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PAPER

Convenient one-pot multicomponent strategy for the synthesis of 6-pyrrolylpyrimidines†

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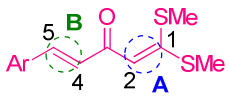
We have developed an easy method to construct diheteroaryls from α-aroylidineketene dithioacetals in a multicomponent fashion. The reaction proceeded with high chemo/regioselectivity to yield 4-alkoxy-6-(4-aryl-1*H*-pyrrol-3-yl)pyrimidin-2-amines under milder conditions. It is found that α-aroylidineketene dithioacetals 2 undergo cycloaddition with (*p*-tolylsulfonyl)methyl isocyanide 3 [TosMIC], guanidine nitrate 5 and alcohol in the presence of NaH/THF to furnish the target 6-pyrrolylpyrimidines 8 in excellent yields.

Pyrimidines are bases present in nucleic acids and play significant roles in medicinal chemistry[1] by exhibiting antibacterial[2], anti-inflammatory[3], cytotoxicity[4], anticancer[5] properties. They have long and distinguished history extending from the day of their discovery and current use in chemotherapy for the treatment of HIV and in other clinical applications. Interestingly, pyrrole derivatives also find significant applications in the field of medicinal chemistry, owing to their pharmacological properties[6] and as synthons for porphyrins[7] / boron-dipyrromethanes (BODIPY)[8] *etc*. Literally, pyrimidine and pyrrole heterocycles combined together as a single molecule could be expected to have excellent biological activity.

Over the past decade α-oxoketene dithioacetals have emerged as versatile intermediates in organic synthesis and they have found applications in the synthesis of substituted and fused aromatic heterocyclic frameworks.[9, 10]

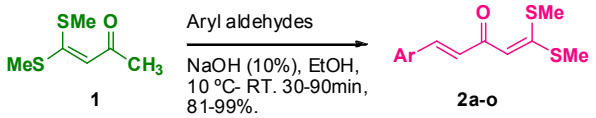


2

Figure 1: General structure of α-aroylidineketene dithioacetals **2**

The α-aroylidineketene dithioacetals[11] **2** are five-carbon 1,5-bielectrophilic species, dense and flexible substitution patterns, and good leaving alkylthio groups open to S_NV-type reactions. The α-aroylidineketene dithioacetals **2** have two different double bonds between C1 - C2 (**A**) and C4 - C5 (**B**). Double bond **A** is push-pull type flanked by two electrons donating methyl sulfanyl and one electron withdrawing carbonyl group and **B** is flanked by electron withdrawing carbonyl and an aryl group (Figure 1). Double bond **A** is more polarized than **B** owing to electron donating characteristics of two methyl sulfanyl groups and have structural features of a α,β-unsaturated carbonyl group with different reactivity towards addition/substitution reactions for the synthesis of a variety of heterocyclic compounds.

α-Aroylidineketene dithioacetals **2** of aromatic substrates are very useful synthons for a variety of heterocycles. To examine the reactivity of β-unsaturated ketones and push-pull alkenes together, we synthesized several α-aroylidineketene dithioacetals **2a-o** by aldol condensation between aryl aldehydes and 4,4-*bis*(methylthio)but-3-en-2-one **1** by following the reported procedure[12] (Scheme 1, Table 1).

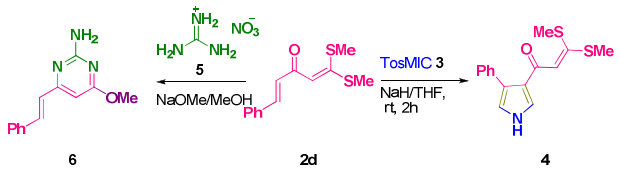


Scheme 1&Table 1: Synthesis of α-aroylidineketene dithioacetals **2a-o.**[a] from **1**

Entry	Ar		Time (min)	Yield[b] %
1	4-OMe-C_6H_4-	2a	30	90[c]
2	2,4-Cl_2-C_6H_3-	2b	30	99
3	3-Cl-C_6H_4-	2c	45	85
4	C_6H_5-	2d	45	81[c]
5	2,4-F_2-C_6H_3-	2e	30	88
6	2-OMe,5-Br-C_6H_3-	2f	40	87
7	4-Cl-C_6H_4-	2g	30	99[c]
8	3,4,5-OMe-C_6H_2-	2h	30	88[c]
9	3-OH-C_6H_4-	2i	40	87
10	3,4-OMe-C_6H_3-	2j	30	89[c]
11	4-CH_3-C_6H_4-	2k	30	90[c]
12	2-F-C_6H_4-	2l	45	92
13	2-furyl-	2m	90	87
14	2-thienyl-	2n	60	86
15	5-Br-C_5H_3N-	2o	60	82

[a]*Optimal Reaction conditions*: **1** (1eq), Ar-CHO (1.1eq), 10% NaOH (1.5eq), Ethanol (5mL), Water (1mL), 10 ºC - RT, 30-90min. [b] Isolated yields after recrystallization . [c]compounds **2a**, **2d**, **2g**, and **2k** [13], **2h** & **2j**[14] are known.

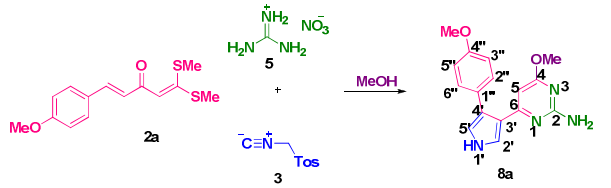
Following our earlier report[15], 3,3-bis(methylthio)-1-(4-aryl-1*H*-pyrrol-3-yl)prop-2-en-1-one **4** was synthesized selectively *via* 1,3-dipolar cycloaddition by involving (*p*-tolylsulfonyl)methyl isocyanide[16] **3** & **2** in the presence of NaH/THF at room temperature (Scheme 2). Similarly, styrylpyrimidines **6** was synthesized by following the reported procedure by mixing guanidine nitrate **5** and **2** under reflux condition (Scheme 2). [17,18]



Scheme 2: Synthesis of **4** & **6** by cycloaddition of **2d** with **3** & **5**

Utilizing the structural features of α-aroylidineketene dithioacetal **2**, we generated novel heterocyclic molecule 4-alkoxy-6-(4-aryl-1*H*-pyrrol-3-yl)pyrimidin-2-amines **8** in a multicomponent fashion with excellent yields. To the best of our knowledge, no such study on the synthesis of diheteroaryls core has been reported by this methodology.

In continuation of our earlier work[15], compound **8a** was synthesized by taking the reaction as a test case to evaluate the cycloaddition of **3**, **5** with **2a** and methanol in a multicomponent fashion. Several reactions were tried to optimize the reaction condition (Scheme 3, Table 2).

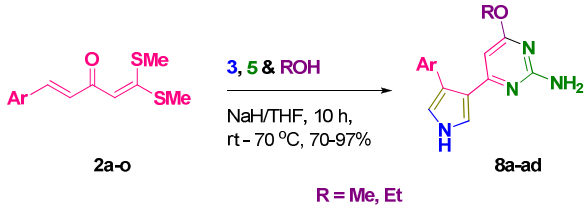


Scheme 3, Table 2: Optimization of reaction conditions for the synthesis of **8a** under multicomponent fashion.

Entry	Bases	Solvents	Temp. (ºC)	Time (h)	Yield (%)
1	NaH	THF	70	10	75[a]
2	NaH	THF	70	15	75[a]
3	NaH	1,4-Dioxane	110	12	40[b]
4	NaH	Benzene	100	12	20[b]
5	NaH	Toluene	110	12	15[b]
6	NaH	DMF	120	12	<5[b]
7	NaH	Xylene	140	12	<5[b]
8	K_2CO_3	Toluene	110	12	--[b]
9	K_2CO_3	THF	70	12	--[b]
10	K_2CO_3	1,4-Dioxane	110	12	--[b]
11	DBU	THF	70	12	<5[b]
12	DBN	THF	70	12	--[b]

[a] Isolated yields after column chromatography, [b] starting material **2a** recovered

A model cycloaddition reaction between **3**, **5** with **2a** and methanol in the presence of NaH/THF at RT-70 ºC for 10h was explored in our initial effort (entry 1, Table 2). Indeed, the reaction occurs to give the desired product **8a** in good yield. The yield of product does not change, even the reaction continued up to 15 h (entry 2, Table 2). In contrast, reactions taking in other solvents, such as 1,4-dioxane, toluene, benzene dimethylformamide (DMF) and xylene, occur with very poor yield even prolonged the reaction time (entry 3-7, Table 2). The cycloaddition did not take place, when the reactions were performed using other bases like K_2CO_3, DBU and DBN (entry 8-12, Table 2).



Scheme 4, **Table 3:** Synthesis of **8a-ad** in a multicomponent fashion by reacting **2** with **3**, **4** and alcohol[a]

Entry	Ar		R	Yield[b](%)
1	4-OMe-C_6H_4-	8a	Me	75
2	4-OMe-C_6H_4-	8b	Et	87
3	2,4-Cl_2-C_6H_3-	8c	Me	85
4	2,4-Cl_2-C_6H_3-	8d	Et	89
5	3-Cl-C_6H_4-	8e	Me	97
6	3-Cl-C_6H_4-	8f	Et	95
7	C_6H_5-	8g	Me	85
8	C_6H_5-	8h	Et	83
9	2,4-F_2-C_6H_3-	8i	Me	80
10	2,4-F_2-C_6H_3-	8j	Et	82
11	2-OMe,5-Br-C_6H_3-	8k	Me	70
12	2-OMe,5-Br-C_6H_3-	8l	Et	72
13	4-Cl-C_6H_4-	8m	Me	87
14	4-Cl-C_6H_4-	8n	Et	89
15	3,4,5-OMe-C_6H_2-	8o	Me	84
16	3,4,5-OMe-C_6H_2-	8p	Et	87
17	3-OH-C_6H_4-	8q	Me	77
18	3-OH-C_6H_4-	8r	Et	78
19	3,4-OMe-C_6H_3-	8s	Me	85
20	3,4-OMe-C_6H_3-	8t	Et	82
21	4-CH_3-C_6H_4-	8u	Me	88
22	4-CH_3-C_6H_4-	8v	Et	86
23	2-F-C_6H_4-	8w	Me	88
24	2-F-C_6H_4-	8x	Et	90
25	2-furyl-	8y	Me	83
26	2-furyl-	8z	Et	85
27	2-thienyl-	8aa	Me	87
28	2-thienyl-	8ab	Et	87
29	5-Br-C_5H_3N-	8ac	Me	78
30	5-Br-C_5H_3N-	8ad	Et	75

[a]**2a-o** (1eq), NaH (2eq), TosMIC **3** (1.5eq), guanidine nitrate **5** (2eq), alcohol (3ml) (v/v), RT- 70 ºC, 10 h. [b] Isolated yields

The cyclization was optimized with **8**, which was obtained by cyclocondensation of **2a**, **3**, **5** and alcohol in a multicomponent fashion in excellent yields (Scheme 4). Ensuring studies showed that the efficiency of formation of this product was highly solvent as well as base dependent. Importantly, the reaction in NaH/THF yields 75% of **8a** in a highly chemo/regioselective manner. To explore the scope of this novel strategy, we consecutively

investigated the cycloaddition of **2a-o** with **3**, **5** and alcohol by following the optimized condition **8a-ad** obtained in excellent yields 70-97% (Table 3).

The ^{1}H NMR spectrum of **8a** was taken as example and analysed their chemical shifts. The ^{1}H NMR spectrum assigned to two singlets at δ 3.66 and 3.74 ppm for two methoxy groups at C-4 & C-4"respectively. The free amino proton at C-2 position appeared as singlet at δ 6.24 ppm and at the same time N*H* proton of pyrrole ring displayed broad singlet at δ 11.11 ppm. We also noticed that, the chemical shift appeared at δ 5.58 ppm for C-5 proton shifted slightly upfield when it was compared with the chemical shift of simple pyrimidine molecule (δ ~6.46 ppm). This shift of upfield may be due to the shielding effect of pyrrole ring at C-6 position. The ^{13}C NMR of **8a** displayed fourteen signals, with diagnostic signal at δ 52.9 and 55.2 ppm assignable to two methoxy groups at C-4 and C-4". In addition to support the analytical data, the structure of **8e** was confirmed on the basis of single-crystal X-ray structure analysis (Figure 2).[19]

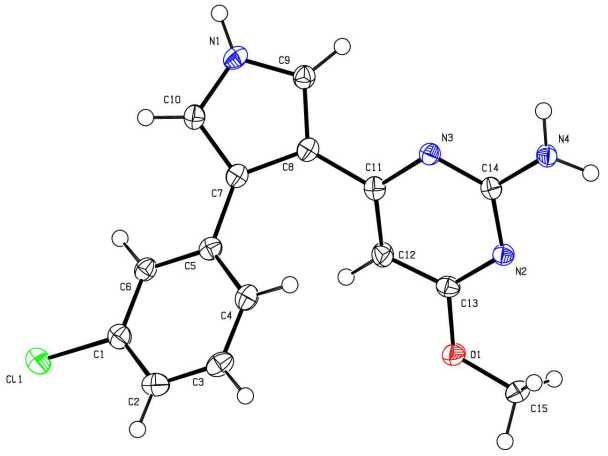
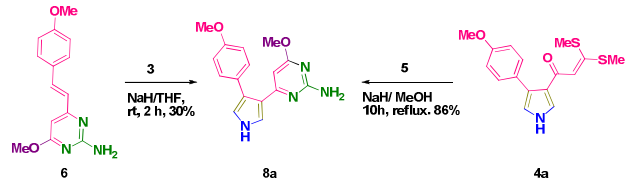


Figure 2: ORTEP representation of **8e**

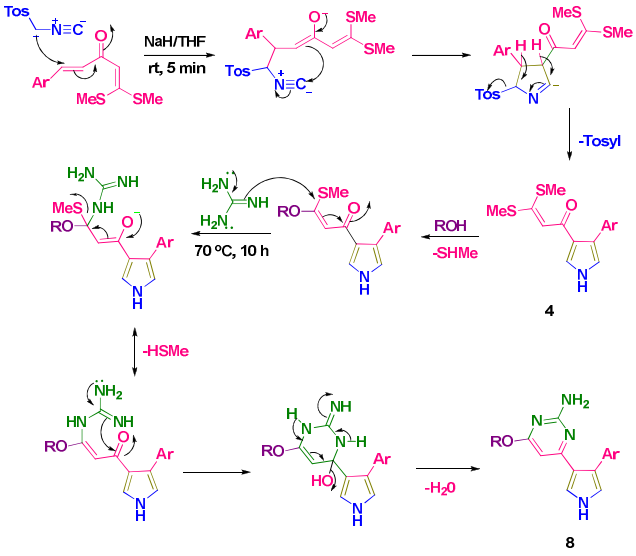
The compounds **8e**, **8f**, **8v** and **8d** were isolated in highest yields at the level of 97, 95, 90 and 89% respectively. Also, we have synthesized few triheteroaryl derivatives **8y-ad** by introducing five & six member heterocycles such as 2-furyl, 2-thienyl and pyridine instead of phenyl group at C-4" position (Table 3, entry 25-30). Interestingly, without any decomposition all the triheteroaryl compounds **8y-ad** was obtained as a single product in very good yields. The R group was fixed as a methyl/ethyl at C-4 position of **8** appropriately. The yield of the product **8a-ad** was varied while changing the substitutions by electron donating/withdrawing groups in the phenyl ring. All other structure of 6-pyrrolylpyrimidines **8a-ad** were analysed by ^{1}H, & ^{13}C NMR, and Mass spectroscopy.

On the other way, the 1,3-dipolar cycloaddition between **3** and **6** was employed in the presence of NaH/THF at RT for 2h to afford **8a** in very poor yield 30% (Scheme 5). Subsequently, **4a** was cyclized with guanidine nitrate **5** to afford **8a** in 86% yield (Scheme 5). Though the compound **8a** obtained in good yield from **2a** *via* **4a** but the cycloaddition proceeds in multi-steps. To avoid the multi-steps as well as the processing time, we focused our interest to synthesis of **8a-ad** *via* multicomponent fashion.



Scheme 5: Stepwise Synthesis of **8a** from **4a** & **6**

A postulated reaction pathway for the formation of 4-alkoxy-6-(4-aryl-1*H*-pyrrol-3-yl)pyrimidin-2-amines **8a-ad** is illustrated (Scheme 6). To evaluate the cycloaddition in a multicomponent fashion, **3**, **5** with **2a** was combined together in the presence of NaH/THF at RT. Interestingly, **3** undergoes 1,3-dipolar cycloaddition selectively with double bond **B** of **2** and followed by removal of tosyl group to yield the corresponding **4**. The 1,3-dipolar cycloaddition did not take place with push-pull alkene because, the double bond **A** of **2** is more polarized than **B** by owing to two electrons donating methyl sulfanyl and one electron withdrawing carbonyl group and it makes the C-1 as electron rich. Thus, the chemo/regioselecive formation of **4** was obtained on less polarized double bond **B** of **2**. On the other hand, **5** was did not reacted with **2** at RT and it needs more vigorous conditions to undergo Michael addition. Hence, the temperature was raised gradually up to 70 °C. During this period of time alcohol was added and replaced one MeSH group from **4** and then **5** undergoes Michael addition with push-pull alkene followed by intramolecular cyclization by removal of one MeSH group to afford **8** in excellent yields.



Scheme 6: Plausible mechanism for the formation of **8**

Conclusions

In summary, we have described the development of efficient formation of 4-alkoxy-6-(4-aryl-1*H*-pyrrol-3-yl)pyrimidin-2-amines **8a-ad** *via* multicomponent approach with high chemo/regioselectivity. The salient features of our method are

facile introduction of various substitutions in a one-step process from readily preparable starting materials **2a-o**. The 6-pyrrolylpyrimidines **8a-ad** was characterized by using ^{1}H & ^{13}C NMR, mass spectroscopy and single crystal X-ray analysis.

Experimental Section

General Experimental

Melting points were determined on melting point apparatus equipped with thermometer were uncorrected. Unless stated otherwise, solvents and chemicals were obtained from commercial sources and used without further purification. The ^{1}H and ^{13}CNMR spectra of the new compounds were measured at 400MHz, 300MHz and 100MHz, 75MHz respectively using Bruker NMR instrument in DMSO-d_6, $CDCl_3$ and the chemical shifts are reported as δ values (ppm) relative to tetramethylsilane. IR values were measured by Thermo Nicolet 6700 FT IR Spectrometer using ATR (attenuated total reflection) KBr Cell. Mass analysis was done in Agilent LC-MS instruments and spectra were recorded in positive and negative mode. Elemental analysis recorded on Thermofinnigan flash 2000 organic elemental CHNS analyser. Petroleum ether employed in column chromatographic purification refers to the fraction which boils at 40-60 ºC.

1.General procedure for the synthesis of 4,4-bis(methylthio)but-3-en-2-one 1*:*

A solution of acetone (100g, 1.721 mol) in carbon disulphide (131g, 1.721 mol) was added to a suspension of sodium-*tert*-butoxide (331g, 3.442 mol) in benzene (500 ml) while keeping the reaction temperature not exceeding 10 ^{0}C. The reaction mixture was stirred at RT for 3h and methyl iodide (489g, 3.442 mol) was added at 10 ^{0}C. The resulting reaction mixture was stirred at RT overnight. The reaction mixture was diluted with ethyl acetate and washed twice with water. The organic layer was dried over sodium sulphate, filtered and concentrated in vacuum. The crude product was washed well with hexane to give 172g of 4,4-bis(methylthio)but-3-en-2-one in 65% yield as a pale yellow crystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.20 (s, 3H), 2.45 (s, 3H), 2.47 (s, 3H), 6.04 (s, 1H). LC-MS calcd. m/z 162, found 163 $[(M+1)]^{+}$.

2. General procedure for the preparation of 1,1-bis(methylthio)-5-arylpenta-1,4-dien-3-one (2a-o)

To a solution of 4,4-bis(methylthio)but-3-en-2-one **1** (1eq) in ethanol (5 ml) was added NaOH (1.5eq) and aryl aldehyde (1.1eq) under constant stirring. After the starting material was consumed by TLC, the reaction mixture was poured into ice water and the resulting solid was filtered, washed well with water (20 ml). The solid material obtained was crystallized from ethanol to furnish 1,1-bis(methylthio)-5-arylpenta-1,4-dien-3-one **2a-o** in 81-99% as a yellow solid.

(*E*)-1,1-bis(methylthio)-5-(4-methoxyphenyl)penta-1,4-dien-3-one (2a)[13]

Yellow solid; yield: 90% (3.1 g). mp 104-106 ^{0}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.48 (s, 3H), 2.56 (s, 3H), 3.79 (s, 3H), 6.45 (s, 1H), 6.93 (d, *J* = 16 Hz, 1H), 6.98 (d, *J* = 8 Hz, 2H), 7.45 (d, *J* = 15.9 Hz, 1H), 7.64 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.8, 17.2, 55.8, 114.2, 114.9, 126.2, 128.0, 130.3, 140.4, 161.3, 163.5, 183.7. IR (ATR KBr cell, cm^{-1}) 1581, 1644. LC-MS calcd.m/z 280, found 281 $[(M+1)]^{+}$.

(*E*)-5-(2,4-dichlorophenyl)-1,1-bis(methylthio)penta-1,4-dien-3-one (2b)

Pale yellow solid; yield: 99% (3.9 g). mp 126 ^{0}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.40 (s, 3H), 2.45 (s, 3H), 5.29-5.31 (m, 1H), 5.55 (s, 1H), 6.17 (s, 1H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.50 (s, 1H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.8, 17.3, 114.3, 128.4, 129.4, 129.9, 131.8, 132.3, 133.9, 135.0, 135.3, 166.3, 182.6. IR (ATR KBr cell, cm^{-1}) 1500, 1650. HRMS (ESI-TOF) calcd for $C_{13}H_{12}Cl_2OS_2Na$ $[M+Na]^{+}$ 340.9604, found 340.9601.

(*E*)-5-(3-chlorophenyl)-1,1-bis(methylthio)penta-1,4-dien-3-one (2c)

Pale yellow solid; yield: 85% (3 g). mp 136 ^{0}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.46 (s, 3H), 2.57 (s, 3H), 6.49 (s, 1H), 7.17 (d, *J* = 16 Hz, 1H), 7.43-7.47 (m, 3H), 7.62-7.65 (m, 1H), 7.79 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.8, 17.3, 113.9, 127.3, 127.9, 129.9, 130.1, 131.2, 134.2, 137.8, 138.6, 165.2, 183.3. IR (ATR KBr cell, cm^{-1}) 1567, 1632. HRMS (ESI-TOF) calcd for $C_{13}H_{13}Cl_2OS_2Na$ $[M+Na]^{+}$ 306.9994, found 306.9993.

(*E*)-1,1-bis(methylthio)-5-phenylpenta-1,4-dien-3-one (2d) [13]

Pale yellow solid; yield: 81% (2.5 g). mp 150 ^{0}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.52 (s, 6H), 6.23 (s, 1H), 6.82 (d, *J* = 16Hz, 1H), 7.35-7.40 (m, 3H), 7.55-7.57 (m, 2H), 7.61 (d, *J* = 16 Hz, 1H), LC-MS calcd.m/z: 252, found 253 $[(M+1)]^{+}$.

(*E*)-5-(2,4-difluorophenyl)-1,1-bis(methylthio)penta-1,4-dien-3-one (2e)

Pale yellow solid; yield: 88% (3.1 g). mp 152-154 ^{0}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.44 (s, 3H), 2.56 (s, 3H), 6.45 (s, 1H), 7.11 (d, *J* = 16 Hz, 1H), 7.15-7.18 (m, 1H), 7.31-7.35 (m, 1H), 7.47 (d, *J* = 15.6 Hz, 1H) 7.89 (q, *J* = 15.6 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.3, 16.7, 104.3, 104.8, 112.2, 112.3, 112.5, 113.6, 119.4, 119.5, 130.5, 130.3, 130.4, 159.5, 161.6, 162.1, 164.1, 164.3, 165.1, 182.5. IR (ATR KBr cell, cm^{-1}) 1460, 1630. HRMS (ESI-TOF) calcd for $C_{13}H_{12}F_2OS_2Na$ $[M+Na]^{+}$ 309.0195, found 309.0194.

(*E*)-5-(5-bromo-2-methoxyphenyl)-1,1-bis(methylthio)penta-1,4-dien-3-one (2f)

Pale yellow solid; yield: 87% (3.9 g). mp.156-158 ^{0}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.45 (s, 3H), 2.56 (s, 3H), 3.86 (s, 3H), 6.44 (s, 1H), 7.04 (d, *J* = 8.8 Hz, 1H), 7.15 (d, *J* = 16.4 Hz, 1H), 7.51 (d, *J* = 8.8 Hz, 1H) 7.61 (d, *J* = 15.6 Hz, 1H), 7.88 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.8, 17.2, 56.5, 112.8, 114.6, 126.1, 129.9, 130.1, 133.2, 134, 157.4, 165, 183.3. IR (ATR KBr cell, cm^{-1}) 1469, 1642. HRMS (ESI-TOF) calcd for $C_{14}H_{15}BrO_2S_2Na$ $[M+Na]^{+}$ 380.9595,found 380.9594.

(*E*)-5-(4-chlorophenyl)-1,1-bis(methylthio)penta-1,4-dien-3-one (2g) [13]

Yellow solid; yield: 99% (3.4 g). mp 144 ^{0}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.46 (s, 3H), 2.48 (s, 3H), 6.47 (s, 1H), 7.07 (d, *J* = 16 Hz, 1H), 7.44-7.48 (m, 3H), 7.69 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.3, 16.7, 113.4, 128.8,

128.9, 129.7, 133.9, 134.3, 138.4, 164.4, 182.8. IR (ATR KBr cell, cm^{-1}), 1598, 1646; LC-MS calcd. m/z: 284, found 285 $[(M+1)]^+$.

(*E*)-1,1-bis(methylthio)-5-(3,4,5-trimethoxyphenyl)penta-1,4-dien-3-one (2h) [14]

Pale yellow solid; yield: 88% (3.7 g). mp 140-142 ^{0}C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.52 (s, 3H), 2.53 (s, 3H), 3.87 (s, 3H), 3.93 (s, 6H), 6.45 (s, 1H), 7.02 (s, 2H), 7.03 (d, *J* = 15.6 Hz, 1H), 7.26 (s, 1H), 7.42 (d, *J* = 15.8 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.3, 16.8, 55.9, 60.1, 105.6, 113.5, 127.3, 130.5, 139.1, 140.3, 153.1, 163.7, 183.1. IR (ATR KBr cell, cm^{-1}) 1578, 1640; LC-MS calcd. m/z 340, found 341$[(M+1)]^+$.

(*E*)-5-(3-hydroxyphenyl)-1,1-bis(methylthio)penta-1,4-dien-3-one (2i)

Pale yellow solid; yield: 87% (2.9 g). mp 156-158 ^{0}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.43 (s, 3H), 2.56 (s, 3H), 6.47 (s, 1H), 6.79 (d, *J* = 10.0 Hz, 1H), 6.95 (d, *J* = 15.6 Hz, 1H), 7.01 (s, 1H), 7.08 (d, *J* = 7.6 Hz, 1H), 7.19 (t, *J* = 8 Hz, 1H), 7.37 (d, *J* = 16 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.7, 17.2, 114.1, 114.9, 117.6, 119.6, 128.4, 130.4, 136.8, 140.6, 158.2, 164.5, 183.6. IR (ATR KBr cell, cm^{-1}) 1470, 1600. HRMS (ESI-TOF) calcd for $C_{13}H_{14}O_2S_2Na$ $[M+Na]^+$ 289.0333,found 289.0331.

***(E)*-5-(3,4-dimethoxyphenyl)-1,1-bis(methylthio)penta-1,4-dien-3-one (2j)** [14]

Pale yellow solid; yield: 89% (3.4 g). mp 125-127 ^{0}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.42 (s, 3H), 2.56 (s, 3H), 3.78 (s, 3H), 3.80 (s, 3H) 6.44 (s, 3H), 6.95 (d, *J* = 15.8 Hz, 1H), 6.97 (d, *J* = 8.31 Hz, 2H), 7.21 (d, *J* = 10.5 Hz, 1H), 7.29 (s, 1H) 7.42 (d, *J* = 15.9 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.8, 17.2, 56.1, 110.5, 112.1, 114.1, 123.2, 126.3, 128.2, 140.8, 149.4, 151.1, 163.5, 183.7. IR (ATR KBr cell, cm^{-1}) 1565, 1637. UPLC-MS calcd. m/z 310, found 311$[(M+1)]^+$.

(*E*)-1,1-bis(methylthio)-5-*p*-tolylpenta-1,4-dien-3-one (2k) [13]

Pale yellow solid; yield: 90% (2.9 g). mp 130 ^{0}C.^{1}H NMR (400 MHz, DMSO-d_6): δ 2.31 (s, 3H), 2.43 (s, 3H), 2.56 (s, 3H), 6.46 (s, 1H), 7.00 (d, *J* = 16.40 Hz, 1H), 7.21 (d, *J* = 7.6 Hz, 2H), 7.43 (d, *J* = 16 Hz, 2H), 7.55 (d, *J* = 8 Hz, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.8, 17.2, 21.5, 114.1, 127.6, 128.5, 129.9, 132.7, 140.3, 140.4, 164.1, 183.7. IR (ATR KBr cell, cm^{-1}) 1477, 1604. LC-MS calcd. m/z 264, found 265 $[(M+1)]^+$

(*E*)-5-(2-fluorophenyl)-1,1-bis(methylthio)penta-1,4-dien-3-one (2l)

Pale yellow solid; yield: 92% (3 g). mp 109 ^{0}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.45 (s, 3H), 2.57 (s, 3H), 6.47 (s, 3H), 7.15 (d, *J* = 15.60 Hz, 1H), 7.23-7.29 (m, 2H), 7.42-7.46 (m, 1H), 7.53 (d, *J* = 16.4 Hz, 1H), 7.79 (t, *J* = 8 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 15.1, 17.2, 113.1, 115.9, 116.2, 123.2, 123.3, 124.3, 129.4, 129.8, 130.9, 131.1, 133.8, 159.7, 163.1, 166.1, 183.7. IR (ATR KBr cell, cm^{-1}) 1502, 1544, 1618. HRMS (ESI-TOF) calcd for $C_{13}H_{13}FOS_2Na$ $[M+Na]^+$ 291.0290, found 291.0289.

(*E*)-5-(furan-2-yl)-1,1-bis(methylthio)penta-1,4-dien-3-one (2m)

Low melting solid; yield: 87% (2.6 g). mp 109 ^{0}C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.42 (s, 3H), 2.54 (s, 3H), 6.43 (s, 1H), 6.60 (bs, 1H), 6.75 (d, *J* = 15.60 Hz, 1H), 6.87 (bs, 1H), 7.29 (d, *J* = 15.60 Hz, 1H), 7.81 (bs, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.8, 17.2, 113.3, 114.1, 115.7, 125.7, 127.4, 145.8, 151.7, 164.4, 183.1. IR (ATR KBr cell, cm^{-1}) 1465, 1642. HRMS (ESI-TOF) calcd for $C_{11}H_{12}O_2S_2Na$ $[M+Na]^+$ 263.0176, found 263.0173.

(*E*)1,1-bis(methylthio)-5-(thiphen-2-yl)-penta-1,4-dien-3-one (2n)

Brown solid; yield: 86% (2.7 g). mp 90 ^{0}C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.43 (s, 3H), 2.55 (s, 3H), 6.42 (s, 1H), 6.86 (d, *J* = 15.6 Hz, 1H), 7.48 (s, 1H), 7.49 (d, *J* = 16 Hz, 1H), 7.59-7,61 (m, 1H) 7.89 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.8, 17.2, 56.0, 113.8, 125.9, 128.1, 128.2, 129.3, 134.5, 138.8, 164.0, 183.9. IR (ATR KBr cell, cm^{-1}) 1567, 1634. HRMS (ESI-TOF) calcd for $C_{11}H_{12}OS_3Na$ $[M+Na]^+$ 278.9948, found 278.9945.

(*E*)-5-(5-bromopyridin-3-yl)-1,1-bis(methylthio)penta-1,4-dien-3-one (2o)

Pale yellow solid; yield: 82% (3.3 g). mp 146 ^{0}C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.43 (s, 3H), 2.56 (s, 3H), 6.46 (s, 1H), 7.29 (d, *J* = 16.00 Hz, 1H), 7.45 (d, *J* = 16.00 Hz, 1H), 8.41 (s, 3H), 8.66 (s, 1H), 8.82 (s, 1H).^{13}C NMR (100 MHz, DMSO-d_6) δ 14.8, 17.2, 56.1, 112.2, 114.5, 121.1, 123.7, 128.3, 128.5, 131.9, 135.2, 158.4, 164.2, 183.9. IR (ATR KBr cell, cm^{-1}) 1165, 1488, 1590, 1646. HRMS (ESI-TOF) calcd for $C_{12}H_{12}BrNOS_2Na$ $[M+Na].^+$ 351.9441, found 351.9449.

3. General procedure for the Synthesis of 8a *via* 1,3-dipolar cycloaddition followed by cyclisation.

Step i; Synthesis of 4 by reacting 2a with 3: To a stirred and cleaned suspension of NaH (60% suspension in oil (0.10g, 0.00427mol)) in dry THF (2 ml) at 0 ^{0}C was added a mixture of TosMIC **3** (1.04g, 0.0053mol) and (*E*)-1-(4-methoxyphenyl)-5,5-bis(methylthio)pent-1-en-3-one **2a** (1g, 0.00357mol) in dry THF (5ml) during 15 min. The reaction mixture was then allowed to stir at room temperature for 10 min. After completion of the reaction (TLC), the mixture was carefully acidified with dilute acetic acid (pH 6.5) and extracted with ethyl acetate (3x20 ml). The combined organic phase was washed with water (15ml), brine (10ml), dried over anhydrous Na_2SO_4 filtered and concentrated in *vacuo*. The crude product was purified through column chromatography using silica gel (60-120 mesh) with increasing amounts of ethyl acetate: petroleum-ether (3:7) as eluent. Pale yellow solid; yield: 1 g (89%); mp.156 ^{0}C.^{1}H NMR (400 MHz, DMSO-d_6): δ 2.18 (s, 3H), 2.37 (s, 3H), 3.76 (s, 3H), 6.30 (s, 1H), 6.81 (s, 1H), 6.90 (d, *J* = 8.60 Hz, 2H), 7.28 (d, *J* = 8.60 Hz, 2H), 7.54 (s, 1H), 11.44 (s, 1H).^{13}C NMR (100 MHz, DMSO-d_6) δ 14.6, 16.4, 55.6, 113.7, 114.1, 119.1, 124.1, 124.4, 124.9, 128.8, 130.7, 158.3, 158.6, 182.3. LC-MS calcd.m/z 319, found 320 $[(M+1)]^+$. IR (ATR KBr cell, cm^{-1}), 1474, 1599, 3355.

Step-ii; Synthesis of 8a by reacting 4 and 5: To a stirred and cleaned suspension of sodium hydride (60% suspension in oil 0.03g, 0.00113mol) in dry methanol (5 ml) at 0 ^{0}C was added guanidine nitrate 5 (0.23g, 0.00188mol) and the reaction mixture was allowed to stir at room temperature for 15mins. And then 1-(4-(4-methoxyphenyl)-1*H*-pyrrol-3-yl)-3,3-bis(methylthio)prop-2-en-1-one (0.3g, 0.000939 mol) 4a was added and allowed to reflux for 8-10h. The solvent was removed from the reaction mixture under the reduced pressure. Water was added (5 ml) and

the aqueous phase was extracted using ethyl acetate. The organic layer was washed with water (2×5ml) and brine (2×5ml) and dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was subjected to column chromatography on silica gel (100-120mesh) using ethyl acetate: petroleum-ether (8:2) to afford the pure compound 8a in 86% (0.21g) yield.

4. General procedure for the preparation of 4-alkoxy-6-(4-(4-aryl)-1*H*-pyrrol-3-yl)pyrimidin-2-amine (8a-ad)

To a stirred suspension of sodium hydride (60% suspension in oil (2eq) in dry THF (5 ml) at 0 ^{0}C was added 1,1-bis(methylthio)-5-arylpenta-1,4-dien-3-one **2** (1eq), TosMIC **3** (1.5eq) followed by guanidine nitrate **5** (2eq) and the reaction mixture was allowed to stir at RT for 5 min. Later, alcohol (3mL (v/v)) was added and allowed to reflux for 10 h. The solvent was removed from the reaction mixture under reduced pressure. The reaction mixture was extracted with ethyl acetate. The organic layer was washed with water (2×5ml) and brine (2×5ml) and dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was subjected to column chromatography on silica gel (100-120mesh) using ethyl acetate: petroleum-ether (1:1) to afford the pure compounds **8a-ad** in excellent yields 70-97%.

4-methoxy-6-(4-(4-methoxyphenyl)-1*H*-pyrrol-3-yl)pyrimidin-2-amine (8a)

Colourless solid; yield: 75% (0.24 g). mp 180 ^{0}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.66 (s, 3H), 3.74 (s, 3H), 5.59 (s, 1H), 6.23 (s, 2H), 6.74 (s, 1H), 6.88 (d, *J* = 8.8 Hz, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 7.25 (s, 1H), 11.11 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 52.9, 55.5, 92.7, 114.1, 118.8, 120.7, 121.0, 123.2, 129.1, 130.4, 158.1, 163.5, 163.6, 170.3. IR (ATR KBr cell, cm^{-1}), 1770, 2350, 3500. LC-MS calcd. m/z 296, found 297 [(M+1)]$^+$. Anal. Calcd for $C_{16}H_{16}N_4O_2$: C, 64.85; H, 5.44; N, 18.91; Found: C, 64.82; H, 5.39; N, 18.89.

4-ethoxy-6-(4-(4-methoxyphenyl)-1*H*-pyrrol-3-yl)pyrimidin-2-amine (8b)

Colourless solid; yield: 87% (0.29 g). mp 142 ^{0}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.17 (t, *J* = 7.2 Hz, 3H), 3.75 (s, 3H), 4.15 (q, *J* = 7.2 Hz, 2H), 5.58 (s, 1H), 6.17 (s, 1H), 6.74 (s, 1H), 6.88 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 7.25 (s, 1H), 11.11 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.9, 55.5, 61.1, 92.7, 114.0, 118.8, 120.7, 121.0, 123.2, 129.1, 130.4, 158.1, 163.5, 163.6, 169.9. IR (ATR KBr cell, cm^{-1}), 1890, 2360, 3379. LC-MS calcd.m/z 310, found 311 [(M+1)]$^+$. Anal. Calcd for $C_{17}H_{18}N_4O_2$: C, 65.79; H, 5.85; N, 18.05; Found: C, 65.72; H, 5.79; N, 18.01.

4-methoxy-6-(4-(2,4-dichlorophenyl-1*H*-pyrrol-3-yl)pyrimidin-2-amine (8c)

Colourless solid; yield: 85% (0.27 g). mp 152 ^{0}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.65 (s, 3H), 5.33 (s, 1H), 6.17 (s, 2H), 6.81 (s, 1H), 7.31-7.41 (m, 3H), 7.62 (s, 1H), 11.31 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 52.9, 91.0, 119.0, 119.9, 120.7, 121.6, 127.5, 129.1, 132.4, 133.9, 134.9, 135.2, 163.1, 163.5, 170.5. IR (ATR KBr cell, cm^{-1}), 1800, 2320, 3470. LC-MS calcd.m/z 335, found 336 [(M+1)]$^+$. Anal. Calcd for $C_{15}H_{12}Cl_2N_4O$: C, 53.75; H, 3.61; N, 16.72; Found: C, 53.71; H, 3.59; N, 16.69.

4-ethoxy-6-(4-(2,4-dichlorophenyl-1*H*-pyrrol-3-yl)pyrimidin-2-amine (8d)

Colourless solid; yield: 89% (0.28 g). mp 156 ^{0}C, ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.15-1.22 (t, *J* = 7.2 Hz, 3H), 4.12 (q, *J* = 7.2 Hz, 2H), 5.34 (s, 1H), 6.10 (s, 2H), 6.80 (s, 1H), 7.31-7.41 (m, 3H), 7.61 (s, 1H), 11.30 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.8, 61.1, 91.2, 118.9, 119.9, 120.7, 121.7, 127.5, 129.1, 132.4, 133.9, 134.8, 135.3, 163.2, 163.4, 170.2. IR (ATR KBr cell, cm^{-1}), 1683, 2300, 2900, 3320. UPLC-MS calcd. m/z 349, found 350 [(M+1)]$^+$. Anal. Calcd for $C_{16}H_{14}Cl_2N_4O$: C, 55.03; H, 4.04; N, 16.04; Found: C, 55.00; H, 4.01; N, 15.99.

4-methoxy-6-(4-(3-chlorophenyl-1*H*-pyrrol-3-yl)pyrimidin-2-amine (8e)

Colourless solid; yield: 97% (0.31 g). mp 122 ^{0}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.69 (s, 3H), 5.65 (s, 1H), 6.24 (s, 2H), 6.95 (s, 1H), 7.22-7.32 (m, 5H), 11.34 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 52.6, 92.5, 119.2, 120.3, 121.0, 121.4, 125.4, 127.2, 127.8, 129.7, 132.6, 138.4, 162.9, 163.1, 169.9. IR (ATR KBr cell, cm^{-1}), 1860, 2372, 3174. LC-MS calcd.m/z 300, found 301 [(M+1)]$^+$. Anal. Calcd for $C_{15}H_{13}ClN_4O$: C, 59.91; H, 4.36; N, 18.63; Found: C, 59.87; H, 4.28; N, 18.57.

4-ethoxy-4-(4-(3-chlorophenyl-1*H*-pyrrol-3-yl)pyrimidin-2-amine (8f)

Colourless solid; yield: 95% (0.31 g). mp 186 ^{0}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.19 (t, *J* = 7.2 Hz, 3H), 4.18 (q, *J* = 7.2 Hz, 2H), 5.64 (s, 1H), 6.20 (s, 2H), 6.95 (s, 1H), 7.23-7.32 (m, 5H), 11.36 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 19.2, 65.4, 97.5, 123.9, 125.8, 126.1, 130.1, 131.9, 132.6, 134.5, 137.4, 143.2, 167.8, 174.3. IR (ATR KBr cell, cm^{-1}), 1840, 2370, 3320. LC-MS calcd.m/z 311, found 312 [(M+1)]$^+$. Anal. Calcd for $C_{16}H_{15}ClN_4O$: C, 61.05; H, 4.80; N, 17.80; Found: C, 61.01; H, 4.75; N, 17.77.

4-methoxy-6-(4-phenyl-1*H*-pyrrol-3-yl)pyrimidin-2-amine (8g)

Colourless solid; yield: 85% (0.27 g). mp 174 ^{0}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.66 (s, 3H), 5.58 (s, 1H), 6.23 (s, 2H), 6.83 (s, 1H), 7.19 (s, 1H), 7.19-7.32 (m, 6H), 11.19 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 52.5, 92.3, 118.6, 120.2, 120.7, 123.0, 125.7, 128.0, 128.7, 136.2, 163.0, 163.1, 169.8. IR (ATR KBr cell, cm^{-1}), 1760, 2380, 3420. LC-MS calcd. m/z 266, found 267 [(M+1)]$^+$. Anal. Calcd for $C_{15}H_{14}N_4O$: C, 67.65; H, 5.30; N, 21.04; Found: C, 67.59; H, 5.23; N, 21.00.

4-ethoxy-6-(4-phenyl-1*H*-pyrrol-3-yl)pyrimidin-2-amine (8h)

Colourless solid; yield: 83% (0.28 g). mp 126 ^{0}C, ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.18 (t, *J* = 7.2 Hz, 3H), 4.14 (q, *J* = 7.2 Hz, 2H), 5.57 (s, 1H), 6.18 (s, 2H), 6.82 (s, 1H), 7.18-7.32 (m, 6H), 11.29 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.4, 60.6, 92.5, 118.6, 120.3, 120.7, 122.9, 125.8, 128.0, 128.7, 136.3, 163.1, 169.5. IR (ATR KBr cell, cm^{-1}), 1670, 2680, 3392. LC-MS calcd. m/z 280, found 281. [(M+1)]$^+$. Anal. Calcd for $C_{16}H_{16}N_4O$: C, 68.55; H, 5.75; N, 19.99; Found: C, 68.50; H, 5.69; N, 19.91. (Two carbon signal merged with one another)

4-methoxy-6-(2,4-difluorophenyl-1*H*-pyrrol-3-yl)pyrimidin-2-amine (8i)

Colourless solid; yield: 80% (0.27 g). mp 150 ^{0}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.67 (s, 3H), 5.52 (s, 1H), 6.16 (s, 2H), 6.85 (s, 1H), 7.05-7.07 (m, 1H), 7.15-7.21 (m, 1H), 7.29-7.53 (m, 2H),

11.31 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 53.0, 91.3, 104.2, 104.6, 111.4, 111.6, 115.2, 120.1, 121.0, 121.6, 133.1, 158.3, 160.0, 161.4, 161.6, 163.5, 170.5. IR (ATR KBr cell, cm^{-1}), 1868, 2360, 3418. LC-MS calcd. m/z 302, found 303 $[(M+1)]^+$. Anal. Calcd for $C_{15}H_{12}F_2N_4O$: C, 59.60; H, 4.00; N, 18.53; Found: C, 59.55; H, 3.93; N, 18.50.

4-ethoxy-6-(2,4-difluorophenyl-1*H*-pyrrol-3-yl)pyrimidin-2-amine (8j)

Colourless solid; yield: 82% (0.29 g). mp 160 ^{0}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.86 (t, *J* = 7.2 Hz, 3H), 4.15 (q, *J* = 7.2 Hz, 2H), 5.52 (s, 1H), 6.10 (s, 2H), 6.84 (s, 1H), 7.02-7.07 (m, 1H), 7.15-7.21 (m, 1H), 7.29-7.35 (m, 2H), 11.30 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.9, 61.1, 91.5, 104.6, 111.4, 111.7, 115.2, 120.1, 121.1, 121.6, 133.2, 158.3, 159.8, 161.4, 163.1, 163.2, 163.5, 170.2. IR (ATR KBr cell, cm^{-1}), 2360, 2989, 3436. LC-MS calcd. m/z 316, found 317 $[(M+1)]^+$. Anal. Calcd for $C_{16}H_{14}F_2N_4O$: C, 60.75; H, 4.46; N, 17.71; Found: C, 60.71; H, 4.43; N, 17.65.

4-methoxy-6-(4-(5-bromo-2-methoxyphenyl)-1*H*-pyrrol-3-yl)pyrimidin-2-amine (8k)

Colourless solid; yield: 70% (0.22 g). mp 182 ^{0}C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.52 (s, 3H), 3.74 (s, 3H) 5.44 (s, 1H), 6.14 (s, 2H), 6.78 (s, 1H), 6.94 (d, *J* = 8.8 Hz, 1H), 7.28 (d, *J* = 14.8 Hz, 2H), 7.42 (d, *J* = 8.8 Hz ,1H), 11.17 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 52.9, 55.8, 91.1, 111.9, 113.8, 117.9, 120.4, 121.7, 128.5, 130.7, 133.5, 156.8, 163.3, 170.5. IR (ATR KBr cell, cm^{-1}), 2360, 3362. LC-MS calcd. m/z 375, found 376 $[(M+1)]^+$. Anal. Calcd for $C_{16}H_{15}BrN_4O_2$: C, 51.22; H, 4.03; N, 14.93; Found: C, 51.12; H, 3.99; N, 14.86.

4-ethoxy-6-(4-(5-bromo-2-methoxyphenyl)-1*H*-pyrrol-3-yl)pyrimidin-2-amine (8l)

Colourless solid; yield: 72% (0.23 g). mp 170 ^{0}C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.18 (t, *J* = 7.2 Hz, 3H) 3.52 (s, 3H), 4.14 (q, *J* = 7.2 Hz, 2H), 5.44 (s, 1H), 6.07 (s, 2H), 6.77 (s, 1H), 6.94 (d, *J* = 8.8 Hz, 1H), 7.26 (d, *J* = 12 Hz, 2H), 7.41 (d, *J* = 8.8 Hz, 1H), 11.16 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.9, 55.8, 60.9, 91.4, 111.9, 113.8, 117.8, 120.4, 121.9, 128.6, 130.6, 133.4, 156.8, 163.4, 163.7, 170.1. IR (ATR KBr cell, cm^{-1}), 1868, 2360, 3365. LC-MS calcd.m/z 389, found 390 $[(M+1)]^+$. Anal. Calcd for $C_{17}H_{17}BrN_4O_2$: C, 52.46; H, 4.40; N, 14.39; Found: C, 52.41; H, 4.33; N, 14.30.

4-methoxy-6-(4-(4-chlorophenyl-1*H*-pyrrol-3-yl)pyrimidin-2-amine (8m)

Colourless solid; yield: 87% (0.28 g). mp 194 ^{0}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.69 (s, 3H), 5.63 (s, 1H), 6.26 (s, 2H), 6.89 (s, 1H), 7.25 (s, 1H), 7.34 (q, *J* = 8.4 Hz, 4H), 11.34 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 53.0, 92.9, 119.4, 120.8, 121.5, 122.1, 128.4, 130.8, 135.6, 163.5, 163.6, 170.4. IR (ATR KBr cell, cm^{-1}), 1867, 2369, 3420. LC-MS calcd.m/z 300, found 301 $[(M+1)]^+$. Anal. Calcd for $C_{15}H_{13}ClN_4O$: C, 59.91; H, 4.36; N, 18.63; Found: C, 59.80; H, 4.27; N, 18.51. (Two carbons merged with one another).

4-ethoxy-6-(4-(4-chlorophenyl-1*H*-pyrrol-3-yl)pyrimidin-2-amine (8n)

Colourless solid; yield: 89% (0.3 g). mp 174 ^{0}C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.20 (t, *J* = 7.2 Hz, 3H), 4.17 (q, *J* = 7.2 Hz, 2H), 5.62 (s, 1H), 6.20 (s, 2H), 6.89 (s, 1H), 7.24 (s, 1H), 7.34 (q, *J* = 8.8 Hz, 4H), 11.25 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.9, 61.2, 93.1, 119.4, 120.8, 121.5, 122.1, 128.4, 130.7, 135.6, 163.6, 163.6, 170.1. IR (ATR KBr cell, cm^{-1}), 1844, 2360, 3387. LC-MS calcd.m/z 314, found 315 $[(M+1)]^+$. Anal. Calcd for $C_{16}H_{15}ClN_4O$: C, 61.05; H, 4.80; N, 17.80; Found: C, 60.88; H, 4.72; N, 17.71. (Two carbons merged with one another).

4-methoxy-6-(4-(3,4,5-trimethoxyphenyl)-1*H*-pyrrol-3-yl)pyrimidin-2-amine (8o)

Colourless solid; yield: 84% (0.26 g). mp 168 ^{0}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.65 (s, 3H), 3.69 (s, 9H), 5.74 (s, 1H), 6.24 (s, 2H), 6.59 (s, 2H), 6.89 (s, 1H), 7.23 (s, 1H), 11.18 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 53.2, 56.1, 60.9, 94.9, 106.3, 118.2, 120.7, 120.9, 124.3, 131.1, 136.7, 152.8, 162.5, 170.8. IR (ATR KBr cell, cm^{-1}), 1800, 2370, 3495. LC-MS calcd.m/z 356, found 357 $[(M+1)]^+$. Anal. Calcd for $C_{18}H_{20}N_4O_4$: C, 60.66; H, 5.66; N, 15.72; Found: C, 60.59; H, 5.58; N, 15.62.

4-ethoxy-6-(4-(3,4,5-trimethoxyphenyl)-1*H*-pyrrol-3-yl)pyrimidin-2-amine (8p)

Colourless solid; yield: 87% (0.28 g). mp 170 ^{0}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.18 (t, *J* = 7.2 Hz, 3H), 3.69 (s, 9H), 4.16 (q, *J* = 7.2 Hz, 2H), 5.72 (s, 1H), 6.21 (s, 2H), 6.60 (s, 2H), 6.89 (s, 1H), 7.23 (s, 1H), 11.18 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.4, 56.1, 60.8, 61.7, 95.0, 106.3, 118.1, 120.6, 120.9, 124.3, 131.1, 136.6, 152.8, 162.6, 162.8, 170.5. IR (ATR KBr cell, cm^{-1}), 1790, 2400, 3298. LC-MS calcd.m/z 370, found 371 $[(M+1)]^+$. Anal. Calcd for $C_{19}H_{22}N_4O_4$: C, 61.61; H, 5.99; N, 15.13; Found: C, 61.50; H, 5.92; N, 15.04.

4-methoxy-6-(4-(3-hydroxyphenyl)-1*H*-pyrrol-3-yl)pyrimidin-2-amine (8q)

Colourless solid; yield: 77% (0.24g). mp 148-150 ^{0}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.67 (s, 3H), 5.62 (s, 1H), 6.23 (s, 2H), 6.62 (d, *J* = 8 Hz, 1H), 6.69 (s, 2H), 6.77 (s, 1H), 7.09 (t, *J* = 8 Hz, 1H), 7.24 (s, 1H), 9.21 (s, 1H), 11.14 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.9, 52.5, 92.4, 112.9, 115.7, 118.4, 119.6, 120.2, 120.6, 121.9, 123.2, 127.1, 128.9, 129.7, 138.1, 143.5, 156.9, 162.9, 163.1, 169.8. IR (ATR KBr cell, cm^{-1}), 1650, 2200, 3200. LC-MS calcd.m/z 282, found 283 $[(M+1)]^+$. Anal. Calcd for $C_{15}H_{14}N_4O_2$: C, 63.82; H, 5.00; N, 19.85; Found: C, 63.74; H, 4.89; N, 19.78.

4-ethoxy-6-(4-(3-hydroxyphenyl)-1*H*-pyrrol-3-yl)pyrimidin-2-amine (8r)

Colourless solid; yield: 78% (0.26 g). mp 126 ^{0}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.19 (t, *J* = 7.2 Hz, 3H), 4.14 (q, *J* = 7.2 Hz, 2H), 5.60 (s, 1H), 6.18 (s, 2H), 6.61 (d, *J* = 7.6 Hz, 1H), 6.72 (s, 1H), 6.76 (s, 1H), 7.07 (t, *J* = 8 Hz, 1H), 7.23 (s, 1H), 9.21 (s, 1H), 11.13 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.4, 60.6, 92.5, 112.9, 115.7, 118.4, 119.6, 120.3, 120.6, 123.2, 127.1, 128.9, 129.6, 137.6, 156.9, 163.0, 163.1, 169.5. IR (ATR KBr cell, cm^{-1}), 1750, 2300, 3470. LC-MS calcd.m/z 296, found 297 $[(M+1)]^+$. Anal. Calcd for $C_{16}H_{16}N_4O_2$: C, 64.85; H, 5.44; N, 18.91; Found: C, 64.79; H, 5.35; N, 18.83.

4-methoxy-6-(4-(3,4-dimethoxyphenyl)-1*H*-pyrrol-3-yl)pyrimidin-2-amine (8s)

Colourless solid; yield: 85% (0.27 g). mp 182 ^{0}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.66 (s, 6H), 3.74 (s, 3H), 5.66 (s, 1H), 6.23 (s, 2H), 6.79-6.81 (m, 2H), 6.86-6.93 (m, 2H), 7.25 (s, 1H), 11.13 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 52.5, 55.4, 55.5, 92.3, 111.7, 113.1, 118.3, 120.2, 120.5, 120.8, 122.9, 128.8, 147.2, 148.2, 163.1, 169.9; IR (ATR KBr cell, cm^{-1}), 1790, 2490, 3220; LC-MS calcd. m/z 326, found 327 [(M+1)]$^+$. Anal. Calcd for $C_{17}H_{18}N_4O_3$: C, 62.57; H, 5.56; N, 17.17; Found: C, 62.49; H, 5.45; N, 17.10.

4-ethoxy-6-(4-(3,4-dimethoxyphenyl)-1*H*-pyrrol-3-yl)pyrimidin-2-amine (8t)

Colourless solid; yield: 82% (0.27g). mp 180 ^{0}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.19 (t, *J* = 7.2 Hz, 3H), 3.66 (s, 3H), 3.74 (s, 3H), 4.16 (q, *J* = 7.2 Hz, 2H), 5.65 (s, 1H), 6.17 (s, 2H), 6.78-6.82 (m, 2H), 6.86-6.90 (m, 2H), 7.23 (s, 1H), 11.12 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 55.3, 55.5, 60.5, 92.5, 111.7, 113.3, 118.3, 120.2, 120.5, 120.7, 122.9, 128.9, 147.2, 148.2, 163.0, 163.2, 169.5. IR (ATR KBr cell, cm^{-1}), 1820, 2500, 3390; LC-MS calcd.m/z 340, found 341 [(M+1)]$^+$. Anal. Calcd for $C_{18}H_{20}N_4O_3$: C, 63.52; H, 5.92; N, 16.46; Found: C, 63.42; H, 5.83; N, 16.39

4-methoxy-6-(4-*p*-tolyl-1*H*-pyrrol-3-yl)pyrimidin-2-amine (8u)

Colourless solid; yield: 88% (0.28 g). mp 150 ^{0}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.36 (s, 3H), 3.66 (s, 3H), 5.60 (s, 1H), 6.23 (s, 2H), 6.77 (s, 1H), 7.09-7.16 (m, 4H), 7.25 (s, 1H), 11.15 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 21.5, 52.9, 92.8, 118.9, 120.7, 121.2, 123.4, 127.7, 130.3, 133.8, 135.3, 163.5, 163.6, 170.3. IR (ATR KBr cell, cm^{-1}), 1720, 2300, 3630; LC-MS calcd.m/z 280, found 281 [(M+1)]$^+$. Anal. Calcd for $C_{16}H_{16}N_4O$: C, 68.55; H, 5.75; N, 19.99; Found: C, 68.48; H, 5.69; N, 19.90.

4-ethoxy-6-(4-*p*-tolyl-1*H*-pyrrol-3-yl)pyrimidin-2-amine (8v)

Colourless solid; yield: 86% (0.29 g). mp 170-172 ^{0}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.18 (t, *J* = 6.8 Hz, 3H), 2.33 (s, 3H), 4.12 (q, *J* = 7.2 Hz, 2H), 5.59 (s, 1H), 6.17 (s, 2H), 6.77 (s, 1H), 7.11 (d, *J* = 8 Hz, 2H),7,16 (d, *J* = 7.6 Hz, 2H), 7.24 (s, 1H), 11.14 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.9, 21.2, 61.1, 92.9, 118.9, 120.7, 121.2, 123.4, 129.1, 133.8, 135.3, 163.6, 169.9; IR (ATR KBr cell, cm^{-1}), 1854, 2330, 3570; LC-MS calcd.m/z 294, found 295 [(M+1)]$^+$. Anal. Calcd for $C_{17}H_{18}N_4O$: C, 69.37; H, 6.16; N, 19.03; Found: C, 69.28; H, 6.10; N, 18.92.

4-methoxy-6-(4-(2-fluorophenyl)-1*H*-pyrrol-3-yl)pyrimidin-2-amine (8w)

Colourless solid; yield: 88% (0.28 g). mp 172 ^{0}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.65 (s, 3H), 5.48 (s, 1H), 6.17 (s, 2H), 6.85 (s, 1H), 7.18 (d, *J* = 7.6 Hz, 2H), 7.27-7.34 (m, 3H), 11.29 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 50.7, 89.8, 113.3, 113.6, 114.1, 117.6, 118.7, 119.5, 120.1, 122.3, 122.5, 125.5, 126.2, 130.1, 156.2, 159.5, 161.2, 168.5. IR (ATR KBr cell, cm^{-1}), 1633, 2360, 3380. LC-MS calcd.m/z 284, found 285 [(M+1)]$^+$. Anal. Calcd for $C_{15}H_{13}FN_4O$: C, 63.37; H, 4.61; N, 19.71; Found: C, 63.25; H, 4.52; N, 19.57.

4-ethoxy-6-(4-(2-fluorophenyl)-1*H*-pyrrol-3-yl)pyrimidin-2-amine (8x)

Colourless solid; yield: 90% (0.3 g). mp 130 ^{0}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.17 (t, *J* = 7.2 Hz, 3H), 4.12 (q, *J* = 6.4 Hz, 2H), 5.47 (s, 1H), 6.12 (s, 2H), 6.84 (s, 1H), 7.13-7.18 (m, 2H), 7.28-7.33 (m, 3H), 11.30 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.3, 61.8, 94.1, 115.3, 115.6, 116.9, 119.6, 120.5, 123.7, 127.9, 128.1, 131.9, 158.4, 161.7, 162.6, 162.9, 170.8. IR (ATR KBr cell, cm^{-1}), 1795, 2288, 3400. LC-MS calcd.m/z 298, found 299 [(M+1)]$^+$. HRMS (ESI-TOF) calcd for $C_{16}H_{15}FN_4O$ [M+H]$^+$ 299.1308, found 299.1307.

4-methoxy-6-(4-(furan-2-yl)-1*H*-pyrrol-3-yl)pyrimidin-2-amine (8y)

Pale yellow solid; yield: 83% (0.24 g). mp 168 ^{0}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.73 (s, 3H), 5.80 (s, 1H), 6.30 (s, 2H), 6.45 (s, 1H), 6.53 (s, 1H), 7.01 (s, 1H), 7.29 (s, 1H), 7.56 (s, 1H), 11.30 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 53.1, 92.1, 107.2, 111.6, 113.2, 119.7, 120.9, 121.4, 141.5, 150.3, 163.1, 163.5, 170.6. IR (ATR KBr cell, cm^{-1}), 1420, 2300, 3100. LC-MS calcd.m/z 256, found 257 [(M+1)]$^+$. Anal. Calcd for $C_{13}H_{12}N_4O_2$: C, 60.93; H, 4.72; N, 21.86; Found: C, 60.79; H, 4.64; N, 21.79.

4-ethoxy-6-(4-(furan-2-yl)-1*H*-pyrrol-3-yl)pyrimidin-2-amine (8z)

Pale yellow solid; yield: 85% (0.26 g). mp 126 ^{0}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.22 (t, *J* = 7.2 Hz, 3H), 4.22 (q, *J* = 6.4 Hz, 2H), 5.79 (s, 1H), 6.26 (s, 2H), 6.44 (s, 1H), 6.54 (s, 1H), 7.01 (s, 1H), 7.29 (s, 1H), 7.56 (s, 1H), 11.29 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.4, 61.8, 94.8, 106.5, 110.9, 113.8, 118.8, 120.6, 120.8, 140.7, 149.5, 162.6, 162.7, 170.8, IR (ATR KBr cell, cm^{-1}), 1485, 2239, 3465. LC-MS calcd.m/z 270, found 271 [(M+1)]$^+$. Anal. Calcd for $C_{14}H_{14}N_4O_2$: C, 62.21; H, 5.22; N, 20.73; Found: C, 62.09; H, 5.17; N, 20.63.

4-methoxy-6-(4-(thiophen-2-yl)-1*H*-pyrrol-3-yl)pyrimidin-2-amine (8aa)

Colourless solid; yield: 87% (0.28 g). mp 170-172 ^{0}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.70 (s, 3H), 5.74 (s, 1H), 6.27 (s, 2H), 6.89 (s, 1H), 7.08 (d, *J* = 5.2 Hz, 1H), 7.24 (s, 1H), 7.42-7.47 (m, 2H), 11.16 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 92.5, 118.2, 119.2, 121.1, 121.4, 125.5, 129.4, 129.6, 136.8, 163.5, 163.7, 170.5. IR (ATR KBr cell, cm^{-1}), 1597, 1800, 2365, 3400. LC-MS calcd.m/z 272, found 273 [(M+1)]$^+$. HRMS (ESI-TOF) calcd for $C_{13}H_{12}N_4OS$ [M+H]$^+$ 273.0810, found 273.0812.

4-ethoxy-6-(4-(thiophen-2-yl)-1*H*-pyrrol-3-yl)pyrimidin-2-amine (8ab)

Colourless solid; yield: 87% (0.29 g). mp 140-142 ^{0}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.21 (t, *J* = 7.2 Hz, 3H), 4.16 (q, *J* = 7.6 Hz, 2H), 5.73 (s, 1H), 6.23 (s, 2H), 6.88 (s, 1H), 7.10 (d, *J* = 4.6 Hz, 1H), 7.24 (s, 1H), 7.45-7.47 (m, 2H), 11.15 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.9, 61.1, 92.7, 118.1, 119.2, 121.0, 121.1, 121.2, 125.5, 129.6, 136.9, 163.5, 163.7, 170.1. IR (ATR KBr cell, cm^{-1}), 1559, 1645, 2209, 3406. LC-MS calcd.m/z 286, found 287 [(M+1)]$^+$. Anal. Calcd for $C_{14}H_{14}N_4OS$: C, 58.72; H, 4.93; N, 19.57; Found: C, 58.65; H, 4.84; N, 19.47.

4-methoxy-6-(4-(5-bromopyridin-3yl)-1*H*-pyrrol-3-yl)pyrimidin-2-amine (8ac)

Colourless solid; yield: 78% (0.25 g). mp 158-160 ^{0}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.74 (s, 3H), 5.82 (s, 1H), 6.22 (s, 2H),

7.13 (s, 1H), 7.30 (s, 1H), 7.94 (s, 1H), 8.51 (s, 2H), 11.43 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 53.2, 92.9, 118.0, 120.1, 120.6, 121.1, 122.0, 134.4, 137.9, 147.2, 147.8, 163.3, 163.6, 170.6. IR (ATR KBr cell, cm^{-1}), 1468, 1820, 2220, 3280, LC-MS calcd.m/z 347, found 348 $[(M+1)]^+$. Anal. Calcd for $C_{14}H_{12}BrN_5O$. C, 48.57; H, 3.49; N, 20.23; Found: C, 48.44; H, 3.41; N, 20.14.

4-ethoxy-6-(4-(5-bromopyridin-3yl)-1*H*-pyrrol-3-yl)pyrimidin-2-amine (8ad)

Colourless solid; yield: 75% (0.25 g). mp 126 ^{0}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.23 (t, *J* = 7.2 Hz, 3H), 4.21 (q, *J* = 7.2 Hz, 2H), 5.81 (s, 1H), 6.17 (s, 2H), 7.17 (s, 1H), 7.31 (s, 1H), 7.95 (s, 1H), 8.46 (s, 2H), 11.43 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.9, 61.2, 93.0, 118.0, 120.1, 120.5, 121.0, 121.9, 134.5, 137.8, 147.1, 147.8, 158.2, 163.6, 170.2. IR (ATR KBr cell, cm^{-1}), 1440, 1860, 2300, 3320. LC-MS calcd. m/z 294, found 295 $[(M+1)]^+$. Anal. Calcd for $C_{15}H_{14}BrN_5O$: C, 50.02; H, 3.92; N, 19.44; Found: C, 49.92; H, 3.88; N, 19.32.

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Notes and references

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Convenient One-Pot Multicomponent Strategy for the Synthesis of 6-Pyrrolylpyrimidines†

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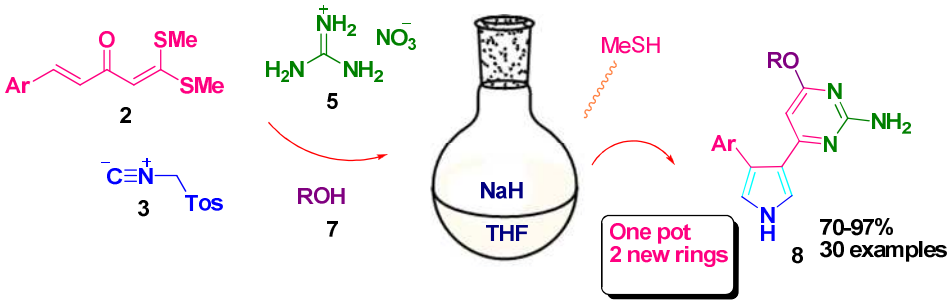

Abstract: We have developed an easy method to construct diheteroaryls from *α*-aroylidineketene dithioacetals in a multicomponent fashion. The reaction proceeded with high chemo/regioselectivity to yield 4-alkoxy-6-(4-aryl-1*H*-pyrrol-3-yl)pyrimidin-2-amines under milder conditions. It is found that *α*-aroylidineketene dithioacetals 2 undergo cycloaddition with (*p*-tolylsulfonyl)methyl isocyanide 3 [TosMIC], guanidine nitrate 5 and alcohol in the presence of NaH/THF to furnish the target 6-pyrrolylpyrimidines 8 in excellent yields.