

## Three-component process for the synthesis of 4-amino-5-pyrimidinecarbonitriles under thermal aqueous conditions or microwave irradiation

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### Abstract

The three-component reaction of malononitrile, aldehydes and N-unsubstituted amidines, is extended to the formation of 4-amino-5-pyrimidinecarbonitrile derivatives. The reaction occurs in water at reflux or under microwave heating, in the presence of sodium acetate. This method provides a new route to produce pyrimidine derivatives in good to excellent yields.

**Keywords:** Malononitrile, amidines, 4-amino-5-pyrimidinecarbonitriles, three-component reaction

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### Introduction

The development of efficient and mild methods for heterocyclic compound synthesis represents a broad area of organic chemistry.<sup>1,2</sup> Structures containing such units often play an essential role due to of their biological activity, particularly in cancer and virus research.<sup>3-6</sup> Among these heterocycles, pyrimidine derivatives are an important class in pharmaceutical discovery.<sup>7,8</sup> Some such compounds are analgesics,<sup>9</sup> antihypertensives,<sup>10</sup> antipyretics,<sup>11</sup> and anti-inflammatory drugs.<sup>12</sup> Pyrimidines occur in some pesticides,<sup>13</sup> herbicides, and plant growth regulators.<sup>14</sup> Consequently, synthetic methodologies for synthesis of novel pyrimidines or pyrimidine-fused compounds are of particular interests in the medicinal and agrochemical areas.<sup>15,16</sup>

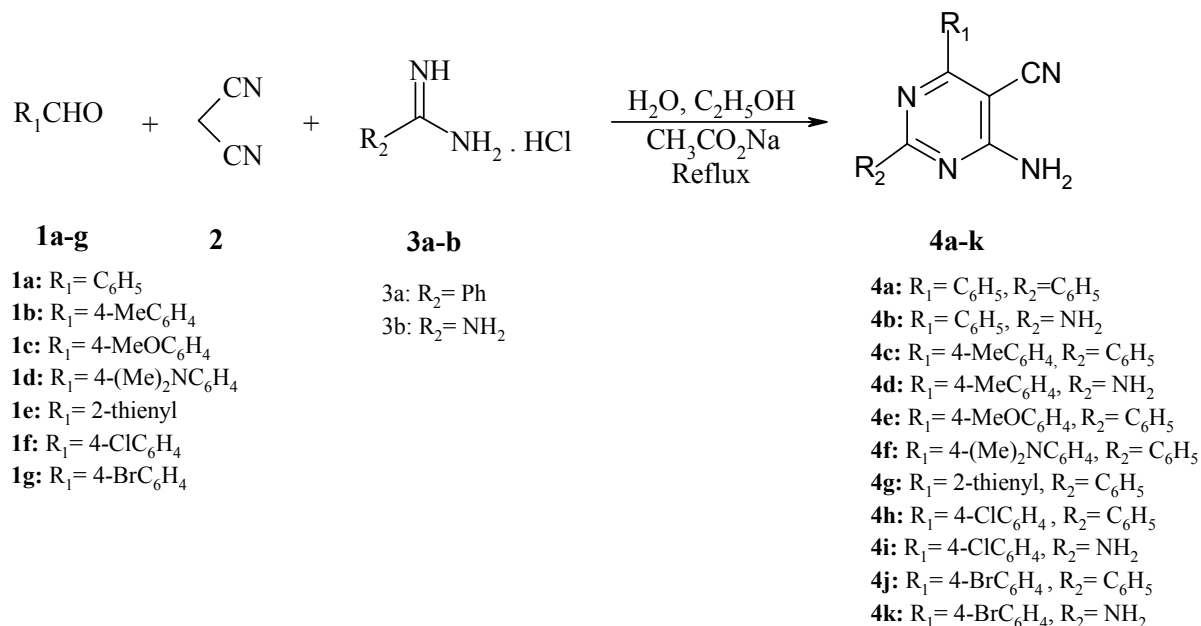
Although some pyrimidine synthesetic routes have been known for a long time, the development of alternative and more efficient strategies is of considerable relevance.<sup>17-20</sup> The increasing importance of pyrimidines and their derivatives as intermediates for the synthesis of biologically and industrially useful compounds prompted us to synthesize 4-amino-5-pyrimidinecarbonitrile derivatives.

Multicomponent reactions (MCRs) are of increasing importance. In situations where a premium is put on speed, diversity, and efficiency in the drug discovery process, MCR strategies

offer significant advantages over conventional linear type syntheses. MCRs leading to interesting heterocyclic scaffolds are particularly useful for the creation of diverse chemical libraries of 'drug-like' molecules for biological screening. The combination of three or more small molecular weight building blocks in a single operation leads to high combinatorial efficacy.<sup>21,22</sup>

## Results and Discussion

In connection with our ongoing work in the development of new synthetic routes to heterocyclic compounds, using 1,3-bielectrophiles and binucleophiles, such as 1,3-dicarbonyl compounds and enaminones,<sup>23-27</sup> herein we report the three-component reaction of aromatic aldehydes **1**, malononitrile **2** and amidines **3** in water at reflux and in the presence of an equivalent amount of sodium acetate for 6-8 h, allowing the one-pot formation of 2-amino-5-pyrimidinecarbonitriles **4** in good yields (Scheme 1).



### Scheme 1

In order to optimize the reaction conditions for preparing compounds **4**, the synthesis of 4-amino-2,6-diphenyl-5-pyrimidinecarbonitrile **4a** was carried out under different reaction conditions. Reaction of benzaldehyde **1a**, malononitrile **2** and benzamidine hydrochloride **3a** in DMSO at reflux in the presence of a catalytic amount of triethylamine was too slow and the yield was low, for example, even after 16 h compound **4a** was obtained in only 40% yield, as compared to yield of 78% in 6 h under thermal aqueous conditions.

The use of water as solvent in organic chemistry has received increasing attention in the last decade. The enhanced reactivity and selectivity observed in some reactions have been rationalized by various authors as being a consequence of hydrophobic effects and enforced hydrophobic interactions.<sup>28-31</sup> When the reaction was carried out in alcoholic solution good yields were obtained due to the solubility of all the reagents in alcohol solvent.

Microwave-assisted solvent-free synthesis in organic reactions has been of growing interest as an efficient, economic and clean procedure ("green chemistry").<sup>32</sup> Based on our previous studies on the use of microwave irradiation,<sup>33</sup> the effects of solvent and base catalyst for preparing compounds **4a** and **4b** under different reaction conditions and microwave irradiation were investigated. Firstly, reactions were carried out under solvent-free microwave-assisted conditions in the presence of a catalytic amount of sodium acetate (method A) and without a catalyst (method B). Secondly, other reactions were performed in a toluene in the presence of a catalytic amount of sodium acetate (method C) or triethylamine (method D). Finally, the three-component reaction was carried out in water and in the presence of a catalytic amount of sodium acetate (method E). Results from these methods are presented in Table 1. As shown in Table 1, the yields were markedly affected by the solvent and catalyst. Optimum results were obtained when reactions were carried out in toluene and in the presence of a catalytic amount of triethylamine (method D).


The same product was obtained under thermal aqueous conditions or microwave irradiation. The results of these reactions under thermal aqueous conditions or with microwave irradiation were summarized in Table 2.

**Table 1.** Synthesis of **4a** and **4b** under different reaction conditions and with microwave irradiation

Entry	Method	Compd.	Time/sec	Yield%
1	A	<b>4a</b>	300	70
2	A	<b>4b</b>	60	78
3	B	<b>4a</b>	600	52
4	B	<b>4b</b>	480	60
5	C	<b>4a</b>	90	74
6	C	<b>4b</b>	40	79
7	D	<b>4a</b>	40	90
8	D	<b>4b</b>	25	92
9	E	<b>4a</b>	40	73
10	E	<b>4b</b>	30	79

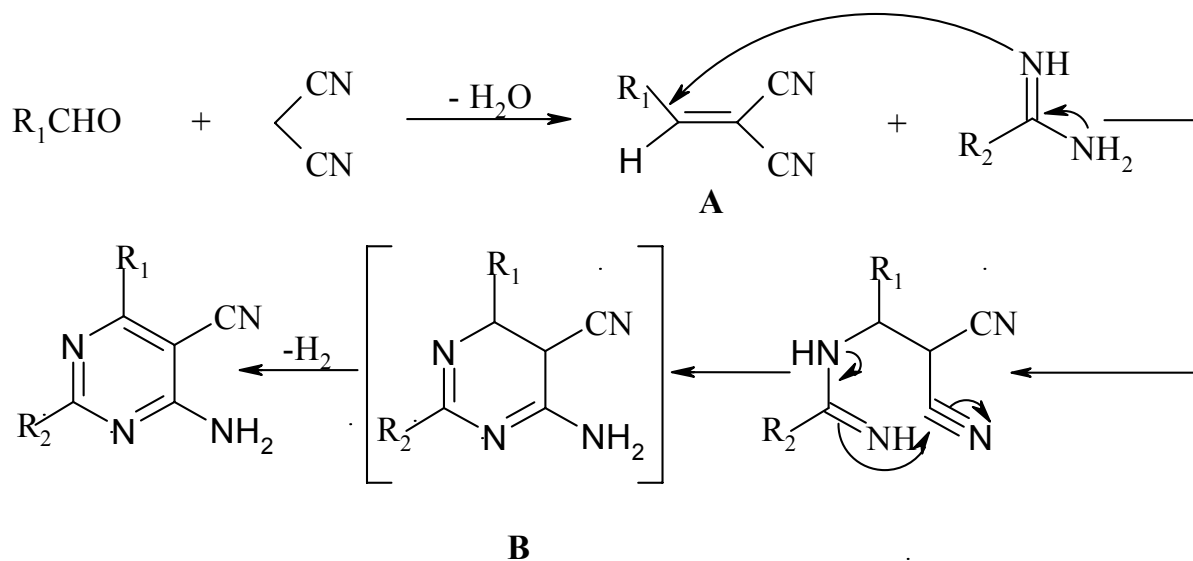
All reactions were carried out with 300W microwave irradiation.

**Table 2.** Synthesis of **4a-k** under thermal conditions and microwave irradiation

Compd No.	R1	R2	Thermal conditions (Method I)		Microwave irradiation (Method II)	
			Time (h)	Yield (%)	Time (Sec)	Yield(%)
4a	C <sub>6</sub> H <sub>5</sub>	Ph	6	78	40	90
4b	C <sub>6</sub> H <sub>5</sub>	NH <sub>2</sub>	5	81	25	92
4c	4-MeC <sub>6</sub> H <sub>4</sub>	Ph	4	79	50	84
4d	4-MeC <sub>6</sub> H <sub>4</sub>	NH <sub>2</sub>	5	64	45	90
4e	4-MeOC <sub>6</sub> H <sub>4</sub>	Ph	8	60	60	78
4f	4-Me <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	Ph	12	78	120	86
4g		Ph	6	46	60	67
4h	4-ClC <sub>6</sub> H <sub>4</sub>	Ph	4	73	35	75
4i	4-ClC <sub>6</sub> H <sub>4</sub>	NH <sub>2</sub>	3	82	30	96
4j	4-BrC <sub>6</sub> H <sub>4</sub>	Ph	4	80	35	89
4k	4-BrC <sub>6</sub> H <sub>4</sub>	NH <sub>2</sub>	4	78	30	85

All reactions were carried out under 300W microwave irradiation.

The complete process represents an example of a one-pot process with sequential steps (often referred to as tandem or cascade reaction) where reagents and catalysts are mixed together and experimental conditions are adjusted in such a way as to promote the reaction cascade.<sup>28</sup> Thus the benzylidenemalononitrile **A** containing an electron-poor C=C double bond is produced by rapid Knoevenagel condensation of malononitrile with the aromatic aldehyde, the formation of the benzylidenemalononitrile being monitored by TLC (*n*-hexane/diethyl ether as eluent). The second step is followed by Michael addition, cycloaddition, isomerization, aromatization to afford the 4-amino-5-pyrimidinecarbonitriles **4**. Intermediate **B** is not stable and was not isolated from the reaction mixture. It must be easily oxidized by air to produce compound **4**. We believe the driving force for such a transformation is the aromaticity of these final products (Scheme 2).



## Scheme 2

Structures **4a-k** were established on the basis of IR measurements which showed the presence of CN at region  $2235\text{-}2238\text{ cm}^{-1}$  and two sharp bands at  $3500\text{-}3450$  and  $3390\text{-}3380\text{ cm}^{-1}$  due to asymmetric and symmetric vibrations of the  $\text{NH}_2$  group. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR and mass spectra were also in accordance with the proposed structures.

In conclusion, we have developed a new, rapid and simple multicomponent cyclocondensation protocol for the synthesis of biologically active pyrimidinecarbonitriles in water as a solvent at reflux in good yields. Also, we observed that these heterocyclic compounds can be prepared in a microwave oven in excellent yields and in short reaction times.

## Experimental Section

**General Procedures.** Melting points were determined on an Gallenkamp melting point apparatus and are uncorrected. IR spectra were measured on a Mattson 1000 FT-IR spectrometer.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were determined on a BRUKER DRX-300 AVANCE spectrometer at 300.13 and 75.47 MHz, respectively. MS spectra were recorded on a Shimadzu QP 1100EX mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses were performed using a Heracus CHN-O-Rapid analyzer.

### General procedure for the preparation of 4-amino-5- pyrimidinecarbonitriles in water at reflux (Method I) and under microwave irradiation (Method II)

**Method I.** A mixture of aldehyde **1** (2 mmol), malononitrile **2** (2 mmol), amidine hydrochloride (2 mmol) and sodium acetate (2 mmol) in  $\text{H}_2\text{O}$  (50 mL) and ethanol (5 mL) was refluxed with

stirring for the time reported in Table 2 (the progress of the reaction being monitored by TLC and using *n*-hexane/ethyl acetate as an eluent). The product **4** precipitated from the reaction mixture after cooling, and the solid was filtered and recrystallized from ethanol.

**Method II.** A mixture of aldehyde **1** (2 mmol), malononitrile **2** (2 mmol) and an amidine hydrochloride (2 mmol) in toluene (5 mL) containing triethylamine (3–4 drops) was placed in a 15 mL high pressure glass tube and placed in a 250 mL beaker. After microwave irradiation at 300 W in the microwave oven for the period of time shown in Table 1, the reaction mixture was allowed to cool to ambient temperature. The product was purified as in Method I. Since guanidinium hydrochloride is insoluble in toluene, more triethylamine was used in this case.

**4-Amino-2,6-diphenyl-5-pyrimidinecarbonitrile (4a).** White crystals; mp 210-212 °C; [Found: C, 74.69 ; H, 4.35; N, 20.33% C<sub>17</sub>H<sub>12</sub>N<sub>4</sub> requires C, 74.98; H, 4.44; N, 20.57%];  $\nu_{\max}$  (KBr) 3478, 3344 (NH<sub>2</sub>), 2212 (CN), 1641, 1617 (C=N), 1542 (Ar) cm<sup>-1</sup>;  $\delta_{\text{H}}$  (300 MHz, DMSO-d<sub>6</sub>) 7.52-8.41 (m, Ar and NH<sub>2</sub>);  $\delta_{\text{C}}$  (75 MHz, DMSO-d<sub>6</sub>) 84.89 (C5), 116.89 (CN), 128.89, 128.99, 129.00, 129.09, 131.42, 132.05, 137.00, 137.04, 164.46, 165.06, 168.63; MS, *m/z* (%): 272 (M<sup>+</sup>, 100), 169 (87), 142 (32), 104 (57), 77 (59), 51 (35).

**2,4-Diamino-6-phenyl-5-pyrimidinecarbonitrile (4b).** Yellow crystals; mp 228-300 °C(dec.); [Found: C, 62.32; H, 4.30; N, 32.9% C<sub>11</sub>H<sub>9</sub>N<sub>5</sub> requires C, 62.55; H, 4.29; N, 33.16%];  $\nu_{\max}$  (KBr) 3478, 3379, 3329 (2NH<sub>2</sub>), 2212 (CN), 1691, 1617 (C=N), 1542 (Ar) cm<sup>-1</sup>;  $\delta_{\text{H}}$  (300 MHz, DMSO-d<sub>6</sub>) 7.14 (4H,broad, 2NH<sub>2</sub>), 7.50-7.73 (5H, m, Ar);  $\delta_{\text{C}}$  (75 MHz, DMSO-d<sub>6</sub>) 79.07 (C5), 117.85 (CN), 128.03,128.05, 130.13, 137.03, 162.87, 164.91, 169.33; MS, *m/z* (%): 211 (M<sup>+</sup>, 100), 169 (28), 77 (8), 60 (15), 43 (50).

**4-Amino-6-(4-methylphenyl)-2-phenyl-5-pyrimidinecarbonitrile (4c).** White crystals; mp 210 °C. [Found: C, 75.32 ; H, 4.81; N, 19.43% C<sub>18</sub>H<sub>14</sub>N<sub>4</sub> requires C, 75.51; H, 4.93; N, 19.57%];  $\nu_{\max}$  (KBr) 3478 (NH), 3478, 3329 (NH<sub>2</sub>), 2212 (CN), 1641 (C=N), 1542 (Ar) cm<sup>-1</sup>;  $\delta_{\text{H}}$  (300 MHz, DMSO-d<sub>6</sub>) 2.38 (3H, s, CH<sub>3</sub>), 7.35-8.41 (11H, m, Ar and NH<sub>2</sub>);  $\delta_{\text{C}}$  (75 MHz, DMSO-d<sub>6</sub>) 21.48 (CH<sub>3</sub>), 84.48 (C5), 117.05 (CN), 128.87, 128.94, 129.04, 129.51, 131.97, 134.20, 137.06, 141.47, 164.40, 165.15, 168.35; MS, *m/z* (%) 286 (M<sup>+</sup>, 100), 183 (90), 140 (18), 104 (34), 77 (23), 51 (15).

**2,4-Diamino-6-(4-methylphenyl)-5-pyrimidinecarbonitrile (4d).** Yellow crystals; mp 130 °C. [Found: C, 63.69 ; H, 4.78; N, 30.92% C<sub>12</sub>H<sub>11</sub>N<sub>5</sub> requires C, 63.99; H, 4.92; N, 31.09%];  $\nu_{\max}$  (KBr) 3478, 3379, 3155 (2NH<sub>2</sub>), 2212 (CN), 1666 (C=N), 1551 (Ar) cm<sup>-1</sup>;  $\delta_{\text{H}}$  (300 MHz, DMSO-d<sub>6</sub>) 2.40 (3H, s, CH<sub>3</sub>), 7.09 (4H, broad, 2NH<sub>2</sub>), 7.43 (2H, d, Ar), 7.86 (d, 2H, Ar);  $\delta_{\text{C}}$  (75 MHz, DMSO-d<sub>6</sub>) 21.93 (CH<sub>3</sub>), 80.73 (C5), 118.57 (CN), 128.59, 130.62, 134.80, 140.53, 163.45, 165.56, 169.67; MS, *m/z* (%):225 (M<sup>+</sup>, 100), 183 (48), 155 (15), 140 (20), 91 (35), 77 (24), 43 (68).

**4-Amino-6-(4-methoxyphenyl)-2-phenyl-5-pyrimidine-carbonitrile (4e).** White crystals; mp 213 °C; [Found: C, 71.25; H, 4.62; N, 18.23% C<sub>18</sub>H<sub>14</sub>N<sub>4</sub>O requires C, 71.51; H, 4.67; N, 18.53%];  $\nu_{\max}$  (KBr) 3479, 3354 (NH<sub>2</sub>), 2212 (CN), 1641, 1617 (C=N), 1542 (Ar) cm<sup>-1</sup>;  $\delta_{\text{H}}$  (300 MHz, DMSO-d<sub>6</sub>) 3.85 (3H, OCH<sub>3</sub>), 7.11-8.39 (11H, m, Ar and NH<sub>2</sub>);  $\delta_{\text{C}}$  (75 MHz, DMSO-d<sub>6</sub>) 55.90 (OCH<sub>3</sub>), 83.82 (C5), 114.37, 117.27, 128.84, 128.96, 129.16, 130.88, 131.95, 137.12,

162.03, 164.26, 165.24, 167.67; MS, *m/z* (%): 302 ( $M^+$ , 100), 258 (32), 199 (75), 169 (15), 129 (18), 104 (35), 77 (25), 45 (22).

**4-Amino-6-[4-(dimethylamino)phenyl]-2-phenyl-5-pyrimidinecarbonitrile (4f).** Red crystals; mp 162 °C; [Found: C, 72.18 ; H, 5.41; N, 22.11%  $C_{19}H_{17}N_5$  requires C, 72.36; H, 5.43; N, 22.21%];  $\nu_{max}$  (KBr) 3478, 3332 ( $NH_2$ ), 2212 (CN), 1617 (C=N), 1542 (Ar)  $cm^{-1}$ ;  $\delta_H$  (300 MHz, DMSO- $d_6$ ) 3.08 (6H, s,  $N(CH_3)_2$ ), 6.81-8.39 (11H, m, Ar and  $NH_2$ );  $\delta_C$  (75 MHz, DMSO- $d_6$ ) 40.80 ( $CH_3$ ), 69.07 (C5), 111.58 (CN), 112.22, 115.98, 116.74, 119.19, 128.78, 128.89, 130.45, 134.04, 154.74, 159.27, 164.23; MS, *m/z* (%) 315( $M^+$ , 100), 212(25), 104(41), 77(26), 51(12).

**4-Amino-2-phenyl-6-(2-thienyl)-5-pyrimidinecarbonitrile (4g).** yellow crystals; mp 200 °C. [Found: C, 64.61 ; H, 3.58; N, 20.03%  $C_{15}H_{10}N_4S$  requires C, 64.73; H, 3.62; N, 20.13%];  $\nu_{max}$  (KBr) 3478, 3329 ( $NH_2$ ), 2212 (CN), 1640 (C=N), 1544 (Ar)  $cm^{-1}$ ;  $\delta_H$  (300 MHz, DMSO- $d_6$ ) 7.31-8.39(m, Ar and  $NH_2$ );  $\delta_C$  (75 MHz, DMSO- $d_6$ ) 80.59(C5), 117.15 (CN), 128.74, 129.03, 129.47 130.52, 132.16, 133.23, 136.64, 141.41, 159.98, 164.29, 165.21; MS, *m/z* (%): 278 ( $M^+$ , 90), 175 (100), 133 (15), 104 (45), 77 (24), 45 (18).

**4-Amino-6-(4-chlorophenyl)-2-phenyl-5-pyrimidine-carbonitrile (4h).** White crystals; mp 222 °C; [Found: C, 66.22; H, 3.58; N, 18.09%  $C_{17}H_{11}ClN_4$  requires C, 66.56; H, 3.61; N, 18.26%];  $\nu_{max}$  (KBr) 3478, 3354 ( $NH_2$ ), 2212 (CN), 1641, 1616 (C=N), 1542 (Ar) $cm^{-1}$ ;  $\delta_H$  (300 MHz, DMSO- $d_6$ ) 7.53-8.40 (m, Ar and  $NH_2$ );  $\delta_C$  (75 MHz, DMSO- $d_6$ ) 84.89 (C5), 116.73 (CN), 128.89, 129.01, 129.11, 130.98, 132.12, 135.80, 136.31, 136.89, 164.46, 164.99, 167.38; MS, *m/z* (%) 306 ( $M^+$ , 100), 203 (70), 104 (32), 77 (20), 51 (15).

**2,4-Diamino-6-(4-chlorophenyl)-5-pyrimidinecarbonit-nitrile (4i).** White crystals; mp 229-231 °C(dec.); [Found: C, 53.55; H, 3.12; N, 28.32%  $C_{11}H_8ClN_5$  requires C, 53.78; H, 3.28; N, 28.51%];  $\nu_{max}$  (KBr) 3485, 3478, 3379, 3180 ( $2NH_2$ ), 2212 (CN), 1681, 1617 (C=N), 1551 (Ar)  $cm^{-1}$ ;  $\delta_H$  (300 MHz, DMSO- $d_6$ ) 7.18 (4H, broad,  $2NH_2$ ), 7.56 (2H, d, Ar), 7.77 (2H, d, Ar);  $\delta_C$  (75 MHz, DMSO- $d_6$ ) 76.35 (C5), 118.23 (CN), 128.76, 130.47, 135.51, 136.32, 163.39, 165.39, 168.66; MS, *m/z* (%) 245 ( $M^+$ , 100), 203 (35), 75 (14), 50 (10), 43 (47).

**4-Amino-6-(4-bromophenyl)-2-phenyl-5-pyrimidine-carbonitrile (4j).** White crystals; mp = 235-238 °C. [Found: C, 57.88 ; H, 3.09 ; N, 15.84%  $C_{17}H_{11}BrN_4$  requires C, 58.14; H, 3.16; N, 15.95%];  $\nu_{max}$  (KBr): 3478, 3329 ( $NH_2$ ), 2212 (CN), 1641, 1542  $^{-1}cm$ .  $\delta_H$  (300 MHz, DMSO- $d_6$ ) 7.50-8.35 (m, Ar and  $NH_2$ );  $\delta_C$  (75 MHz, DMSO- $d_6$ ) 84.82 (C5), 116.69 (CN), 125.18, 128.89, 128.95, 131.09, 131.99, 132.11, 136.06, 136.77, 164.53, 164.97, 167.45; MS, *m/z* (%) 353 ( $M+2$ , 100), 351 ( $M^+$ , 100), 270 (22), 249 (75), 247 (75), 168 (25), 141 (23), 104 (75), 77(55), 51(35).

**2,4-Diamino-6-(4-bromophenyl)-5-pyrimidinecarbonitrile (4k).** Yellow crystals; mp >240 °C dc. [Found: C, 45.38 ; H, 2.62 ; N, 23.93%  $C_{11}H_8BrN_5$  requires C, 45.54; H, 2.78; N, 24.14%];  $\nu_{max}$  (KBr): 3429, 3379, 3156 ( $2NH_2$ ), 2212 (CN), 1691, 1617 (C=N), 1542 (Ar)  $cm^{-1}$ .  $\delta$  (300 MHz, DMSO- $d_6$ ) 6.71-7.67 (m, Ar and  $NH_2$ ); MS, *m/z* (%) 290 ( $M^+$ , 100), 249 (25), 210 (15), 168 (45), 141 (45), 104 (65), 77 (50), 60 (25), 43 (35).

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## References and Footnotes

1. Keay, J. G.; Toomey, J. E. *Progress in Heterocyclic Chemistry*; Suschitzky, H.; Scriven, E. F. V., Eds.; Pergamon: Oxford, 1993; Vol. 5, p 202.
2. Ciufolini, M. A. *Advances in Heterocyclic Natural Product Synthesis*; Pearson, W. H.; Ed.; JAI: London, 1996; p3.
3. Wnuk, S. F.; Lewandowska, E.; Companioni, D. R.; Garcí'a, P. I., Jr.; Secrist, J. A. III. *Org. Biomol. Chem.* **2004**, *2*, 120.
4. Cushman, M.; Sambaiah, T.; Jin, G.; Illarionov, B.; Fischer, M.; Bacher, A. *J. Org. Chem.* **2004**, *69*, 601.
5. De Clercq, E. *Anticancer Res.* **1986**, *6*, 549.
6. De Clercq, E.; Bernaerts, R. *J. Biol. Chem.* **1987**, *262*, 14905.
7. Shishoo, C. J.; Shirsath, V. S.; Rathod, I. S.; Yande, V. D. *Eur. J. Med. Chem.* **2000**, *35*, 351.
8. Chambhare, R.V.; Khadse, B. G.; Bobde, A. S.; Bahekar, R. H. *Eur. J. Med. Chem.* **2003**, *38*, 89.
9. Hassan, N. A. *Molecules* **2000**, *5*, 827.
10. Pemmsin, M.; Lnu-Due, C.; Hoguet, F.; Gaultier, C.; Narcisse, J. *Eur. J. Chem.* **1988**, *23*, 543.
11. Cannito, A.; Pemmsin, M.; Lnu-Due, C.; Hoguet, F.; Gaultier, C.; Narcisse, J. *Eur. J. Chem.* **1990**, *25*, 635.
12. Smith, P. A. S.; Kan, R. O. *J. Org. Chem.* **1964**, *29*, 2261.
13. Nega, S.; Aionso, J.; Diazj, A.; Junquere, F. *J. Heterocycl. Chem.* **1990**, *27*, 269;
14. Shishoo, C. J.; Jain, K. S. *J. Heterocycl. Chem.* **1992**, *29*, 883.
15. Peters, J. U.; Hunziker, D.; Fischer, H.; Kansy, M.; Weber, S.; Kritter, S.; Muller, A.; Ricklin, F.; Boehringer, M.; Poli, S. M.; Csato, M.; Loeffler, B. M. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3575.
16. Peters, J. U.; Weber, S.; Kritter, S.; Weiss, P.; Wallier, A.; Zimmerli, D.; Boehringer, M.; Steger, M.; Loeffler, B. M. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3579.
17. Katritzky, A. R.; Soloduchko, J.; Belyakov, S. *ARKIVOC* **2000**, (i), 37.
18. Spivey, A. C.; Srikanan, R.; Diaper, C. M.; Turner, D. J. *Org. Biomol. Chem.* **2003**, *1*, 1638.
19. Bratus'ek, U.; Meden, A.; Svete, J.; Stanovnik, B. *ARKIVOC* **2003**, (v), 77.
20. Bowman, M. D.; Jeske, R. C.; Blackwell, H. E. *Org. Lett.* **2004**, *6*, 2019.
21. Weber, L. *Drug Disc. Today* **2002**, *7*, 143.



22. Dömling, A. *Curr. Opin. Chem. Biol.* **2002**, *6*, 306.
23. Sheibani, H.; Bernhardt, P, V.; Wentrup, C. *J. Org. Chem.* **2005**, *70*, 5859.
24. Sheibani, H.; Mosslemin, M. H.; Behzadi, S.; Islami, M. R.; Saidi, K. *Synthesis* **2006**, 435.
25. Sheibani, H.; Mosslemin, M. H.; Behzadi, S.; Islami, M. R.; Foroughi, H.; Saidi, K. *ARKIVOC* **2005**, (xv), 88.
26. Sheibani, H.; Islami, M. R.; Hassanpour, A.; Hosseininasab, F. A. *ARKIVOC* **2006**, (xv), 68.
27. Sheibani, H.; Islami, M. R.; Hosseininasab, F. A.; Hassanpour, A. *ARKIVOC* **2006**, (xv), 175.
28. For review on organic synthesis in water see: Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159.
29. Li, C. J. *Chem. Rev.* **1993**, *93*, 2023.
30. Breslow, R.; Groves, K.; Mayer, M. U. *Org. Lett.* **1999**, *1*, 117.
31. Blokzijl, W.; Blandamer, M. J.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1991**, *113*, 4241.
32. Gedye, R.; Smith, F.; Westaway, K. C.; Ali, H.; Baldisera, L.; Laberge, L.; Rousell, J. *Tetrahedron Lett.* **1986**, *27*, 279.
33. Khabazzadeh, H.; Moordini Nejad, R.; Sheibani, H.; Saidi, K. *Catal. Commun.* **2007**, *8*, 1411.