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Synthesis of unsymmetrically tetrasubstituted pyrroles and studies of AIEE in pyrrolo[1,2-a]pyrimidine derivatives†

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Pyrroles are among the most important heterocycles in pharmaceuticals and agrochemicals. Construction of pyrrole scaffolds with different substituents and a free NH group, however, is challenging. Herein, a metal-free method for the synthesis of unsymmetrically tetrasubstituted NH-pyrroles using a consecutive chemoselective double cyanation is reported. The desired pyrroles were obtained with yields up to 99% and good functional group tolerance. Mechanistic studies identified a reaction mechanism that features a subtle sequence of first cyano-addition and migration, followed by cyano-addition and aromatization to afford the pyrrole skeleton. Pyrrolo[1,2-a]pyrimidines are synthesized as the synthetic applications of NH-pyrroles, and these pyrrolo[1,2-a]pyrimidines exhibit unpredicted time-dependent aggregation-induced emission enhancement (AIEE) properties.

Introduction

As one of the major challenges and driving forces for the development of innovative pharmaceuticals and agrochemicals, efficient construction of structurally diverse and highly functionalized heterocycles has long been a highly cited research field.[1] As prevalent key motifs in bioactive natural molecules, pyrrole and its derivatives have diverse applications in therapeutically active compounds, such as the heavily used drugs, lipitor, sutent, and molindone (Fig. 1a).[2] As core structures, these valuable polysubstituted pyrroles show that production of polysubstituted pyrrole scaffolds, especially with unsymmetrically disposed substituents and diverse functional groups, is highly sought.

Classically, pyrroles can be synthesized by the Paal–Knorr reaction[3] or the Hantzsch reaction.[4] Many other syntheses of pyrroles have been established,[5] including powerful coupling strategies realized by transition-metals[5] and the van Leusen

pyrrole synthesis.[6] However, the major disadvantages of these protocols lie in their requirement for substrate pre-functionalization, substituent deficiency and formation of by-products. Synthesis of pyrrole scaffolds with unsymmetrical tetrasubstituents[7] can be considerably difficult, and it is even
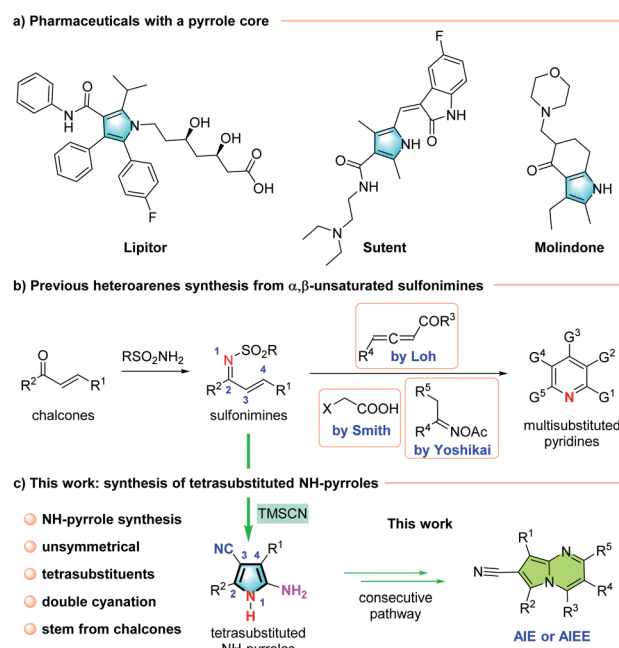

Fig. 1 Pharmaceutically significant pyrroles and synthesis of heteroarenes from α,β-unsaturated sulfonimines.

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more challenging to obtain polysubstituted pyrroles with an unprotected free NH group, so called NH-pyrroles.[8] Examples such as the base-catalyzed cyclization of propargyl enamines by Wan's group,[9] the rhodium-catalyzed tandem reaction of α-diazo oxime ethers by Park et al.,[10] a visible-light-induced formal [3 + 2] cycloaddition by Xiao et al.[11] and an electrochemical heterocoupling between two structurally diverse enamines reported by Roy and De Sarkar[12] have disclosed excellent methods with which to synthesize polysubstituted NH-pyrroles. Nevertheless, only carbon substituents can be introduced into pyrroles with these methods, and procedures for the generation of NH-pyrroles with diverse functionalities are extremely rare.
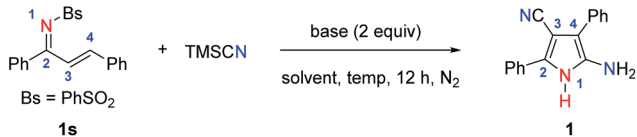
On the basis of the widely used synthesis of commercially available chalcones,[13] we have developed an efficient method for the synthesis of polysubstituted NH-pyrroles directly from α,β-unsaturated sulfonimines, which have been shown by Loh,[14] Smith,[15] and Yoshikai[16] to be good precursors for the construction of multisubstituted pyridines (Fig. 1b). Judging by the proposed mechanism, an interesting consecutive chemoselective double cyanation should be important in this strategy. This reaction provides access to unsymmetrically tetrasubstituted pyrroles and tolerates functional groups, such as a free NH group that can be further substituted (Fig. 1c). In addition, the pyrrolo[1,2-a]pyrimidine derivatives that were synthesized from NH-pyrroles exhibit unpredicted time-dependent aggregation-induced emission enhancement (AIEE) properties.

The initial screening and optimization of this pyrrole synthesis was carried out with an α,β-unsaturated sulfonimine (**1s**) as the model substrate and TMSCN. As shown in Table 1,

the desired tetrasubstituted NH-pyrrole (**1**) can be easily generated when the reaction was performed in DMF at 80 °C with Cs_2CO_3 as the base (Table 1, entry 1). Screening of other alternative inorganic or organic bases showed that Cs_2CO_3 gave the best results (Table 1, entries 2 and 3 vs. entry 1). Decreasing or increasing the reaction temperature resulted in a lower yield (Table 1, entries 4 and 5). When anhydrous DMSO was used as the solvent, the best isolated yield of the NH-pyrrole (**1**) was 80% (Table 1, entry 6). While other solvents fail to improve the efficiency of the reaction, protic EtOH completely terminated the reaction (Table 1, entries 7 and 8). In the absence of a base, no reaction occurred (Table 1, entry 9), and finally, when the Bs ($PhSO_2$) protecting group was replaced by a toluene sulfonyl group (Ts), the NH-pyrrole (**1**) was obtained in 73% yield (Table 1, entry 10). Other cyanide sources[17] such as $Zn(CN)_2$, $K_3[Fe(CN)_6]$ and ^tBuCN have been studied, but only $Zn(CN_2)$ could afford the target molecule in 41% yield.

With the optimized conditions in hand, we explored the substrate scope and the limitations of the reaction. As shown by the results in Fig. 2, the reaction exhibits good functional group compatibility, and a variety of unsymmetrically tetrasubstituted NH-pyrroles can be obtained from α,β-unsaturated sulfonimines. Electron-donating substituents at the para-position of the aryl group (the C=C side) are well-tolerated and give the corresponding products (**1–4**) in yields of 67–91%. The reaction proceeds smoothly with weak electron-withdrawing substituents, leading to the desired pyrroles (**5–7, 10**) in yields ranging from 72 to 96%. Compounds with ortho- and meta-methoxy substituents afford **9** and **11**, respectively, in high yields. For

Table 1 Reaction optimization[a]

Entry	Base	Solvent	Temp (°C)	Yield[b] (%)
1	Cs_2CO_3	DMF	80	68
2	K_2CO_3, Na_2CO_3, t-BuONa, or KF	DMF	80	17–43[c]
3	TEA, DBU, DMAP, or DABCO	DMF	80	0–29[d]
4	Cs_2CO_3	DMF	70	47
5	Cs_2CO_3	DMF	85	62
6	Cs_2CO_3	DMSO	80	82 (80)[e]
7	Cs_2CO_3	DMAc, MeCN, NMP, 1,4-dioxane, or THF	80	18–57[f]
8	Cs_2CO_3	EtOH	80	0
9		DMSO	80	0
10	Cs_2CO_3	DMSO	80	73[g]
11	Cs_2CO_3	DMSO	80	41[h]
12	Cs_2CO_3	DMSO	80	0[i]
13	Cs_2CO_3	DMSO	80	0[j]

[a] Reaction conditions: sulfonimine **1s** (0.2 mmol, 1 equiv.), TMSCN (2.2 equiv.), base (2 equiv.), anhydrous solvent (1.5 mL), 80 °C, 12 h, under a nitrogen atmosphere. [b] Yields were determined by GC-MS analysis of the crude product using 1,4-dimethoxybenzene as an internal standard. [c] Yields with K_2CO_3, Na_2CO_3, t-BuONa, and KF were 43%, 17%, 32%, and 37%, respectively. [d] Yields with TEA, DBU, DMAP, and DABCO were 4%, 29%, trace, and 12%, respectively. [e] Isolated yield in parentheses. [f] Yields with DMAc, MeCN, NMP, 1,4-dioxane, and THF were 49%, 57%, 29%, 18% and 45%, respectively. [g] N-((1E,2E)-1,3-Diphenylallylidene)-4-methylbenzenesulfonamide was used instead of **1s** (Bs was replace by Ts). [h] $ZnCN_2$ was used instead of TMSCN. [i] $K_3Fe(CN)_6$ was used instead of TMSCN. [j] ^tBuCN was used instead of TMSCN.
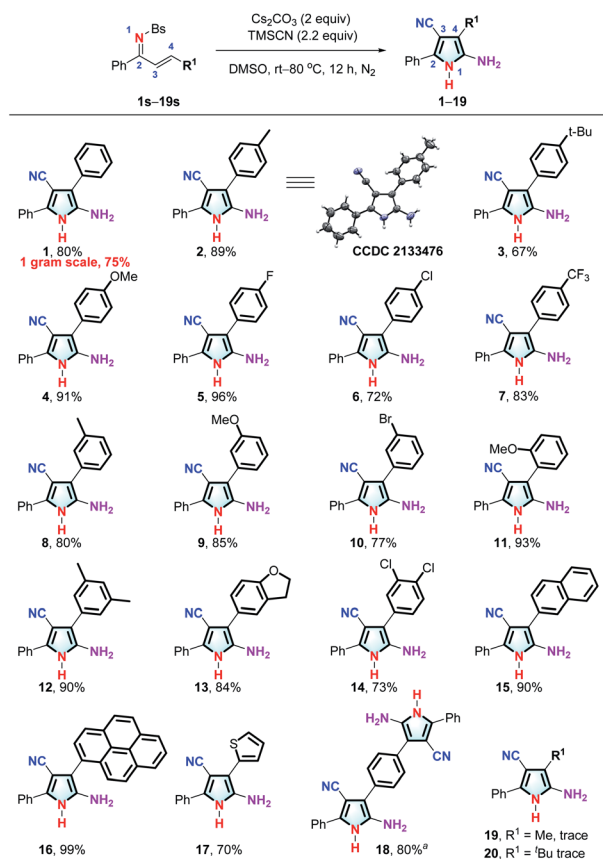
Fig. 2 Substrate scope of carbon substituents. Reaction conditions: sulfonimine (0.5 mmol, 1 equiv.), TMSCN (2.2 equiv.), Cs_2CO_3 (2 equiv.), anhydrous DMSO (4 mL), 80 °C, 12 h, under a nitrogen atmosphere. [a] TMSCN (4.4 equiv.) and Cs_2CO_3 (4 equiv.) were used instead.

Fig. 3 Substrate scope of substituents on the C=N side. Reaction conditions: sulfonimine (0.5 mmol, 1 equiv.), TMSCN (2.2 equiv.), Cs_2CO_3 (2 equiv.), anhydrous DMSO (4 mL), 80 °C, 12 h, under a nitrogen atmosphere.

substrates with a disubstituted aryl group, the reaction affords the corresponding pyrroles (**12–14**) in good to excellent yields. In addition to compounds with a phenyl ring, other aryl substituents are also tolerated. For example, naphthyl, pyrenyl, and thienyl groups are entirely compatible, leading to reactions which can convert the substrates into the corresponding NH-pyrroles (**15–17**) in excellent yields. Interestingly, when the C2-symmetric substrate, *N*-((1*E*,2*E*)-1,3-diphenylallylidene)benzene-sulfon-amide (**18s**) is employed in the reaction, both sides of the α,β-unsaturated sulfonimine moiety are involved in the formation of the pyrrole skeleton, and the reaction provides a C2-symmetric product (**18**) with two pyrrole substituents in 80% yield. However, when the R^1 group is an alkyl group (Me and *t*Bu), the desired NH-pyrrole (**19, 20**) was not detected. The structure of the NH-pyrrole (**2**) was confirmed by X-ray single crystal diffraction analysis.

Subsequently, the scope of another substituent on the C=N side of the α,β-unsaturated sulfonimines was explored (Fig. 3). Substrates with electron-rich substituents (**21s–24s**) and electron-deficient substituents (**25s–29s**) at the *para*-position of the aromatic ring afforded the corresponding unsymmetrically tetra-substituted NH-pyrroles (**21–29**) in yields of 75–99%. While substrates with a 3-chlorophenyl substituent (**30s**) afford the desired product in 69% yield, 3,5-dimethylphenyl (**31s**) and
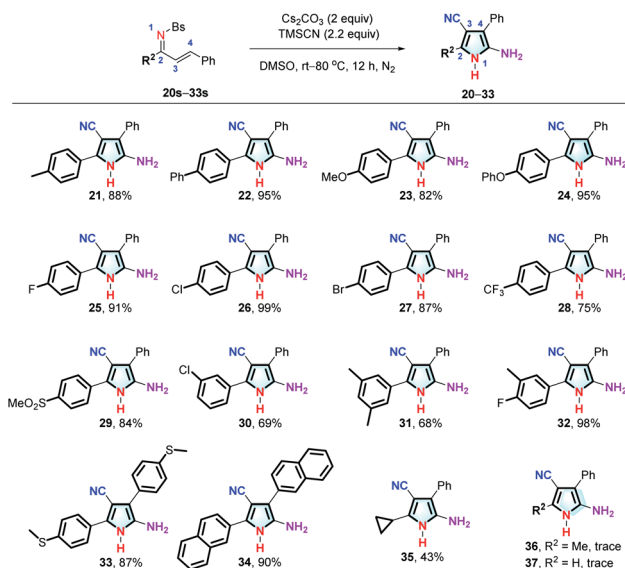
4-fluoro-3-methylphenyl (**32s**) substituents are also well tolerated. Bis(4-(methylthio)phenyl (**33**)) and dinaphthyl (**34**) NH-pyrroles with the same substituents at the C=C or the C=N side could be obtained in good yield. When R^2 is cyclopropyl, the corresponding product **35** can be obtained with 43% yield. However, when R^2 is hydrogen and methyl, no trace of the corresponding NH-pyrrole (**36, 37**) is detected.
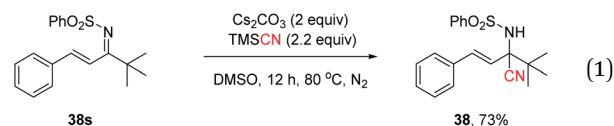
Unexpectedly, distinct from the reaction with diaryl-substituted α,β-unsaturated sulfonimines, a substrate with a *tert*-butyl group next to the C=N bond (**38s**) afforded only the 1,2-cyano addition product (**38**) in 73% yield (eqn (1)), presumably as a result of the considerable steric hindrance.[18] This result suggested that this reaction might entail an initial 1,2-addition step.

In order to gain some insight into the mechanism of the reaction, several control experiments were conducted (Fig. 4). First, when the reaction of **8s** was conducted at rt, the 1,2-cyano addition product (**39**) was generated almost quantitatively in 2 min (Fig. 4a), a result similar to that obtained with substrate **38s**.[18] A reasonable hypothesis is that the reaction at rt of an α,β-unsaturated sulfonimine and TMSCN might undergo 1,2-addition to afford the corresponding cyano sulfonamide. Second, upon subjecting **39** to the standard conditions (with 1.2 equiv. of TMSCN), the corresponding NH-pyrrole (**8**) was isolated in 55% yield (Fig. 4b). Even in the absence of TMSCN, the cyano sulfonamide (**39**) can be converted into the NH-pyrrole (**8**)
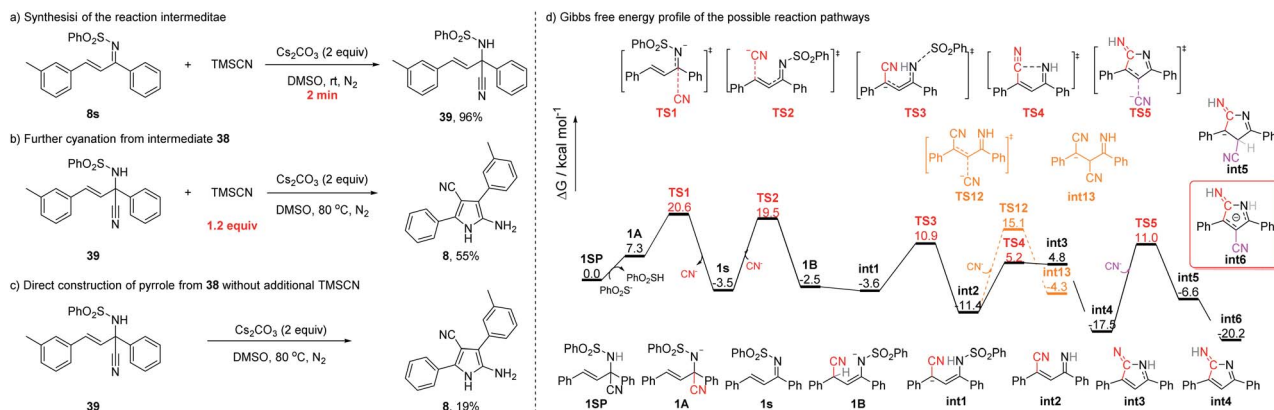
Fig. 4 Experimental and theoretical studies on the reaction mechanism.

(Fig. 4c), implying that the 1,2-addition of the cyano group is reversible at higher temperatures.

Theoretical studies have also been conducted on the basis of the experimental results to investigate the reaction mechanisms of cyclization and double cyanation. Density functional theory (DFT) calculations were performed at the B3LYP-D3(SMD)/Def2-TZVP//B3LYP-D3/Def2-SVP level of theory. Since the reaction can be carried out starting from **39** without additional TMSCN but with much lower yields, the calculation of reversible CN elimination from **1SP** was initially considered. Deprotonation of **1SP** should be an easy process under the base reaction conditions, and the intermediate **1A** can then eliminate the cyanide ion *via* **TS1** with a barrier of 13.3 kcal mol⁻¹ to afford **1s** (Fig. 4d). The isolated CN⁻ ion therefore can add onto the carbon C4 of **1s** to deliver the intermediate **1B** through the transition state **TS2**, however, with a slightly higher barrier of 23.0 kcal mol⁻¹, indicating that there may be a competition between 1,2- and 1,4-addition of **1s** to reverse to the **1SP** or forward to the pyrrole without external TMSCN at high temperature.

Several plausible pathways starting from intermediate **1B** have been examined (see the ESI for more details), and the rearranged intermediate **int1** with a relative free enthalpy −3.6 kcal mol⁻¹ was found to be the more favorable conformation than **1B**. Then, **int1** can undergo the desulfurization rather than the second CN⁻ addition to afford **int2** *via* the transition state **TS3** with a barrier of 14.5 kcal mol⁻¹. Next, the transition state of cyclization, **TS4**, was found to be a much lower state along the reaction pathway than that of **TS12** (the second CN⁻ addition).

Finally, the annulated intermediate **int3** then should perform the proton transfer to afford intermediate **int4** with a free enthalpy of −17.5 kcal mol⁻¹. The second cyanide then can add onto **int4** *via* the transition state **TS5** to deliver the intermediate **int5** which will rearrange to the aromatic conformer **int6** with a much stable free energy of −20.2 kcal mol⁻¹.

On the basic of these mechanistic studies, a plausible reaction mechanism was proposed and is shown in Fig. 5. Initially, a first cyanation occurs on the imine moiety to generate the

cyano sulfonamide **A**.[18] Upon heating, elimination of the cyano group from **A** takes place,[19] regenerating the α,β-unsaturated sulfonimine, which will undergo 1,4-Michael addition to afford **B**. Intermediate **B** undergoes proton transfer and then deprotects the sulfone group to form intermediate **D**. Then, intramolecular 5-*exo*-dig cyclization provides an intermediate **E** which undergoes a second cyanation to offer intermediate **F**. Finally, the thermodynamically stable NH-pyrrole is formed by aromatization and protonation.

The synthetic value of the unsymmetrically tetrasubstituted NH-pyrroles was demonstrated by the construction of various multisubstituted pyrrolo[1,2-*a*]pyrimidines. As shown in Fig. 6, a wide range of fused aza-arenes (**40–51**) can be developed from the NH-pyrroles and diketones.

As known from the literature, pyrrole-containing fluorescent materials generally exhibit aggregation-caused quenching characteristics. Surprisingly, these pyrrole-containing materials exhibit AIE properties, and a remarkable fluorescence enhancement phenomenon was observed for most of these pyrrolo[1,2-*a*]pyrimidines in a mixed THF/water solvent (Fig. 7).[20] For example, following the pioneering AIE studies by Tang *et al.*,[21] the fluorescence intensity of compound **40** was measured and found to be slightly reduced before f_w (water fraction) reached 60%. A sudden rise in fluorescence intensity occurred when f_w increased from 80% to 95%, indicating an AIE behaviour. Unexpectedly, it was found that the fluorescence generated by aggregation continued to increase with time. In order to gain insight into this unusual phenomenon, several
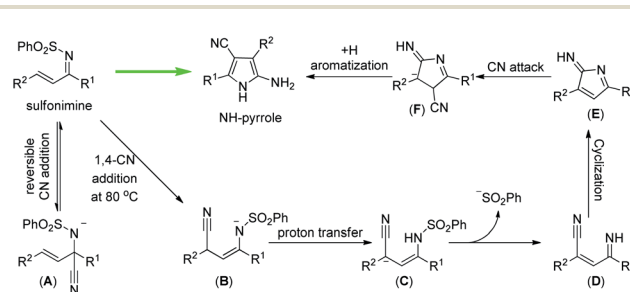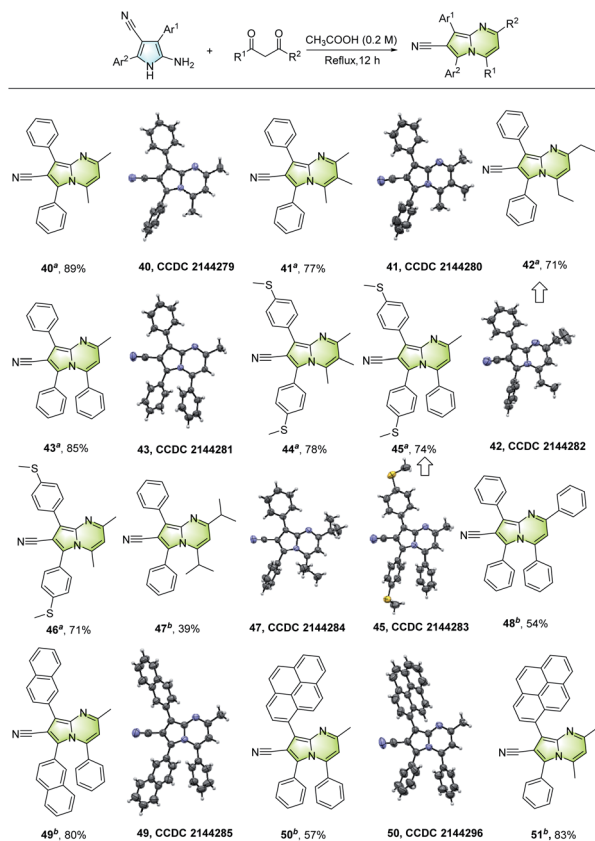

Fig. 5 Proposed mechanism.

Fig. 6 Construction of AIE-active multisubstituted pyrrolo[1,2-a]pyrimidines. [a]AIEE. [b]AIE.

Fig. 7 (a) The emission intensity at 518 nm of **40** in THF/water mixtures (0.1 mg mL^{-1}) with different f_w. (b) Time-dependent photoluminescence (PL) spectra in THF/water mixtures (f_w = 90%, 0.2 mg mL^{-1}). (c) Control experiment; fluorescence intensity at 437 nm light for 5 min (pink line) and in the dark for 5 min (green line); (d) transient photoluminescence decay spectra in THF and water mixtures (f_w = 90%, 0.1 mg mL^{-1}) freshly prepared (black line) and after 30 min (red line); λ_{ex} = 437 nm. (e) Fluorescence quantum yield of THF and water mixtures (f_w = 90%, 0.1 mg mL^{-1}) (I) freshly prepared and (II) after 30 min, THF solution (0.1 mg mL^{-1}) (III), solid powder (IV) and crystal particles (V). (f) XRD spectra of **40** powder, prepared by centrifugation of the THF and water mixtures (f_w = 90%, 0.1 mg mL^{-1}); (g) molecular packing in single crystals of **40**, and (h) molecular packing in single crystals of **49**.

carefully designed experiments were performed. First, when the aggregate in THF/water (10 : 90) solution was irradiated or kept in the dark for the same period of time, similar fluorescence intensities were obtained, indicating that an unexpected radiation time-dependent fluorescence enhancement had occurred. Further studies revealed that irradiation has very little effect on the intensity enhancement, and temperature was a minor factor. Second, upon photoactivation, the fluorescence lifetime of the THF/water (10 : 90) solution of **40** was prolonged from 3.529 ns to 9.966 ns. It was also shown that a solution in THF (0.1 mg mL^{-1}) of compound **40** emitted green light with a maximum at 511 nm and a low fluorescence quantum yield,[22] but the efficiencies of its solution in THF/water (10 : 90) and its crystal form reach 40% and 36%, respectively. Interestingly, the fluorescence of the THF/water solution of **47–51** is not time independent, which is thus different from **40**. To investigate this difference, single crystal structures of these compounds were studied. As depicted in Fig. 7, a face-to-tail pyrrolo[1,2-a]pyrimidine stacking mode is present in crystals of **40**, **41**, **42**, **43**, and **45** and absent for **47**, **49** and **50**. Molecular packing in single crystals of **40** is shown in Fig. 7h as an example of face-to-tail packing of pyrrolo[1,2-a]pyrimidines. This trend is consistent with the AIE or AIEE properties. Interestingly, a π–π interaction of the naphthalene rings is found in crystalline **49**. The different single crystal packing models of **40** and **49** might be responsible for the distinction in the fluorescence phenomena. So, the
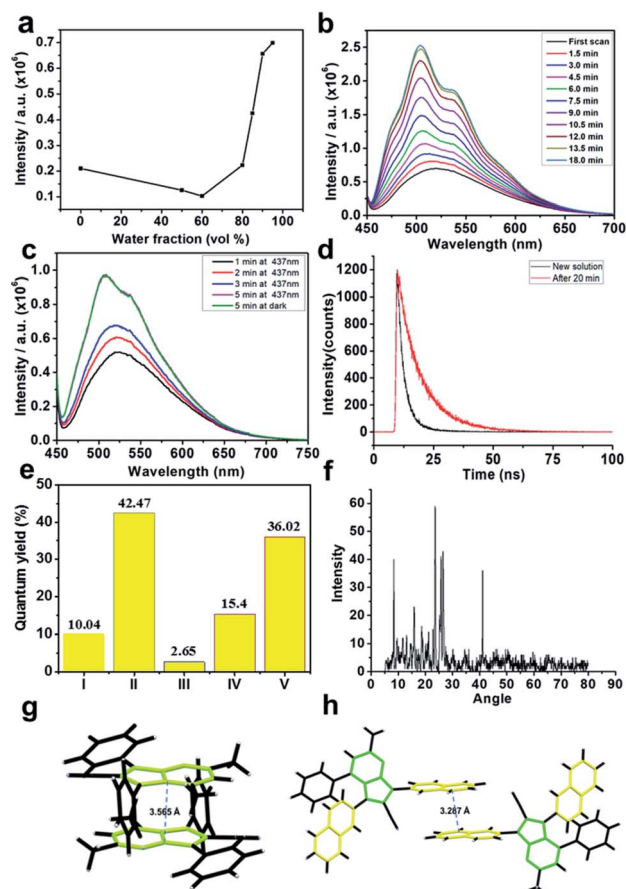
multisubstituted pyrrolo[1,2-a]pyrimidines represent a new kind of AIE luminogens with an unusual time-dependent fluorescence enhancement.

Conclusions

We have developed an efficient transition metal-free approach to the synthesis of a variety of unsymmetrically tetrasubstituted NH-pyrroles from chalcone derivatives. A consecutive double cyanation of α,β-unsaturated sulfonimines followed by aromatization is proposed as a plausible pathway. The feasible conversion of the kinetic intermediate into the corresponding thermodynamically stable NH-pyrrole might be the key to the success of this method. Pyrrolo[1,2-a]pyrimidines are

synthesized as examples of synthetic applications of NH-pyrroles and these pyrrolo[1,2-*a*]pyrimidines exhibit unpredicted time-dependent aggregation-induced emission enhancement properties.

Data availability

All experimental and characterization data, as well as DFT calculation data are available in the ESI.†

Author contributions

H. Bao, D. Li and W.-M. Wan directed the investigations. H. Bao and Y. Li prepared the manuscript. T. Li and C. Ye performed the synthetic experiments and analyzed the experimental data. M.-F. Chiou completed the theoretical calculations. M. Su, M. Xue, X. Yuan and C. Wang performed the synthetic experiments. T. Li and M.-F. Chiou contributed equally.

Conflicts of interest

There are no conflicts to declare.

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