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New Procedures for the Synthesis of Heterocyclic Substituted and 2,4-Difunctionalized Pyrimidines

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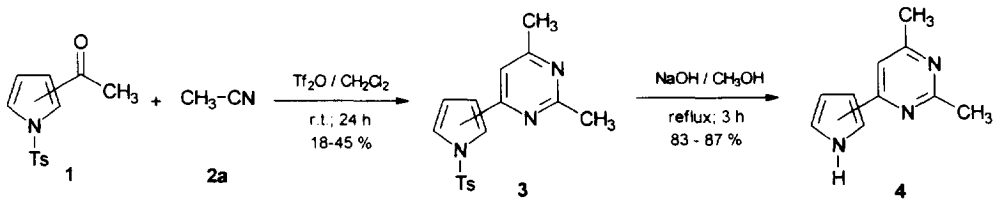
Abstract: *N*-Tosyl-2- and -3-acetylpyrrols **1** or *N*-tosyl-2-pyrrolidone **5** were condensed with cyano compounds in the presence of triflic anhydride (Tf_2O) to yield heteroarylpyrimidines. 2,4-Difunctionalized pyrimidines were obtained by reaction of the corresponding 2,4-bis(methylsulfonyl)pyrimidines with nucleophiles.

One of the more prominent types of heterocyclic compounds is constituted by 2,4-difunctionalized pyrimidines, because many of them are components of naturally occurring products like nucleic acids, and others have found applications in pharmaceuticals and pesticides.[1-4] Pyrimidines are normally prepared by Pinner synthesis, which consists in the condensation of a N-C-N fragment with a C-C-C fragment.[5] A disadvantage of this method is the use of very complicated starting materials for the synthesis of highly substituted pyrimidines.[5]

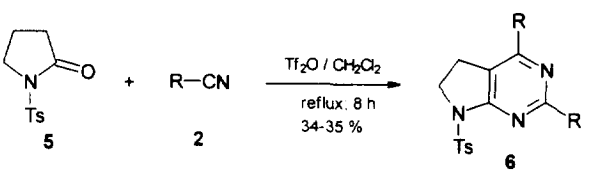
We have found that the cyclisation of ketones with nitriles in the presence of Tf_2O is a very useful method for the preparation of alkyl and arylpyrimidines.[6] We present here a new methodology for the preparation of 2,4-disubstituted pyrimidines based on cyclisation of functionalized precursors followed, when desired, by transfunctionalization reactions of the obtained pyrimidines. As target molecules we have selected a series of challenging compounds, which have biological interests and are difficult to prepare according to the usual procedures.

The reaction of alkyl aryl ketones with nitriles in the presence of Tf_2O,[6] however, fails in the case of aromatic heterocyclic ketones.[7] Thus, the reaction of methyl 2-acetylpyrrole with acetonitrile (**2**) led to *N*-triflylsubstituted pyrrole salts,[7] due to the electrophilic attack of Tf_2O to the heterocyclic nitrogen. We have found that the reaction of *N*-protected analogues *N*-tosyl-2- and -3-acetylpyrroles **1** with Tf_2O affords the derived 2,4-dimethyl-6-(*N*-tosyl-2- or -3-pyrrolyl)pyrimidine **3**, which can be easy hydrolyzed to the free base **4** (Scheme 1)



Scheme 1

The reaction of amides with Tf_2O takes place via iminium salts,[8] and these intermediates were also formed in the presence of nitriles.[7] However, this reaction can also be conducted for the formation of pyrimidines by employing *N*-protected starting products. Thus, the reaction of tertiary *N*-tosyl-amides, which are neither nucleophilic nor able to be dehydrated, leads to the corresponding pyrimidines in moderate yields as elaborated for *N*-tosyl-2-pyrrolidone (**5**) (Scheme 2). This reaction is a very convenient method for the synthesis of 5,6-dihydropyrrolo[2,3-*d*]pyrimidines **6**, which are interesting intermediates for the preparation of anticancer drugs.[4,9]

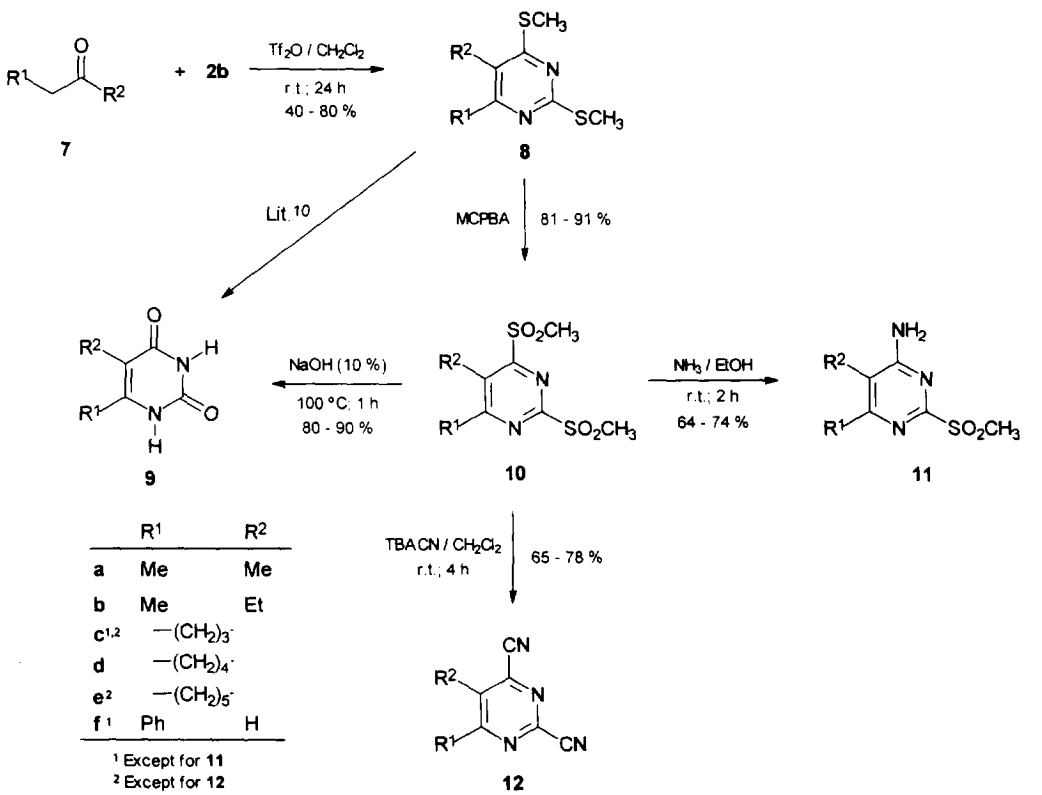


a = CH_3
b = SCH_3

Scheme 2

A strategical step in the synthesis of functionalized pyrimidines is the oxidation of the methylthio group to methylsulfonyl group because it can be easily substituted by nucleophiles like alkoxy and amino groups.[5] Investigations on monosubstituted pyrimidines at the C-2 or C-4 positions have shown that the nucleophilic substitution of a methylsulfonyl group at C-4 takes place faster than the substitution at C-2. Therefore, it is possible to introduce two identical or different substituents starting from 2,4-bis(methylthio)-pyrimidines. Developing this strategy, we report here on the nucleophilic substitution reactions of 2,4-bis-(methylsulfonyl)pyrimidines **10**, obtained by oxidation of the corresponding 2,4-bis(methylthio)pyrimidines

8. The compounds **8** were prepared by reaction of aliphatic, cyclic or aromatic ketones **7** with Tf_2O and methyl thiocyanate **2b**, following our general method.[6c] The results are shown in Scheme 3.



Scheme 3

The basic hydrolysis of the bis(methylsulfonyl)pyrimidines **10** affords the uracils **9** in very good yields. This method is an alternative to the direct hydrolysis of the bis(methylthio)pyrimidines **8** under acidic conditions.[10] The relative substitution of the methyl sulfonyl group at C-4 can be achieved by ammonolysis of **10** yielding the mixed substituted products **11**. However, the reaction with tetrabutylammonium cyanide (TBACN) could not be stopped at the first step and the only obtained products were the dicyanopyrimidines **12**.

In summary, we have shown that our method for the preparation of aryl- and alkyl-pyrimidines can be convenienthly used in the synthesis of the title compounds.

EXPERIMENTAL SECTION

All reagents were commercial grade and were used as received unless otherwise indicate. Column chromatography was performed on Merck Silica Gel 60 [70-230 mesh]. Infrared (Ir) spectra were recorded on a Perkin Elmer 710B scanning spectrophotometer. ^{1}H and ^{13}C MNR spectra were recorded on a Varian XL 300 spectrometer with signal positions referenced to tetramethylsilane (TMS). Mass spectra were recorded on HP-5989 spectrometer at 70 eV. The elemental analysis were recorded on a Perkin-Elmer 2400 analizer. Melting points were obtained using a Mel-Temp capillary melting point apparatus. All melting points are uncorrected.

Preparation of tosylpyrrolylpyrimidines **3**.

Tosylpyrrolylpyrimidines **3** were obtained by our general method.[6a] Tosylpyrrolylketones **1** were prepared as reported in the literature.[11]

2,4-Dimethyl-6-(1-tosyl-2-pyrrolyl)pyrimidine. (18 %). m.p.: 145-146 ° C. Ir (KBr, ν cm^{-1}) 1595, 1550, 1450, 1400, 1380, 1200, 1180, 1155, 1100. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.66 (d, J= 8.2 Hz, 2H), 7.51 (dd, J= 3.3, 1.7 Hz, 1H), 7.25 (d, J= 8.2 Hz, 2H), 7.19 (s, 1H), 6.58 (dd, J= 3.5 and 1.7 Hz, 1H), 6.33 (dd, J= 3.5, 3.3 Hz, 1H), 2.55 (s, 3H), 2.50 (s, 3H), 2.38 (s, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 166.88, 166.78, 157.37, 144.99, 136.52, 133.46, 129.64, 127.44, 127.03, 118.92, 117.26, 112.35, 25.2, 24.35, 21.75. MS: *m/z* (%) 327 (3, M^{+}), 263 (35), 155 (19), 91 (100). *Anal. Calcd. for*: $C_{17}H_{17}N_3O_2S$: C, 62.37; H, 5.23; N, 12.83. *Found*: C, 62.20; H, 5.29; N, 12.73.

2,4-Dimethyl-6-(1-tosyl-3-pyrrolyl)pyrimidine. (45 %). m.p.: 125-127 ° C. Ir (KBr, ν cm^{-1}) 3160, 1600, 1580, 1540, 1495, 1370, 1175, 1060. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.84 (dd, J=2.3, 1.8 Hz, 1H), 7.27 (d, J= 8.3 Hz, 2H), 7.77 (d, J= 8.3 Hz, 2H), 7.19 (dd, J= 3.2, 2.3 Hz, 1H), 7.03 (s, 1H), 6.77 (dd, J= 3.2, 1.8 Hz, 1H), 2.64 (s, 3H), 2.44 (s, 3H), 2.37 (s, 3H). ^{13}C-NMR (75 Mz, $CDCl_3$) δ 167.99, 167.12, 159.10, 145.64, 135.59, 130.26, 127.67, 127.23, 121.96, 120.76, 112.73, 111.80, 25.82, 24.35, 21.75. MS: *m/z* (%) 327 (3, M^{+}), 155 (19), 91 (100). *Anal. Calcd. for*: $C_{17}H_{17}N_3O_2S$: C, 62.37; H, 5.23; N, 12.83. *Found*: C, 62.20; H, 5.29; N, 12.73.

Preparation of pyrrolylpyrimidines **4**.

General Procedure. To a solution of **3** (2.7 mmol) in methanol (10 mL) was added slowly NaOH (5 M) (5 mL). The mixture was refluxed for 3 h. Methanol was removed in vacuo and the remaining slurry was extracted with ethyl acetate and washed with brine. The organic phase was dried over Mg_2SO_4, filtered

and concentrated in vacuo to give the crude product, that was purified by column chromatography on silica gel.

2,4-Dimethyl-6-(2-pyrrolyl)pyrimidine. (83 %). m.p.: 161-163 ° C. Ir (KBr, ν cm^{-1}) 3120 , 1600, 1540, 1430, 1380, 1130. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.78 (br.s, 1H), 7.04 (s, 1H), 6.87 (m, 1H), 6.77 (m, 1H), 6.24 (dd, J= 2.6, 6.2 Hz, 1H), 2.56 (s, 3H), 2.39 (s,3H). ^{13}H-NMR (75 MHz, $CDCl_3$) δ 167.42, 166.46, 156.32, 129.59, 121.49, 111.00, 110.62, 110.22, 26.11, 24.31. MS: *m/z* (%) 173 (100, $M^{\cdot+}$), 172 (11), 92 (22), 91 (51), 66 (12), 65 (8). *Anal. Calcd. for*: $C_{10}H_{11}N_3$: C, 69.33; H, 6.40; N, 24.27. *Found*: C, 69.02; H, 6.24; N, 24.28.

2,4-Dimethyl-6-(3-pyrrolyl)pyrimidine. (87 %). m.p.: 140-141 ° C. Ir (KBr, ν cm^{-1}) 3120, 1600, 1520, 1430, 1380. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.87 (br.s, 1H), 7.57 (m, 1H), 7.09 (s, 1H), 6.85 (dd, J=4.8, 2.4 Hz, 1H), 6.75 (m, 1H), 2.68 (s, 3H), 2.47 (s, 3H). ^{13}H-NMR (75 MHz, $CDCl_3$) δ 167.56, 166.32, 161.38, 123.07. 119.72, 119.54, 112.20, 107.30, 26.17, 24.18. MS: *m/z* (%) 173 (100, $M^{\cdot+}$), 172 (9), 92 (20), 91 (63).

Preparation of dihydropyrrolopyrimidines **6**.

N-Tosyl-2-pyrrolidinone **5** was prepared as reported in the literature.[12] Dihydropyrrolopyrimidines **6** were prepared by our general method.[6a,6c]

2,4-Dimethyl-7-tosyl-5,6-dihydropyrrolo[2,3-d]pyrimidine. (35%). m.p.: 137-138 ° C. Ir (KBr, ν cm^{-1}) 1600, 1400, 1355, 1160, 1095. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.02 (d , J= 8.3 Hz, 2H), 7.30 (d, J= 8.3 Hz, 2 H), 4.07 (t, J= 8.5 Hz, 2H), 2.97 (t, J= 8.5 Hz, 2H), 2.60 (s, 3H), 2.41 (s, 3H), 2.27 (s, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$) 166.91, 162.79, 160.67, 144.77, 134.76, 129.49, 128.45, 115.69, 48.17, 23.13, 26.09, 21.75, 21.20. MS: *m/z* (%) 304 (19, M+1), 240 (13), 239 (81), 238 (100), 148 (15), 122 (27), 121 (13), 107 (12), 91 (74), 66 (24), 65 (46). *Anal. Calcd. for*: $C_{15}H_{17}N_3O_2S$: C, 59.39; H, 5.65; N, 13.80. *Found*: C, 58.90; H, 5.70; N, 13.70.

2,4-Bis(methylthio)-7-tosyl-5,6-dihydropyrrolo[2,3-d]pyrimidine. (34 %). m.p.: 157-159 ° C. Ir (KBr, ν cm^{-1}) 1600, 1575, 1540, 1400, 1370, 1345, 1280, 1180, 1040. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.94 (d, J= 8.2 Hz , 2H), 7.29 (d, J= 8.2 Hz, 2H), 4.07 (t, J= 8.5 Hz, 2H), 2.82 (t, J=8.5 Hz, 2H), 2.55 (s, 3H), 2.50 (2, 3H), 2.40 (s, 3H). ^{13}H-NMR (75 MHz, $CDCl_3$) δ 170.75, 163.31, 160.27, 144.85, 134.86, 129.62, 128.28, 111.91, 48.59, 22.87, 21.73, 14.47, 11.90. MS: *m/z* (%) 367 (22, $M^{\cdot+}$), 334 (10), 303 (28), 288 (18), 212 (100), 179 (15), 155 (13), 139 (16), 112 (55), 92 (31), 91 (97), 85 (16), 65 (60). *Anal. Calcd. for*: $C_{15}H_{17}N_3O_2S_3$: C, 49.05; H, 4.60; N, 11.44. *Found*: C, 49.03; H, 4.62; N, 11.48.

Methylthiopyrimidines was obtained by our general method.[6c]

5-Ethyl-6-methyl-2,4-bis(methylthio)pyrimidine **8b**. (65 %). mp : 36-37 °C. Ir (CCl_4, ν cm^{-1}) 1535, 1350, 1315, 1275. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.48 (q, J= 7.5 Hz, 2H), 2.45 (s, 3 H), 2.26 (s, 3H), 2.21 (s, 3H), 1.20 (t, J= 7.5 Hz, 3H). ^{13}H-NMR (75 MHz, $CDCl_3$) δ 168.12, 167.53, 162.06, 126.61, 21.27, 21.26, 14.24, 13.00, 12.17. MS: *m/z* (%) 214 (100, M^{+}), 199.62 (62), 181 (89), 153 (20), 135 (12), 67 (23). *Anal. Calcd. for*: $C_9H_{14}N_2S_2$: C, 50.45; H, 6.59; N, 13.08. *Found*: C, 50.45; H, 6.59; N, 13.08.

2,4-Bis(methylthio)-6,7,8,9-tetrahydro-5H-cyclohepta[d]pyrimidine **8e**. (50 %). m.p.: 40-42 °C. Ir (CCl_4, ν cm^{-1}) 1545, 1450, 1350, 1305. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.81 (m, 4H), 2.69 (m, 2H), 2.56 (s, 3H), 2.52 (s, 3H), 1.82 (m, 2H), 1.59 (m, 4H). ^{13}H-NMR (75 MHz, $CDCl_3$) δ 168.72, 167.58, 167.08, 127.03, 38.23, 32.30, 28.28, 26.63, 25.78, 14.78, 13.38. MS: *m/z* (%) 240 (100, M^{+}), 225 (45), 207 (85), 179 (17). *Anal. Calcd. for*: $C_{11}H_{16}N_2S_2$: C, 54.98; H, 6.72; N, 11.67. *Found*: C, 55.03; H, 6.45; N, 11.26.

Preparation of methylsulfonylpyrimidines **10**

General procedure. To a stirred solution of 2,4-bis(methylthio)pyrimidine **8** (3.2 mmol) in anhydrous CH_2Cl_2 (60 mL) was added slowly MCPBA (13 mmol). The mixture was magnetically stirred at room temperature for 2 h. $Na_2S_2O_3$ (5 %) solution (50 mL) was then added, and the layers were shaken and separated. The aqueos phase was estracted with CH_2Cl_2 (3X100 mL), and the combined organic layers were washed with saturated $NaHCO_3$ solution (50 mL), and dried over $MgSO_4$.The solvent was removed in vacuo and the product was washed with methanol.

5,6-Dimethyl-2,4-bis(methylsulfonyl)pyrimidine **10a**. (86 %). m.p.: 189-191 °C. Ir (KBr, ν cm^{-1}) 1561, 1530, 1320, 1140. ^{1}H-NMR (300 MHz, DMSO) δ 3.49 (s, 3H), 3.56 (2.71 (s, 3 H), 2.71 (s, 3H), 2.63 (s, 3H). ^{13}C-NMR (75 MHz, DMSO) δ 174.58, 161.86, 161.23, 130.12, 39.69, 38.95, 22.86, 13.08. MS: *m/z* (%) 264 (32, M^{+}), 249 (15), 200 (38), 123 (64), 107 (58), 96 (36), 80 (61). *Anal. Calcd. for*: $C_8H_{12}N_2O_4S_2$: C, 36.35; H, 4.58; N, 10.60. *Found*: C, 36.56; H, 4.40; N, 10.51.

5-Ethyl-6-methyl-2,4-bis(methylsulfonyl)pyrimidine **10b**. (90 %). m.p.: 160-162 ° C. Ir (KBr, ν cm^{-1}) 1530, 1310, 1130. ^{1}H-NMR (300 MHz, DMSO) δ 3.55 (s, 3H), 3.48 (s, 3H), 3.14 (q, J= 7.4 Hz, 2H), 2.75 (s, 3H), 1.21 (t, J= 7.4 Hz, 3H). ^{13}C-NMR (75 MHz, DMSO) δ 174.18, 162.45, 161.36, 135.03, 40.02, 38.98, 21.90, 19.90, 12.81. MS: *m/z* (%) 278 (8, M^{+}), 263 (10), 215 (46), 199 (39), 197 (55), 155 (18), 135 (22), 96 (14). *Anal. Calcd. for*: $C_9H_{14}N_2O_4S_2$: C, 38.84; H, 5.07; N, 10.06. *Found*: C, 38.90; H, 4.86; N, 10.11.

2,4-Bis(methylsulfonyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine **10c**. (85 %). m.p.: 210 ° C dec.. Ir (CCl_4, ν cm^{-1}) 1540, 1315, 1150. ^{1}H-NMR (300 MHz, CD_2Cl_2) δ 3.42 (t , J= 7.7 Hz, 2H), 2.35 (s, 3H), 3.34 (s, 3H), 3.22 (t, J= 7.7 Hz, 2H), 2.32 (q, J= 7.7 Hz). ^{13}C-NMR (75 MHz, DMSO) δ 183.9, 163.9, 158.5, 135.8, 39.6, 39.3, 33.9, 32.8, 32.0. *Anal. Calcd. for*: $C_9H_{12}N_2O_4S_2$: C, 39.12; H, 4.38; N, 10.14. *Found*: C, 39.39; H, 4.35; N, 10.16.

2,4-Bis(methylsulfonyl)-5,6,7,8-quinazoline **10d**. (80 %). m.p.: 175-176 ° C. Ir (KBr, ν cm^{-1}) 1555, 1530, 1305, 1140. ^{1}H-NMR (300 MHz, DMSO) δ 3.53 (s , 3H), 3.47 (s, 3H), 3.15 (m, 3H), 3.05 (m, 2H), 1.85 (m, 4H). ^{13}C-NMR (75 MHz, DMSO) δ 173.84, 162.09, 161.28, 130.69, 39.63, 39.10, 32.58, 32.55, 20.43, 20.29. MS: *m/z* (%) 290 (69, $M^{\cdot+}$), 211 (11), 165 (37), 131 (31), 122 (46), 147 (28), 121 (30). *Anal. Calcd. for*: $C_{10}H_{14}N_2O_4S_2$: C, 41.37; H, 4.86; N, 9.65. *Found*: C, 41.45; H, 4.80; N, 9.54.

2,4-Bis(methylsulfonyl)-6,7,8,9-tetrahydro-5H-cyclohepta[d]pyrimidine **10e**. (81 %). m.p.: 156-157 ° C. Ir (KBr, ν cm^{-1}) 1550, 1520, 1315, 1155. ^{1}H-NMR (300 MHz, DMSO) δ 3.56 (s, 3H), 3.49 (s, 3H), 3.25 (m, 4H), 1.67 (m, 2H), 1.57 (m, 4H). ^{13}C-NMR (75 MHz, DMSO) δ 179.67, 161.69, 161.21, 135.77, 39.73, 38.92, 37.98, 30.84, 26.20, 25.20., 24.64. MS: *m/z* (%) 304 (61, $M^{\cdot+}$), 289 (70), 244 (63), 241 (74), 169 (39). *Anal. Calcd. for*: $C_{11}H_{16}N_2O_4S_2$: C, 43.41; H, 5.30; N, 9.21. *Found*: C, 43.28; H, 5.08; N, 9.05.

2,4-Bis(methylsulfonyl)-6-phenylpyrimidine **10f**. (95 %). m.p.: 220 ° C dec.. Ir (KBr, ν cm^{-1}) 1570, 1510, 1310, 1140. ^{1}H-NMR (300 MHz, DMSO) δ 8.6 (s, 1H), 8.4 (m, 2H), 7.7 (m, 3H) 3.6 (s, 3H), 3.5 (s, 3H). ^{13}C-NMR (75 MHz, DMSO) δ 168.54, 167.16, 165.75, 133, 68, 133.47, 129.47, 128.36, 115.05, 39.70, 38.78. *Anal. Calcd. for*: $C_{12}H_{11}N_2O_4S_2$: C, 53.00; H, 4.45; N, 16.86. *Found*: C, 52.80; H, 6.34; N, 16.52.

Preparation of 1H,3H-Pyrimidine-2,4-diones **9**.

General procedure. To a 50 mL of NaOH (10 %) solution was added 2,4-bis(methylsulfonyl)pyrimidine **10** (5 mmol). The mixture was refluxed for 1h. Then HCl (10 %) is added until pH=2, and the resulting solid was filtered and washed with CH_2Cl_2.

5,6-Dimethyl-1H,3H-pyrimidin-2,4-dione **9a**. (86 %). m.p.: 296-297 ° C (Lit.[13] m.p.:300 °C dec.). Ir (KBr, ν cm^{-1}) 1710, 1650. ^{1}H-NMR (300 MHz, DMSO) δ 10.90 (br s , 1H), 10.60 (br s, 1H), 2.00 (s, 3H), 1.70 (s, 3H). ^{13}C-NMR (75 MHz, DMSO) δ 164.58, 150.72, 147.40, 103.99, 16.13, 9.46. MS: *m/z* (%) 140 (100, $M^{\cdot+}$), 97 (8), 82 (8), 69 (79), 55 (14). *Anal. Calcd. for*: $C_6H_8N_2$: C, 51.42; H, 5.75; N, 19.99. *Found*: C, 51.48; H, 5.70; N, 19.90.

5-Ethyl-6-methyl-1H,3H-pyrimidin-2,4-dione **9b**. (82 %). m.p.: 308-309 ° C. Ir (KBr, ν cm^{-1}) 1725, 1680. ^{1}H-NMR (300 MHz, DMSO) δ 10.89 (br s, 1H), 10.58 (br s, 1H), 2.20 (q, J= 7.3 Hz, 2H), 2.04

(s, 3H), 0.90 (t, J= 7.3 Hz, 3H). ^{13}C-NMR (75 MHz, DMSO) δ 169.94, 156.53, 153.04, 116.03, 23.03, 21.35, 19.22. MS: *m/z* (%) 154 (42, M^{+}), 153 (7), 139 (100), 110 (7), 96 (69).

6,7-Dihydro-1H,3H,5H-cyclopenta[d]pyrimidin-2,4-dione **9c**. (85 %). m.p.: 280 ° C dec (Lit.[14] m.p. > 300 °C). Ir (KBr, ν cm^{-1}) 1690, 1650. ^{1}H-NMR (300 MHz, DMSO) δ 11.02 (br.s, 1H), 10.71 (br.s, 1H), 2.69 (t, J= 7.3 Hz, 2H), 2.43 (t, J= 7.3 Hz, 2H), 1.94 (q, J= 7.1 Hz, 4H). ^{13}C-NMR (75 MHz, DMSO) δ 162.08, 156.07, 152.35, 109.65, 31.05, 26.41, 20.98. MS: *m/z* (%) 152 (100, M^{+}), 151 (29), 109 (50), 81 (18).

5,6,7,8-Tetrahydro-1H,3H-quinazolin-2,4-dione **9d**. (84 %). m.p.: 320-321 ° C (Lit.[15] m.p.: 321-323 °C). Ir (KBr, ν cm^{-1}) 1700, 1640. ^{1}H-NMR (300 MHz, DMSO) δ 10.85 (br s, 1H), 10.57 (br s, 1H), 2.27 (m, 2H), 2.10 (m, 2H), 1.57 (8m, 4 H). ^{13}C-NMR (75 MHz, DMSO) δ 164.31, 150.79, 148.79, 105.61, 25.61, 21.26,20.94, 20.39. MS: *m/z* (%) 166 (100, M^{+}), 165 (60), 152 (5), 138 (21), 122 (28), 95 (45).

6,7,8,9-Tetrahydro-1H,3H,5H-cyclohepta[d]pyrimidin-2,4-dione **9e**. (80 %). m.p.: 260 ° C dec.. Ir (KBr, ν cm^{-1}) 1720, 1625. ^{1}H-NMR (300 MHz, DMSO) δ 10.91 (br s , 1H), 10.62 (br s, 1H), 2.41 (m, 2H), 1.70 (m, 2H), 1.52 (m, 2H), 1.37 (m, 2H). ^{13}C-NMR (75 MHz, DMSO) δ 164.13, 152.79, 150.70, 110.35, 31.55, 31.36, 26.39, 24.72, 22.53 . MS: *m/z* (%) 180 (97, M^{+}), 179 (19), 165 (100), 152 (87), 151 (83), 126 (19), 109 (19).

6-Phenyl-1H,3H-pyrimidin-2,4-dione **9f**. (90 %). m.p.: 282-284 ° C (Lit.[10] 273-275 °C). Ir (KBr, ν cm^{-1}) 1700, 1660. ^{1}H-NMR (300 MHz, DMSO) δ 11.14 (br.s, 1H), 11.10 (br.s, 1H), 7.69 (m, 2H), 7.49 (m, 3H), 5.80 (s, 1H). ^{13}C-NMR (75 MHz, DMSO) δ 164.33, 152.72, 152.10, 131.85, 131.29, 129.03, 127.17, 98.32. MS: *m/z* (%) 188 (100, M^{+}), 187 (7), 145 (31), 117 (27).

Preparation of 4-amino-2-(methylsulfonyl)pyrimidines **11**.

General procedure. 5 mmol of **10** was dissolved soft-heating in ethanol (50 mL) and NH_3 is bubbled through the solution for 2h. The solvent was then removed in vacuo and the crude product was hydrolysed with NaOH (10 %) (10 mL) giving a solid that was filtered and washed with CH_2Cl_2.

4-Amino-5,6-dimethyl-2-(methylsulfonyl)pyrimidine **11a**. (68 %). m.p.: 154-156 ° C. Ir (KBr, ν cm^{-1}) 3590, 3410, 3320, 3210, 1645, 1580, 1310, 1150. ^{1}H-NMR (300 MHz, DMSO) δ 7.28 (br s, 2 H), 3.20 (s, 3H), 2.32 (s, 3H), 2.00 (s, 3H). ^{13}C-NMR (75 MHz, DMSO) δ 162.92, 162.01, 161.65, 112.78, 38.80, 21.50, 11.78 . MS: *m/z* (%) 201 (16, M^{+}), 186 (11), 137 (11), 122 (43), 81 (100), 82 (5). *Anal. Calcd. for*: $C_7H_{11}N_3O_2S$: C, 41.78; H, 5.51; N, 20.89. *Found*: C, 41.54; H, 5.29; N, 20.17.

4-Amino-5-ethyl-6-methyl-2-(methylsulfonyl)pyrimidine **11b**. (70 %). m.p.: 145-147 ° C. Ir (KBr, ν cm^{-1}) 3590, 3420, 3320, 3210, 1650, 1590, 1320, 1155. ^{1}H-NMR (300 MHz, DMSO) δ 7.33 (br s, 2H),

3.20 (s, 2H), 2.49 (q, J= 7.4 Hz, 2H), 2.34 (s, 3H), 1.00 (t, J= 7.4 Hz, 3H). ^{13}C-NMR (75 MHz, DMSO) δ 162.35, 162.14, 161.54, 118.30, 38.40, 20.82, 18.53, 11.48. MS: *m/z* (%) 215 (27, M^{+}), 200 (16), 152 (8), 151 (17), 137 (12), 136 (76), 95 (100).

4-Amino-2-(methylsulfonyl)-5,6,7,8-tetrahydroquinazoline **11d**. (64 %). m.p.: 191-193 ° C. Ir (KBr, ν cm^{-1}) 3435, 3340, 3220, 1650, 1590, 1480, 1440, 1300. ^{1}H-NMR (300 MHz, DMSO) δ 7.25 (br s, 2H), 3.19 (s, 3H), 2.61 (m, 2H), 2.32 (m, H), 1.74 (m, 4H). ^{13}C-NMR (75 MHz, DMSO) δ 162.66, 162.06, 114.18, 38.82, 31.19, 22.47, 21.49, 21.29. MS: *m/z* (%) 227 (17, M^{+}), 212 (12), 163 (14), 148 (100), 106 (13).

4-Amino-2-(methylsulfonyl)-6,7,8,9-tetrahydro-5H-cyclohepta[d]pyrimidine **11e**. (62 %). m.p.: 159-160 ° C. Ir (KBr, ν cm^{-1}) 3410, 3310, 3210, 1645, 1580, 1480, 1440, 1140. ^{1}H-NMR (300 MHz, DMSO) δ 7.30 (br s, 2H), 3.20 (s, 3H), 2.79 (m, 2H), 2.62 (m, 2H), 1.79 (m, 2H), 1.51 (m, 4H). ^{13}C-NMR (75 MHz, DMSO) δ 168.94, 162.38, 119.12, 38.95, 37.26, 31.59, 25.86, 25.20, 24.75. MS: *m/z* (%) 241 (6, M^{+}), 263 (20), 262 (10), 163 (20), 147 (19), 118 (35).

Preparation of 2,4-Dicyanopyrimidines **12**.

General procedure. To solution of 2,4-bis(methylsulfonyl)pyrimidine **10** (5 mmol) in anhydrous CH_2Cl_2 (50 mL) was added tetrabutylammonium cyanide (10 mmol). The mixture was magnetically stirred at room temperature for 4 h, after that was washed with water and dried over $MgSO_4$. The solvent was removed in vacuo and the crude product was purified by flash cromatography on silica gel eluting with hexanes/ethyl acetate (3:1).

2,4-Dicyano-5,6-dimethylpyrimidine **12a**. (78 %). oil. Ir (CCl_4, ν cm^{-1}) 1550, 1400, 1340, 1320, 1155, 1120. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.63 (s, 3H), 2.55 (s, 3H). ^{13}C-NMR (75 MHz, DMSO) δ 171.67, 142.32, 141.08, 137.09, 114.86, 113.73, 23.04, 16.10. MS: *m/z* (%) 158 (100, M^{+}), 157 (18), 131 (18), 105 (16), 104 (11).

2,4-Dicyano-5-ethyl-6-methylpyrimidine **12b**. (73 %). oil. Ir (CCl_4, ν cm^{-1}) 1550, 1485, 1375. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.70 (s, 3H), 2.95 (q, J= 7.6 Hz, 2H), 1.30 (t, J= 7.6 Hz, 3H). ^{13}C-NMR (75 MHz, DMSO) δ 170.88, 142.60, 142.09, 141.13, 114.77, 113.53, 23.48, 22.34, 13.43. MS: *m/z* (%) 172 (52, M^{+}), 171 (19), 157 (33), 132 (10), 131 (66). *Anal. Calcd. for*: $C_9H_8N_4$: C, 62.76; H, 4.69; N, 32.55. *Found*: C, 62.69; H, 4.59; N, 32.22.

2,4-Dicyano-5,6,7,8-tetrahydroquinazoline **12d**. (65 %). oil. Ir (CCl_4, ν cm^{-1}) 1550, 1420, 1420, 1380, 1355. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.97 (m , 4H), 1.91 (m, 4H). ^{13}C-NMR (75 MHz, DMSO) δ 171.95, 142.36, 141.59, 137.54. 114.83, 113.20, 32.29, 25.95, 21.23, 20.99. MS: *m/z* (%) 184 (100, M^{+}), 183 (83), 169 (65), 158 (24), 157 (21), 156 (24), 144 (35), 131 (11).

2,4-Dicyano-6-phenylpyrimidine **12f**. (65 %). m.p.: 177-178 ° C. Ir (KBr, ν cm^{-1}) 1575, 1420, 1360, 1340. ^{1}H-NMR (300 MHz, DMSO) δ 9.13 (s , 1H), 8.30 (m, 2H), 7.67 (m, 3H). ^{13}C-NMR (75 MHz, DMSO) δ 166.54, 144.30, 141.78, 133.48, 132.85, 129.47, 127.85, 123.89, 115.22, 114.97. MS: *m/z* (%) 206 (89, M^+), 205 (10), 154 (100), 128 (11), 127 (59), 103 (33), 102 (24), 77 (50). *Anal. Calcd. for*: $C_9H_8N_4$: C, 62.76; H, 4.69; N, 32.55. *Found*: C, 62.69; H, 4.59; N, 32.22.

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