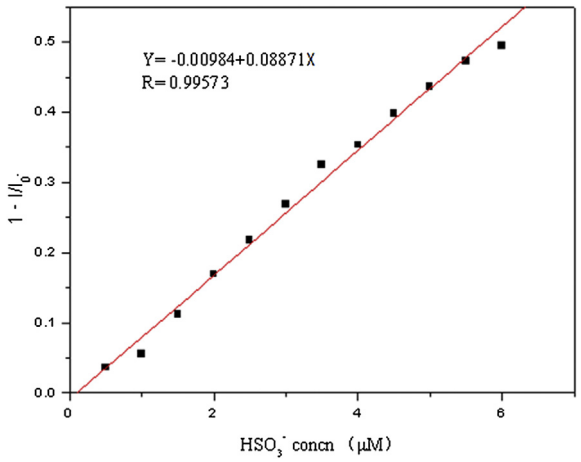



**Fig. 13.** Calibration graph for bisulfite anion. Working conditions: pH 7.20, reaction time 10 s.

## 3. Conclusions

In summary, we have investigated AIE mechanism of 2-phenylisothiazolo[5,4-*b*]pyridin-3(2*H*)-one, and have verified the ICT effect has great influence on the luminescence. Through crystal analysis and theoretical calculation, we finally confirmed the dimmer (excimer)-induced-AIE mechanism. By using this AIE compound, we developed a high sensitive and selective sub-micron particle bisulfite anion probe. Because of the high response speed and simplicity for analysis, we believe this probe may be applied in a variety of real samples in the future.

## 4. Experimental section

### 4.1. General

All chemicals purchased were used without purification. THF of analytical grade and de-ionized water were used throughout the experiment as solvents. $^1$H NMR spectra were recorded on a Bruker Avance 400 (400 MHz) or 300 (300 MHz) spectrometer, using $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal standard. $^{13}$C NMR spectra were recorded on a Bruker Avance 100 (100 MHz) or 75 (75 MHz) spectrometer, using $CDCl_3$ as

solvent and tetramethylsilane (TMS) as internal standard. Melting points were determined on an XD-4 digital micro melting point apparatus. HEPES buffer solutions (pH 7.2) were prepared using 20 mM HEPES and the proper amount of aqueous sodium hydroxide using a pH meter. HRMS spectra were determined on a Q-TOF6510 spectrograph (Agilent). Single crystal X-ray diffraction was made on a Rigaku RAXIS-SPIDER IP diffractometer at 50 kV and 20 mA and data collection was performed at 293 K by using graphite-monochromated Mo-Kα radiation ($\lambda$=0.71073 Å). The nanoparticle diameter was measured by the Zetasizer 2000 (Marven, UK). Fluorescent measurements were collected on a Hitachi F-4500 luminescence spectrophotometer with a 150 W Xe lamp. Calculations were conducted by using the Gaussian 03 program.

### 4.2. General experimental procedure for the preparation of 2-phenylisothiazolo[5,4-*b*]pyridin-3(2*H*)-one (1a)

To a solution of 2-mercaptonicotinic acid (3.1 g, 20 mmol) in $CH_2Cl_2$ (80 mL) thionyl chloride (3 mL) was added, the solution was refluxed for 2.5 h (oil bath). The mixture was evaporated in vacuo, and the solvent and thionyl chloride were removed, yellow solid was obtained. The yellow solid was dissolved by $CH_2Cl_2$ (50 mL), then aniline (1.86 g, 20 mmol) dissolved in 30 mL $CH_2Cl_2$ was added dropwise to the ice bath solution. The mixture was stirred overnight, then $H_2O$ (100 mL) was added and the mixture was filtered and extracted with $CH_2Cl_2$ (3×50 mL). The combined organic layers were washed by chilled water (3×100 mL), dried by $Na_2SO_4$, filtered, and evaporated in vacuo. The crude product was purified by flash chromatography on silica gel (hexane/EtOAc=5:1). Compound **1a** was obtained as white plate crystals (1.96 g, 43%).

*4.2.1. 2-Phenylisothiazolo[5,4-b]pyridin-3(2H)-one (**1a**).* White crystal, mp 137–138 °C, yield 43%. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.81 (dd, 1H, $J$=1.5, 4.8 Hz), 8.40 (d, 1H, $J$=8.1 Hz), 7.70 (d, 2H, $J$=7.5 Hz), 7.50 (t, 2H, $J$=7.8 Hz), 7.44 (t, 1H, $J$=3.9 Hz). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 162.5, 161.9, 154.0, 136.7, 135.3, 129.5, 127.5, 124.9, 121.0. HRMS calcd for $C_{12}H_8N_2OS$ [$(M+H)^+$], 229.0391; found, 229.0425.

*4.2.2. 2-(4-Methoxyphenyl)isothiazolo[5,4-b] pyridine-3(2H)-one (**1b**).* Yellow acicular crystal, yield 40%, mp 169–171 °C. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.80 (d, 1H, $J$=3.3 Hz), 8.34 (dd, 1H, $J$=1.2, 7.8 Hz), 7.58–7.53 (m, 2H), 7.40 (dd, 1H, $J$=4.6, 7.8 Hz), 7.02–6.97 (m, 2H), 3.85 (s, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 162.7, 162.0, 159.0, 153.9, 135.2, 129.0, 121.0, 119.6, 114.7, 55.6. HRMS calcd for $C_{13}H_{10}N_2O_2S$ [$(M+H)^+$], 259.0497; found, 259.0536.

*4.2.3. 2-(4-Fluorophenyl)isothiazolo[5,4-b]pyridin-3(2H)-one (**1c**).* White acicular crystal, mp 188–190 °C, yield 33%. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.83 (dd, 1H, $J$=1.2, 4.8 Hz), 8.36 (dd, 1H, $J$=1.2, 7.8 Hz), 7.68–7.63 (m, 2H), 7.42 (dd, 1H, $J$=4.8, 7.8), 7.21–7.16 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 162.7 (d, $J_{C-F}$=12 Hz), 161.8, 160.3, 154.1, 135.4, 133.0, 132.4 (d, $J_{C-F}$=2.9 Hz), 127.1 (d, $J_{C-F}$=8.5 Hz), 121.1, 119.5, 116.5 (d, $J_{C-F}$=23 Hz). HRMS calcd for $C_{12}H_7FN_2OS$ [$(M+H)^+$], 247.0297; found, 247.0334.

*4.2.4. 2-Phenylbenzo[d]isothiazol-3(2H)-one (**1d**).* White crystal, yield 31%. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.11 (d, 1H, $J$=7.8 Hz), 7.73–7.70 (m, 2H), 7.69–7.65 (m, 1H), 7.59 (d, 1H, $J$=8.0 Hz), 7.52–7.43 (m, 3H), 7.32 (t, 1H, $J$=7.4 Hz). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 164.1, 139.9, 137.3, 132.3, 129.4, 127.2, 127.0, 125.8, 124.9, 124.6, 120.1. HRMS calcd for $C_{13}H_9N_2OS$[$(M+H)^+$], 228.0438; found, 228.0472.


## Acknowledgements

We are grateful to National Natural Science Foundation of China (Nos. 21172131, 21272141, 21072117) for financial support of this research.


## Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.07.038.

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