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AN EXPERIMENTAL STUDY OF SPECIAL LEAVING GROUP BEHAVIOR IN THE REACTION OF ARYLIDENEBARBITURIC ACIDS WITH CARBON NUCLEOPHILES

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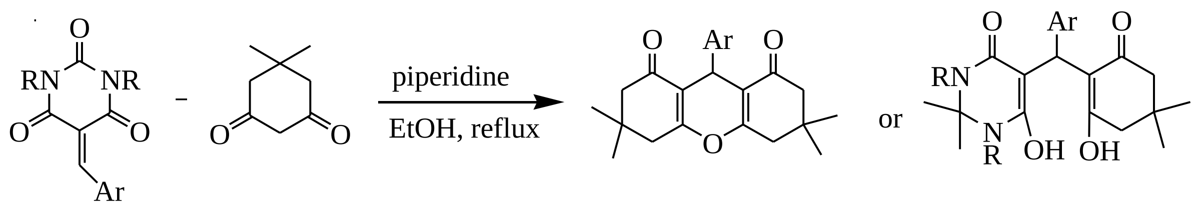
Abstract – The reaction of benzylidenebarbituric acid and 1,3-dimethylbenzylidenebarbituric acid with malononitrile as well as with dimedone in piperidine is investigated. In reaction with malononitrile, substituted pyridine-3,5-dicarbonitriles are obtained, while with dimedone, xanthenes and/or 6-hydroxy-5-((2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)(aryl)methyl)-1,3-dimethyl pyrimidine-2,4(1*H*,3*H*)-dione derivatives are isolated.

Benzylidenebarbituric acids which are potential organic oxidizers[1,2] are used in preparation of oxadeazaflavines,[3] unsymmetrical synthesis of disulphides,[4] synthesis of Merocyanine dyes[5] and as antibacterial agents.[6] Benzylidenebarbiturate derivatives such as benzylidene(thio)barbiturate-β-D-glycosides act as mushroom tyrosinase inhibitors.[7,8] Furthermore, benzylidenebarbituric acids are important building blocks in the synthesis of pyrazolo[3,4-*d*]pyrimidines and pyrido[2,3-*d*]pyrimidines,[9-11] which show a broad spectrum of biological activities.[12-14] Some of these compounds have also been studied as nonlinear optical materials.[15]

The nucleophilic attack at the electron-deficient double bond of Michael acceptors has long been a field of great interest in physical organic chemistry.[16,17] Benzylidenebarbituric and thiobarbituric acids are characterized by their strongly polarized exocyclic double bond with a positive partial charge on the arylidene carbon.[18,19]

The reaction of enones **1a-e** with two equivalents of dimedone (**2**) in the presence of an excess piperidine in EtOH furnished xanthene derivatives **3a-e**. Under the same conditions the *N*,*N*-dimethylderivatives **1f-j** gave 6-hydroxy-5-((2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)(aryl)methyl)-1,3-dimethyl-pyrimidine-2,4-(1*H*,3*H*)-dione derivatives **4f-j**, while the compounds **1k** and **1l** did not react at all (Scheme 1 and Table 1).



1a-l **2** **3a-e** **4f-j**

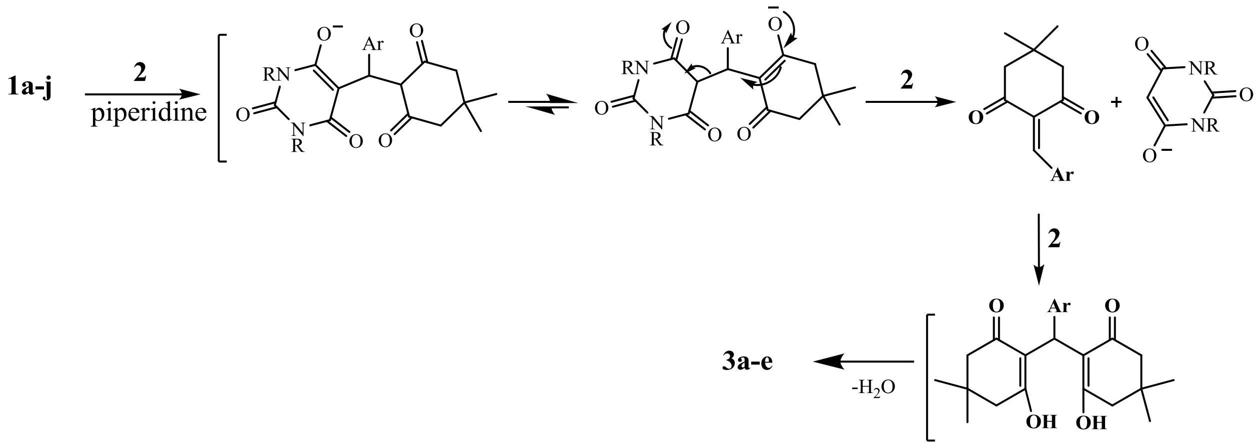
Scheme 1

Table 1. Reaction of enones **1a-l** with dimedone (**2**)

1	R	Ar	product	Yield (%)
a	H	C_6H_5-	**3a**	75
b	H	4-$MeOC_6H_4$-	**3b**	45
c	H	4-ClC_6H_4-	**3c**	79
d	H	2-ClC_6H_4-	**3d**	80
e	H	4-MeC_6H_4-	**3e**	71
f	Me	C_6H_5-	**4f**	70
g	Me	4-MeC_6H_4-	**4g**	65
h	Me	4-ClC_6H_4-	**4h**	68
i	Me	3-$O_2NC_6H_4$-	**4i**	73
j	Me	4-BrC_6H_4-	**4j**	69
k	Me	4-$MeOC_6H_4$-	**--**	--
l	Me	2,4-$MeOC_6H_4$-	**--**	--

Along with the formation of products **3a-e**, barbiturate salts precipitate from the reaction mixture. No such precipitations were observed in formation of **4f-j**. To investigate further, the reaction of **1b,c,e** with 1,3-indanedione was also carried out which lead to the corresponding 2-benzylidene-1,3-indanediones **5b,c,d** containing no barbituric acid moiety.

The formation of xanthenes **3** could be rationalized by an initial Micheal addition of **2**, followed by a sequence involving concurrent retro-Micheal elimination of the barbiturate moiety, followed by the second Micheal addition of **2** and cyclization (Scheme 2).



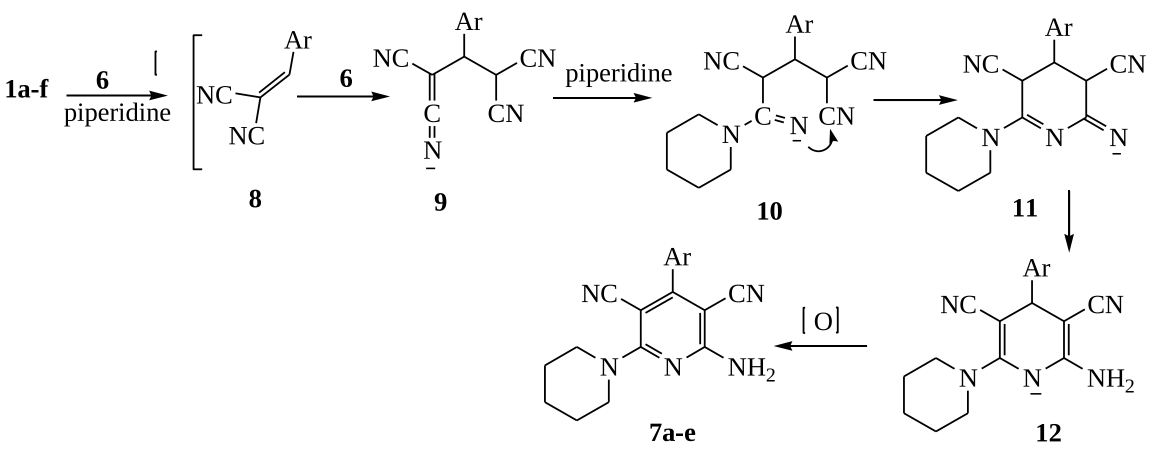
Scheme 2

The presence of hydrogens or nitrogen atoms is clearly a determining factor in the type of products formed. The reaction of enones **1a-f** with two equivalent of malononitrile (**6**) in presence of an excess amount of piperidine in EtOH afforded pyridinedinitrile derivatives **7a-e** in 45-65% yields, presumably through a similar addition-elimination-addition sequence as dimedone **2** and final cyclization as shown (Scheme 3 and Table 2).

Table 2. Reaction of enones **1a-f** with malononitrile

1	R	Ar	product	Yield (%)
a	H	C_6H_5-	**7a**	60
b	H	4-MeOC_6H_5-	**7b**	45
c	H	4- ClC_6H_5-	**7c**	63
d	H	2-ClC_6H_5-	**7d**	65
e	H	4-MeC_6H_5-	**7e**	53
f	Me	C_6H_5-	**7a**	58

In products isolated from the reactions **1a-f** with malononitrile, barbituric acid units are absent. A possible mechanism[20] is shown in Scheme 3.



Scheme 3

The reaction of arylidenebarbituric acids with dimedone was found to give two types of products depending upon the presence of N-H bonds or otherwise. Starting materials **1a-e** gave xanthenes where as **1f-j** gave substituted pyrimidinediones. Similar results were obtained from the reaction of malononitrile with arylidenbarbituric acids except for compound **1f**.

EXPERIMENTAL

1. Instruments and characterization

Melting points were measured on an Electrothermal 9200 apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DRX-300 AVANCE spectrometer at 300.13 MHz. IR spectra were recorded on a Bomem MB-Series FTIR. Electrospray ionization (ESI) mass spectrometry (MS) experiments were performed on Finnigan-MAT-8430 mass spectrometer, at 70 eV, in m/z. Elemental analyses were carried out on a Heraeus CHN-O-Rapid analyzer.

2. General procedure for the preparation of 5-((aryl)(2-hydroxy-6-oxocyclohex-1-enyl)methyl)-6-hydroxy-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (4f-j).

Piperidine (8 mmol) was added dropwise to a solution of enone **1** (2 mmol) and dimedone (**2**, 4 mmol) in absolute EtOH (15 mL) at room temperature. The reaction mixture was refluxed until the disappearance of the starting material (4-6 h), (monitored by TLC), solution was evaporated and was diluted with H_2SO_4 (10%) (15 mL), precipitate solid product was recrystallized from water/acetone.

2.1. 6-Hydroxy-5-((2-hydroxy-6-oxocyclohex-1-enyl)(phenyl)methyl)-1,3-dimethylpyrimidine-2,4-(1*H*,3*H*)-dione (4f). Yield 70%. Mp 186-188 °C. IR (KBr cm^{-1}) 2200-3383, 1700, 1631, 1616. ^{1}H NMR ($CDCl_3$) δ: 1.15 (s, 3H, Me), 1.28 (s, 3H, Me), 2.30-2.54 (m, 4H, $2CH_2$), 3.36 (s, 3H, N-Me), 3.45 (s, 3H, N-Me), 5.58 (s, 1H, CH), 7.12-7.33 (m, 5H, aryl), 10.6 (br, 1H, OH), 12.85 (s, 1H, OH). ^{13}C NMR ($CDCl_3$) δ: 27.1, 28.9, 29.2, 29.7, 31.12, 33.6, 45.7, 47.0, 92.4, 116.4, 126.2, 126.5, 128.3, 137.2, 150.7, 162.3, 164.2, 190.6, 191.5. MS: m/z (%) = 384 (M^+, 68), 263 (8), 243 (26), 227 (100), 171 (14), 156 (22), 129 (12), 116 (19), 102 (27), 83 (13), 71 (9), 55 (14), 42 (33). Anal. Calcd for $C_{21}H_{24}N_2O_5$: C, 65.61; H, 6.29; N, 7.29. Found: C, 65.71; H, 6.32; N, 7.08.

2.2. 6-Hydroxy-5-((2-hydroxy-6-oxocyclohex-1-enyl)(p-tolyl)methyl)-1,3-dimethylpyrimidine-2,4-(1*H*,3*H*)-dione (4g). Yield 68%. Mp 176-179 °C. IR (KBr cm^{-1}) 2200-3200, 1703, 1604. ^{1}H NMR ($CDCl_3$) δ: 1.10 (s, 3H, Me), 1.27 (s, 3H, Me), 2.32 (s, 3H, Me-aryl), 2.34-2.53 (m, 4H, $2CH_2$), 3.35 (s, 3H, N-Me), 3.44 (s, 3H, N-Me), 5.53 (s, 1H, CH), 7.01 (d, J = 7.7 Hz, 2H, aryl) 7.10 (d, J = 8.1 Hz, 2H, aryl), 11.0 (br, 1H, OH), 12.8 (s, 1H, OH). ^{13}C NMR ($CDCl_3$) δ: 20.9, 27.1, 28.8, 29.2, 29.9, 31.2, 33.2, 46.9, 50.7, 92.5, 116.5, 126.4, 129.0, 133.9, 135.6, 150.7, 162.3, 164.1, 190.7, 191.4. MS: m/z (%) = 398 (M^+, 6), 364 (17), 349 (12), 273 (21), 257 (18), 241 (25), 227 (100), 171 (21), 156 (30), 129 (14), 115 (49), 97 (17), 83 (29), 69 (46), 57 (30), 43 (39). Anal. Calcd for $C_{22}H_{26}N_2O_5$: C, 66.32; H, 6.58; N, 7.03. Found: C, 65.99; H, 6.58; N, 7.03.

2.3. 5-((4-Chlorophenyl)(2-hydroxy-6-oxocyclohex-1-enyl)methyl)-6-hydroxy-1,3-dimethyl-pyrimidine-2,4(1*H*,3*H*)-dione (4h). Yield 62%. Mp 176 °C. IR (KBr cm^{-1}) 2200-3385, 1703, 1604. ^{1}H NMR ($CDCl_3$) δ: 1.13 (s, 3H, Me), 1.26 (s, 3H, Me), 2.29-2.53 (m, 4H, $2CH_2$), 3.35 (s, 3H, N-Me), 3.44 (s, 3H, N-Me), 5.50 (s, 1H, CH), 7.05 (d, *J* = 11.4 Hz, 2H, aryl) 7.25 (d, *J* = 11.4 Hz, 2H, aryl), 9.50 (br, 1H, OH), 12.79 (s, 1H, OH). ^{13}C NMR ($CDCl_3$) δ: 27.1, 28.9, 29.1, 29.9, 31.2, 33.3, 46.0, 46.5, 47.0, 92.2, 116.1, 128.0, 128.4, 131.9, 135.8, 150.6, 162.3, 146.1, 191.1, 191.2. MS: m/z (%) = 418 (M^+, 7), 400 (11), 289 (30), 207 (15), 186 (13), 167 (43), 149 (100), 80 (48), 64 (59), 41 (43). Anal. Calcd for $C_{21}H_{23}N_2O_5Cl$: C, 60.22; H, 5.53; N, 6.69. Found: C, 60.83; H, 5.43; N, 6.75.

2.4. 6-Hydroxy-5-((2-hydroxy-6-oxocyclohex-1-enyl)(3-nitrophenyl)methyl)-1,3-dimethyl-pyrimidine-2,4(1*H*,3*H*)-dione (4i). Yield 59%. Mp 180-182 °C. IR (KBr cm^{-1}) 2200-3392, 1703, 1609. ^{1}H NMR ($CDCl_3$) δ: 1.16 (s, 3H, Me), 1.33 (s, 3H, Me), 2.32-2.58 (m, 4H, $2CH_2$), 3.36 (s, 3H, N-Me), 3.47 (s, 3H, N-Me), 5.58 (s, 1H, CH), 7.47 (d, *J* = 4.5 Hz, 2H, aryl), 8.02 (d, *J* = 1.1 Hz, H, aryl), 8.09 (m, 1H, aryl), 9.80 (br, 1H, OH), 12.79 (s, 1H, OH). ^{13}C NMR ($CDCl_3$) δ: 27.0, 28.9, 29.3, 29.9, 31.2, 33.72, 46.1, 46.9, 91.5, 115.7, 121.4, 122.4, 129.2, 132.7, 139.9, 148.5, 150.5, 162.4, 164.2, 191.4, 191.6. MS: m/z (%) = 429 (M^+, 11), 378 (11), 289 (27), 273 (60), 256 (100), 242 (15), 226 (44), 189 (19), 156 (61), 129 (29), 115 (28), 101 (37), 69 (21), 55 (43), 42 (89). Anal. Calcd for $C_{21}H_{23}N_3O_7$: C, 58.71; H, 5.40; N, 9.79. Found: C, 58.94; H, 5.41; N, 9.56.

2.5. 5-((4-Bromophenyl)(2-hydroxy-6-oxocyclohex-1-enyl)methyl)-6-hydroxy-1,3-dimethyl-pyrimidine-2,4(1*H*,3*H*)-dione (4j). Yield 70%. Mp 193-195 °C. IR (KBr cm^{-1}) 2200-3391, 1705, 1607. ^{1}H NMR ($CDCl_3$) δ: 1.14 (s, 3H, Me), 1.26 (s, 3H, Me), 2.29-2.53 (m, 4H, $2CH_2$), 3.35 (s, 3H, N-Me), 3.44 (s, 3H, N-Me), 5.48 (s, 1H, CH), 7.00 (d, *J* = 8.5 Hz, 2H, aryl) 7.41 (d, *J* = 8.5 Hz, 2H, aryl), 9.65 (br, 1H, OH), 12.70 (s, 1H, OH). ^{13}C NMR ($CDCl_3$) δ: 27.1, 29.2, 29.5, 29.9, 31.2, 33.3, 46.0, 46.9, 92.1, 116.1, 120.0, 128.5, 131.2, 136.4, 150.6, 162.3, 164.1, 191.1, 191.2. MS: m/z (%) = 464 (M^+, 33), 462 (33), 323 (20), 307 (53), 227 (100), 209 (7), 196 (10), 171 (26), 141 (11), 115 (23), 101 (16), 83 (16), 69 (10), 55 (20), 42 (40). Anal. Calcd for $C_{21}H_{23}N_2O_5Br$: C, 54.44; H, 5.40; N, 6.05. Found: C, 54.86; H, 5.44; N, 6.04.

3. General procedure for the preparation of 9-(aryl)-3,4,6,7-tetrahydro-3,3,6,6-tetramethyl-anthracene-1,8(2*H*,5*H*,9*H*,10*H*)-dione (3a-e).

Piperidine (8 mmol) was added dropwise to a solution of enone **1** (2 mmol) and dimedone (**2**, 4 mmol) in absolute EtOH (15 mL) at room temperature. The reaction mixture was refluxed until the disappearance of the starting material (3.5-5 h), (monitored by TLC) and barbituric acid salt was filtered off. The filtrate was evaporated and was diluted with H_2SO_4 (10%) (15 mL), precipitate solid product was recrystallized from water/acetone.

3.1. 3,4,6,7-Tetrahydro-3,3,6,6-tetramethyl-9-phenyl-2*H*-xanthene-1,8(5*H*,9*H*)-dione (3a). Yield 75%. Mp 199-203 °C. IR (KBr cm^{-1}) 2958, 1677, 1662, 1623. ^{1}H NMR (acetone) δ: 0.96 (s, 6H, $CH(Me)_2$), 1.08 (s, 6H, $CH(Me)_2$), 2.02-2.55 (m, 8H, $4CH_2$), 4.64 (s, 1H, CH), 7.04-7.26 (m, 5H, aryl). ^{13}C NMR (acetone) δ: 27.1, 32.5, 32.6, 41.0, 51.1, 115.9, 126.9, 128.5, 129.3, 145.6, 163.4, 196.2. Anal. Calcd for $C_{23}H_{26}O_3$: C, 78.85; H, 7.42; N, 0.00. Found: C, 78.30; H, 7.60; N, 0.21.

3.2. 3,4,6,7-Tetrahydro-9-(4-methoxyphenyl)-3,3,6,6-tetramethyl-2*H*-xanthene-1,8(5*H*,9*H*)-dione (3b). Yield 45%. Mp 245-247 °C. IR (KBr cm^{-1}) 2953, 1679, 1678, 1659, 1619. ^{1}H NMR (DMSO-d_6) δ: 0.88 (s, 6H, $CH(Me)_2$), 1.02 (s, 6H, $CH(Me)_2$), 2.02-2.52 (m, 8H, $4CH_2$), 3.66 (s, 3H, OMe), 4.44 (s, 1H, CH), 6.75 (d, *J* = 8.6 Hz, 2H, aryl), 7.05 (d, *J* = 8.6 Hz, 2H, aryl). ^{13}C NMR (DMSO-d_6) δ: 26.4, 28.6, 30.2, 31.8, 48.3, 50.0, 113.2, 114.6, 128.9, 136.4, 162.6, 196.0. Anal. Calcd for $C_{24}H_{28}O_4$: C, 75.79; H, 7.37; N, 0.00. Found: C, 75.60; H, 7.30; N, 0.15.

3.3. 9-(4-Chlorophenyl)-3,4,6,7-tetrahydro-3,3,6,6-tetramethyl-2*H*-xanthene-1,8(5*H*,9*H*)-dione (3c). Yield 79%. Mp 214-217 °C. IR (KBr cm^{-1}) 2951, 1679, 1662, 1624. ^{1}H NMR (DMSO-d_6) δ: 0.88 (s, 6H, $CH(Me)_2$), 0.97 (s, 6H, $CH(Me)_2$), 2.09-2.59 (m, 8H, $4CH_2$), 4.48 (s, 1H, CH), 7.16 (d, *J* = 8.5 Hz, 2H, aryl), 7.26 (d, *J* = 8.5 Hz, 2H, aryl). ^{13}C NMR (DMSO-d_6) δ: 26.5, 28.6, 30.9, 31.8, 49.9, 113.9, 127.8, 129.9, 130.7, 143.2, 163.0, 196.0. Anal. Calcd for $C_{23}H_{25}O_3Cl$: C, 71.78; H, 6.50; N, 0.00. Found: C, 72.2; H, 6.47; N, 0.09.

3.4. 9-(2-Chlorophenyl)-3,4,6,7-tetrahydro-3,3,6,6-tetramethyl-2*H*-xanthene-1,8(5*H*,9*H*)-dione (3d). Yield 80%. Mp 217-218 °C. IR (KBr cm^{-1}) 2959, 1680, 1655, 1625. ^{1}H NMR (DMSO-d_6) δ: 0.9 (s, 6H, $CH(Me)_2$), 1.03 (s, 6H, $CH(Me)_2$), 2.06-2.6 (m, 8H, $4CH_2$), 4.82 (s, 1H, CH), 7.08-7.26 (m, 4H, aryl). ^{13}C NMR (DMSO-d_6) δ: 26.3, 28.6, 30.5, 31.6, 50.0, 113.1, 126.4, 127.7, 129.4, 131.9, 132.8, 140.7, 168.2, 195.8. Anal. Calcd for $C_{23}H_{25}O_3Cl$: C, 71.78; H, 6.50; N, 0.00. Found: C, 71.30; H, 6.61; N, 0.07.

3.5. 3,4,6,7-Tetrahydro-9-(4-methylphenyl)-3,3,6,6-tetramethyl-2*H*-xanthene-1,8(5*H*,9*H*)-dione (3e). Yield 45%. Mp 222-225°C. IR (KBr cm^{-1}) 2950, 1677, 1676, 1660, 1617. ^1H NMR (DMSO-d_6) δ: 1.00 (s, 6H, $C(Me)_2$), 1.11 (s, 6H, $C(Me)_2$), 1.99-2.22 (m, 8H, $4CH_2$), 2.44 (s, 3H, Me), 4.6 (s, 1H, CH), 6.69 (d, *J* = 8.6 Hz, 2H, aryl), 7.13 (d, *J* = 8.6 Hz, 2H, aryl). ^{13}C NMR (DMSO-d_6) δ: 22.5, 26.4, 28.5, 30.2, 31.8, 50.1, 113.0, 114.6, 128.7, 136.2, 163.6, 197.0. Anal. Calcd for $C_{24}H_{28}O_3$: C, 79.09; H, 7.74; N, 0.00. Found: C, 78.73; H, 7.65; N, 0.09.

4. General procedure for the preparation 2-(benzyliden)-2*H*-indene-1,3-dione (5b,c,e)

Piperidine (8 mmol) was added dropwise to a solution of enone **1** (2 mmol) and 2*H*-indene-1,3-dione (2 mmol) in absolute EtOH (15 mL) at room temperature. The reaction mixture was refluxed until the disappearance of the starting material (5-7 h), (monitored by TLC) and barbituric acid salt was filtered off. The filtrate was evaporated and was diluted with H_2SO_4 (10%) (15 mL), precipitate solid product was recrystallized from hot EtOH.

4.1. 2-(4-Methoxybenzylidene)-2*H*-indene-1,3-dione (5b). Yield 68%. Mp 156-157 °C. IR (KBr cm^{-1}) 1725, 1680. ^1H NMR (CDCl3) δ: 3.9 (s, 3H, OMe), 7.02 (d, *J* = 8.9 Hz, 2H, aryl), 7.58 (s, 1H, =CH), 7.79 (m, 2H, aryl), 7.98 (m, 2H, aryl), 8.55 (d, *J* = 8.9 Hz, 2H, aryl), ^{13}C NMR (CDCl3) δ: 55.6, 123.1, 123.5, 126.4, 126.5, 134.8, 135.1, 137.2, 139.9, 142.3, 146.8, 188.3, 190.8. Anal. Calcd for $C_{17}H_{12}O_3$: C, 77.26; H, 4.58; N, 0.00. Found: C, 77.73; H, 4.65; N, 0.06.

4.2. 2-(4-Chlorobenzylidene)-2*H*-indene-1,3-dione (5c). Yield 72%. Mp 172-174 °C. IR (KBr cm^{-1}) 1727, 1690. ^1H NMR (CDCl3) δ: 7.47 (d, *j* = 8.5 Hz, 2H, aryl), 7.81 (s, 1H, =CH), 7.83 (m, 2H, aryl), 8.01 (m, 2H, aryl), 8.41 (d, *J* = 8.5 Hz, 2H, aryl), ^{13}C NMR (CDCl3) δ: 123.3, 123.4, 129.1, 129.4, 135.3, 135.5, 139.5, 140.1, 142.5, 145.1,188.9, 189.9. Anal. Calcd for $C_{16}H_9ClO_2$: C, 71.52; H, 3.38; N, 0.00. Found: C, 71.67; H, 3.15; N, 0.08.

4.3. 2-(4-Methylbenzylidene)-2*H*-indene-1,3-dione (5e). Yield 80%. Mp 146-147 °C. IR (KBr cm^{-1}) 1726, 1683. ^1H NMR (CDCl3) δ: 2.46 (s, 3H, Me), 7.32 (d, *J* = 8.1 Hz, 2H, aryl), 7.81(m, 2H, aryl), 7.88 (s, 1H, =CH), 8.01 (m, 2H, aryl), 8.40 (d, *J* = 8.2 Hz, 2H, aryl). ^{13}C NMR (CDCl3) δ: 22.09, 123.2, 128.2, 129.6, 130.6, 134.5, 135.0, 135.2, 140.0, 142.5, 144.6, 147.1, 189.2, 190.5. Anal. Calcd for $C_{17}H_{12}O_2$: C, 82.24; H, 4.87; N, 0.00. Found: C, 81.89; H, 4.70; N, 0.04.

5. General procedure for the preparation of 2-amino-4-(2-aryl)-6-(piperidinyl)-pyridine-3,5-dicarbonitriles (7a-e).

Piperidine (8 mmol) was added dropwise to a solution of enone **1** (2 mmol) and malononitrile (**6**, 4 mmol) in absolute EtOH (15 mL) at room temperature. The reaction mixture was refluxed until the disappearance of the starting material (8-10 h), (monitored by TLC) and barbituric acid salt was filtered off. The filtrate was evaporated and was diluted with water (15 mL), precipitate solid product was recrystallized from water/acetone. In some cases column chromatography was used using ethylacetate/chloroform mixture as eluent.

5.1. 2-Amino-4-phenyl-6-(piperidin-1-yl)pyridine-3,5-dicarbonitrile (7a). Yield 60%. Mp 203-205 °C. IR (KBr cm^{-1}) 3474, 3325, 3222, 2202, 1624, 1583, 1567. ^{1}H NMR (DMSO-d6) δ: 1.61 (m, 6H, piperidine), 3.71 (m, 4H, piperidine), 7.44-7.53 (m, 7H, aryl and NH2). ^{13}C NMR (DMSO-d6) δ: 24.9, 26.6, 49.4, 81.8, 82.5, 117.2, 118.8, 129.5, 129.7, 130.9, 136.3, 160.8, 161.7, 162.8. MS: m/z (%) = 303 (M^+, 1), 302 (3), 277 (4), 238 (100), 213 (3), 183 (3), 162 (24), 145 (3), 127 (19), 103 (15), 84 (17), 56 (8), 41 (9). Anal. Calcd for $C_{18}H_{17}N_5$: C, 71.28; H, 5.65; N, 23.09. Found: C, 71.78; H, 6.01; N, 22.76.

5.2. 2-Amino-4-(4-methoxyphenyl)-6-(piperidin-1-yl)pyridine-3,5-dicarbonitrile (7b). Yield 45%. Mp 198-200 °C. IR (KBr cm^{-1}) 3512, 3401, 2196, 1602, 1580, 1554. ^{1}H NMR (acetone) δ: 1.65 (m, 6H, piperidine), 3.76 (m, 4H, piperidine), 3.87 (s, 3H, OMe), 6.71 (s, 2H, NH_2), 7.06 (d, J = 6.8 Hz, 2H, aryl), 7.49 (d, J = 6.8 Hz, 2H, aryl). ^{13}C NMR (acetone) δ: 25.1, 26.7, 49.7, 55.7, 81.7, 83.8, 114.7, 116.9, 118.4, 128.5, 131.4, 161.1, 162.1, 162.4, 162.5. MS: m/z (%) = 333 (M^+, 68), 332 (100), 318 (23), 304 (9), 182 (14), 125 (23), 84 (8), 55 (7), 41 (5). Anal. Calcd for $C_{19}H_{19}N_5O$: C, 68.45; H, 5.74; N, 21.01. Found: C, 67.92; H, 5.69; N, 21.50.

5.3. 2-Amino-4-(4-chlorophenyl)-6-(piperidin-1-yl)pyridine-3,5-dicarbonitrile (7c). Yield 63%. Mp 218-220 °C. IR (KBr cm^{-1}) 3470, 3331, 3326, 2209, 1628, 1576, 1530. ^{1}H NMR (acetone) δ: 1.65 (m, 6H, piperidine), 3.79 (m, 4H, piperidine), 6.82 (s, 2H, NH_2), 7.54-7.61 (m, 4H, aryl). ^{13}C NMR (acetone) δ: 25.0, 26.6, 49.6, 81.3, 83.3, 116.4, 118.0, 129.6, 131.5, 132.1, 135.4, 136.4, 160.9, 161.5, 161.9. MS: m/z (%) = 337 (M^+, 46), 336 (100), 308 (10), 294 (41), 281 (5), 219 (5), 84 (7), 69 (8), 55 (7), 41 (8). Anal. Calcd for $C_{18}H_{16}N_5Cl$: C, 64.00; H, 4.77; N, 20.73. Found: C, 63.90; H, 4.71; N, 20.47.

5.4. 2-Amino-4-(2-chlorophenyl)-6-(piperidin-1-yl)pyridine-3,5-dicarbonitrile (7d). Yield 65%. Mp 188-189 °C. IR (KBr cm^{-1}) 3467, 3327, 3321, 2207, 1622, 1572, 1531. ^{1}H NMR (acetone) δ: 1.65 (m, 6H, piperidine), 3.80 (m, 4H, piperidine), 6.85 (s, 2H, NH_2), 7.47-7.61 (m, 4H, aryl). ^{13}C NMR (acetone) δ: 25.0, 26.6, 49.4, 83.0, 84.1, 115.8, 117.4, 128.3, 130.6, 131.1, 132.0, 132.6, 135.8, 160.3, 160.6, 161.2. MS: m/z (%) = 337 (M^+, 75), 308 (33), 302 (100), 294 (9), 281 (9), 260 (15), 247 (19), 219 (20), 165 (13), 84 (21), 55 (12), 41 (15). Anal. Calcd for $C_{18}H_{16}N_5Cl$: C, 64.00; H, 4.77; N, 20.73. Found: C, 64.06; H, 4.71; N, 20.77.

5.5. 2-Amino-6-(piperidin-1-yl)-4-p-tolylpyridine-3,5-dicarbonitrile (7e). Yield 53%. Mp 198 °C. IR (KBr cm^{-1}) 3479, 3327, 3221, 2201, 1623, 1579, 1556, 1535. ^{1}H NMR ($CDCl_3$) δ: 1.69 (m, 6H, piperidine), 2.41 (s, 3H, Me) 3.79 (m, 4H, piperidine), 5.35 (s, 2H, NH_2), 7.30 (d, J = 8.1 Hz, 2H, aryl), 7.39 (d, J = 8.1 Hz, 2H, aryl). ^{13}C NMR ($CDCl_3$) δ: 21.5, 24.4, 25.9, 49.2, 81.5, 83.5, 116.7, 117.8, 128.6, 129.5, 131.8, 140.7, 159.4, 161.2, 162.4. MS: m/z (%) = 317 (M^+, 56), 316 (100), 302 (17), 288 (9), 219 (4), 179 (4), 84 (8), 69 (8), 55 (5), 41 (7). Anal. Calcd for $C_{19}H_{19}N_5$: C, 71.90; H, 6.03; N, 22.07. Found: C, 72.09; H, 6.20; N, 21.69.

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