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I_2-Catalyzed Multicomponent Reactions for Accessing Densely Functionalized Pyrazolo[1,5-*a*]pyrimidines and Their Disulphenylated Derivatives

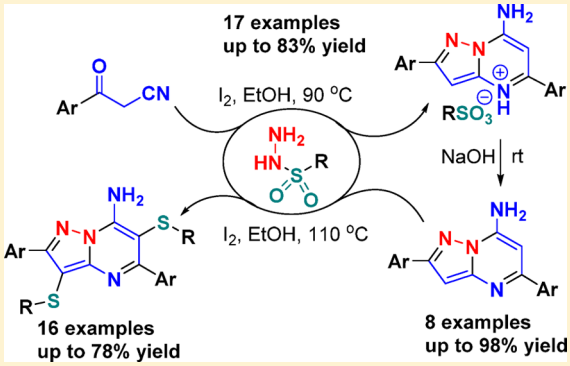
Jun Sun,[†,§] Jiang-Kai Qiu,[†,§] Bo Jiang,[*,‡] Wen-Juan Hao,[‡] Cheng Guo,[*,†] and Shu-Jiang Tu[*,‡]

[†]College of Chemistry and Molecular Engineering, Biotechnology and Pharmaceutical Engineering, Nanjing Tech University, Nanjing 211816, P. R. China

[‡]School of Chemistry and Chemical Engineering, Jiangsu Key Laboratory of Green Synthetic Chemistry for Functional Materials, Jiangsu Normal University, Xuzhou 221116, P. R. China

Supporting Information

ABSTRACT: New I_2-catalyzed multicomponent bicyclization reactions of *β*-ketonitriles with sulfonyl hydrazides have been established, providing a direct and metal-free access toward unreported pyrazolo[1,5-*a*]pyrimidin-4-ium sulfonates. The latter could be quantitatively converted into densely functionalized pyrazolo[1,5-*a*]pyrimidines in the presence of bases. Using sulfonyl hydrazides as a sulfenylating agent, the resulting pyrazolo[1,5-*a*]pyrimidines enabled I_2-catalyzed unprecedented disulphenylations to access fully substituted pyrazolo[1,5-*a*]pyrimidines through direct C(sp^2)−H bond bifunctionalization.



INTRODUCTION

Pyrazolo[1,5-*a*]pyrimidines, standing for a class of significant heterocycles, have been extensively utilized in pharmaceutical chemistry and material science.[1] For instance, pyrazolo[1,5-*a*]pyrimidines present a key structural motif in the anxiolytic agent ocinaplon and the hypnotic drugs zaleplon and indiplon as well as in the fungicide pyrazophos (Figure 1). Besides, aryl-

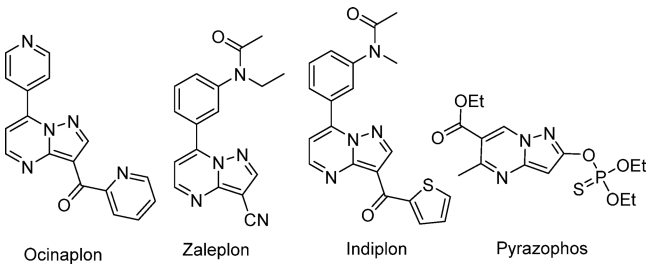


Figure 1. Examples of pyrazolo[1,5-*a*]pyrimidine-containing drugs.

substituted pyrazolo[1,5-*a*]pyrimidines are well-known to display a broad spectrum of biological activities, such as being antitumor[2] and anti-inflammatory agents,[3] hepatitis C virus inhibitors, and estrogen receptor ligands,[4] as well as high affinity for translocator protein (TSPO).[5] The importance of these compounds has stimulated great efforts to create methodology for their syntheses. Typically, the synthesis of pyrazolo[1,5-*a*]pyrimidines are through catalytic intermolecular cyclization between aminopyrazoles and bifunctional reagents, such as 1,2-allenic ketones,[6] enaminones,[7] 1,3- or 1,5-dicarbonyl compounds,[8] *β*-keto nitriles,[9] *β*-halovinyl aldehydes,[10] etc. Recently, Aggarwal et al. reported the *p*-TsOH catalyzed synthesis of pyrazolo[1,5-*a*]pyrimidines from 3-aryl-3-oxopropanonitriles and hydrazine hydrate in a one-pot, two-step manner.[11] Despite these advances, to the best of our knowledge, the utilization of three-component bicyclization involving disulphenylation for the construction of fully substituted pyrazolo[1,5-*a*]pyrimidines has not yet been documented.

Sulphenylation reactions become a powerful and reliable synthetic strategy for C−S bond formation.[12] Recently, sulphonyl hydrazides, possessing a stable nature and high reactivity, serve as readily available and eco-friendly sulphenylation agents for the synthesis of sulfur-containing compounds.[13] Tian and co-workers reported an interesting I_2-catalyzed sulphenylation reaction of sulphonyl hydrazides with indoles for the synthesis of indole thioethers (Scheme 1a).[14] Subsequently, several groups developed various I_2-catalyzed sulphenylations of the electron-rich aryl or heterocyclic rings using sulphonyl hydrazides as a sulphenylation agent.[15] Very recently, we also reported a three-component sulphenylation for accessing fully substituted pyrazoles using readily available *β*-ketonitriles, arylhydrazines, and sulphonyl hydrazides

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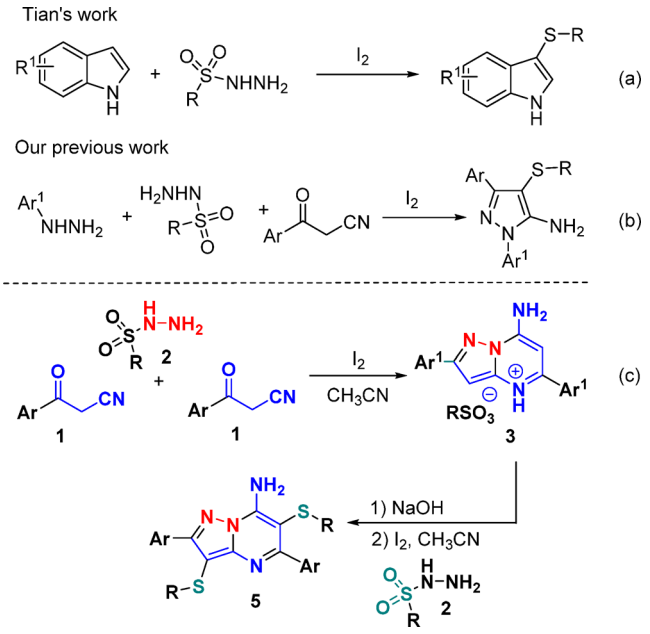
Scheme 1. Profiling Applications of Sulphenylation

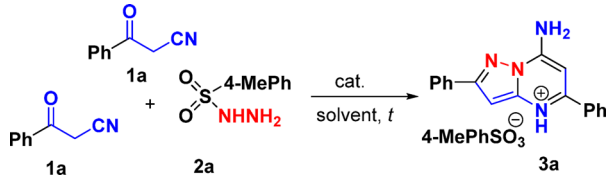


(Scheme 1b).[16] To continue our efforts in this project and catalytic domino bicyclizations,[17] we found that when *β*-ketonitriles were subjected to a reaction with sulphonyl hydrazides in a 2:1 mol ratio, the reaction occurred in an unexpected bicyclization direction to give densely functionalized 7-aminopyrazolo[1,5-*a*]pyrimidin-4-ium sulfonates **3**, which could be quantitatively converted into the corresponding 7-aminopyrazolo[1,5-*a*]pyrimidines **4** by reacting with suitable bases (Scheme 1c). Considering the valuable potential of 7-aminopyrazolo[1,5-*a*]pyrimidines with two electron-rich heterocyclic motifs, we decided to probe the feasibility of its disulphenylation with sulphonyl hydrazides in a one-pot manner. Delightedly, the reaction proceeded smoothly in I_2 catalysis, affording a series of unprecedented fully substituted pyrazolo[1,5-*a*]pyrimidines **5** (Scheme 1c). During these reaction processes, sulphonyl hydrazides were served as both a bicyclization component and a sulphenylation reagent. Herein, we report this interesting exploration.

RESULTS AND DISCUSSION

Our initial investigation began with the three-component reaction of 3-oxo-3-phenylpropanenitrile (**1a**) with *p*-toluenesulfonyl hydrazide (**2a**) without inert gas protection. The reaction was conducted by using 10 mol % of I_2 as a catalyst in EtOH at 70 °C to give an unexpected 7-aminopyrazolo[1,5-*a*]pyrimidin-4-ium sulfonate **3a** in a 29% chemical yield (Table 1, entry 1). Increasing the loading of the I_2 catalyst to 20 mol % facilitated the reaction rate and gave a higher yield (53%, entry 2), whereas a visible drop in the yield was observed when the amount of I_2 was further increased to 30 mol % (entry 3). A subsequent evaluation of reaction temperatures was conducted (entries 2, 4, and 5). The reaction worked more effectively at 90 °C, delivering the bicyclic product **3a** in 75% yield (entry 4). The yield leveled off when the temperature was further elevated to 100 °C (entry 5). Afterward, we utilized other solvents, such as acetonitrile (CH_3CN), 1,2-dichloroethane (DCE), tetrahydrofuran (THF), and 1,4-dioxane as well as toluene, to investigate the solvent effect on the reaction outcomes in this I_2-catalyzed bicyclization (entry 4 vs entries 6−10), and we found that all these solvents were inferior to EtOH in terms of reaction yields (entry 4).

Table 1. Optimization of Reaction Conditions for Forming Product 3a[a]

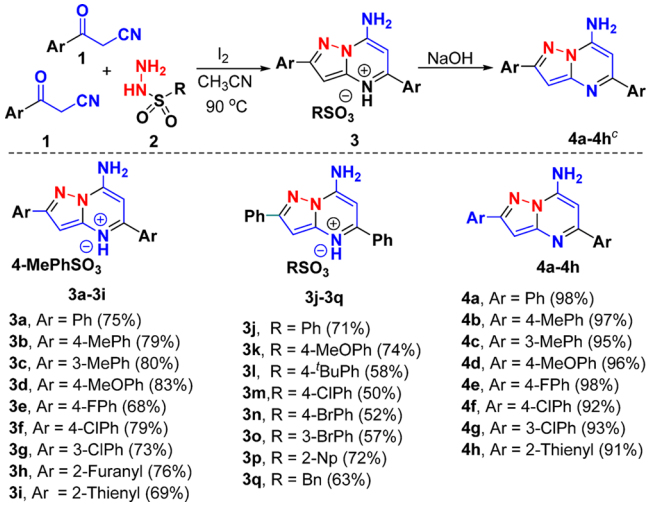


entry	cat. (mol %)	solvent	*t*/°C	yield (%)[b]
1	I_2 (10)	EtOH	70	29
2	I_2 (20)	EtOH	70	53
3	I_2 (30)	EtOH	70	47
4	I_2 (20)	EtOH	90	75
5	I_2 (20)	EtOH	100	70
6	I_2 (20)	CH_3CN	90	59
7	I_2 (20)	DCE	90	45
8	I_2 (20)	THF	90	31
9	I_2 20)	1,4-dioxane	90	29
10	I_2 (20)	toluene	90	48

[a]Reaction conditions: All reactions were performed with **1a** (2.4 mmol), **2a** (1 mmol), catalyst, and solvent (3.0 mL) in the sealed reaction tube under air conditions. [b]Isolated yield based on **2a**.

With the optimization of conditions in hand, we then set out to evaluate the generality and scope of this I_2-catalyzed bicyclization toward the formation of pyrazolo[1,5-*a*]-pyrimidin-4-ium sulfonates. This transformation demonstrated wide substrate scope in terms of the *β*-ketonitriles and sulphonyl hydrazides under the optimized conditions (Scheme 2). Various aryl-substituted *β*-ketonitriles with electron-donating (methyl, methoxy) and electron-withdrawing (fluoride and chloride) groups successfully afforded the correspond-

Scheme 2. Three-Component Synthesis of Pyrazolo[1,5-*a*]pyrimidines[a,b]



3a, Ar = Ph (75%)
3b, Ar = 4-MePh (79%)
3c, Ar = 3-MePh (80%)
3d, Ar = 4-MeOPh (83%)
3e, Ar = 4-FPh (68%)
3f, Ar = 4-ClPh (79%)
3g, Ar = 3-ClPh (73%)
3h, Ar = 2-Furanyl (76%)
3i, Ar = 2-Thienyl (69%)

3j, R = Ph (71%)
3k, R = 4-MeOPh (74%)
3l, R = 4-^{t}BuPh (58%)
3m,R = 4-ClPh (50%)
3n, R = 4-BrPh (52%)
3o, R = 3-BrPh (57%)
3p, R = 2-Np (72%)
3q, R = Bn (63%)

4a, Ar = Ph (98%)
4b, Ar = 4-MePh (97%)
4c, Ar = 3-MePh (95%)
4d, Ar = 4-MeOPh (96%)
4e, Ar = 4-FPh (98%)
4f, Ar = 4-ClPh (92%)
4g, Ar = 3-ClPh (93%)
4h, Ar = 2-Thienyl (91%)

[a]Reaction conditions: All reactions were performed with **1** (2.4 mmol), **2** (1.0 mmol), I_2 (0.2 mmol), and EtOH (3.0 mL) in the sealed reaction tube at 90 °C under air conditions for 5.0 h. [b]Isolated yield is based on **2**. [c]Reaction conditions: All reactions were performed with **3** (0.5 mmol), NaOH (10% aqueous, 10 mL) at room temperature for 30 min.

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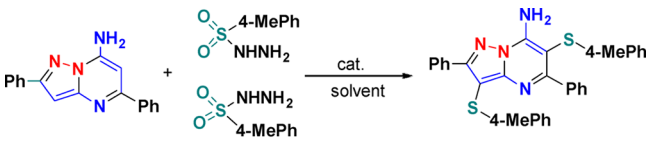
ing products **3b**−**3g** in synthetically useful yields. The electronic nature of the substituents of *β*-ketonitriles exerted an important influence on the reaction efficiency and the obtained chemical yields, and in cases of electron-rich substituents such as methyl and methoxy, the reactions are more facilitated leading to the higher yields compared to their electron-poor counterparts. For instance, treatment of **1d** carrying a methoxy group with sulphonyl hydrazides **2a** gave access to the corresponding product **3d** in 83% yield. In contrast, the presence of a fluoro group resulted in a relatively lower chemical yield (68%). Notably, furan and thiophene functionalized pyrazolo[1,5-*a*]pyrimidin-4-ium sulfonates **3h** and **3i** were successfully obtained under the optimal conditions, which proved the good tolerance of the current bicyclization to heteroaryl functionalized *β*-ketonitriles. After the utilization of various *β*-ketonitriles, we turned our attention to expand the reaction scope using various sulphonyl hydrazides. Substituents with different electronic properties such as methoxy, *tert*-butyl, chloro, and bromo in the *meta*- or *para*-position on the phenyl ring of sulfonyl hydrazides were compatible in the present I_2-catalyzed bicyclization. Similarly, 2-naphthyl (2-Np) and benzyl (Bn) sulfonyl hydrazides can also enable the reaction to work effectively, leading to 72% and 63% yields of the product **3p** and **3q**, respectively. The resulting pyrazolo[1,5-*a*]pyrimidin-4-ium sulfonates **3a**−**3q** were subjected to 10% aqueous sodium hydroxide, which could quantitatively yield the free pyrazolo-[1,5-*a*]pyrimidines **4a**−**4h**. The structures of products **3** and **4** have been determined by NMR and HR-MS spectral analysis. In the case of product **3h**, its structure has been further confirmed by X-ray diffractional analysis.

After our successful achievement with the free pyrazolo[1,5-*a*]pyrimidines **4** having two electron-rich pyrazole and aminopyrimidine motifs, we decided to employ them as starting materials to react with sulfonyl hydrazides to investigate the feasibility of I_2-catalyzed disulphenylation. The one-pot reaction of **4a** with **2a** was conducted under the conditions described above (Table 2, entry 1), but without the observations of the expected disulphenylated pyrazolo[1,5-*a*]pyrimidines **5a**. When the loading of iodine was increased to 40 mol %, the expected product **5a** was obtained, albeit with a very low yield (18%). Furthermore, increasing the loading of iodine could improve the yield of product **5a** (entry 3). After careful optimizations (entries 4−11), we were pleased to observe that using 50 mol % of I_2 and elevating the temperature to 110 °C showed remarkable improvement in the reaction efficiency and gave an optimal outcome (68%, entry 4).

Using the acceptable reaction conditions, the scope and limitation of this I_2-catalyzed domino disulphenylation were evaluated by treating a variety of the preformed pyrazolo[1,5-*a*]pyrimidines **4** with a range of sulfonyl hydrazides **2** (Scheme 3). Upon repeating the reaction with sulfonyl hydrazides **2a**, various pyrazolo[1,5-*a*]pyrimidines **4** carrying either electronically neutral, rich, or poor groups at the *para*- or *meta*-position of phenyl ring all readily participated in this disulphenylation, delivering the collection of fully substituted pyrazolo[1,5-*a*]pyrimidines (**5a**−**5d**) with yields ranging from 51% to 73%. Heteroarylated pyrazolo[1,5-*a*]pyrimidines **4h** could also be accommodated, thus confirming the reaction efficiency, as 2-thienyl product **5f** was obtained in a 59% yield.

Next, the scope of sulfonyl hydrazides **2** was explored by the adoption of these two examples of representative pyrazolo[1,5-*a*]pyrimidines **4a** and **4e** as the coupling partner. Satisfyingly, the reaction proceeded smoothly with various functional groups attached by the aryl moiety of sulfonyl hydrazides **2** under the above-mentioned conditions. The variety of substituents of arylsulfonyl hydrazides, including methoxy, *t*-butyl, fluoro, chloro and bromo, would be compatible with the catalytic system. The presence of a strong electron-rich substituent (methoxy) at the *para* position seemed to improve the reaction

Table 2. Optimization of Reaction Conditions for Forming Product 5a[a]

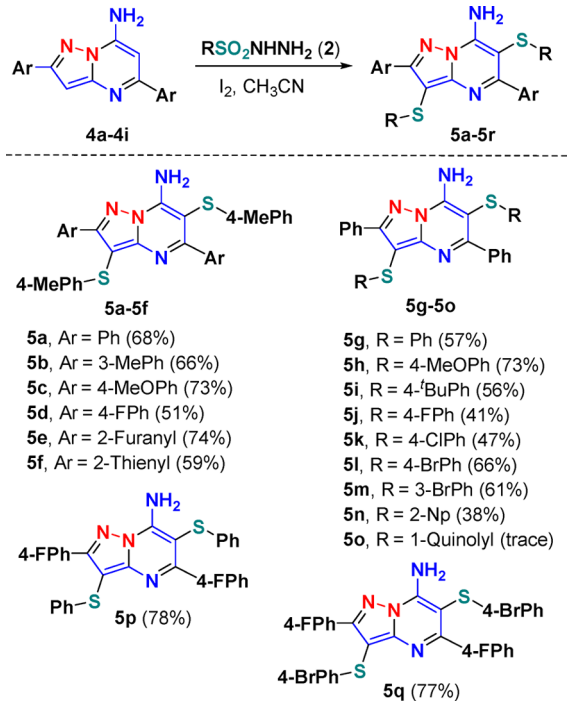


4a **2a** **5a**

entry	cat. (mol %)	solvent	*t*/°C	yield (%)[b]
1	I_2 (20)	EtOH	90	ND
2	I_2 (40)	EtOH	90	18
3	I_2 (50)	EtOH	90	30
4	I_2 (50)	EtOH	110	68
5	I_2 (50)	EtOH	130	49
6	I_2 (75)	EtOH	110	63
7	I_2 (100)	EtOH	110	60
8	I_2 (50)	CH_3CN	110	41
9	I_2 (50)	DCE	110	33
10	I_2 (50)	1,4-dioxane	110	25
11	I_2 (50)	EtOH	110	54[c]

[a]Reaction conditions: **4a** (0.25 mmol), **2a** (0.6 mmol), and solvent (2.5 mL). [b]Isolated yield. [c]HOAc (0.25 mol).

Scheme 3. Scope of Three-Component Disulphenylation[a,b]



[a]Reaction conditions: All reactions were performed with **4** (0.25 mmol), **2** (0.6 mmol), I_2 (0.125 mmol), and EtOH (2.5 mL) in the sealed reaction tube at 110 °C under air conditions for 6 h. [b]Isolated yield based on **4**.

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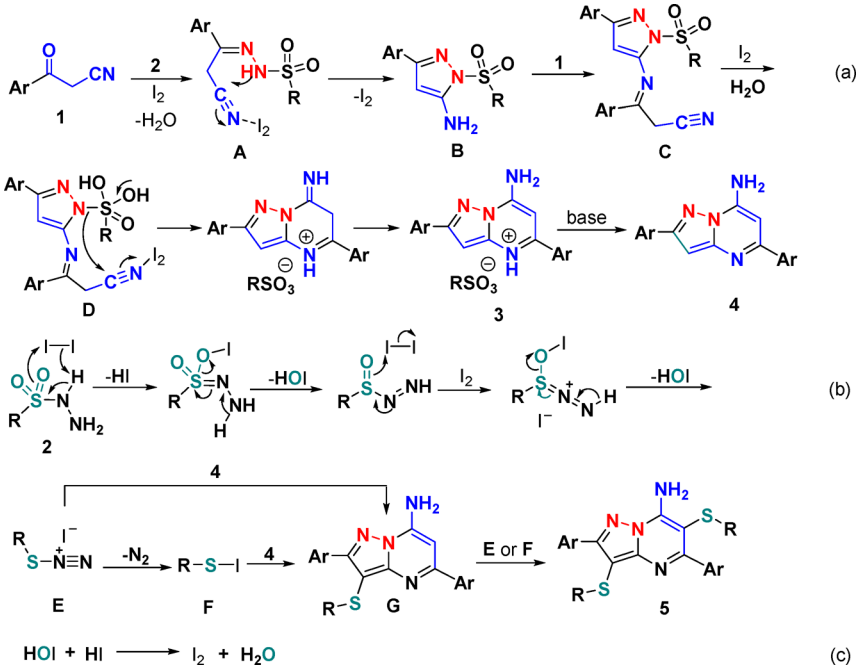
Scheme 4. Proposed Mechanism



efficiency, as the corresponding disulphenylated product **5h** could be isolated in a slightly higher yield (73%). However, a sterically demanding 2-naphthyl analogue (**2i**) proved to be more reluctant to undergo the desired reaction, so that **5n** could only be obtained in 38% yield. Unluckily, 1-quinolyl counterpart **2j** was not a good substrate for this disulphenylation, which was transformed into a trace amount of product **5o** and failed to be isolated. Note that this is the first reported method for the mutlicomponent synthesis of these new fully substituted pyrazolo[1,5-*a*]pyrimidines through a sequential I_2-catalyzed bicyclization and disulphenylation pathway in a simple three-step manner. Single-crystal X-ray diffraction analysis of **5q** was conducted for further structural confirmation.

On the basis of the above-mentioned observations and reported survey,[13−15] reasonable mechanisms for the formation of products **3**, **4**, and **5** are proposed in Scheme 4. In the presence of the I_2 catalyst, *β*-ketonitriles are first subjected to a reaction with sulfonyl hydrazides to generate in situ pyrazole intermediates **B**, followed by reacting with another molecule of *β*-ketonitriles, affording intermediates **C**. Intermediates **C** undergo the cleavage of the N−S bond and intramolecular 5-*exo*-*dig* cyclization to form pyrazolo[1,5-*a*]pyrimidin-4-ium sulfonates **3**, which are quantitatively converted into compounds **4** in the presence of 10% aqueous sodium hydroxide (Scheme 4a). Second, sulphonyl hydrazides **2** mediated by molecular iodine are continuously transformed into thiodiazonium **E** by the elimination of HI and HOI.[13] **E** releases nitrogen to yield intermediates **F**. Then, two continuous Friedel−Crafts-type reactions between intermediates **E** or **F** and electron-rich pyrazolo[1,5-*a*]pyrimidines **4** occur to deliver final disulphenylated pyrazolo[1,5-*a*]pyrimidines **5** (Scheme 4b). Lastly, the released HI would be treated with HOI to regenerate in situ the iodine catalyst to complete the catalytic cycle (Scheme 4c).

In conclusion, we have developed a new iodine-catalyzed three-component bicyclization of *β*-ketonitriles with sulphonyl hydrazides, by which a wide range of functionalized pyrazolo[1,5-*a*]pyrimidin-4-ium sulfonates can be synthesized in a highly regioselective manner. Furthermore, sulfonyl hydrazides were also successfully applied as an alternative sulfenylating agent, enabling I_2-catalyzed unprecedented disulphenylations to access fully substituted pyrazolo[1,5-*a*]pyrimidines through direct C(sp^2)−H bond functionalization. A detailed application of resulting pyrazolo[1,5-*a*]pyrimidines is currently underway in our laboratory.

EXPERIMENTAL SECTION

General Procedure for the Synthesis of Products 3, 4, and 5. *Example for the Synthesis of* ***3a.*** 3-Oxo-3-phenylpropanenitrile (**1a**, 2.4 mmol, 348 mg) and 4-methylbenzenesulfonohydrazide (**2a**, 1.0 mmol, 186 mg) were introduced in a sealed 10 mL reaction tube, and I_2 (0.2 mmol, 50 mg) and EtOH (3.0 mL) were then successively added. Then, the mixture was stirred at 90 °C for 5 h. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature. Then, the organic solvent was concentrated by a rotary evaporator, and the residue was washed with ethyl acetate to afford the pure product **3a**.

*7-Amino-2,5-diphenylpyrazolo[1,5-a]pyrimidin-4-ium 4-Methylbenzenesulfonate (**3a**).* White solid, 344 mg, 75% yield; mp >300 °C; ^{1}H NMR (400 MHz, DMSO-d_6; *δ*, ppm) 9.61 (s, 2H), 8.16−8.14 (m, 2H), 7.94−7.91 (m, 2H), 7.70−7.66 (m, 3H), 7.58−7.51 (m, 5H), 7.13 (d, *J* = 8.0 Hz, 2H), 7.05 (s, 1H), 6.66 (s, 1H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6; *δ*, ppm) 156.9, 152.4, 151.1, 146.0, 142.8, 138.2, 132.5, 132.3, 131.6, 130.5, 129.8, 129.4, 128.6, 128.1, 127.2, 126.0, 89.5, 88.2, 21.2. IR (KBr, *ν*, cm^{-1}) 3077, 1661, 1635, 1446, 1219, 1122; HRMS (ESI-TOF) *m*/*z* calcd for $C_{18}H_{15}N_4^+$, 287.1291; found, 287.1280.

*7-Amino-2,5-di-p-tolylpyrazolo[1,5-a]pyrimidin-4-ium 4-Methylbenzenesulfonate (**3b**).* White solid, 384 mg, 79% yield; mp >300 °C; ^{1}H NMR (400 MHz, DMSO-d_6; *δ*, ppm) 9.58 (s, 2H), 8.03 (d, *J* = 7.2 Hz, 2H), 7.81 (d, *J* = 6.8 Hz, 2H), 7.53−7.45 (m, 4H), 7.36 (d, *J* = 6.8 Hz, 2H), 7.13 (d, *J* = 6.8 Hz, 2H), 6.97 (s, 1H), 6.63 (s, 1H), 2.43 (s, 3H), 2.39 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6; *δ*, ppm) 156.9, 152.1, 151.0, 146.0, 142.8, 142.6, 140.2, 138.2, 130.4, 130.0, 129.3, 128.8, 128.6, 128.0, 127.1, 126.0, 89.1, 87.6, 21.5, 21.5, 21.2 IR (KBr, *ν*, cm^{-1}) 3142, 3082, 1660, 1635, 1448, 1219, 1119. HRMS (ESI-TOF) *m*/*z* calcd for $C_{20}H_{19}N_4^+$, 315.1604; found, 315.1604.

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*7-Amino-2,5-di-m-tolylpyrazolo[1,5-a]pyrimidin-4-ium 4-Methylbenzenesulfonate (**3c**).* White solid, 389 mg, 80% yield; mp >300 °C; 1H NMR (400 MHz, DMSO-d_6; δ, ppm) 9.65 (s, 2H), 7.97 (s, 1H), 7.92 (d, *J* = 7.6 Hz, 1H), 7.73−7.69 (m, 2H), 7.56−7.49 (m, 4H), 7.45−7.42 (m, 1H), 7.32 (d, *J* = 7.6 Hz, 1H), 7.13 (d, *J* = 8.0 Hz, 2H), 6.99 (s, 1H), 6.66 (s, 1H), 2.44 (s, 3H), 2.42 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 156.9, 152.4, 151.4, 151.1, 145.9, 142.8, 132.5, 132.3, 131.6, 130.5, 129.8, 129.4, 128.2, 127.2, 125.8, 124.8, 89.5, 88.2, 34.8, 31.5. IR (KBr, ν, cm^{-1}) 3138, 1666, 1635, 1484, 1238, 1157. HRMS (ESI-TOF) *m*/*z* calcd for $C_{20}H_{19}N_4^+$, 315.1604; found, 315.1609.

*7-Amino-2,5-bis(4-methoxyphenyl)pyrazolo[1,5-a]pyrimidin-4-ium 4-Methylbenzenesulfonate (**3d**).* White solid, 430 mg, 83% yield; mp >300 °C; 1H NMR (400 MHz, *DMSO-d*$_6$; δ, ppm) 9.47 (s, 2H), 8.08 (d, *J* = 8.8 Hz, 2H), 7.89 (d, *J* = 8.8 Hz, 2H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 8.8 Hz, 2H), 7.13−7.10 (m, 4H), 6.92 (s, 1H), 6.57 (s, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 162.8, 161.2, 156.8, 151.6, 150.9, 146.1, 138.2, 129.9, 128.7, 128.5, 126.0, 124.0, 115.3, 114.8, 88.6, 87.0, 56.1, 55.8, 21.2. IR (KBr, ν, cm^{-1}) 3140, 1662, 1632, 1485, 1254, 1161, 1086. HRMS (ESI-TOF) *m*/*z* calcd for $C_{20}H_{19}N_4O_2^+$, 347.1503; found, 347.1495.

*7-Amino-2,5-bis(4-fluorophenyl)pyrazolo[1,5-a]pyrimidin-4-ium 4-Methylbenzenesulfonate (**3e**).* White solid, 336 mg, 68% yield; mp >300 °C; 1H NMR (400 MHz, DMSO-d_6; δ, ppm) 9.56 (s, 2H), 8.21−8.17 (m, 2H), 8.00−7.97 (m, 2H), 7.53−7.48 (m, 4H), 7.42−7.38 (m, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 7.03 (s, 1H), 6.65 (s, 1H), 2.29 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 164.6 (J_{CF} = 249.0 Hz), 163.6 (J_{CF} = 245.7 Hz), 155.9, 151.5, 150.9, 145.9, 143.1, 138.3, 130.8 (J_{CF} = 9.1 Hz), 129.4 (J_{CF} = 8.5 Hz), 128.6, 128.3 (J_{CF} = 2.9 Hz), 125.95, 116.9 (J_{CF} = 22.0 Hz), 116.4 (J_{CF} = 21.6 Hz), 89.50, 88.08, 21.23. IR (KBr, ν, cm^{-1}) 3096, 1671, 1605, 1449, 1219, 1173, 1011. HRMS (ESI-TOF) *m*/*z* calcd for $C_{18}H_{13}F_2N_4^+$, 323.1103; found, 323.1107.

*7-Amino-2,5-bis(4-chlorophenyl)pyrazolo[1,5-a]pyrimidin-4-ium 4-Methylbenzenesulfonate (**3f**).* White solid, 416 mg, 79% yield; mp >300 °C; 1H NMR (400 MHz, DMSO-d_6; δ, ppm) 9.23 (s, 2H), 8.16 (d, *J* = 8.4 Hz, 2H), 7.97 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 8.8 Hz, 2H), 7.63 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.06 (s, 1H), 6.63 (s, 1H), 2.29 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 155.3, 152.3, 150.4, 146.1, 138.1, 136.7, 134.8, 131.0, 129.8, 129.7, 129.5, 128.8, 128.5, 126.0, 90.3, 87.6, 21.2. IR (KBr, ν, cm^{-1}) 3050, 1675, 1640, 1483, 1222, 1163, 681. HRMS (ESI-TOF) *m*/*z* calcd for $C_{18}H_{13}Cl_2N_4^+$, 355.0512; found, 355.0510.

*7-Amino-2,5-bis(3-chlorophenyl)pyrazolo[1,5-a]pyrimidin-4-ium 4-Methylbenzenesulfonate (**3g**).* White solid, 384 mg, 73% yield; mp 274−275 °C; 1H NMR (400 MHz, DMSO-d_6; δ, ppm) 9.45 (s, 2H), 8.23−8.22 (m, 1H), 8.11−8.09 (m, 1H), 8.01−8.00 (m, 1H), 7.89−7.87 (m, 1H), 7.73−7.71 (m, 1H), 7.68−7.64 (m, 1H), 7.60−7.51 (m, 4H), 7.14−7.12 (m, 3H), 6.71 (s, 1H), 2.29 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 155.2, 151.5, 150.7, 145.8, 144.0, 138.3, 135.3, 134.3, 134.3, 134.0, 131.8, 131.6, 131.3, 130.0, 128.6, 127.8, 126.8, 126.5, 126.0, 125.8, 90.3, 88.3, 21.2. IR (KBr, ν, cm^{-1}) 3050, 1666, 1633, 1481, 1222, 1162, 678. HRMS (ESI-TOF) *m*/*z* calcd for $C_{18}H_{13}Cl_2N_4^+$, 355.0512; found, 355.0502.

*7-Amino-2,5-di(furan-2-yl)pyrazolo[1,5-a]pyrimidin-4-ium 4-Methylbenzenesulfonate (**3h**).* White solid, 332 mg, 76% yield; mp 26−261 °C; 1H NMR (400 MHz, DMSO-d_6; δ, ppm) 9.51 (s, 2H), 8.15 (d, *J* = 1.2 Hz, 1H), 7.93 (d, *J* = 1.2 Hz, 1H), 7.58 (d, *J* = 3.6 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 3.2 Hz, 1H), 7.14 (d, *J* = 8.0 Hz, 2H), 6.87−6.86 (m, 1H), 6.76 (s, 1H), 6.73−6.72 (m, 1H), 6.68 (s, 1H), 2.29 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 151.0, 148.7, 148.1, 146.9, 146.1, 145.9, 145.2, 142.6, 142.0, 138.3, 128.6, 126.0, 115.5, 114.0, 112.7, 111.3, 89.0, 84.8, 21.2. IR (KBr, ν, cm^{-1}) 3122, 1667, 1637, 1486, 1243, 1148, 1119. HRMS (ESI-TOF) *m*/*z* calcd for $C_{14}H_{11}N_4O_2^+$, 267.0877; found, 267.0881.

*7-Amino-2,5-di(thiophen-2-yl)pyrazolo[1,5-a]pyrimidin-4-ium 4-Methylbenzenesulfonate (**3i**).* White solid, 324 mg, 69% yield; mp 272−273 °C; 1H NMR (400 MHz, DMSO-d_6; δ, ppm) 9.01 (s, 2H), 7.95−7.93 (m, 2H), 7.83−7.82 (m, 1H), 7.73−7.72 (m, 1H), 7.52 (d, *J* = 8.0 Hz, 2H), 7.33−7.31 (m, 1H), 7.24−7.22 (m, 1H), 7.13 (d, *J* = 8.0 Hz, 2H), 6.87 (s, 1H), 6.59 (s, 1H), 2.29 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 152.0, 150.1, 147.5, 145.9, 144.6, 138.3, 134.9, 132.2, 129.8, 129.5, 128.6, 128.4, 126.0, 89.8, 86.0, 21.3. IR (KBr, ν, cm^{-1}) 3093, 1660, 1633, 1461, 1219, 1169, 570. HRMS (ESI-TOF) *m*/*z* calcd for $C_{14}H_{11}N_4S_2^+$, 299.0420; found, 299.0417.

*7-Amino-2,5-diphenylpyrazolo[1,5-a]pyrimidin-4-ium Benzenesulfonate (**3j**).* White solid, 316 mg, 71% yield; mp 280−281 °C; 1H NMR (400 MHz, DMSO-d_6; δ, ppm) 9.67 (s, 2H), 8.16−8.13 (m, 2H), 7.93−7.90 (m, 2H), 7.70−7.64 (m, 5H), 7.58−7.51 (m, 3H), 7.36−7.32 (m, 3H), 7.05 (s, 1H), 6.68 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 156.9, 152.2, 151.1, 148.5, 142.6, 132.5, 132.1, 131.6, 130.5, 129.8, 129.4, 129.0, 128.2, 127.2, 125.9, 89.4, 88.3. IR (KBr, ν, cm^{-1}) 3106, 1671, 1636, 1443, 1227, 1171. HRMS (ESI-TOF) *m*/*z* calcd for $C_{18}H_{15}N_4^+$, 287.1286; found, 287.1296.

*7-Amino-2,5-diphenylpyrazolo[1,5-a]pyrimidin-4-ium 4-Methoxybenzenesulfonate (**3k**).* White solid, 350 mg, 74% yield; mp 287−288 °C; 1H NMR (400 MHz, DMSO-d_6; δ, ppm) 9.57 (s, 2H), 8.15 (d, *J* = 6.8 Hz, 2H), 7.94−7.92 (m, 2H), 7.69−7.66 (m, 3H), 7.59−7.52 (m, 5H), 7.05 (s, 1H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.66 (s, 1H), 3.75 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 164.5, 161.6, 157.2, 155.8, 146.1, 137.1, 136.4, 135.2, 134.6, 134.2, 132.9, 132.3, 131.9, 118.0, 94.3, 92.8, 60.4. IR (KBr, ν, cm^{-1}) 3157, 3073, 1661, 1633, 1445, 1257, 1184, 1124. HRMS (ESI-TOF) *m*/*z* calcd for $C_{18}H_{15}N_4^+$, 287.1286; found, 287.1302.

*7-Amino-2,5-diphenylpyrazolo[1,5-a]pyrimidin-4-ium 4-(tert-Butyl)benzenesulfonate (**3l**).* Yellow solid, 290 mg, 58% yield; mp 283−284 °C; 1H NMR (400 MHz, DMSO-d_6; δ, ppm) 9.60 (s, 2H), 8.16−8.14 (m, 2H), 7.94−7.91 (m, 2H), 7.68−7.66 (m, 3H), 7.58−7.52 (m, 5H), 7.35−7.33 (m, 2H), 7.05 (s, 1H), 6.67 (s, 1H), 1.27 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 157.0, 152.2, 151.1, 145.8, 142.4, 139.3, 138.7, 138.3, 133.1, 132.0, 131.5, 131.1, 129.7, 129.3, 128.6, 128.5, 127.6, 126.0, 125.3, 124.4, 89.3, 88.2, 21.5, 21.4, 21.2. IR (KBr, ν, cm^{-1}) 3049, 1668, 1634, 1446, 1223, 1165. HRMS (ESI-TOF) *m*/*z* calcd for $C_{18}H_{15}N_4^+$, 287.1286; found, 287.1290.

*7-Amino-2,5-diphenylpyrazolo[1,5-a]pyrimidin-4-ium 4-Chlorobenzenesulfonate (**3m**).* White solid, 239 mg, 50% yield; mp 273−274 °C; 1H NMR (400 MHz, DMSO-d_6; δ, ppm) 9.57 (s, 2H), 8.15 (d, *J* = 7.2 Hz, 2H), 7.94−7.92 (m, 2H), 7.68−7.61 (m, 5H), 7.58−7.52 (m, 3H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.05 (s, 1H), 6.64 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 156.9, 152.5, 151.0, 147.6, 143.0, 133.5, 132.4, 131.7, 130.4, 129.8, 129.4, 128.2, 128.2, 127.9, 127.2, 89.5, 88.1. IR (KBr, ν, cm^{-1}) 3079, 1659, 1632, 1446, 1229, 1171, 673. HRMS (ESI-TOF) *m*/*z* calcd for $C_{18}H_{15}N_4^+$, 287.1286; found, 287.1290.

*7-Amino-2,5-diphenylpyrazolo[1,5-a]pyrimidin-4-ium 4-Bromobenzenesulfonate (**3n**).* White solid, 272 mg, 52% yield; mp >300 °C; 1H NMR (400 MHz, DMSO-d_6; δ, ppm) 9.59 (s, 2H), 8.17−8.15 (m, 2H), 7.93−7.91 (m, 2H), 7.70−7.65 (m, 3H), 7.59−7.51 (m, 7H), 7.05 (s, 1H), 6.63 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 156.9, 152.3, 151.1, 147.9, 142.7, 132.5, 132.2, 131.6, 131.1, 130.5, 129.8, 129.4, 128.2, 128.1, 127.2, 122.2, 89.4, 88.2. IR (KBr, ν, cm^{-1}) 3148, 3074, 1659, 1632, 1445, 1226, 1188, 566. HRMS (ESI-TOF) *m*/*z* calcd for $C_{18}H_{15}N_4^+$, 287.1286; found, 287.1296.

*7-Amino-2,5-diphenylpyrazolo[1,5-a]pyrimidin-4-ium 3-Bromobenzenesulfonate (**3o**).* White solid, 298 mg, 57% yield; mp 281−282 °C; 1H NMR (400 MHz, DMSO-d_6; δ, ppm) 9.61 (s, 2H), 8.17−8.14 (m, 2H), 7.93−7.91 (m, 2H), 7.74−7.67 (m, 4H), 7.63−7.51 (m, 5H), 7.34−7.30 (m, 1H), 7.05 (s, 1H), 6.63 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 156.9, 152.4, 151.1, 150.9, 142.7, 132.5, 132.3, 131.7, 131.6, 130.7, 130.5, 129.8, 129.4, 128.7, 128.2, 127.2, 125.0, 121.4, 89.4, 88.2. IR (KBr, ν, cm^{-1}) 3142, 1660, 1632, 1445, 1238, 1173, 584. HRMS (ESI-TOF) *m*/*z* calcd for $C_{18}H_{15}N_4^+$, 287.1286; found, 287.1292.

*7-Amino-2,5-diphenylpyrazolo[1,5-a]pyrimidin-4-ium Naphthalene-2-sulfonate (**3p**).* White solid, 356 mg, 72% yield; mp >300 °C; 1H NMR (400 MHz, DMSO-d_6; δ, ppm) 9.64 (s, 2H), 8.20 (s, 1H), 8.15−8.13 (m, 2H), 7.98−7.96 (m, 1H), 7.92−7.87 (m, 4H), 7.77−7.75 (m, 1H), 7.68−7.65 (m, 3H), 7.57−7.51 (m, 5H), 7.04 (s, 1H), 6.66 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 156.9,

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152.3, 151.1, 145.9, 142.7, 133.2, 132.6, 132.5, 132.2, 131.6, 130.5, 129.8, 129.4, 128.9, 128.2, 127.9, 127.9, 127.2, 127.0, 126.8, 124.6, 124.4, 89.4, 88.2. IR (KBr, ν, cm^{-1}) 3115, 1663, 1628, 1444, 1234, 1161. HRMS (ESI-TOF) m/z calcd for $C_{18}H_{15}N_4^+$, 287.1286; found, 287.1296.

*7-Amino-2,5-diphenylpyrazolo[1,5-a]pyrimidin-4-ium Phenylmethanesulfonate (**3q**).* Yellow solid, 289 mg, 63% yield; mp 220−221 °C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 9.55 (s, 2H), 8.16−8.13 (m, 2H), 7.95−7.92 (m, 2H), 7.69−7.66 (m, 3H), 7.58−7.52 (m, 4H), 7.32−7.17 (m, 4H), 7.05 (s, 1H), 6.67 (s, 1H), 3.76 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 156.8, 152.4, 151.0, 143.0, 135.7, 132.4, 131.7, 130.7, 130.4, 129.8, 129.4, 128.1, 127.9, 127.2, 126.6, 89.6, 88.1, 58.0. IR (KBr, ν, cm^{-1}) 3059, 1662, 1633, 1446, 1220, 1179. HRMS (ESI-TOF) m/z calcd for $C_{18}H_{15}N_4^+$, 287.1286; found, 287.1291.

*Example for the Synthesis of **4a**.* The resultant compound **3a** (0.5 mmol, 230 mg) was poured into 10% NaOH aqueous (10 mL). The solution was stirred for 30 min and then was extracted with CH_2Cl_2 (3 × 10 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated by a rotary evaporator to afford the pure product **4a**.

*2,5-Diphenylpyrazolo[1,5-a]pyrimidin-7-amine (**4a**).* White solid, 140 mg, 98% yield; mp 274−275 °C. ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 7.87 (d, J = 6.8 Hz, 2H), 7.72 (d, J = 8.2 Hz, 2H), 7.58−7.54 (m, 2H), 7.43−7.32 (m, 4H), 7.10 (d, J = 8.0 Hz, 2H), 7.02 (d, J = 8.0 Hz, 2H), 5.77 (s, 2H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 156.1, 154.9, 150.8, 148.5, 138.7, 133.5, 130.1, 129.2, 129.2, 128.6, 127.2, 126.6, 92.0, 84.9; IR (KBr, ν, cm^{-1}) 3319, 3025, 1652, 1574. HRMS (ESI-TOF) m/z calcd for $C_{18}H_{15}N_4$ [M + H]$^+$, 287.1292; found, 287.1295.

*2,5-Di-p-tolylpyrazolo[1,5-a]pyrimidin-7-amine (**4b**).* White solid, 152 mg, 97% yield; mp 262−263 °C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 7.98−7.94 (m, 4H), 7.77 (s, 2H), 7.33−7.30 (m, 4H), 6.85 (s, 1H), 6.61 (s, 1H), 2.39 (s, 3H), 2.37 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 179.7, 160.8, 159.6, 155.5, 153.2, 144.4, 143.3, 140.7, 135.5, 134.5, 134.5, 131.8, 131.3, 96.2, 89.3, 30.6, 26.1, 26.1. IR (KBr, ν, cm^{-1}) 3303, 3018, 1647, 1570. HRMS (ESI-TOF) m/z calcd for $C_{20}H_{19}N_4$ [M + H]$^+$, 315.1605; found, 315.1620.

*2,5-Di-m-tolylpyrazolo[1,5-a]pyrimidin-7-amine (**4c**).* White solid, 149 mg, 95% yield; mp 224−225 °C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 7.93 (s, 1H), 7.89−7.76 (m, 5H), 7.42−7.37 (m, 2H), 7.29 (d, J = 7.6 Hz, 1H), 7.24 (d, J = 7.6 Hz, 1H), 6.90 (s, 1H), 6.62 (s, 1H), 2.42 (s, 3H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 156.2, 155.0, 150.8, 148.5, 138.7, 138.3, 138.3, 133.4, 130.7, 129.8, 129.0, 127.7, 127.1, 124.3, 123.9, 91.9, 84.9, 21.6, 21.6. IR (KBr, ν, cm^{-1}) 3285, 1629, 1561. HRMS (ESI-TOF) m/z calcd for $C_{20}H_{19}N_4$ [M + H]$^+$, 315.1605; found, 315.1609.

*2,5-Bis(4-methoxyphenyl)pyrazolo[1,5-a]pyrimidin-7-amine (**4d**).* White solid, 166 mg, 96% yield; mp 224−225 °C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.02−7.99 (m, 4H), 7.64 (s, 2H), 7.08−7.05 (m, 4H), 6.79 (s, 1H), 6.54 (s, 1H), 3.84 (s, 3H), 3.83 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 161.0, 160.2, 155.7, 154.7, 150.8, 148.3, 131.1, 128.6, 127.9, 126.1, 114.5, 114.5, 91.0, 84.0, 55.7, 55.7. IR (KBr, ν, cm^{-1}) 3110, 2963, 1629, 1566, 1244. HRMS (ESI-TOF) m/z calcd for $C_{20}H_{19}N_4O_2$ [M + H]$^+$, 347.1503; found, 347.1514.

*2,5-Bis(4-fluorophenyl)pyrazolo[1,5-a]pyrimidin-7-amine (**4e**).* White solid, 158 mg, 98% yield; mp 238−239 °C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.14−8.08 (m, 4H), 7.82 (s, 2H), 7.37−7.32 (m, 4H), 6.92 (s, 1H), 6.61 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 163.6 (J_{CF} = 245.3 Hz), 163.0 (J_{CF} = 243.9 Hz), 155.1, 154.0, 150.8, 148.5, 135.1 (J_{CF} = 2.9 Hz), 130.0 (J_{CF} = 2.9 Hz), 129.4 (J_{CF} = 8.5 Hz), 128.7 (J_{CF} = 8.3 Hz), 116.1 (J_{CF} = 21.4 Hz), 116.0 (J_{CF} = 21.4 Hz), 91.91, 84.75. IR (KBr, ν, cm^{-1}) 3285, 3163, 1630, 1566, 1236. HRMS (ESI-TOF) m/z calcd for $C_{18}H_{13}F_2N_4$ [M + H]$^+$, 323.1103; found, 323.1113.

*2,5-Bis(4-chlorophenyl)pyrazolo[1,5-a]pyrimidin-7-amine (**4f**).* White solid, 163 mg, 92% yield; mp 255−256 °C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.11−8.06 (m, 4H), 7.92 (s, 2H), 7.59−7.56 (m, 4H), 6.97 (s, 1H), 6.65 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 159.7, 158.5, 155.5, 153.4, 142.2, 139.6, 138.6, 137.1, 134.0, 133.9, 133.7, 133.0, 97.0, 89.7. HRMS (ESI-TOF) m/z calcd for $C_{18}H_{13}Cl_2N_4$ [M + H]$^-$, 355.0517; found, 355.0520. IR (KBr, ν, cm^{-1}) 3284, 3169, 1637, 1560, 780. HRMS (ESI-TOF) m/z calcd for $C_{18}H_{13}Cl_2N_4$ [M + H]$^+$, 355.0512; found, 355.0520.

*2,5-Bis(3-chlorophenyl)pyrazolo[1,5-a]pyrimidin-7-amine (**4g**).* White solid, 165 mg, 93% yield; mp 232−233 °C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.19−8.18 (m, 1H), 8.09−8.08 (m, 1H), 8.05−8.03 (m, 1H), 8.00−7.97 (m, 1H), 7.91 (s, 2H), 7.56−7.47 (m, 4H), 7.05 (s, 1H), 6.65 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 154.6, 153.5, 150.7, 148.6, 140.7, 135.6, 134.1, 134.1, 131.1, 129.8, 129.0, 126.9, 126.1, 125.8, 125.3, 92.7, 85.2. IR (KBr, ν, cm^{-1}) 3282, 3170, 1628, 1559, 764. HRMS (ESI-TOF) m/z calcd for $C_{18}H_{13}Cl_2N_4$ [M + H]$^+$, 355.0512; found, 355.0517.

*2,5-Di(thiophen-2-yl)pyrazolo[1,5-a]pyrimidin-7-amine (**4h**).* Yellow solid, 136 mg, 91% yield; mp 259−260 °C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 7.71−7.67 (m, 5H), 7.63−7.62 (m, 1H), 7.20−7.18 (m, 2H), 6.78 (s, 1H), 6.54 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 151.7, 150.6, 150.2, 148.2, 144.4, 136.5, 129.7, 128.8, 128.4, 127.2, 126.7, 126.6, 91.4, 83.6. IR (KBr, ν, cm^{-1}) 3294, 1628, 1590, 594. HRMS (ESI-TOF) m/z calcd for $C_{14}H_{11}N_4S_2$ [M + H]$^+$, 299.0420; found, 299.0428.

*Example for the Synthesis of **5a**.* The preformed pyrazolo[1,5-*a*]pyrimidines **4a** (0.25 mmol, 71 mg) and 4-methylbenzenesulfonohydrazide (**2a**, 0.6 mmol, 111 mg) were introduced in a sealed 10 mL reaction tube, I_2 (0.125 mmol, 31 mg) and EtOH (2.5 mL) were then successively added, and the mixture was stirred at 110 °C for 6 h. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature. Then, the organic solvent was concentrated by a rotary evaporator, and the residue was purified by column chromatography (eluents, petroleum ether/ethyl acetate 30:1) to afford the pure product **5a**.

*2,5-Diphenyl-3,6-bis(p-tolylthio)pyrazolo[1,5-a]pyrimidin-7-amine (**5a**).* White solid, 90 mg, yield 68%; mp 196−197 °C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.39 (s, 2H), 8.14−8.12 (m, 2H), 7.49−7.45 (m, 5H), 7.39−7.34 (m, 3H), 7.09−7.00 (m, 6H), 6.95 (d, J = 8.0 Hz, 2H), 2.23 (s, 3H), 2.20 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 164.7, 157.6, 151.2, 151.1, 140.0, 135.4, 135.3, 134.8, 133.6, 132.6, 130.3, 130.2, 129.7, 129.3, 129.1, 128.8, 128.7, 127.9, 126.2, 125.9, 92.7, 89.8, 20.9, 20.9. IR (KBr, ν, cm^{-1}) 3356, 3349, 1610, 1582, 1574, 697; HRMS (ESI-TOF) m/z calcd for $C_{32}H_{27}N_4S_2$ [M + H]$^+$, 531.1672; found, 531.1659.

*2,5-Di-m-tolyl-3,6-bis(p-tolylthio)pyrazolo[1,5-a]pyrimidin-7-amine (**5b**).* White solid, 92 mg, yield 66%; mp 204−205 °C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.37 (s, 2H), 7.96 (s, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.36−7.32 (m, 1H), 7.27−7.18 (m, 5H), 7.10−7.00 (m, 6H), 6.95 (d, J = 8.4 Hz, 2H), 2.34 (s, 3H), 2.26 (s, 3H), 2.23 (s, 3H), 2.20 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 164.9, 157.7, 151.2, 151.0, 140.0, 137.9, 136.9, 135.5, 135.3, 134.9, 133.8, 132.5, 130.3, 130.2, 130.2, 129.9, 129.7, 129.3, 128.7, 127.7, 126.4, 126.3, 126.1, 125.9, 92.9, 89.9, 21.6, 21.5, 20.9, 20.9. IR (KBr, ν, cm^{-1}) 3421, 1611, 1582, 1575, 698; HRMS (ESI-TOF) m/z calcd for $C_{34}H_{31}N_4S_2$ [M + H]$^+$, 559.1979; found, 559.1977.

*2,5-Bis(4-methoxyphenyl)-3,6-bis(p-tolylthio)pyrazolo[1,5-a]pyrimidin-7-amine (**5c**).* White solid, 108 mg, yield 73%; mp 181−182 °C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.27 (s, 2H), 8.11 (d, J = 8.8 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 7.10−6.99 (m, 8H), 6.96−6.90 (m, 4H), 3.80 (s, 3H), 3.76 (s, 3H), 2.23 (s, 3H), 2.20 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 163.9, 160.6, 160.2, 157.3, 151.1, 135.6, 135.3, 134.8, 133.7, 132.2, 131.1, 130.3, 130.2, 130.0, 126.0, 125.8, 125.0, 114.3, 113.3, 91.8, 89.2, 55.7, 55.6, 20.9, 20.9. IR (KBr, ν, cm^{-1}) 3490, 3380, 1602, 1572, 1526, 1247, 616; HRMS (ESI-TOF) m/z calcd for $C_{34}H_{31}N_4O_2S_2$ [M + H]$^+$, 591.1883; found, 591.1871.

*2,5-Bis(4-fluorophenyl)-3,6-bis(p-tolylthio)pyrazolo[1,5-a]pyrimidin-7-amine (**5d**).* White solid, 72 mg, yield 51%; mp 149−150 °C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.44 (s, 2H), 8.21−8.17 (m, 2H), 7.56−7.53 (m, 2H), 7.36−7.31 (m, 2H), 7.22−7.17 (m, 2H), 7.09−7.04 (m, 4H), 7.00 (d, J = 8.4 Hz, 2H), 6.95 (d, J = 8.0 Hz, 2H), 2.23 (s, 3H), 2.20 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm)

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163.2 (J_{CF} = 245.5 Hz), 163.6, 162.8 (J_{CF} = 244.5 Hz), 156.6, 151.2, 151.0, 136.4, 136.3, 135.4, 135.2, 134.9, 133.4, 131.6 (J_{CF} = 8.4 Hz), 130.8 (J_{CF} = 8.4 Hz), 130.3 (J_{CF} = 5.0 Hz), 129.0 (J_{CF} = 3.1 Hz), 126.2, 125.9, 115.9 (J_{CF} = 21.4 Hz), 114.8 (J_{CF} = 21.5 Hz), 92.5, 89.9, 20.9, 20.9. IR (KBr, ν, cm^{-1}) 3444, 3381, 1620, 1601, 1578, 1222, 612; HRMS (ESI-TOF) m/z calcd for $C_{32}H_{25}F_2N_4S_2$ $[M + H]^+$, 567.1484; found, 567.1502.

*2,5-Di(furan-2-yl)-3,6-bis(p-tolylthio)pyrazolo[1,5-a]pyrimidin-7-amine (**5e**).* Yellow solid, 94 mg, yield 74%; mp 225−226 °C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.37 (s, 2H), 7.89−7.86 (m, 2H), 7.33 (d, J = 3.6 Hz, 1H), 7.18 (d, J = 3.2 Hz, 1H), 7.11 (d, J = 8.0 Hz, 2H), 7.07−7.03 (m, 6H), 6.65−6.64 (m, 1H), 6.60−6.59 (m, 1H), 2.23 (s, 3H), 2.21 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 152.4, 151.7, 150.7, 150.0, 146.3, 145.3, 144.4, 135.5, 134.9, 134.8, 133.1, 130.4, 130.2, 126.1, 126.0, 116.1, 112.7, 112.4, 91.8, 87.5, 20.9, 20.9. IR (KBr, ν, cm^{-1}) 3463, 3356, 1608, 1582, 1566, 1084, 594. HRMS (ESI-TOF) m/z calcd for $C_{28}H_{23}N_4O_2S_2$ $[M + H]^+$, 511.1257; found, 511.1268.

*2,5-Di(thiophen-2-yl)-3,6-bis(p-tolylthio)pyrazolo[1,5-a]pyrimidin-7-amine (**5f**).* Yellow solid, 80 mg, yield 59%; mp 245−246 °C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.34 (s, 2H), 8.08−8.07 (m, 1H), 7.98−7.97 (m, 1H), 7.71−7.68 (m, 2H), 7.19−7.17 (m, 1H), 7.12 (d, J = 8.0 Hz, 4H), 7.09−7.05 (m, 5H), 2.23 (s, 3H), 2.21 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 155.6, 153.1, 151.5, 150.6, 142.5, 135.5, 135.2, 134.8, 134.1, 133.0, 131.4, 131.3, 130.5, 130.2, 129.1, 128.2, 128.1, 128.0, 126.6, 125.9, 91.9, 87.6, 20.9. IR (KBr, ν, cm^{-1}) 3473, 3361, 1605, 1585, 1524, 572; HRMS (ESI-TOF) m/z calcd for $C_{28}H_{23}N_4S_4$ $[M + H]^+$, 543.0801; found, 543.0812.

*2,5-Diphenyl-3,6-bis(phenylthio)pyrazolo[1,5-a]pyrimidin-7-amine (**5g**).* White solid, 72 mg, yield 57%; mp 199−200 °C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.45 (s, 2H), 8.14−8.11 (m, 2H), 7.49−7.45 (m, 5H), 7.38−7.34 (m, 3H), 7.30−7.22 (m, 4H), 7.16−7.05 (m, 6H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 164.8, 157.7, 151.3, 151.2, 140.0, 139.0, 137.2, 132.5, 129.8, 129.6, 129.6, 129.3, 129.1, 128.8, 128.7, 127.9, 125.9, 125.8, 125.6, 125.5, 92.1, 89.3. IR (KBr, ν, cm^{-1}) 3434, 3306, 1622, 1576, 581; HRMS (ESI-TOF) m/z calcd for $C_{30}H_{23}N_4S_2$ $[M + H]^+$, 503.1359; found, 503.1382.

*3,6-Bis((4-methoxyphenyl)thio)-2,5-diphenylpyrazolo[1,5-a]pyrimidin-7-amine (**5h**).* White solid, 103 mg, yield 73%; mp 168−169 °C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.38 (s, 2H), 8.16−8.13 (m, 2H), 7.54−7.46 (m, 5H), 7.44−7.39 (m, 3H), 7.10 (d, J = 8.8 Hz, 2H), 7.00 (d, J = 8.8 Hz, 2H), 6.85−6.82 (m, 4H), 3.69 (s, 3H), 3.67 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 164.5, 158.4, 158.0, 157.4, 151.0, 150.9, 140.1, 132.6, 129.7, 129.6, 129.3, 129.1, 128.8, 128.7, 128.3, 127.9, 127.4, 115.3, 93.9, 91.2, 55.6, 55.6. IR (KBr, ν, cm^{-1}) 3453, 3347, 1610, 1581, 1573, 1244, 569; HRMS (ESI-TOF) m/z calcd for $C_{32}H_{27}N_4O_2S_2$ $[M + H]^+$, 563.1570; found, 563.1591.

*3,6-Bis((4-(tert-butyl)phenyl)thio)-2,5-diphenylpyrazolo[1,5-a]pyrimidin-7-amine (**5i**).* White solid, 86 mg, yield 56%; mp 251−252 °C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.39 (s, 2H), 8.18−8.15 (m, 2H), 7.53−7.45 (m, 5H), 7.40−7.34 (m, 3H), 7.30−7.24 (m, 4H), 7.03 (d, J = 8.8 Hz, 2H), 6.97 (d, J = 8.4 Hz, 2H), 1.22 (s, 3H), 1.20 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 164.7, 157.6, 151.1, 151.0, 148.6, 148.2, 140.0, 135.5, 133.5, 132.6, 129.8, 129.5, 129.1, 128.9, 128.7, 127.9, 126.5, 126.5, 125.8, 125.7, 92.7, 89.7, 34.6, 34.5, 31.5. IR (KBr, ν, cm^{-1}) 3488, 3376, 1610, 1582, 1574, 569; HRMS (ESI-TOF) m/z calcd for $C_{38}H_{39}N_4S_2$ $[M + H]^+$, 615.2611; found, 615.2620.

*3,6-Bis((4-fluorophenyl)thio)-2,5-diphenylpyrazolo[1,5-a]pyrimidin-7-amine (**5j**).* White solid, 55 mg, yield 41%; mp 193−194 °C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.48 (s, 2H), 8.12−8.10 (m, 2H), 7.49−7.46 (m, 5H), 7.40−7.37 (m, 3H), 7.17−7.14 (m, 2H), 7.12−7.07 (m, 6H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 164.8, 161.0 (J_{CF} = 240.9 Hz), 161.96 (J_{CF} = 240.7 Hz), 157.5, 151.3, 151.1, 139.9, 134.4 (J_{CF} = 2.8 Hz), 132.6 (J_{CF} = 2.7 Hz), 132.4, 129.8, 129.3, 129.1, 128.9, 128.66, 128.3 (J_{CF} = 7.9 Hz), 127.9, 127.8 (J_{CF} = 7.9 Hz), 116.6 (J_{CF} = 22.0 Hz), 92.6, 89.9. IR (KBr, ν, cm^{-1}) 3434, 3290, 1603, 1583, 1573, 1228, 623; HRMS (ESI-TOF) m/z calcd for $C_{30}H_{21}F_2N_4S_2$ $[M + H]^+$, 539.1171; found, 539.1182.

*3,6-bis((4-chlorophenyl)thio)-2,5-diphenylpyrazolo[1,5-a]pyrimidin-7-amine (**5k**).* White solid, 67 mg, yield 47%; mp 218−219 °C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.51 (s, 2H), 8.10−8.08 (m, 2H), 7.51−7.44 (m, 5H), 7.39−7.28 (m, 7H), 7.14−7.07 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 164.9, 157.6, 151.3, 151.2, 139.9, 138.1, 136.4, 132.4, 130.4, 130.1, 129.9, 129.5, 129.2, 128.9, 128.6, 127.9, 127.5, 127.3, 91.7, 89.0. IR (KBr, ν, cm^{-1}) 3435, 3292, 1603, 1583, 1573, 763, 578; HRMS (ESI-TOF) m/z calcd for $C_{30}H_{21}Cl_2N_4S_2$ $[M + H]^+$, 571.0580; found, 571.0595.

*3,6-Bis((4-bromophenyl)thio)-2,5-diphenylpyrazolo[1,5-a]pyrimidin-7-amine (**5l**).* White solid, 109 mg, yield 66%; mp 230−231 °C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.52 (s, 2H), 8.11−8.08 (m, 2H), 7.51−7.42 (m, 8H), 7.41−7.35 (m, 4H), 7.07−7.01 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 164.9, 157.6, 151.3, 151.2, 139.9, 138.7, 137.0, 132.4, 132.3, 129.9, 129.2, 129.2, 128.9, 128.6, 128.0, 127.8, 127.6, 118.6, 118.3, 91.6, 88.8. IR (KBr, ν, cm^{-1}) 3436, 3292, 1603, 1584, 1573, 665, 577; HRMS (ESI-TOF) m/z calcd for $C_{30}H_{21}Br_2N_4S_2$ $[M + H]^+$, 658.9569; found, 658.9572.

*3,6-Bis((3-bromophenyl)thio)-2,5-diphenylpyrazolo[1,5-a]pyrimidin-7-amine (**5m**).* White solid, 100 mg, yield 61%; mp 148−149 °C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.56 (s, 2H), 8.12−8.09 (m, 2H), 7.52−7.45 (m, 5H), 7.40−7.32 (m, 4H), 7.30−7.26 (m, 3H), 7.24−7.17 (m, 2H), 7.12−7.10 (m, 1H), 7.05−7.03 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 165.0, 157.6, 151.4, 151.2, 141.7, 140.1, 139.8, 132.3, 131.5, 131.5, 129.9, 129.2, 129.1, 128.9, 128.7, 128.6, 128.4, 128.1, 128.0, 127.7, 124.6, 124.6, 122.8, 122.7, 91.3, 88.6. IR (KBr, ν, cm^{-1}) 3411, 3280, 1607, 1582, 1571, 675, 584; HRMS (ESI-TOF) m/z calcd for $C_{30}H_{21}Br_2N_4S_2$ $[M + H]^+$, 658.9569; found, 658.9562.

*3,6-Bis(naphthalen-1-ylthio)-2,5-diphenylpyrazolo[1,5-a]pyrimidin-7-amine (**5n**).* White solid, 60 mg, yield 38%; mp 229−230 °C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.52 (s, 2H), 8.18−8.15 (m, 2H), 7.87−7.81 (m, 5H), 7.76 (d, J = 8.0 Hz, 1H), 7.59−7.57 (m, 2H), 7.50−7.41 (m, 9H), 7.36−7.26 (m, 5H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 164.9, 157.7, 151.5, 151.4, 140.0, 136.7, 135.0, 133.9, 133.9, 132.6, 131.5, 131.4, 129.2, 129.1, 128.9, 128.7, 128.1, 127.9, 127.4, 127.3, 127.1, 125.9, 125.8, 124.6, 124.6, 122.9, 92.0, 88.9. IR (KBr, ν, cm^{-1}) 3438, 3306, 1602, 1575, 577; HRMS (ESI-TOF) m/z calcd for $C_{38}H_{27}N_4S_2$ $[M + H]^+$, 603.1672; found, 603.1674.

*2,5-Bis(4-fluorophenyl)-3,6-bis(phenylthio)pyrazolo[1,5-a]pyrimidin-7-amine (**5p**).* White solid, 105 mg, yield 78%; mp 184−185 °C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.49 (s, 2H), 8.21−8.17 (m, 2H), 7.55−7.52 (m, 2H), 7.36−7.32 (m, 2H), 7.29−7.14 (m, 7H), 7.13−7.05 (m, 5H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 163.8, 163.2 (1 J_{CF} = 245.5 Hz), 162.8 (J_{CF} = 244.5 Hz), 156.7, 151.3, 151.1, 138.7, 137.0, 136.3, 136.3, 131.6 (J_{CF} = 8.4 Hz), 130.8 (J_{CF} = 8.4 Hz), 129.6 (J_{CF} = 4.5 Hz), 129.0 (J_{CF} = 3.1 Hz), 125.9, 125.8, 125.6, 115.9 (J_{CF} = 21.4 Hz), 114.8 (J_{CF} = 21.5 Hz), 92.0, 89.3. IR (KBr, ν, cm^{-1}) 3469, 3358, 1614, 1598, 1577, 1221, 611; HRMS (ESI-TOF) m/z calcd for $C_{30}H_{21}F_2N_4S_2$ $[M + H]^+$, 539.1171; found, 539.1190.

*3,6-Bis((4-bromophenyl)thio)-2,5-bis(4-fluorophenyl)pyrazolo-[1,5-a]pyrimidin-7-amine (**5q**).* White solid, 134 mg, yield 77%; mp 196−197 °C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.56 (s, 2H), 8.17−8.13 (m, 2H), 7.52−7.49 (m, 2H), 7.45−7.40 (m, 4H), 7.37−7.33 (m, 2H), 7.22−7.17 (m, 2H), 7.06−7.01 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 163.3 (J_{CF} = 245.8 Hz), 163.9, 162.8 (J_{CF} = 244.7 Hz), 156.6, 151.3, 151.2, 138.4, 136.8, 136.2, 136.1, 132.4, 131.5 (J_{CF} = 8.4 Hz), 130.8 (J_{CF} = 8.4 Hz), 128.8 (J_{CF} = 3.1 Hz), 127.8, 127.6, 118.7, 118.4, 116.0 (J_{CF} = 21.4 Hz), 114.9 (J_{CF} = 21.5 Hz), 91.4, 88.9. IR (KBr, ν, cm^{-1}) 3453, 3344, 1605, 1577, 1229, 566; HRMS (ESI-TOF) m/z calcd for $C_{30}H_{19}Br_2F_2N_4S_2$ $[M + H]^+$, 694.9381; found, 694.9396.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00332.

^{1}H and ^{13}C NMR spectra for all pure products (PDF)

X-ray crystal data for **3h** (CIF)

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X-ray crystal data for **5q** (CIF)

AUTHOR INFORMATION

Corresponding Authors

*E-mail: guocheng@njtech.edu.cn (C.G.).
*E-mail: jiangchem@jsnu.edu.cn (B.J.).
*E-mail: laotu@jsnu.edu.cn (S.J.T.).

Author Contributions

§J.S. and J.-K.Q. contributed equally.

Notes

The authors declare no competing financial interest.

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