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ORIGINAL PAPER

Efficient Construction of Pyrazolo[1,5-*a*]pyrimidine Scaffold and its Exploration as a New Heterocyclic Fluorescent Platform

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Abstract An efficient, fast and facile pyrazolo[1,5-*a*]pyrimidine synthetic protocol has been established by the condensation of aminopyrazoles with 1,3-dicarbonyl components in $AcOH/H_2SO_4$ system. The pyrazolo[1,5-*a*]pyrimidine sulfides were selectively oxidized to the sulfones via a temperature-controlled stepwise oxidative fashion. The correlation between the substitution patterns of these pyrazolo[1,5-*a*]pyrimidines and their fluorescent spectroscopic properties were further examined, which provided the fundamentals for their potential applications in the development of new fluorescent probes. Red-shifts were easily achieved by the incorporation of unsaturated groups at the 5- and 7-positions, which suggested an approach for synthesizing long wavelength pyrazolo[1,5-*a*]pyrimidine dyes. The fluorescent spectroscopic properties were found to be sensitive to the hydroxy-containing and carbonyl-containing media such as alcohol and acetone, which helps to confirm the promising perspectives of further investigations in this area.

Keywords Fluorophore · Heterocycle · Pyrazolo[1,5-*a*]pyrimidine · Fluorescence

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Introduction

Fluorescent sensors are widely appreciated in the field of chemistry, biology, and environmental sciences because of their simplicity, high sensitivity and low detection limits [1–3]. Various different fluorophores are required as applications of fluorescent probe increase, which makes the development of new fluorescent sensor platforms a high priority [4–7]. On the other hand, pyrazolo[1,5-*a*]pyrimidines have attracted increasing attention due to their fundamental roles in a large number of pharmaceutical agents with a diverse range of biological and physiological activities [8–10] such as anticancer [11], corticotrophin-releasing hormone antagonists [12], antifungals [13] and KDR kinase inhibitors [14]. The special binding sites of pyrazolo[1,5-*a*]pyrimidine core facilitate its binding affinity to hormones, enzymes and proteins. Therefore, the availability of the fluorescent pyrazolo[1,5-*a*]pyrimidine platform would be an advance for their bio-analytic studies. In connection with our ongoing project aiming at the development of various functional heterocycles [15–18], we wish to describe here our recent approach for the synthesis of pyrazolo[1,5-*a*]pyrimidines along with studies of their fluorescent properties, which have potential for applications in the design of certain fluorescent sensors for its special binding sites and diverse spectral properties.

Experimental

All reactions were performed using oven-dried glassware under a positive atmosphere of dry nitrogen. Common reagents and materials were purchased from commercial sources and purified by recrystallization or distillation.

Analytical thin layer chromatography was performed with 0.2 mm coated commercial silica gel plates (Kiesselgel 60 GF254). NMR spectra were measured on a Bruker XL-300 (^{1}H, 300 MHz and ^{13}C, 75 MHz). Data for ^{1}H are reported as follows: chemical shift (ppm), integration, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad), coupling constant (Hz) and number. Data for ^{13}C NMR are reported in terms of chemical shift (ppm). Infrared (IR) spectra were recorded on a Perkin Elmer 500 FT-IR spectrophotometer and are reported in terms of frequency of absorption (cm^{-1}). Elemental analyses were performed on Yanaco-CHN CORDER elementary analyzer. UV-Vis spectra were recorded on a Shimazu 2401 spectrophotometer. The fluorescence spectra were measured with a Hitachi F-4500 fluorescence spectrophotometer. Melting points were measured on a Thomas–Hoover apparatus and were not corrected.

General procedure for the pyrazolo[1,5-*a*]pyrimidine construction

To a solution of **1** (1.0 mmol) in 5 mL of acetic acid, 1,3-disubstituted-1,3-diones (**2**, 1.1 mmol) and two drops of concentrated sulfuric acid (98%) were added. The solution was stirred at 50 °C for 5 min, and added with 10 ml of water and 20 ml of dichloromethane sequentially. The aqueous layer was separated, and extracted with dichloromethane (20 ml×3). The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The products **3** were isolated by flash chromatography on silica gel (200–300 mesh, gradient elution 30–50% ethyl acetate in heptanes; Scheme 1).

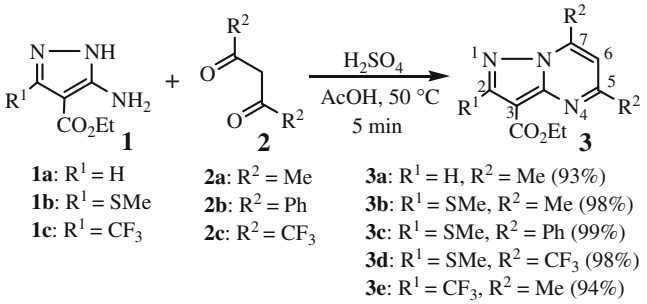
3a: 93% yield; white solid; mp=94–95 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ=8.48 (s, 1H), 6.73 (s, 1H), 4.39 (q, *J*=7.1 Hz, 2H), 2.76 (s, 3H), 2.67 (s, 3H), 1.39 (t, *J*=7.1 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ=162.8, 162.6, 148.0, 146.9, 146.3, 110.3, 102.0, 60.2, 25.2, 17.2, 14.5 ppm; FTIR (KBr) 3057, 2,984, 1,710, 1,625, 1,225, 712 cm^{-1}. Anal. calcd for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98; N, 19.17. Found: C, 60.19; H, 6.12; N, 19.35.

3b: 98% yield; white solid; mp=168–170 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ=6.56 (s, 1H), 4.37 (q, *J*=7.1 Hz, 2H), 2.63 (s, 3H), 2.56 (s, 3H), 2.54 (s, 3H), 1.38 (t, *J*=7.1 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ=163.1, 162.1, 158.6, 149.3, 145.3, 109.3, 98.8, 60.2, 25.1, 16.9, 14.5, 13.3 ppm; FTIR (KBr) 3,062, 2,988, 1,713, 1,629, 1,553, 1,512, 1,437, 1,380, 1,342, 1,248, 1,154, 1,044, 795, 713 cm^{-1}. Anal. calcd for $C_{12}H_{15}N_3O_2S$: C, 54.32; H, 5.70; N, 15.84. Found: C, 54.27; H, 5.88; N, 15.72.

3c: 99% yield; pale yellow solid; mp=148–150 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ=8.25–8.22 (m, 2H), 8.12–8.09 (m, 2H), 7.59–7.50 (m, 6H), 7.45 (s, 1H), 4.47 (q, *J*=7.1 Hz, 2H), 2.57 (s, 3H), 1.51 (t, *J*=7.1 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ=163.3, 159.8, 158.4, 150.4, 146.3, 136.7, 131.3, 131.0, 130.7, 129.6, 129.0, 128.6, 127.5, 105.2, 99.7, 60.3, 14.6, 13.4 ppm; FTIR (KBr) 3,052, 2,980, 2,916, 1,685, 1,607, 1,554, 1,486, 1,457, 1,375, 1,221, 1,193, 1,157, 1,069, 774, 691 cm^{-1}. Anal. calcd for $C_{22}H_{19}N_3O_2S$: C, 67.84; H, 4.92; N, 10.79. Found: C, 67.78; H, 4.99; N, 10.95.

3d: 98% yield; white solid; mp=184–185 °C; ^{1}H NMR (300 MHz, CF_3CO_2D) δ=8.26 (s, 1H), 5.17 (q, *J*=7.1 Hz, 1H), 3.34 (s, 3H), 2.13 (t, *J*=7.1 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CF_3CO_2D) δ=165.1, 164.3, 150.0 (q, $_2J_{CF}$=38.7 Hz), 149.9, 136.4, 135.8, 119.8 (q, $_1J_{CF}$=274.7 Hz), 118.6 (q, $_1J_{CF}$=274.7 Hz), 100.9, 63.0, 12.4, 12.1 ppm; FTIR (KBr) 3,082, 2,987, 2,935, 1,708, 1,624, 1,565, 1,467, 1,372, 1,280, 1,214, 1,029, 881, 678 cm^{-1}. Anal. calcd for $C_{12}H_9F_6N_3O_2S$: C, 38.61; H, 2.43; N, 11.26. Found: C, 38.43; H, 2.62; N, 11.15.

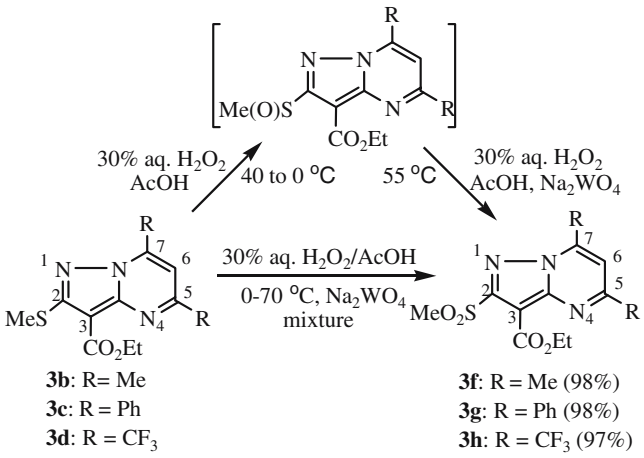
3e: 94% yield; white solid; mp=115–116 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ=6.81 (s, 1H), 4.37 (q, *J*=7.1 Hz, 2H), 2.72 (s, 3H), 2.64 (s, 3H), 1.35 (t, *J*=7.1 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ=164.1, 161.0, 148.8, 146.6, 145.8 (q, $_2J_{CF}$=39.5 Hz), 120.7 (q, $_1J_{CF}$=270.7 Hz, CF_3), 111.9, 100.1, 60.8, 25.3, 16.7, 13.9 ppm; FTIR (KBr) 1,713, 1,629, 1,554, 1,512, 1,437, 1,379, 1,343, 1,245, 1,180, 1,046, 878, 846, 795, 712 cm^{-1}. Anal. calcd for $C_{12}H_{12}F_3N_3O_2$: C, 50.18; H, 4.21; N, 14.63. Found: C, 50.11; H, 4.28; N, 14.79.



Scheme 1 Synthesis of pyrazolo[1,5-*a*]pyrimidines **3a**–**3e**

General procedure for the temperature-controlled selective sulfide oxidation

To a solution of sulfides (1.0 mmol) in 5 mL of acetic acid, aqueous hydrogen peroxide (30%, 1.0 mmol) was added dropwise at 40→0 °C. After which the mixture was stirred at 0 °C overnight (6–8 hours including the addition period),



Scheme 2 Synthesis of pyrazolo[1,5-*a*]pyrimidines **3f**–**3h**

and then added with sodium tungstate (Na_2WO_4, 0.1 mmol) and more aqueous hydrogen peroxide (30%, 1.5 mmol) at 55 °C. The mixture was then stirred vigorously at 55 °C for 20 min, and added with 10 mL of water at room temperature. The mixture was extracted with ethyl acetate (20 mL×3). The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The corresponding sulfones were isolated by flash chromatography on silica gel (200–300 mesh, gradient elution 50%→70% ethyl acetate in heptanes; Scheme 2).

3f: 98% yield; white solid; mp=162–163 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ=6.88 (s, 1H), 4.44 (q, *J*=6.9 Hz, 2H), 3.44 (s, 3H), 2.75 (s, 3H), 2.66 (s, 3H), 1.41 (t, *J*=6.9 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ=164.6, 161.0, 155.0, 148.5, 146.8, 112.6, 101.0, 61.4, 42.8, 25.4, 16.9, 14.1 ppm; FTIR (KBr) 3,074, 3,004, 1,707, 1,630, 1,547, 1,472, 1,439, 1,381, 1,319, 1,233, 1,174, 1,145, 1,047, 973, 871, 790, 765 cm^{-1}. Anal. calcd for $C_{12}H_{15}N_3O_4S$: C, 48.47; H, 5.08; N, 14.13. Found: C, 48.44; H, 4.98; N, 14.20.

3g: 98% yield; white solid; mp=223–224 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ=8.28–8.25 (m, 2H), 8.14–8.10 (m, 2H), 7.64 (s, 1H), 7.60–7.54 (m, 6H), 4.49 (q, *J*=7.1 Hz, 2H), 3.10 (s, 3H), 1.51 (t, *J*=7.1 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ=162.8, 162.1, 160.1, 149.9, 148.4, 136.2, 131.9, 131.6, 129.9, 129.7, 129.2, 129.0, 127.8, 107.4, 100.6, 61.0, 40.7, 14.4 ppm; FTIR (KBr) 2,976, 1,678, 1,607, 1,549, 1,490, 1,462, 1,375, 1,220, 1,162, 1,067, 773, 691 cm^{-1}. Anal. calcd for $C_{22}H_{19}N_3O_4S$: C, 62.69; H, 4.54; N, 9.97. Found: C, 62.56; H, 4.69; N, 9.78.

3h: 97% yield; white solid; mp=124–125 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.72 (s, 1H), 4.47 (q, *J*=7.1 Hz, 2H), 3.13 (s, 3H), 1.44 (t, *J*=7.1 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ=165.6, 160.5, 150.3 (q, $_2J_{CF}$=38.8 Hz), 147.8, 137.3 (q, $_2J_{CF}$=39.5 Hz), 119.5 (q, $_1J_{CF}$=276.3 Hz), 118.3 (q, $_1J_{CF}$=276.1 Hz), 105.0, 104.9, 62.0, 40.5, 14.1 ppm; FTIR (KBr) 3,044, 1,696, 1,561, 1,463, 1,353, 1,326, 1,277, 1,218, 1,177, 1,147, 1,116, 1,088, 1,021, 677 cm^{-1}. Anal. calcd for $C_{12}H_9F_6N_3O_4S$: C, 35.56; H, 2.24; N, 10.37. Found: C, 35.49; H, 2.31; N, 10.24.

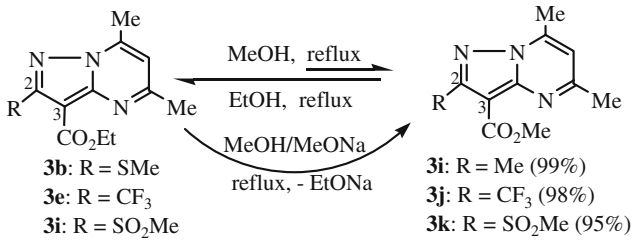
General procedure for transesterification of ethyl esters to methyl esters

To a solution of ethyl esters (2.0 mmol) in 10 ml of methanol, sodium methoxide (3.0 mmol) was added at 0 °C. The mixture was stirred at reflux for 6 h, quenched with 5 ml of aqueous ammonium chloride, and extracted with dichloromethane (20 ml×3). The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The corresponding methyl esters were isolated by flash chromatography on silica gel (200–300 mesh, gradient elution 30–70% ethyl acetate in heptanes; Scheme 3).

3i: 99% yield; white solid; mp=180–181 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ=6.59 (s, 1H), 3.90 (s, 3H), 2.65 (s, 3H), 2.57 (s, 3H), 2.55 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ=163.6, 162.2, 159.1, 149.0, 145.6, 109.4, 98.6, 51.5, 25.1, 17.0, 13.2 ppm; FTIR (KBr) 2,923, 1,682, 1,623, 1,556, 1,460, 1,369, 1,239, 1,207, 1,139, 1,047, 788 cm^{-1}. Anal. calcd for $C_{11}H_{13}N_3O_2S$: C, 52.57; H, 5.21; N, 16.72. Found: C, 52.49; H, 5.38; N, 16.57.

3j: 98% yield; white solid; mp=118–119 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ=6.84 (s, 1H), 3.91 (s, 3H), 2.73 (s, 3H), 2.65 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ=164.6, 161.1, 149.3, 146.3, 146.1 (q, $_2J_{CF}$=38.7 Hz), 120.7 (q, $_1J_{CF}$=274.7 Hz, CF_3), 111.7, 100.2, 52.1, 25.3, 14.0 ppm; FTIR (KBr) 1,683, 1,624, 1,557, 1,460, 1,368, 1,236, 1,140, 1,049, 789 cm^{-1}. Anal. calcd for $C_{11}H_{10}F_3N_3O_2$: C, 48.36; H, 3.69; N, 15.38. Found: C, 48.31; H, 3.88; N, 15.24.

3k: 95% yield; white solid; mp=164–166 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ=6.91 (s, 1H), 3.90 (s, 3H), 3.43



Scheme 3 Synthesis of pyrazolo[1,5-*a*]pyrimidines **3i**–**3k**

(s, 3H), 2.76 (s, 3H), 2.65 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ=165.1, 161.1, 155.5, 148.2, 147.1, 112.7, 100.8, 52.7, 42.9, 25.5, 14.0 ppm; FTIR (KBr) 2,939, 1,676, 1,624, 1,550, 1,420, 1,370, 1,224, 1,146, 1,050, 783 cm^{-1}. Anal. calcd for $C_{11}H_{13}N_3O_4S$: C, 46.63; H, 4.63; N, 14.83. Found: C, 46.51; H, 4.87; N, 14.56.

Results and discussion

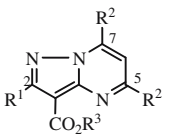
Synthesis of pyrazolo[1,5-*a*]pyrimidine-type fluorescent dyes

Although the condensation of aminopyrazoles with 1,3-dicarbonyl components in acetic acid system was a straightforward synthetic protocol (Scheme 1), however, it didn't work at room temperature. Similar as the other established pyrazolo[1,5-*a*]pyrimidine construction protocols, they require extended reaction times at high temperature and invariably suffer from low to moderate yields [19–22]. For example, treat aminopyrazole **1a** with 1,3-dicarbonyl component **2a** in acetic acid under reflux (120 °C) for 1 day (Scheme 1), pyrazolo[1,5-*a*]pyrimidine **3a** was obtained in low yield (34%). To our delight, **3a** was obtained in moderate yield (61%) when hydrochloric acid was added to the acetic acid refluxing system, which indicated that the reaction efficiency might be improved by increasing the system's acidity. Considering dehydrating agents should be favorable in this dehydrative cyclization, we envisioned that the addition of a little concentrated sulfuric acid to the reaction mixture would not only increase its acidity but also absorb the water produced, and thereby facilitate the reaction. It was found that condensation of **1a** with **2a** in acetic acid with a little concentrated sulfuric acid under stirring at room temperature for one day afforded **3a** in 90% isolated yield. **3a**–**3e** was obtained in high isolated yields (93–99%) within several minutes when the reaction temperature was 50 °C (Scheme 1).

Interesting this class of molecules is found here to exhibit fluorescent properties. The preliminary results indicated that the fluorescence intensity of two-electron-withdrawing group (trifluoromethyl) substituted pyrazolo[1,5-*a*]pyrimidine **3e** is obviously stronger than its 2-electron-donating group (methylthio) substituted analogue (**3b**). To further examine the structure-fluorescence relationship at its 2-position, pyrazolo[1,5-*a*]pyrimidine sulfides **3b**–**3d** were selectively oxidized to pyrazolo[1,5-*a*]pyrimidine sulfones **3f**–**3h** with 30% aqueous hydrogen peroxide in the presence of sodium tungstate (Na_2WO_4, 10 mmol%, Scheme 2). The oxidation of these organic sulfides to their respective sulfones could be processed in a stepwise fashion through the oxidation intermediate of sulfoxides. Thus in the production of sulfide **3b** to sulfone **3f** in acetic acid system with hydrogen peroxide as oxidant, the sulfide-sulfoxide conversion went well once the reaction temperature was increased to 40 °C, whereas the process didn't go exclusively at 0–40 °C as the sulfoxide–sulfone conversion could take place to some extent, and the interaction of sulfide–sulfoxide and sulfoxide–sulfone conversions decreased the sulfoxide/sulfone selectivity. The sulfoxide–sulfone conversion proceeded rapidly at 55 °C so with the addition of sodium tungstate as catalyst, whereas the process didn't go exclusively at 55–70 °C with sulfide **3b** or the impure sulfoxide intermediate as material, which might also come from the interaction of sulfide–sulfoxide and sulfoxide–sulfone conversions. Interesting, during the addition of hydrogen peroxide the sulfide-sulfoxide conversion still went well when the temperature slowly decreased from 40 °C to 0 °C, otherwise the process didn't go well at 0 °C. Upon the completion of the sulfide–sulfoxide conversion at 0 °C, the sulfoxide was formed in high yield without the formation of the sulfone (**3f**). The sulfoxide intermediate could be transformed completely to sulfone **3f** by simply adding sodium tungstate catalyst and increasing the temperature to 55 °C. Pyrazolo[1,5-*a*]pyrimidines **3g**–**3h** were also obtained in high yields by this selective sulfide oxidation strategy (Scheme 2).

Substituent group at the 3-position of pyrazolo[1,5-*a*]pyrimidines was also changed to examine the structure–fluorescence relationship. The condensations of pyrazolo[1,5-*a*]pyrimidine ethyl esters (**3b**, **3e**–**3f**) with sodium

Table 1 Fluorescent properties of pyrazolo[1,5-*a*]pyrimidines **3a**–**3k**[a]



Entry	Comp	R^1	R^2	R^3	λ_{ex} (nm)	λ_{max} (nm)	I_F
1	3a	H	Me	Et	312.0	407.0	129.8
2	3b	SMe	Me	Et	309.0	412.0	70.1
3	3c	SMe	Ph	Et	344.0	464.0	70.7
4	3d	SMe	CF_3	Et	348.0	-	0
5	3e	CF_3	Me	Et	300.0	396.0	216.0
6	3f	SO_2Me	Me	Et	301.0	396.0	222.6
7	3g	SO_2Me	Ph	Et	319.0	448.0	237.1
8	3h	SO_2Me	CF_3	Et	321.0	-	0
9	3i	SMe	Me	Me	310.0	412.0	63.8
10	3j	CF_3	Me	Me	300.0	396.0	209.0
11	3k	SO_2Me	Me	Me	300.0	396.0	216.6

[a] The experiments were performed in acetonitrile (c=1 *u*M); λ_{ex} (excitation wavelength, the absorption maximum obtained from its UV-vis spectra); λ_{max} (maximum emission wavelength); I_F (relatively fluorescence intensity)

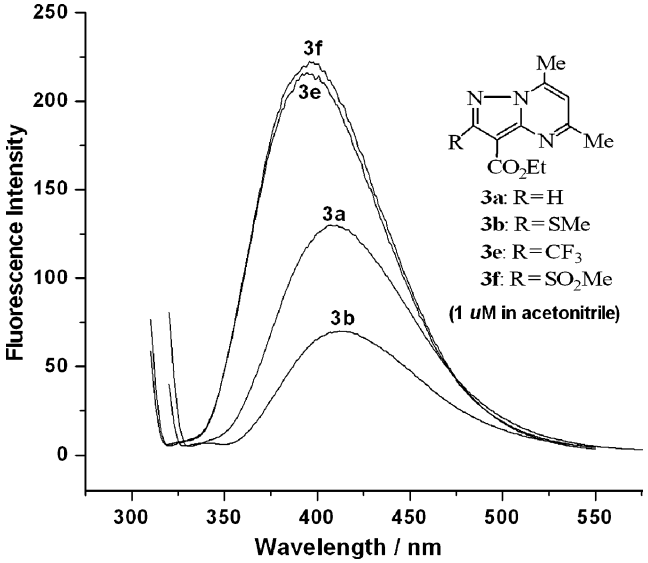


Fig. 1 Part of fluorescence emission spectra of **3**

Table 2 Fluorescent properties of pyrazolo[1,5-*a*]pyrimidine **3e**[a]

Entry	Solvents	λ_{max} (nm)	I_F
1	Acetone	-	0
2	Tetrahydrofuran	407.0	29.1
3	Diethyl ether	397.0	109.6
4	1,4-Dioxane	404.0	190.8
5	Hexane	398.0	141.7
6	Toluene	402.0	150.1
7	Chloroform	397.0	200.7
8	Dichloromethane	398.0	224.0
9	Acetonitrile	396.0	216.0
10	Ethanol	410.0	801.5

[a] Excitation wavelength λ_{ex} (300 nm) is the absorption maximum obtained from its UV-vis spectra; concentration (c=1 *u*M); λ_{max} (maximum emission wavelength); I_F (relatively fluorescence intensity)

methoxide in refluxing methanol afforded pyrazolo[1,5-*a*] pyrimidine methyl esters (**3i**–**3k**) in high isolated yield (95–99%, Scheme 3). Transesterification with a higher alcohol to displace a lower alcohol is an easy process, whereas the reversed process is relatively difficult. Herein, sodium methoxide was found to efficiently facilitate the transesterification of an ethyl ester to a methyl ester.

Structure-fluorescence relationships of pyrazolo[1,5-*a*] pyrimidine-type dyes

With pyrazolo[1,5-*a*]pyrimidines **3a**–**3k** in hand, the correlations between their substitution patterns and their fluorescent spectroscopic properties were subsequently investigated (Table 1). With substituents at the 2-position of pyrazolo[1,5-*a*]pyrimidines, the fluorescence intensity increased with increasing electron-withdrawing strength. With the 2-position bearing a hydrogen atom, **3a** has an absorption maximum centered at 312.0 nm with a corresponding moderate fluorescence emission maximum at 407.0 nm (entry 1). With an electron-donating group such as a methylthio group at the 2-position, the fluorescence intensity of **3b** decreased in comparison to that of **3a** (i.e., 129.8 vs 70.1, entries 1–2). Interestingly, with strong electron-withdrawing groups, trifluoromethyl and methylsulfonyl, at the 2-position, the fluorescence intensities of **3e**–**3f** increased by about 2-fold with slight blue-shifts in comparison to that of **3a** (entries 1, 5–6). Substitution of an ethoxycarbonyl group to a methoxycarbonyl group at the 3-substituent resulted in a slight decrease in fluorescence intensity from 70.1 (**3b**) to 63.8 (**3i**) with no noticeable shift in the fluorescence emission wavelength (λ_{max}=412 nm) maximum (entries 2 and 9). The similar trend was also observed for **3e** and **3g** and **3j**–**3k** (entries 5, 7 and 10–11).

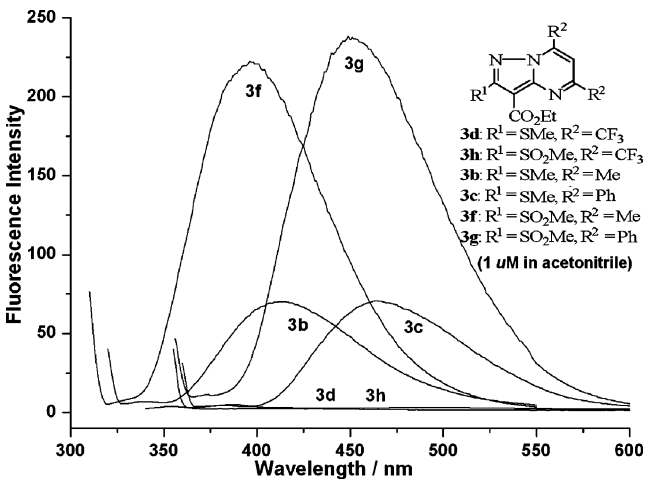


Fig. 2 Part of fluorescence emission spectra of **3**

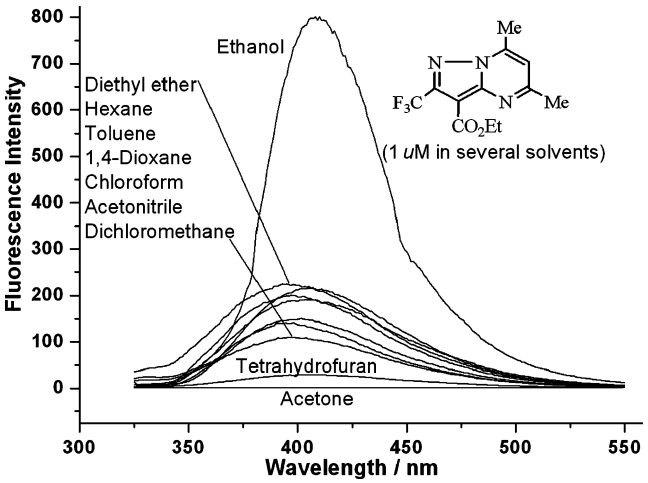


Fig. 3 Part of fluorescence emission spectra of **3e**

Clearly, the nature of the substituent at the 2-position is very important to its fluorescence intensity (Fig. 1). With decreased electron density at their 2-positions [MeS (**3b**)> H (**3a**)>CF_3 (**3e**) ~$MeSO_2$ (**3f**)], the fluorescence intensities increased [70.1 (**3b**)<129.8 (**3a**)<216.0 (**3e**) ~222.6 (**3f**)) with slight blue-shifts (412.0 nm (**3b**)>407.0 nm (**3a**)> 396.0 nm (**3e**–**3f**)).

The natures of the 5- and 7-substituents are also very important to their fluorescence intensities (Fig. 2). On one hand, when the 5- and 7-positions bore strong electron-withdrawing groups such as a trifluoromethyl group, the corresponding pyrazolo[1,5-*a*]pyrimidines (**3d** and **3h**) showed no fluorescence (I_F=0). However, fluorescence is observed for the pyrazolo[1,5-*a*]pyrimidines when the 5- or the 7-postion is occupied by electron donating groups. On the other hand, a noticeable red-shift (52.0 nm) in the emission maximum was observed when the 5- and 7-substituents of **3b** (λ_{max}=412.0 nm) were changed from a methyl group to a phenyl group (**3c**: λ_{max}=464.0 nm). A similar red-shift (52.0 nm) in the emission maximum could also be observed in the case of **3f** (λ_{max}=396.0 nm) and **3g** (λ_{max}=448.0 nm), which suggested approaches for obtaining long wavelength pyrazolo[1,5-*a*]pyrimidine dyes.

The fluorescence spectroscopic properties of pyrazolo[1,5-*a*] pyrimidine-type dyes in various media

The nature of media was found to be very important to the fluorescence intensities of these pyrazolo[1,5-*a*]pyrimidines. Pyrazolo[1,5-*a*]pyrimidine **3e**, for example, was selected to dissolve in several solvents to further study its spectroscopic properties (Table 2). When it was dissolved in acetone (c=1 μM), no fluorescence (I_F=0) was detected (entry 1 and Fig. 3). However, fluorescence is observed for **3e** when it was dissolved in the other selected media (entries 2–10). When **3e** was dissolved in tetrahydrofuran with same concentration, it has an absorption maximum centered at 407.0 nm with a corresponding weak fluorescence emission maximum (29.1 nm, entry 2 and Fig. 3). When **3e** was dissolved in the other non-protonic media such as diethyl ether, 1,4-dioxane, hexane, toluene, chloroform, dichloromethane and acetonitrile, moderate fluorescence emission maxima (109.6–224.0 nm) with absorption maxima centered at 396–404 nm were found (entries 3–9 and Fig. 3). Interestingly, the fluorescence intensity of **3e** in ethanol increased by about fourfold (i.e., 801.5 nm vs 216.0 nm) with slight red-shift in comparison to that in acetonitrile (entries 9–10, and Fig. 3). The preliminary results indicated that the fluorescence spectroscopic properties of pyrazolo[1,5-*a*]pyrimidines was sensitive to alcohols and ketones, which suggested their potential applications in the detections certain materials or alcohol-ketone redox reactions.

Conclusions

In summary, pyrazolo[1,5-*a*]pyrimidines bearing various substituents have been designed and facile synthesized by the condensation of aminopyrazoles with 1,3–dicarbonyl components in $AcOH/H_2SO_4$ system, and a temperature-controlled selective sulfide oxidation. The heterocyclic core has been explored as a new fluorescent platform, in which the preliminary media effect and the structure-fluorescent correlations were found. Based on these fluorescent properties, several pyrazolo[1,5-*a*]pyrimidine class of fluorescent chemosensors have been developed, which will be reported on later.

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