An efficient and chemoselective synthesis of *N*-substituted 2-aminopyridines *via* a microwave-assisted multicomponent reaction†

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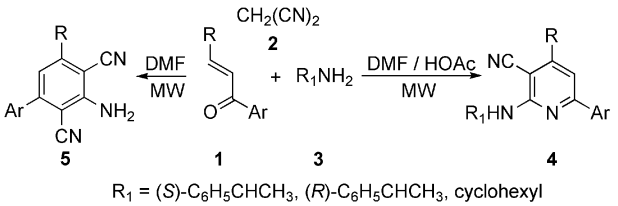
A facile and selective synthesis of *N*-substituted 2-aminopyridines is accomplished *via* microwave-assisted multi-component reactions controlled by the basicity of amine and the nature of solvent. In addition, a possible mechanism accounting for the reaction was proposed.

Introduction

The pyridine ring is one of the most well-known systems among the naturally occurring heterocycles.[1] Pyridine and fused pyridine moieties present in numerous natural products such as quinoline and isoquinoline alkaloids,[2] and nicotine and its analogues.[3] 2-Aminopyridines are promising substituted pyridines which have been shown to be biologically active molecules.[4] Additionally, because of their chelating abilities, 2-aminopyridines are commonly used as ligands in inorganic and organometallic chemistry.[5] If substituted with optically active groups, they could potentially serve as chiral auxiliaries or chiral ligands in asymmetric reactions. For these reasons, 2-aminopyridines are valuable synthetic targets. The synthesis of 2-aminopyridine derivatives has been extensively reviewed.[4–10]

N-Substituted 2-aminopyridines were previously mostly synthesized through: (i) reaction of aliphatic amines with 2-halopyridines or with imidol silyl ethers derived from the corresponding pyridin-2-ones,[11] (ii) aminolysis of 2-alkoxypyridines,[12] (iii) using α,β-unsaturated ketones to react with cyano derivatives and amines,[13] and (iv) reaction of 2-alkoxypyridines with amines in the presence of Et_2AlCl.[14] Of these methods, pathway (i) requires high temperature and high pressure while pathway (ii) involves alkoxypyridines containing activating groups in the pyridine ring under strong basic conditions, high temperatures, and a long reaction time. Method (iii) worked reasonably well with simple secondary amines while it was unable to isolate any of the desired 2-aminopyridine products when anilines or primary amines were used as nucleophiles. Method (iv) demands Et_2AlCl as a catalyst, which needs protection by a nitrogen environment and exclusion of water. Recently, Raghukumar *et al.*[15] have reported the synthesis of *N*-substituted 2-aminopyridines from α,β-unsaturated ketones, malononitrile and amines under mild conditions. However, the major drawback of this method is not only the poor to moderate yields, particularly with long reaction times, but also that it is limited to electron-donating substituents on the phenyl rings in the 3-position of α,β-unsaturated ketones and the stronger basicity of amines such as pyrrolidine, and morpholine. Hence, there is an urgent demand to develop a facile and versatile method for the synthesis of *N*-substituted 2-aminopyridines.

As part of an ongoing development of efficient protocols for the preparation of poly-substituted heterocycles from common intermediates,[16] we recently discovered that *N*-substituted 2-aminopyridines were efficiently synthesized *via* microwave-assisted (MW) chemoselective reactions controlled by the basicity of amine and the nature of solvent (Scheme 1).



Scheme 1

Results and discussion

Choosing an appropriate solvent is of crucial importance not only for successful microwave-promoted synthesis but also for the effective control of chemoselective reactions. For example, chalcone **1a** (1 mmol) reacted with equimolar malononitrile **2** and (*S*)-1-phenylethanamine **3a** in a mixed solvent of DMF and HOAc (volume ratio: 1 : 1), gave two different products (**4a** and **5a**) at 100 °C under microwave irradiation (initial power 100 W and maximum power 200 W) after 4 minutes (Scheme 2). Increasing the HOAc volume ratio of the mixed solvent to 1 : 2 and 1 : 3 resulted in higher yields of products **4a** to 59% and 73%, respectively. When the volume ratio of the mixed solvent was increased to 1 : 4, the compound **4a** was obtained as the main product and only a trace amount of **5a** was formed. Further increase of the volume ratio of the mixed solvent to 1 : 5 and 1 : 6 failed to improve the yield of product **4a**. Only compound **5a** was given if this reaction was carried out in pure DMF (Table 1, entry 8).

Under these optimized chemoselectivity conditions, a series of *N*-substituted 2-aminopyridines were synthesized *via* three-component reactions of chalcones **1**, malononitrile **2** and aliphatic amines **3a–c** in the mixed solvent of DMF and HOAc (volume ratio at 1 : 4) under microwave irradiation. The results are summarized in Table 2. In order to examine the applicability of this three-component cyclocondensation reaction to amines with weak

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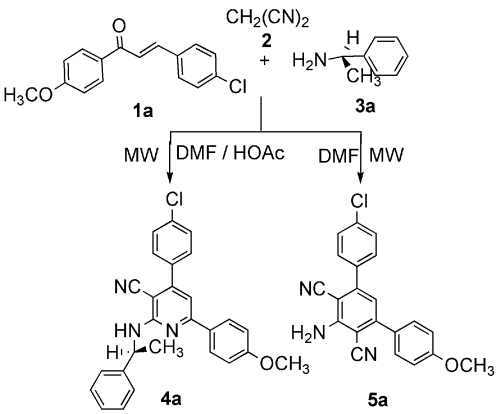
Table 1 Optimization of chemoselectivity conditions in the synthesis of compounds **4a** and **5a**

Entry	Solvent	Volume ratio	Yield[b] (%)	
			4a	**5a**
1	Mixed solvent[a]	1 : 1	45	32
2	Mixed solvent[a]	1 : 2	59	21
3	Mixed solvent[a]	1 : 3	73	10
4	Mixed solvent[a]	1 : 4	86	Trace
5	Mixed solvent[a]	1 : 5	82	Trace
6	Mixed solvent[a]	1 : 6	79	Trace
7	HOAc	—	40	Trace
8	DMF	—	0	45[c] (89)[d]

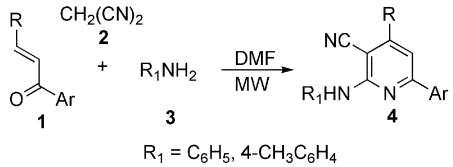
[a] The mixed solvent of DMF and HOAc. [b] Isolated yields. [c] The mole ratio of **1** and **2** is 1 : 1. [d] The mole ratio of **1** and **2** is 1 : 2.

basicity, we employed aromatic amines instead of aliphatic amines to react with the corresponding chalcones and malononitrile in different solvents such as HOAc, DMF and their mixed solvents. The reaction proceeded smoothly. To our delight, only products **4** were observed with the best results in DMF (Scheme 3).

Thus, the question is, why does the selective formation of products **4** occur in the mixed solvent of DMF and HOAc (volume ratio: 1 : 4) when aliphatic amines are employed as nucleophiles, whereas only products **4** are given using HOAc, DMF and their mixture as reaction solvents, when aromatic amines are used as nucleophiles? The chemoselectivity of the reaction should be attributed to the basicity of the reaction solution.



Scheme 2



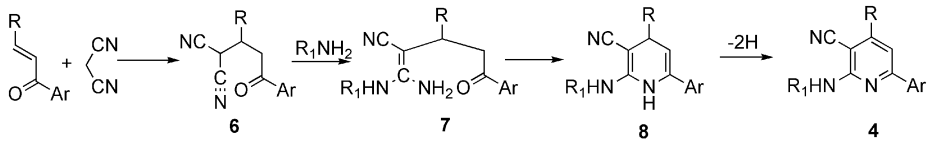
Scheme 3

The addition of a certain amount of HOAc to the reaction mixture made the basicity too low to deprotonate the malononitrile, so the Knoevenagel condensation reaction of malononitrile and **6** could not occur. The free aliphatic amine could undergo nucleophilic attack of **6** to give **7**, which yielded the final product

Table 2 Synthesis of compounds **4** and **5** under microwave irradiation conditions

Entry	Product	R	Ar	**3**	R_1	Time/min	Yield[a] (%)	Mp/°C
1	**4a**	4-ClC_6H_4	4-$CH_3OC_6H_4$	**3a**	(*S*)-$C_6H_5CHCH_3$	4	86	176–178
2	**4b**	4-BrC_6H_4	4-$CH_3OC_6H_4$	**3a**	(*S*)-$C_6H_5CHCH_3$	4	87	158–159
3	**4c**	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	**3a**	(*S*)-$C_6H_5CHCH_3$	6	82	148–150
4	**4d**	4-$CH_3OC_6H_4$	4-ClC_6H_4	**3a**	(*S*)-$C_6H_5CHCH_3$	4	85	165–167
5	**4e**	4-$CH_3OC_6H_4$	4-ClC_6H_4	**3b**	(*R*)-$C_6H_5CHCH_3$	4	83	172–174
6	**4f**	4-ClC_6H_4	4-$CH_3OC_6H_4$	**3b**	(*R*)-$C_6H_5CHCH_3$	4	84	186–187
7	**4g**	4-ClC_6H_4	4-$CH_3OC_6H_4$	**3c**	Cyclohexyl	5	79	201–203
8	**4h**	4-BrC_6H_4	4-FC_6H_4	**3c**	Cyclohexyl	3	84	187–188
9	**4i**	4-$CH_3OC_6H_4$	4-ClC_6H_4	**3c**	Cyclohexyl	4	82	156–158
10	**4j**	4-BrC_6H_4	4-$CH_3OC_6H_4$	**3d**	C_6H_5	6	89	237–238
11	**4k**	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	**3d**	C_6H_5	8	84	188–189
12	**4l**	4-$CH_3OC_6H_4$	4-ClC_6H_4	**3d**	C_6H_5	5	86	226–228
13	**4m**	4-ClC_6H_4	2,4-$Cl_2C_6H_3$	**3d**	C_6H_5	4	84	238–240
14	**4n**	4-$CH_3OC_6H_4$	2-Pyridyl	**3d**	C_6H_5	7	81	216–217
15	**4o**	4-ClC_6H_4	2-Pyridyl	**3d**	C_6H_5	5	85	258–259
16	**4p**	4-ClC_6H_4	4-$CH_3OC_6H_4$	**3e**	4-$CH_3C_6H_4$	6	88	235–237
17	**4q**	4-BrC_6H_4	4-$CH_3OC_6H_4$	**3e**	4-$CH_3C_6H_4$	5	87	230–231
18	**4r**	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	**3e**	4-$CH_3C_6H_4$	9	82	211–213
19	**4s**	4-$CH_3OC_6H_4$	4-ClC_6H_4	**3e**	4-$CH_3C_6H_4$	6	85	239–241
20	**4t**	2-Thiophenyl	4-$CH_3OC_6H_4$	**3e**	4-$CH_3C_6H_4$	8	76	182–184
21	**4x**	4-$CH_3OC_6H_4$	2-Pyridyl	**3e**	4-$CH_3C_6H_4$	7	82	244–245
22	**4y**	4-ClC_6H_4	2-Pyridyl	**3e**	4-$CH_3C_6H_4$	4	88	255–256
23	**5a**	4-ClC_6H_4	4-$CH_3OC_6H_4$	**3a**	(*S*)-$C_6H_5CHCH_3$	4	86	263–265
24	**5b**	4-BrC_6H_4	4-$CH_3OC_6H_4$	**3a**	(*S*)-$C_6H_5CHCH_3$	4	89	267–269
25	**5c**	4-BrC_6H_4	4-FC_6H_4	**3a**	(*S*)-$C_6H_5CHCH_3$	4	90	252–253
26	**5d**	4-$CH_3OC_6H_4$	4-ClC_6H_4	**3b**	(*R*)-$C_6H_5CHCH_3$	6	87	253–254
27	**5e**	4-ClC_6H_4	C_6H_5	**3b**	(*R*)-$C_6H_5CHCH_3$	8	84	269–270
28	**5f**	2,4-$Cl_2C_6H_3$	4-$CH_3OC_6H_4$	**3c**	Cyclohexyl	7	85	217–218
29	**5g**	3-$NO_2C_6H_4$	4-$CH_3OC_6H_4$	**3c**	Cyclohexyl	4	83	234–235

[a] Isolated yields.

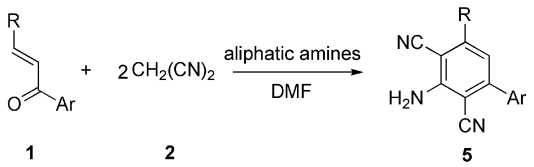


Scheme 4

4 *via* cyclization and aromatization (Scheme 4). A similar case happened to the aryl amine, thus gave similar products. However, in the absence of HOAc, the aliphatic amine acted as a basic catalyst rather than a reactant in the synthesis of compounds **5**.

To further investigate this process, reactions of chalcones **1b**, malononitrile **2**, and amines **3a** were carried out in formic acid ($pK_a = 3.77$)[17] whose pK_a value was lower than that of acetic acid ($pK_a = 4.76$).[17] Surprisingly, we could not get the expected product **4**, instead **6b** was obtained by reaction of chalcones **1b** and malononitrile **2**. The results indicated that amine **3a** might have formed an ammonium salt by reacting with formic acid, losing the nucleophilicity.

In addition, an attempted reaction of **1** and **2** in a 1 : 2 mole ratio with a few drops of aliphatic amines **3a–c** in DMF under microwave irradiation was carried out to give 2,6-dicyanoanilines **5** in good yields (Scheme 5, and Table 2, entries 23–29).



Scheme 5

As shown in Table 2, a study of the electronic effect with various substituents on the phenyl rings of chalcones was conducted. Under our reaction conditions, electron-donating substituents readily provided *N*-substituted 2-aminopyridines **4** in high yields (Table 2, entries 3, 12 and 17). Moreover, electron-withdrawing *N*-substituted 2-aminopyridine derivatives **4** were obtained in high yields as well, as highlighted by halide-containing compounds, which were obtained in 87 and 89% yields, respectively. It is worth noting that this result is significant since there is no literature precedent for the synthesis of 2-arylamino-4-aryl-6-(pyridin-2-yl)pyridine-3-carbonitriles (Table 2, entries 14–15 and 21–22). Furthermore, the reaction is not only suitable for amines but also can be used with chiral amines such as (*S*)-1-phenylethanamine (Table 2, entries 1–4) and (*R*)-1-phenylethanamine (Table 2, entries 5–6).

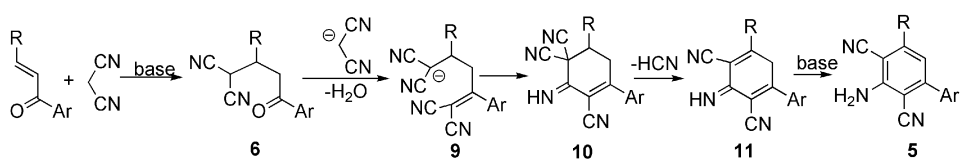
The structures of all of the synthesized compounds were established on the basis of their spectroscopic data. The IR spectrum of compound **4a** showed strong absorptions at 3342 cm^{-1} due to the NH group, and at 2207 cm^{-1} due to the CN group. The ^1H NMR spectrum of **4a** showed a doublet at δ 1.59 due to $-CH_3$ and a singlet at δ 3.82 due to OCH_3 and a triplet at δ 7.20 due to the NH proton (exchanged with D_2O) and a singlet at δ 7.23 due to the CH proton in the pyridine ring. In the IR spectrum of compound **5a**, the appearance of bands at 3466, 3363, 3241 and 2216 cm^{-1} due to the NH_2 and CN triple bond, respectively, and the disappearance of the band at 1685–1710 cm^{-1} due to the C=O group of chalcone confirmed the formation of product. The appearance of a broad singlet at δ 6.84 due to the NH_2 protons (exchanged with D_2O) and a singlet at δ 6.79 due to $H–C_4$ in the ^1H NMR spectrum further confirmed the formation of product.

Proposed reaction mechanism

A mechanism for the formation of the products **4** is outlined in Scheme 4. The reaction occurs *via* an initial formation of the compounds **6** formed by Michael addition reaction of chalcones and malononitrile as shown in Scheme 4, which suffers nucleophilic attack to give the intermediate **7**. The intermediate **7** then cyclizes and subsequently loses a hydrogen molecule to afford the fully aromatized compound **4**. This type of hydrogen loss is well precedented.[18] In order to support the proposed mechanism of **4**, the compound **6b**[19] was prepared independently from chalcones **1b** and malononitrile **2** and then employed in a two-component reaction with (*S*)-1-phenylethanamine **3a** to afford **4b** in 87% yield, while 2,6-dicyanoaniline **5b** was not observed at all. This stimulated us to use the compound **6b** as a substrate to react with (*S*)-1-phenylethanamine **3a** and malononitrile **2** for further study. Impressively, both **4b** and **5b** were formed. Therefore, the formation of **5** is expected to proceed *via* an initial Michael addition reaction of chalcones and malononitrile to afford compound **6**, which further undergoes an *in situ* Knoevenagel condensation reaction with malononitrile **2** to yield the intermediate **9**. The intermediate **9** suffers nucleophilic attack to give intermediate **10**, which eliminates HCN molecular and subsequently aromatizes to afford the product **5** (Scheme 6). This type of HCN loss has been reported.[20]

Conclusion

In summary, we have demonstrated an efficient and practical method for the synthesis of a wide range of *N*-substituted



Scheme 6

2-aminopyridines under mild conditions and have shown the effect of the basicity of amine and the nature of solvent on chemoselectivity. In light of its operational simplicity, simple purification procedure and good yields, this protocol is superior to the existing methods.

Experimental

General

Microwave irradiation was carried out with a microwave oven Emrys™ Creator from Personal Chemistry, Uppsala, Sweden. Melting points were determined in open capillaries and were uncorrected. IR spectra were taken on a FT-IR-Tensor 27 spectrometer in KBr pellets and reported in cm^{-1}. ^1H NMR spectra were measured on a Bruker DPX 400 MHz spectrometer in DMSO-d_6 with chemical shift (δ) given in ppm relative to TMS as internal standard. Elemental analysis was determined by using a Perkin-Elmer 240c elemental analysis instrument.

General procedure for the synthesis of compounds 4 and 5

Preparation of compounds 4a–i. In a 10 mL Emrys™ reaction vial, chalcone (**1**, 1 mmol), malononitrile (**2**, 1 mmol), amine (**3a–c**, 1 mmol), DMF (0.2 mL) and HOAc (0.8 mL) were mixed and then capped. The mixture was irradiated for a given min at 100 °C under microwave irradiation (initial power 100 W and maximum power 200 W). Upon completion, monitored by TLC, the reaction mixture was cooled to room temperature and then poured into cold water. The solid product was collected by Büchner filtration and washed with EtOH (95%), and subsequently dried and recrystallized from EtOH (95%) to give the pure product.

Preparation of compounds 4j–s. In a 10 mL Emrys™ reaction vial, chalcone (**1**, 1 mmol), malononitrile (**2**, 1 mmol), aromatic amine (**3d–e**, 1 mmol) and DMF (1.0 mL) were mixed and then capped. The mixture was irradiated for a given min at 100 °C under microwave irradiation (initial power 100 W and maximum power 200 W). When the reaction was completed (monitored by TLC), the subsequent work-up procedure was the same as that of the above.

Preparation of compounds 5. In a 10 mL Emrys™ reaction vial, chalcone (**1**, 1 mmol), malononitrile (**2**, 2 mmol), amine (**3a–c**, 0.1 mmol) and DMF (1.0 mL) were mixed and then capped. The mixture was irradiated for a given min at 100 °C under microwave irradiation (initial power 100 W and maximum power 200 W). When the reaction was completed (monitored by TLC), the subsequent work-up procedure was the same as that of the above.

2-((*S*)-1-Phenylethylamino)-4-(4-chlorophenyl)-6-(4-methoxyphenyl)pyridine-3-carbonitrile (4a). IR (KBr, ν, cm^{-1}): 3342, 3026, 2973, 2207, 1597, 1488, 1368, 1238, 1093, 1015, 821, 698; ^1H NMR (DMSO-d_6) (δ, ppm): 8.04 (d, $J = 8.8$ Hz, 2H, ArH), 7.68 (d, $J = 8.8$ Hz, 2H, ArH), 7.63 (d, $J = 8.8$ Hz, 2H, ArH), 7.53 (d, $J = 7.6$ Hz, 2H, ArH), 7.40 (d, $J = 7.2$ Hz, 1H, ArH), 7.33 (t, $J = 7.6$ Hz, 2H, ArH), 7.23 (s, 1H, ArH), 7.20 (t, $J = 7.2$ Hz, 1H, NH), 7.01 (d, $J = 8.8$ Hz, 2H, ArH), 5.47–5.43 (m, 1H, CH), 3.82 (s, 3H, OCH_3), 1.59 (d, $J = 6.8$ Hz, 3H, CH_3); Anal. calcd. for $C_{27}H_{22}ClN_3O$; C, 73.71; H, 5.04; N, 9.55; found C, 73.54; H, 5.18; N, 9.69%.

4-(4-Chlorophenyl)-2-(cyclohexylamino)-6-(4-methoxyphenyl)-pyridine-3-carbonitrile (4g). IR (KBr, ν, cm^{-1}): 3378, 2932, 2853, 2209, 1578, 1511, 1486, 1366, 1243, 1089, 823, 778, 668; ^1H NMR (DMSO-d_6) (δ, ppm): 8.14 (d, $J = 8.8$ Hz, 2H, ArH), 7.69 (d, $J = 8.4$ Hz, 2H, ArH), 7.63 (d, $J = 8.4$ Hz, 2H, ArH), 7.23 (s, 1H, ArH), 7.06 (d, $J = 8.8$ Hz, 2H, ArH), 6.62 (d, $J = 7.6$ Hz, 1H, NH), 4.19–4.12 (m, 1H, CH), 3.83 (s, 3H, OCH_3), 1.95 (d, $J = 10.4$ Hz, 2H, CH_2), 1.78 (d, $J = 12.4$ Hz, 2H, CH_2), 1.63–1.20 (m, 6H, CH_2); Anal. calcd. for $C_{25}H_{24}ClN_3O$, C, 71.85; H, 5.79; N, 10.05; found C, 71.99; H, 5.53; N, 10.21%.

4-(4-Bromophenyl)-6-(4-methoxyphenyl)-2-(phenylamino)pyridine-3-carbonitrile (4j). IR (KBr, ν, cm^{-1}): 3324, 2936, 2215, 1607, 1579, 1540, 1496, 1238, 1009, 821; ^1H NMR (DMSO-d_6) (δ, ppm): 9.17 (s, 1H, NH), 8.11 (d, $J = 8.8$ Hz, 2H, ArH), 7.81 (d, $J = 8.8$ Hz, 2H, ArH), 7.69–7.66 (m, 4H, ArH), 7.53 (s, 1H, ArH), 7.38 (t, $J = 7.6$ Hz, 2H, ArH), 7.07–7.04 (m, 3H, ArH), 3.83 (s, 3H, OCH_3); Anal. calcd. for $C_{25}H_{18}BrN_3O$, C, 65.80; H, 3.98; N, 9.21; found C, 65.57; H, 4.12; N, 9.35%.

2-(*p*-Tolylamino)-4,6-bis(4-methoxyphenyl)pyridine-3-carbonitrile (4r). IR (KBr, ν, cm^{-1}): 3321, 3001, 2932, 2836, 2215, 1606, 1540, 1370, 1251, 1170, 825; ^1H NMR (DMSO-d_6) (δ, ppm): 8.96 (s, 1H, NH), 8.10 (d, $J = 8.8$ Hz, 2H, ArH), 7.70 (d, $J = 8.8$ Hz, 2H, ArH), 7.56 (d, $J = 8.4$ Hz, 2H, ArH), 7.45 (s, 1H, ArH), 7.17 (d, $J = 8.4$ Hz, 2H, ArH), 7.14 (d, $J = 8.8$ Hz, 2H, ArH), 7.04 (d, $J = 8.4$ Hz, 2H, ArH), 3.86 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 2.31 (s, 3H, CH_3); Anal. calcd. for $C_{27}H_{23}N_3O_2$, C, 76.94; H, 5.50; N, 9.97; found C, 77.12; H, 5.67; N, 9.79%.

3-(4-Chlorophenyl)-5-(4-methoxyphenyl)-2,6-dicyanoanilines (5a). IR (KBr, ν, cm^{-1}): 3466, 3363, 3241, 2986, 2216, 1645, 1578, 1562, 1464, 1297, 1180, 1093, 1030, 822; ^1H NMR (DMSO-d_6) (δ, ppm): 7.68 (d, $J = 8.4$ Hz, 2H, ArH), 7.62–7.60 (m, 4H, ArH), 7.09 (d, $J = 8.4$ Hz, 2H, ArH), 6.84 (s, 2H, NH_2), 6.79 (s, 1H, ArH), 3.83 (s, 3H, OCH_3); Anal. calcd. for $C_{21}H_{14}ClN_3O$, C, 70.10; H, 3.92; N, 11.68; found C, 70.34; H, 3.71; N, 11.61%.

2-(1-(4-Bromophenyl)-3-(4-methoxyphenyl)-3-oxopropyl)malononitrile (6b). Mp: 123–124 °C; IR (KBr, ν, cm^{-1}): 3014, 2967, 2905, 2250, 1671, 1602, 1574, 1488, 1369, 1223, 1075, 836, 810; ^1H NMR (DMSO-d_6) (δ, ppm): 7.96 (d, $J = 8.8$ Hz, 2H, ArH), 7.59 (d, $J = 8.8$ Hz, 2H, ArH), 7.36 (d, $J = 8.8$ Hz, 2H, ArH), 6.98 (d, $J = 8.8$ Hz, 2H, ArH), 4.69 (d, $J = 5.2$ Hz, 1H, CH), 3.93–3.96 (m, 1H, ArH), 3.88 (s, 3H, OCH_3), 3.53–3.73 (m, 2H, CH_2); Anal. calcd. for $C_{19}H_{15}BrN_2O_2$, C, 59.55; H, 3.95; N, 7.31; found C, 59.68; H, 3.79; N, 7.46%.

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