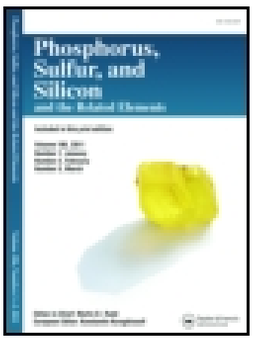

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Synthesis of Novel 4-Phenyl sulfonamido-pyrimidine Derivatives

A New Facile, High Yielding and Efficient Protocol for the Synthesis of Novel 4-Phenylsulfonamido-6-aryl-2-phenylpyrimidine-5-carbonitrile Derivatives

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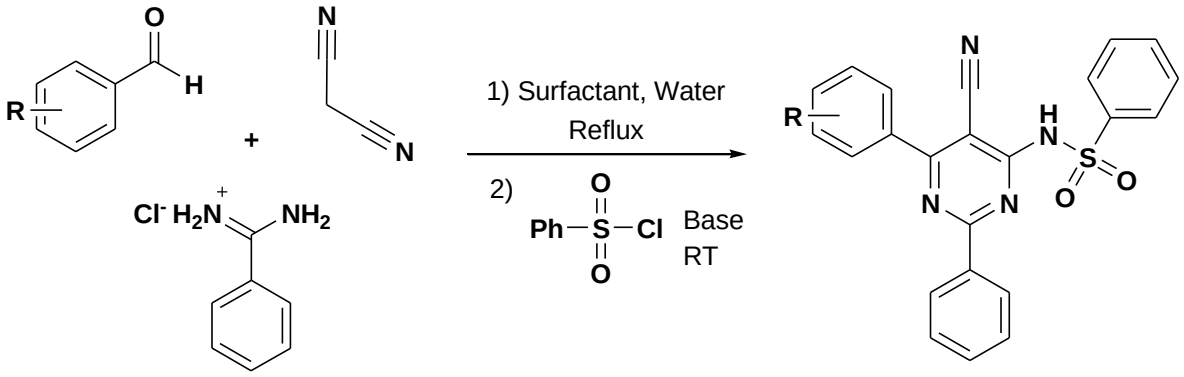
Abstract

A series of novel 4-phenylsulfonamido-6-aryl-2-phenylpyrimidine-5-carbonitrile derivatives have been synthesized through a two-step process. This protocol includes a facile surfactant-mediated methodology for the synthesis of 4-amino-6-aryl-2-phenylpyrimidine-5-carbonitrile derivatives through a one-pot, three-component reaction in the presence of a catalytic amount of cetyltrimethylammonium bromide in water. No additional organic solvents and oxidants were used. The pyrimidine-5-carbonitrile products were then subjected to a direct sulfonylation of 4-amino group to 4-phenylsulfonamide-6-aryl-2-phenylpyrimidine-5-carbonitrile derivatives in the presence of sodium hydride in tetrahydrofuran solution. These new structures were confirmed by ^{1}H- and ^{13}CNMR spectroscopy as well as mass spectrometry and elemental analyses.



Keywords

Heterocycles, sulfonylation, green chemistry, surfactants, 4-sulfonamidopyrimidine-5-carbonitrile.

INTRODUCTION

The pyrimidine moiety is a structural isostere of naturally occurring nucleotides; hence, it has been extensively utilized as a drug scaffold in medicinal chemistry. Our previous studies on the synthesis and biological activity of the pyrimidine ring[1] have demonstrated that this building block reveals extremely potent biological activities. Particularly, its sulfonamide derivatives have emerged as important building blocks in chemotherapeutic agents such as, sulfadiazine, sulfadimethoxine and sulfisomidine [2-4] and as antimicrobial agent such as sulfacytine [5-7] in advanced clinical trials (Figure 1). A great number of methodologies for the synthesis of common pyrimidine derivatives have been reported in the literature recently. [8-13] Because of medicinal importance of sulfonamido pyrimidine derivatives, these compounds have been synthesized through different methods and evaluated for their biological activities. [14-16] Harsh reaction conditions, using harmful organic solvents and reagents and moderate yields of products werefound as the main drawbacks of these reports for the synthesis of pyrimidine derivatives. Recently, much effort has been directed towards using water as an alternative solvent for reasons of cost effectiveness, safety, and environmental concerns for organic reactions. [17,18] The organic syntheses in aqueous media are mostly restricted to reactions with water soluble substrates using special additives. Several research groups have discerned that the addition of surfactants to water may extend this concept to substrates that have poor water solubility.[19,20] It has been emphasized that most of the substrates and the catalyst are aggregated in the spherical spaces called micelles, which act as hydrophobic reaction environments inside water and enable the organic reactions to be accomplished faster.

Hexadecyltrimethylammonium bromide (CTAB) with its C_{16} hydrocarbon chain provides a strong hydrophobic force that can solubilize the organic molecules in water. [21] However, from the viewpoints of practicability and applicability, the surfactant-aided organic synthesis is still at its infancy. To the best of our knowledge, there are only few reports using the strategy of amino group sulfonylation for the synthesis of 4-sulfonamidopyrimidine derivatives. [22-24] Inspired by the significance of 4-sulfonamidopyrimidine derivatives and rare number of synthetic methodologies, we came up with a novel two-step process for the synthesis of this group of compounds. In this protocol, a facile surfactant mediated three-component reaction for the synthesis of 4-amino-6-aryl-2-phenylpyrimidine-5-carbonitrile derivatives in water catalyzed by hexadecyltrimethylammonium bromide was introduced. Then, the products of the first step were subjected to sulfonylation of the 4-amino group using benzensulfonyl chloride catalyzed by NaH.

RESULTS AND DISCUSSION

To achieve the task of preparing novel 4-sulfonamidopyrimidines, we first explored a novel green methodology toward 4-aminopyrimidine related derivatives. Various conditions were investigated in the model reaction using 4-chlorobenzaldehyde with malononitrile and benzamidine hydrochloride under reflux conditions (Scheme 1). Results are summarized in Table 1.

In the absence of any surfactant, only 4-chlorobenzylidiene malononitrile was obtained as intermediate after 90 minutes (Table 1, Entry 1). Addition of 10% mol of cetyltrimethylammonium bromide (CTAB) to the reaction mixture led to the formation of product **4b** in moderate yields. When the amount of CTAB was increased, a gradual increase of

yield reaching a maximum of 98% was obtained (Table 1, Entries 3-5). On the other hand, the use of SDS, Me_4NBr or Bu_4NBr (50 mol% each) gave only marginal increases in the yields in comparison with the case of using CTAB as promoter (Table 1, Entries 6-8).

CTAB provides a strong micellar effect while under the above mentioned conditions Bu_4NBr and other surfactants cannot provide the same effect to the extent CTAB is capable of, thus explaining the decisive advantage of using CTAB over other surfactants in aqueous medium. Using the optimized reaction conditions, further investigations were carried out to expand the scope and limitations of the present methodology (Scheme 2) and the results were summarized in Table 2.

As shown in Table 2, a series of aromatic aldehydes bearing either electron-donating or electron-withdrawing groups on aromatic ring were investigated. The substituents on the aromatic ring did not obviously affect the yields and reaction times under the above mentioned optimal conditions.

Subsequently, the 4-amino-6-aryl-2-phenylpyrimidine-5-carbonitrile derivatives were subjected to direct sulfonylation at amino group with benzenesulfonyl chloride. In the model reaction, various conditions for sulfonylation of 4-amino-6-(4-bromophenyl)-2-phenylpyrimidine-5-carbonitrile **4c** with benzenesulfonyl chloride were investigated (Scheme 3, Table 3).

The best result was obtained using THF as solvent and NaH as the base at room temperature within short reaction time (5 minutes as monitored by TLC analysis, EtOAc:Petrolium ether, 4:1) (Table 3, Entry 9). Extra amounts of NaH and higher temperatures did not lead to improving the process in terms of time and yield of the reaction. So, equimolar amount of NaH and pyrimidine as reactants were used at room temperature in THF as solvent as the optimized reaction

conditions. In order to examine the scope and generality of the present protocol, the other synthesized pyrimidine derivatives were subjected to the sulfonylation process under the optimized conditions. The reactions were accomplished smoothly and cleanly for the other pyrimidine derivatives. The products were obtained in moderate to good yields within a very short reaction time and separated easily from the reaction medium. No further purification was needed for the products as confirmed by spectral analysis (Scheme 4, Table 4).

As indicated in Table 4, aryl substituents at C-6 with various electron demands were able to carry out the reaction simply. In only two cases (Entries 2 and 6, Table 4) the pyrimidine substrates did not undergo the sulfonylation process and no product was formed. Further attempts to activate these two substrates in sulfonylation by increasing the temperature and amount of NaH were failed. Nevertheless, these results show very good level of generality for the synthesis 4-sulfonamidopyrimidine derivatives.

CONCLUSION

In summary, we reported the synthesis of novel 4-phenylsulfonamide-6-aryl-2-phenylpyrimidine-5-carbonitrile derivatives from the reaction of 4-amino-6-aryl-2-phenylpyrimidine-5-carbonitrile with benzensulfonyl chloride for the first time. In this protocol, we have developed an operationally simple and environmentally benign method for the synthesis of pyrimidine derivatives by the multicomponent reaction of aromatic aldehydes, malononitrile and benzamidine hydrochloride in the presence of CTAB in water followed by sulfonylation of the amino substituents using NaH as the base. High yields of the products, short reaction times, using water and CTAB instead of organic solvents and harmful catalysts and the synthesis of novel sulfonamido substituted pyrimidine derivatives for the first time are the advantages of the

present protocol. These compounds are currently under study for revealing their possible bioactivity effects.

EXPERIMENTAL

Melting points were recorded on a Buchi B-540 apparatus. Infrared (IR) spectra were recorded on an ABB Bomem model FTLA200-100 instrument. ^{1}H and ^{13}C NMR spectra were measured with a Bruker DRX-400 Avance spectrometer at 400 and 100 MHz using tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ) are reported relative to TMS, and coupling constants (J) are reported in hertz (Hz). Mass spectra were recorded on a Shimadzu QP 1100 EX mass spectrometer with 70eV ionization potential. Elemental analyses of new compounds were performed with a Vario EL III 0 serial no. 11024054 instrument.

Typical Procedure for the surfactant mediated synthesis of pyrimidine-5-carbonitrile derivatives

Benzamidine hydrochloride (2.0 mmol), benzaldehyde derivative (2.0 mmol) and malononitrile (2.0 mmol) were mixed and poured into a solution of 5 ml water possessing hexadecyltrimethylammonium bromide (0.5 mmol). The reaction mixture was heated under reflux for the specified time (Table 2). The reaction progress was monitored by TLC analysis (various mixtures of ethyl acetate and n-hexane). When the reaction completed, the reaction mixture was allowed to be cooled down; the precipitates were filtered off and washed several times with water. The desired pyrimidine products were obtained with good to excellent yields and characterized by physical and spectral data.

Selected analytical and spectroscopic data for pyrimidine-5-carbonitrile derivatives

4-Amino-2,6-diphenylpyrimidine-5-carbonitrile (4a)

White powder, Mp 217 °C; [lit. Mp 210-212 °C] [25-28]; ^{1}HNMR (400 MHz, DMSO-d_6): δ 8.45-8.49 (m, 2H), 7.91-7.93 (m, 2H), 7.52-7.70 (m, 7H); ^{13}CNMR (100 MHz, DMSO-d_6): δ 169.6, 166.7, 165.2, 136.0, 133.5, 131.8, 129.6, 129.4, 128.9, 117.9, 86.5; IR (KBr, cm^{-1}):ν 3443, 3395, 2230.

4-Amino-6-(4-chlorophenyl)-2-phenylpyrimidine-5-carbonitrile (4b)

Yellow powder, Mp 215 °C; [lit. Mp 222 °C] [25-28]; ^{1}HNMR (400 MHz, DMSO-d_6): δ 8.31 (m, 2H), 7.91 (d, 2H, *J*= 8.5 Hz), 7.69-7.76 (d, 2H, *J*= 8.5 Hz), 7.45-7.51 (m, 5H); ^{13}CNMR (100 MHz, DMSO-d_6):δ 165.3, 164.1, 163.2, 137.4, 136.4, 136.0, 133.6, 131.1, 128.9, 128.3, 128.0, 114.5, 83.9; IR (KBr, cm^{-1}): ν 3382, 3091, 2229.

4-Amino-6-(4-bromophenyl)-2-phenylpyrimidine-5-carbonitrile (4c)

Yellow powder, Mp 230-233 °C; [lit. Mp 234-236 °C] [25-28]; ^{1}HNMR (400 MHz, DMSO-d_6): δ 8.44 (br. s, 2H) 8.30-8.35 (m, 2H), 8.12 (d, 2H, *J*= 8.4 Hz), 7.91 (d, 2H, *J*= 8.4 Hz), 7.58-7.64 (m, 3H); ^{13}CNMR (100 MHz, DMSO- d_6):δ 177.3, 170.2, 169.0, 142.1, 137.0, 134.8, 133.9, 132.5, 131.2, 129.8, 121.8, 116.5, 85.1; IR (KBr, cm^{-1}): ν 3486, 3345, 2221.

4-Amino-6-(4-cyanophenyl)-2-phenylpyrimidine-5-carbonitrile (4d)

White powder, Mp 292-295 °C [lit. Mp 299-300 °C] [29] ; ^{1}HNMR (400 MHz, DMSO-d_6): δ 8.43-8.48 (m, 2H), 8.18-8.23 (m, 2H), 8.09 (d, 2H, *J*= 8.4 Hz), 8.01 (br. s, 2H), 7.55-7.64 (m, 3H); ^{13}CNMR (100 MHz, DMSO-d_6): δ 169.2, 165.6, 164.9, 141.9, 135.2, 133.5, 132.6, 129.8, 129.1, 129.0, 119.4, 117.2, 114.4, 86.7; IR (KBr, cm^{-1}): ν 3477, 3347, 2229, 2201.

4-Amino-6-(4-methoxyphenyl)-2-phenylpyrimidine-5-carbonitrile (4e)

Pale yellow powder, Mp 208 °C; [lit. Mp 213 °C] [25-28]; ^{1}HNMR (400 MHz, DMSO-d_6): δ 8.56-8.60 (m, 2H), 8.11-8.14 (d, 2H, *J*= 9.1 Hz), 7.96 (br. s, 2H), 7.61-7.65 (m, 3H), 7.15 (d, 2H, *J*=

9.1 Hz), 3.77 (s, 3H); ^{13}CNMR (100 MHz, DMSO-d_6): δ 166.2, 163.9, 162.7, 160.1, 138.7, 133.7, 131.6, 129.2, 128.9, 128.1, 115.2, 114.9, 84.6, 54.1; IR (KBr, cm^{-1}): ν 3469, 3341, 3209, 2227.

4-Amino-6-(4-nitrophenyl)-2-phenylpyrimidine-5-carbonitrile (4f)

Yellow powder, Mp 215-217 °C; [lit. Mp 215 °C] [25-28]; ^{1}HNMR (400 MHz, DMSO-d_6): δ 8.71 (d, 2H, *J*= 6.1Hz), 8.59 (d, 2H, *J*= 6.1 Hz), 8.48-8.52 (m, 2H), 8.12 (br. s, 2H), 7.62-7.66 (m, 3H); ^{13}CNMR (100 MHz, DMSO- d_6): δ 172.3, 169.9, 162.7, 143.4, 138.1, 135.8, 132.3, 129.1, 128.3, 122.0, 118.7, 81.6; IR (KBr, cm^{-1}): ν 3436, 3311, 3222, 2221.

4-Amino-6-(3-nitrophenyl)-2-phenylpyrimidine-5-carbonitrile (4g)

Yellow powder, Mp 196-197 °C [lit. Mp 201-202 °C] [29]; ^{1}HNMR (400 MHz, DMSO-d_6): δ 8.68 (s, 1H), 8.58-8.61 (m, 1H), 8.41-8.45 (m, 3H), 8.22 (br, 2H), 7.76-7.83 (m, 1H), 7.53-7.58 (m, 1H), 7.42-7.44 (m, 2H); ^{13}CNMR (100 MHz, DMSO-d_6): δ 167.1, 165.0, 164.3, 146.6, 138.2, 136.2, 135.0, 131.7, 130.3, 128.5, 128.4, 125.4, 123.3, 116.0, 86.1; IR (KBr, cm^{-1}): ν 3492, 3385, 2211.

4-Amino-6-(2-bromophenyl)-2-phenylpyrimidine-5-carbonitrile (4h)

Yellow powder, Mp 247-251 °C; ^{1}HNMR (400 MHz, DMSO-d_6): δ 8.57 (d, *J*= 9Hz), 8.29 (d, 1H, *J*= 8Hz), 8.10 (d, 1H, *J*= 8Hz), 7.79-7.84 (m, 1H), 7.57-7.62 (m, 3H), 7.48 (t, 1H, *J*= 8Hz); ^{13}CNMR (100 MHz, DMSO-d_6): δ 173.2, 165.7, 163.6, 142.9, 140.9, 137.1, 131.5, 130.0, 129.1, 128.3, 127.4, 126.9, 126.0, 118.7, 82.3; IR (KBr, cm^{-1}): ν 3484, 3372, 2224; MS: m/z 317 (84), 271 (59), 214 (56), 168 (67), 156 (100), 141 (91), 104 (71), 103 (72), 76 (72), 57 (45), 43 (44); Elemental analysis: calcd. for $C_{17}H_{11}N_5O_2$: C 64.35, H 3.49, N 22.07; O 10.08; found: C 64.35; H 3.33; N 22.28.

4-Amino-6-(2-chlorophenyl)-2-phenylpyrimidine-5-carbonitrile (4i)

Yellow powder, Mp 200-202 ºC; [lit. Mp196ºC] [25-28]; ^{1}HNMR (400 MHz, DMSO-d_6): δ 8.24-8.28 (m, 2H), 8.01 (br. s, 2H), 7.51-7.59 (m, 3H), 7.43-7.47 (m, 4H); ^{13}CNMR (100 MHz, DMSO-d_6): δ 166.9, 162.0, 160.7, 134.4, 134.3, 132.1, 131.9, 130.0, 129.4, 128.8, 128.1, 127.9, 126.7, 114.0, 86.5; IR (KBr, cm^{-1}): ν 3492, 3342, 2219.

4-Amino-6-(4-methylphenyl)-2-phenylpyrimidine-5-carbonitrile (4j)

White powder, Mp 211 ºC; [lit. Mp 210ºC] [25-28]; ^{1}HNMR (400 MHz, DMSO-d_6): δ 8.59-8.66 (m, 2H), 8.37-8.44 (m, 2H), 7.87-7.90 (d, 2H, *J*= 9.0Hz), 7.69 (br. s, 2H), 7.57-7.61 (m, 3H), 3.26 (s, 3H); ^{13}CNMR (100 MHz, DMSO-d_6): δ 171.1, 166.8, 163.1, 145.3, 137.9, 136.3, 134.0, 132.1, 129.4, 128.6, 128.0, 117.1, 85.5, 21.9; IR (KBr, cm^{-1}): ν 3455, 3367, 2229.

Typical Procedure for the direct sulfonylation of 4-amino-5-pyrimidinecarbonitrile derivatives

A mixture containing 4-aminopyrimidine derivative (2.0 mmol), and NaH (2.0 mmol) in 10 ml THF was stirred for a short period of time at room temperature. Then, benzensulfonyl chloride (2.0 mmol) was added dropwise to the stirring mixture while maintaining the reaction temperature. The formation of product precipitates was started quickly while the benzensulfonyl chloride being added to the reaction mixture. The reaction mixture was stirred for 1 hour at room temperature in order to make sure that the reaction was completed. Then, the solvent was removed *in vacuo* and the solid residues were poured into a 10 ml hydrochloric acid (10% v/v) solution in order to remove the unreacted NaH. The remaining precipitates were then filtered off with a Buchi funnel and washed with ethyl acetate and n-hexane and dried at room temperature. The 4-sulfonamidopyrimidine derivatives were then characterized by physical and spectroscopic

data. The Supplemental Materials contains selected spectroscopic characterization for 5d and 5e (Figures S 1 – S 8)

Selected analytical and spectroscopic data for 4-suilfonamidopyrimidine-5-carbonitrile derivatives

4-Phenylsulfonamide-2,6-diphenylpyrimidine-5-carbonitrile (5a)

White powder, Mp 320 ºC; ^{1}HNMR (400 MHz, DMSO-d_6): δ 8.05-8.08 (m, 2H), 7.86-7.91 (m, 3H), 7.51-7.53 (m, 4H), 7.29-7.43 (m, 6H),; ^{13}CNMR (100 MHz, DMSO-d_6): δ 175.2, 167.2, 162.4, 148.2, 146.0, 137.3, 130.7, 130.2, 129.9, 128.5, 128.4, 128.3, 128.0, 127.9, 127.6, 126.5, 125.4, 118.2, 91.2; MS: m/z 412(9, M^+), 270(19), 259(21), 139(32), 89(82), 63(100), 51(79). IR (KBr, cm^{-1}): ν 3422, 3059, 2214, 1580, 1532. Elemental analysis: calcd. For $C_{23}H_{16}N_4O_2S$ C 66.97, H 3.91, N 13.58; found: C 66.53, H 3.77, N 13.51.

4-Phenylsulfonamide-6-(4-bromophenyl)-2-phenylpyrimidine-5-carbonitrile (5c)

White powder, Mp 354 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.54 (m, 2H), 8.44 (d, 2H, *J*= 9Hz), 7.85 (d, 2H, *J*= 9Hz), 7.79 (d, 2H, *J*= 8Hz), 7.55 (m, 3H), 7.49 (t, J = 8Hz, 1H), 7.45 (m, 2H); ^{13}CNMR (100 MHz, DMSO-d_6): δ 173.2, 167.8, 159.8, 143.6, 141.5, 137.7, 134.2, 132.9, 132.1, 130.7, 130.0, 129.8, 129.3, 126.0, 123.5, 118.6, 83.4; MS: m/z 492(12, $(M+2)^+$), 490(9, M^+), 286(16), 231(67), 183(36), 88(100), 73(75), 75(71), 61(83). IR (KBr, cm^{-1}): ν 3440, 2212, 1591, 1576, 1487. Elemental analysis: calcd. for $C_{23}H_{15}BrN_4O_2S$: C, 56.22; H, 3.08; Br, 16.26; N, 11.40; found: C 55.89; H 3.34; N 11.07.

4-Phenylsulfonamide-6-(4-cyanophenyl)-2-phenylpyrimidine-5-carbonitrile (5d)

White powder, Mp 374-376 ºC; ^{1}HNMR (400 MHz, DMSO-d_6): δ 8.06-8.10 (m, 4H); 8.01-8.03 (m, 2H), 7.92-7.94 (m, 2H), 7.39-7.49 (m, 6H); ^{13}CNMR (100 MHz, DMSO-d_6): δ 166.2, 166.1,

163.1, 146.2, 142.0, 137.8, 132.8, 131.4, 130.5, 129.9, 128.9, 128.5, 128.4, 127.0, 118.9, 118.2, 113.1, 92.2, 79.4; MS: m/z 437(8, M^+), 297(76), 194(100), 104(69), 77(36), 51(17). IR (KBr, cm^{-1}): ν 3471, 2243, 2207, 1627, 1534, 1493. Elemental analysis: calcd. for $C_{24}H_{15}N_5O_2S$: C 65.89, H 3.46, N 16.01; found: C 66.23, H 3.21, N 15.62.

4-Phenylsulfonamido-6-(4-methoxyphenyl)-2-phenylpyrimidine-5-carbonitrile (5e)

White powder, Mp 298 ºC; ^{1}HNMR (400 MHz, DMSO-d_6): δ 8.06-8.08 (m, 2H), 7.88-7.93 (m, 4H), 7.41 (m, 6H), 7.06-7.09 (m, 2H), 3.82 (s, 3H); ^{13}CNMR (100 MHz, DMSO-d_6): δ 166.3, 166.1, 162.2, 160.9, 146.1, 137.7, 130.6, 130.1, 129.8, 129.5, 128.4, 128.0, 127.9, 126.5, 118.6, 113.6, 90.3, 55.3; MS: m/z 442(19, M^+), 83(25), 69(35), 55(100). IR (KBr, cm^{-1}): ν 3483, 3060, 2214, 1603, 1582, 1510, 1450. Elemental analysis: calcd. for $C_{24}H_{18}N_4O_3S$: C 65.14, H 4.10, N 12.66; found: C 65.41, H 3.79, N 12.42.

4-phenylsulfonamido-6-(3-nitrophenyl)-2-phenylpyrimidine-5-carbonitrile (5g)

White powder, Mp 362 ºC; ^{1}HNMR (400 MHz, DMSO-d_6): δ 8.06-8.08(m, 2H), 7.88-7.90 (m, 2H), 7.79-7.81 (d, 2H, *J*=7.7Hz), 7.38-7.41 (m, 6H), 7.32-7.34 (d, 2H, *J*=7.7Hz); ^{13}CNMR (100 MHz, DMSO-d_6): δ 176.4, 167.0, 162.3, 146.1, 140.1, 137.7, 134.5, 130.6, 129.8, 128.8, 128.4, 128.0, 127.9, 126.5, 118.3, 90.9; MS: m/z 457(12, M^+), 392(85), 344(53), 317(77), 77(100). IR (KBr, cm^{-1}): ν 3262, 2217, 1562, 1518, 1458. Elemental analysis: calcd. for $C_{23}H_{15}N_5O_4S$: C 60.39; H 3.31; N 15.31; found: C 60.73, H 3.03, N 15.69.

4-phenylsulfonamido-6-(2-bromophenyl)-2-phenylpyrimidine-5-carbonitrile (5h)

White powder, Mp 286 ºC; ^{1}HNMR (400 MHz, DMSO-d_6): δ 8.00-8.03(m, 2H), 7.90-7.93 (m, 2H), 7.73-7.76 (m, 2H), 7.35-7.53 (m, 8H); ^{13}CNMR (100 MHz, DMSO-d_6): δ 168.5, 164.8, 162.5, 145.9, 138.8, 137.5, 132.6, 130.9, 130.8, 130.3, 130.1, 128.5, 128.1, 128.0, 127.7, 127.6,

126.6, 120.8, 117.0, 93.8,; MS: m/z 492(13, $(M+2)^+$), 490(10, M^+), 308(66), 187(84), 61(100). IR (KBr, cm^{-1}): ν 3452, 2224, 1536, 1479. Elemental analysis: calcd. for $C_{23}H_{15}BrN_4O_2S$: C 56.22; H 3.08; N 11.40; found: C 56.49; H 2.62; N 11.79.

4-phenylsulfonamide-6-(2-chlorophenyl)-2-phenylpyrimidine-5-carbonitrile (5i)

White powder, Mp 388 ºC; ^{1}HNMR (400 MHz, DMSO-d_6): δ 8.03-8.05(m, 2H), 7.93-7.95 (m, 2H), 7.61-7.63 (m, 2H), 7.39-7.56 (m, 8H); ^{13}CNMR (100 MHz, DMSO-d_6): δ 167.7, 165.3, 163.2, 146.4, 138.0, 137.4, 131.7, 131.4, 130.9, 130.6, 130.0, 129.0, 128.6, 128.5, 127.7, 127.1, 117.5, 94.5; MS: m/z 446(14, M^+), 129(57), 69(100). IR (KBr, cm^{-1}): ν 3430, 3057, 2223, 1543, 1474. Elemental analysis: calcd. for $C_{23}H_{15}ClN_4O_2S$: C 61.81; H 3.38; N 12.54; found: C, 61.52; H, 3.73; N, 12.11.

4-phenylsulfonamide-6-(4-methylphenyl)-2-phenylpyrimidine-5-carbonitrile (5j)

White powder, Mp 305 ºC; ^{1}HNMR (400 MHz, DMSO- d_6): δ 8.07-8.10 (m, 2H), 7.90-7.92 (m, 2H), 7.81-7.83 (d, 2H, *J*=8.0Hz), 7.38-7.47 (m, 6H), 7.34-7.36 (d, 2H, *J*=8.0Hz), 2.40 (s, 3H); ^{13}CNMR (100 MHz, DMSO-d6): δ 167.5, 166.4, 162.8, 146.5, 140.5, 138.1, 135.0, 131.1, 130.3, 129.3, 128.9, 128.5, 128.4, 126.9, 118.8, 91.3, 79.4, 21.4; MS: m/z 426(9, M^+), 91(100), 57(82). IR (KBr, cm^{-1}): ν 3426, 2199, 1731, 1537, 1510, 1435. Elemental analysis: calcd. for $C_{24}H_{18}N_4O_2S$: C 67.59; H 4.25; N 13.14; found: C 67.11; H 4.71; N 13.46.

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Table 1 Evaluation of various surfactants toward synthesis of 4-amino-6-(4-chlorophenyl)-pyrimidine-5-carbonitrile as model reaction.

Entry	Catalyst (% mol)	Time (h)	Yield [b] (%)
1	-	24	0
2	CTAB (10)	12	65
3	CTAB (25)	1.5	94
4	CTAB (50)	1.5	98
5	CTAB (60)	1.5	90
6	SDS (50)	12	17
7	TMAB (50)	12	40
8	TBAB (50)	12	52

[a] All reactions were done with 4-chlorobenzaldehyde under reflux

[b] Hexadecyltrimethylammonium bromide (CTAB), Dodecyl sodium sulfate (SDS), Tetramethylammonium bromide(TMAB), Tetrabutylammonium bromide (TBAB)

Table 2 Synthesis of **4(a-j)** catalyzed with CTAB in water under reflux

Entry	Product	R	Time (min.)	Yield[a] (%)
1	**4a**	Ph	60	92
2	**4b**	4-Cl	90	94
3	**4c**	4-Br	90	90
4	**4d**	4-CN	50	95
5	**4e**	4-MeO	50	89
6	**4f**	4-NO_2	80	81
7	**4g**	3-NO_2	90	80
8	**4h**	2-Br	90	92
9	**4i**	2-Cl	80	95
10	**4j**	4-Me	60	98

[a] Isolated yield.

Table 3 Evaluation of various reaction conditions for the sulfonylation of 4-amino-6-(4-bromophenyl)-2-phenylpyrimidine-5-carbonitrile (4c).

Entry	Base[a]	Solvent	Temperature (°C)	Product
1	-	-	r.t	-
2	-	acetonitrile	50	-
3	-	acetonitrile	reflux	-
4	NEt_3	acetonitrile	r.t	-
5	NaH	acetonitrile	r.t	-
6	DBU	acetonitrile	r.t	-
7	NEt_3	DMF	r.t	-
8	NaH	DMF	r.t	-
9	NaH	THF	r.t	**5c** (70%)
10	NEt_3	THF	r.t	**5c** (25%)
11	DBU	THF	r.t	-

[a] Equimolar amount of catalysts and reactant was used.

Table 4 The synthesis of novel 4-sulfonamidopyrimidine derivatives through amino group sulfonylation catalyzed with NaH in THF at r.t.

Entry	Product	R	Yield (%)[a]	M. P. (°C)
1	5a	H	88	320
2	5b	4-Cl	-	-
3	5c	4-Br	92	354
4	5d	4-CN	82	374-376
5	5e	4-MeO	95	298
6	5f	4-NO_2	-	-
7	5g	3-NO_2	91	362
8	5h	2-Br	77	286
9	5i	2-Cl	83	388
10	5j	4-Me	87	305

[a] Isolated yield

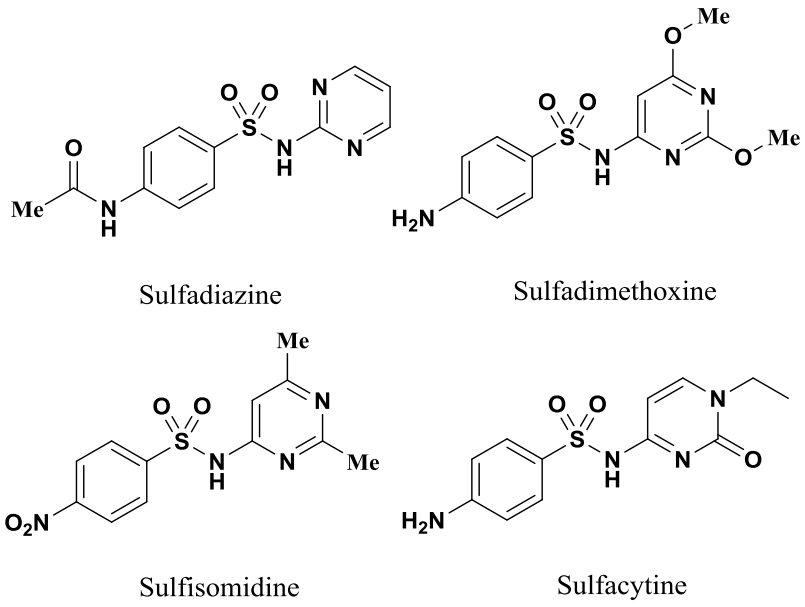
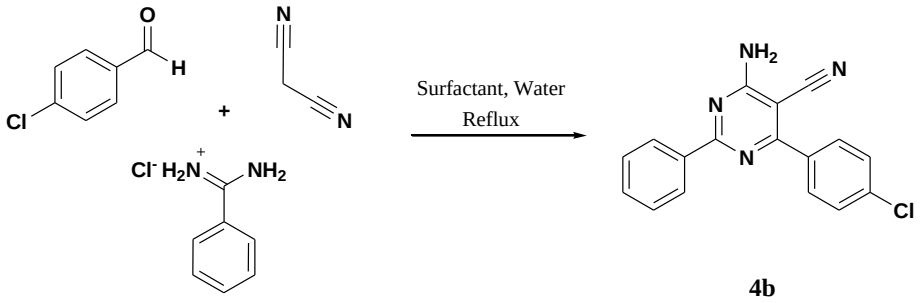
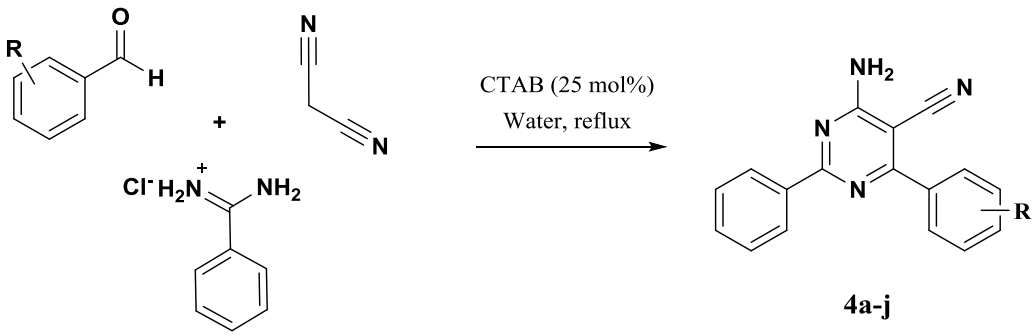


Figure 1 The structures of some common sulfonamide drugs

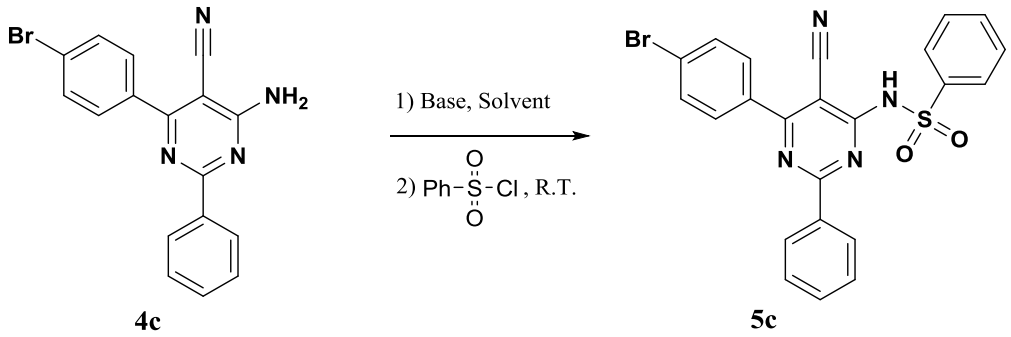


4b

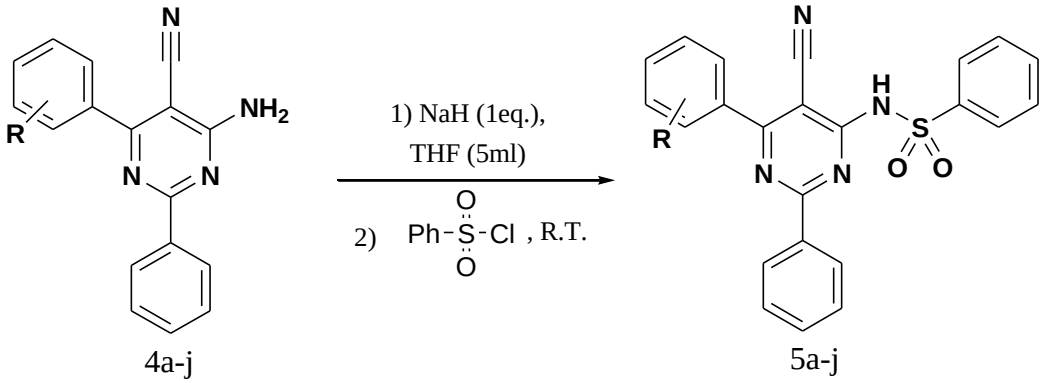
Scheme 1 The study of surfactant mediated synthesis of 4-amino-2,6-diaryl-pyrimidine-5-carbonitrile derivatives



Scheme 2 Synthesis of 4-amino-6-arylpyrimidine-5-carbonitrile derivatives under optimized surfactant mediated conditions



Scheme 3 Evaluation of various reaction conditions for the sulfonylation of amino group toward the synthesis of sulfonamidopyrimidine derivatives



4a-j 5a-j

Scheme 4 Synthesis of novel 4-sulfonamidopyrimidine-5-carbonitrile derivatives through amino group sulfonylation