

Synthesis of 1-Amino-5,6-diaryl-3-cyano-1*H*-pyridin-2-ones and 6,7-Diaryl-4-cyano-3-hydroxy-1*H*-[1,2]diazepines from Isoflavones

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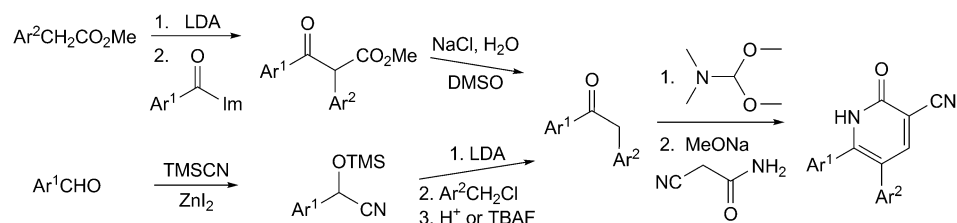
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The one-step cyclocondensation of substituted isoflavones (= 3-phenyl-4*H*-1-benzopyran-4-ones) with cyanoacetohydrazide in the presence of KOH afforded a mixture of 1-amino-5,6-diaryl-3-cyano-1*H*-2-pyridin-2-ones and 6,7-diaryl-4-cyano-3-hydroxy-1*H*-[1,2]diazepines.

Introduction. – Substituted 1*H*-pyridin-2-ones and 1*H*-[1,2]diazepines possess interesting biological and pharmacological activities. For example, 1*H*-pyridin-2-ones have been shown to exhibit antimicrobial [1], antidepressant [2], cardiotoxic [3], and anticancer activities [4], while benzo-annelated 1*H*-[1,2]diazepines play an important role in medicine as tranquilizers [5][6]. The most common synthetic route to 1*H*-pyridin-2-ones [7] involves the cyclocondensation of MeCN derivatives such as cyanoacetate, cyanoacetamide, or malononitrile with an appropriate α,β -unsaturated carbonyl or 1,3-dicarbonyl substrate [8–10]. However, the preparation of 5,6-diaryl-1*H*-pyridin-2-ones requires multistep syntheses and harsher reaction conditions (Scheme 1) [11][12]. The traditional synthesis of 1*H*-[1,2]diazepines [13] usually employed photoinduced ring enlargement of 1-iminopyridinium ylides [14] or reactions of 2,4,6-triarylpyrylium (or thiopyrylium) salts with NH_2NH_2 in H_2O under microwave irradiation [15]. Synthesis of 6,7-diaryl-1*H*-[1,2]diazepines have not been reported.

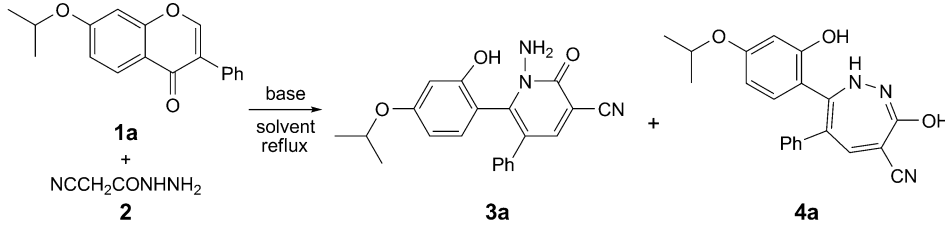
Scheme 1. Methods for the Synthesis of 5,6-Diaryl-3-cyano-1*H*-pyridin-2-ones. LDA, Lithium diisopropylamide; Im, 1*H*-imidazol-1-yl; TMSCN, Me_3SiCN ; TBAF, Bu_4NF .



It is known that the chromone (=4*H*-1-benzopyran-4-one) moiety of isoflavones can generate a 1,3-dicarbonyl equivalent in the presence of a base, which readily reacts with amidines [16], guanidine [17], and hydrazine [18], to form the corresponding 2-substituted pyrimidines and diarylpyrazoles. Recently, we have reported that 2-aminobenzimidazole [19], 3-amino-1,2,4-triazole [20], 3-amino-5-hydroxypyrazole [21], and cyanoacetamide underwent [22] condensations with isoflavones to yield pyrimido[1,2-*a*]benzimidazoles, triazolopyrimidines, pyrazolo[3,4-*b*]pyridines, and 5,6-diaryl-3-cyano-pyridin-2(1*H*)-ones, respectively. These heterocyclic compounds are usually constructed by condensation of isoflavones with substrates containing two N-atoms such as amidines, guanidines, hydrazines, and amino-azoles among others [7][13]. We now report a strategy for the synthesis of 5,6-diaryl-1*H*-pyridin-2-ones and 6,7-diaryl-1*H*-[1,2]diazepines involving the cyclocondensation reactions of isoflavones (**1**) with the active CH₂ C-atom and N-atoms of cyanoacetohydrazide (**2**).

Results and Discussion. – Initially, the reaction between the readily available 4-isopropoxyisoflavone (**1a**) and cyanoacetohydrazide (**2**) was optimized by varying the bases and solvents. The reactions were carried out under reflux, and the results are compiled in *Table 1*. The product of the NaOH-catalyzed condensation with **1a** in EtOH was the expected 1-amino-1*H*-pyridin-2-one derivative **3a**, but it was formed in

Table 1. Optimization of the Cyclocondensation of Isoflavone **1a** with Cyanoacetohydrazide (**2**)^{a)}



| Entry | Solvent ^{b)} | Base | Molar ratios | | Yield [%] ^{c)} | |
|-------|-----------------------|--------------------------------|-----------------------------|-----------|-------------------------|--|
| | | | 1a / 2 /base | 3a | 4a | |
| 1 | EtOH | NaOH | 1 : 1 : 1 | 2 | trace | |
| 2 | MeCN | NaOH | 1 : 1 : 1 | 12 | trace | |
| 3 | DMF | NaOH | 1 : 1 : 1 | 25 | 8 | |
| 4 | BuOH | NaOH | 1 : 1 : 1 | 10 | 3 | |
| 5 | DMSO | NaOH | 1 : 1 : 1 | 25 | 5 | |
| 6 | DMF | KOH | 1 : 1 : 1 | 30 | 10 | |
| 7 | DMF | K ₂ CO ₃ | 1 : 1 : 1 | 15 | trace | |
| 8 | DMF | ^t BuOK | 1 : 1 : 1 | 8 | trace | |
| 9 | DMF | KOH | 1 : 1 : 1.6 ^{d)} | 35 | 15 | |
| 10 | DMF | KOH | 1 : 1.2 : 1.6 ^{e)} | 28 | 11 | |

^{a)} All reactions were carried out on 1-mmol scale of **1a** in the indicated solvent (10 ml) until complete disappearance of **1a**. ^{b)} All reactions were carried out in refluxing solvent. ^{c)} Yields of isolated products.

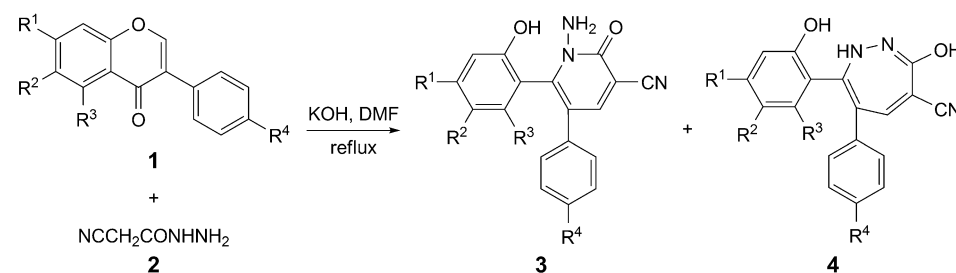
^{d)} Reactions with 1.2, 1.4, or 1.8 equiv. of NaOH gave **3a/4a** in 32/12%, 33/14%, and 30/12% yields, resp.

^{e)} Reactions with 1.4 or 1.6 equiv. of **2** gave **3a/4a** in 25/9% and 22/5% yields, resp.

low yield (*Table 1, Entry 1*). Reactions in different solvents using solid NaOH as the base revealed that DMF gave the highest yield of **3a** (*Entries 1–5*). Careful separation of the crude mixtures on silica-gel column furnished also a second product, whose structure was assigned as 1*H*-[1,2]diazepine derivative **4a**. A similar 4-cyano-3-hydroxy-7-(2-hydroxyphenyl)-1*H*-[1,2]diazepine product has been recently observed in the reaction of chromone-3-carboxylic acid with cyanoacetohydrazide in the presence of EtONa [23]. A comparative study of different bases showed that KOH was the most effective base in producing **3a** and **4a** derivatives (*Entries 6–8*). The highest yields were obtained using **1a/2/KOH** in the ratio of 1:1:1.6 (*Entries 9–10*). In most cases, the cyclocondensation afforded **3a** as the major product, and **4a** was the minor, though, in few instances, 1-amino-1*H*-pyridin-2-one **3a** was obtained as a single product, albeit in low yields (*Entries 1, 2, 7, and 8*).

The cyclocondensation seems to be widely applicable, because reactions between a variety of isoflavones, **1a–1j** and **2** (**1/2/KOH** 1:1:1.6; DMF, 1.5–7 h; reflux) afforded mixtures of 2-amino-1*H*-pyridin-2-ones **3a–3j** and 1,2-diazepines **4a–4j**, respectively in good overall yields (36–60%). The ratio **3/4**, as separated compounds, ranged from 3:1 to 2:1 (*Table 2*). The highest yields of **3a–3j** and **4a–4j** were obtained, when a F-

Table 2. Synthesis of 1-Amino-5,6-diaryl-3-cyano-1*H*-pyridin-2-ones **3a–3j** and 4-Cyano-6,7-diaryl-1*H*-[1,2]diazepines **4a–4j** by Cyclocondensation of Various Isoflavones, **1a–1j** with Cyanoacetohydrazide (**2**) in DMF^a)



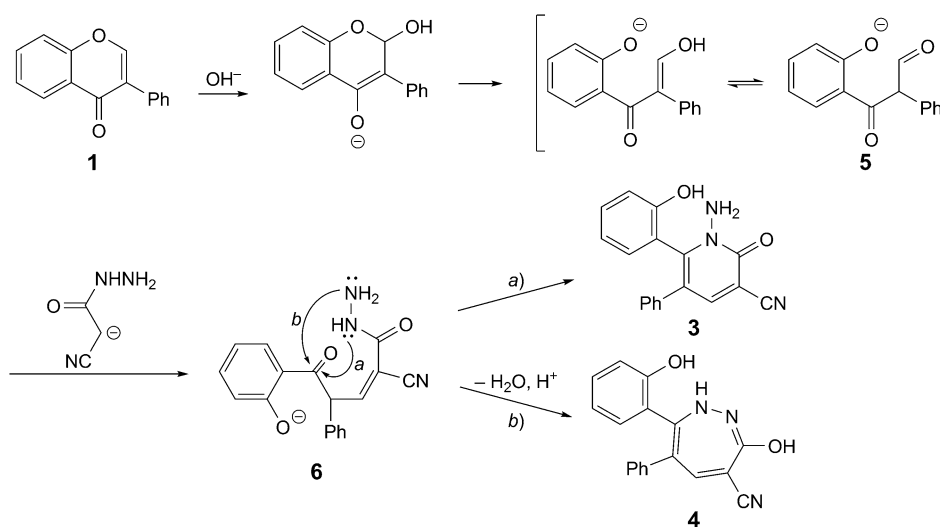
| Entry | Substrate | R ¹ | R ² | R ³ | R ⁴ | Product | | Time [h] | Yield [%] ^b) | |
|-------|-----------|------------------|----------------|----------------|----------------|-----------|-----------|----------|--------------------------|----------|
| | | | | | | 3 | 4 | | 3 | 4 |
| 1 | 1a | ^t PrO | H | H | H | 3a | 4a | 1.5 | 35 ^c) | 15 |
| 2 | 1b | MeO | H | MeO | MeO | 3b | 4b | 2.0 | 32 | 13 |
| 3 | 1c | MeO | H | Me | H | 3c | 4c | 2.5 | 30 | 10 |
| 4 | 1d | OH | H | H | MeO | 3d | 4d | 7.0 | 25 | 9 |
| 5 | 1e | H | F | H | H | 3e | 4e | 3.5 | 40 ^d) | 20 |
| 6 | 1f | H | F | H | Me | 3f | 4f | 3.5 | 38 | 18 |
| 7 | 1g | H | F | H | MeO | 3g | 4g | 4.0 | 37 | 17 |
| 8 | 1h | MeO | H | H | MeO | 3h | 4h | 5.0 | 28 | 12 |
| 9 | 1i | H | H | H | Me | 3i | 4i | 5.5 | 26 | 10 |
| 10 | 1j | BnO | H | H | MeO | 3j | 4j | 4.0 | 31 | 11 |

^a) All reactions were carried out on 1-mmol scale of **1a–1j** (**1/2/KOH** 1:1:1.6) in DMF (10 ml) at reflux until complete disappearance of **1a–1j**. ^b) Yields of isolated products. ^c) At 80° only **3a** (20%) was formed. ^d) At 80°, only **3e** (26%) was formed.

atom as an electron-withdrawing group was present at ring A (*Entries 5–7*), while the yields for isoflavones with electron-donating groups were lower. It is worth mentioning that the condensation at temperature below 80° was chemoselective, and only 2-amino-1*H*-pyridin-2-ones **3** were formed; however, the yields were low (*Entries 1* and 5). At higher temperature the 1*H*-[1,2]diazepine derivatives **4** started to form, and their yields increased gradually with increasing temperature until 150°.

A plausible mechanism for the formation of **3** and **4** is outlined in *Scheme 2*. In brief, base-catalyzed ring opening of the isoflavones [24] should lead to the formation of the 1,3-dicarbonyl intermediate **5**. *Knoevenagel* condensation of **5** with the anion of cyanoacetohydrazide (**2**) would initially form **6**. Subsequent attack of the NH group in **6** (path *a*) on the C=O group, followed by dehydration, would form the six-membered ring of **3**, while attack of the NH₂ group in **6** (path *b*) would lead to the seven-membered ring of **4**.

Scheme 2. Proposed Mechanism for the Formation of **3** and **4**



Conclusions. – We have developed a convenient one-pot procedure for the synthesis of 1-amino-5,6-diaryl-3-cyano-1*H*-pyridin-2-ones and 6,7-diaryl-4-cyano-1*H*-[1,2]diazepines through the condensation of substituted isoflavones with cyanoacetohydrazide (**2**) in the presence of KOH in DMF. The procedure involves base-catalyzed ring opening of the isoflavones and subsequent *Knoevenagel* condensation between the 1,3-dicarbonyl intermediate generated from the isoflavones and **2**, followed by ring closure and dehydration.

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Experiment Part

General. Column chromatography (CC): *Kieselgel 60* (230–400 mesh; *Merck*). TLC: Silica gel *60 GF254* plates (SiO₂); visualization under UV light (254 nm). M.p.: *X-5 Macro* melting-point tester; uncorrected. IR Spectra: *Nicolet 170SX* FT-IR spectrophotometer; KBr pellets; $\bar{\nu}$ in cm⁻¹. ¹H- and ¹³C-NMR spectra: *Bruker Avance 300* at 300 and 75 MHz, resp., in (D₆)DMSO, unless otherwise indicated; δ [ppm] rel. to Me₄Si as internal standard, *J* in Hz. HR-ESI-MS: *Bruker MALDI-TOF/MS* instrument; in *m/z*.

General Procedure for the Synthesis of 1-Amino-5,6-diaryl-3-cyano-1H-pyridin-2-ones 3a–3j and 6,7-Diaryl-4-cyano-1H-[1,2]diazepines 4a–4j. The respective isoflavone **1a–1j** (1 mmol), cyanoaceto-hydrazide (**2**; 109 mg, 1.1 mmol), and solid KOH (90 mg, 1.6 mmol) in DMF (10 ml) were heated at reflux for 1.5–7.0 h. All reactions were monitored by TLC, which showed the disappearance of **1**, indicating the completion of the reaction. The mixture was poured into H₂O (100 ml) and adjusted to neutrality by addition of 5% aq. HCl. The formed brown-red precipitate was filtered off and was purified by CC (CHCl₃/MeOH 60 : 1) to give products **3a–3j** and **4a–4j** as colorless amorphous powders.

1-Amino-6-[2-hydroxy-4-(propan-2-yloxy)phenyl]-2-oxo-5-phenyl-1,2-dihydropyridine-3-carbonitrile (3a). M.p. 240–242°. IR: 3407, 3249, 3083, 2977, 2228, 1631, 1510, 1382, 1141, 991, 855. ¹H-NMR: 1.21 (*d*, *J* = 6.0, 6 H); 4.49 (*sept*, *J* = 6.0, 1 H); 6.09 (*br. s*, 2 H); 6.23 (*d*, *J* = 8.6, 1 H); 6.41 (*s*, 1 H); 6.68 (*d*, *J* = 8.5, 1 H); 7.04–7.18 (*m*, 5 H); 8.10 (*s*, 1 H); 10.35 (*s*, 1 H). ¹H-NMR: (300 MHz, (D₆)DMSO/D₂O): 1.16 (*d*, *J* = 6.0, 6 H); 4.45 (*sept*, *J* = 6.0, 1 H); 6.18 (*d*, *J* = 8.5, 1 H); 6.38 (*s*, 1 H); 6.63 (*d*, *J* = 8.5, 1 H); 7.00 (*m*, 2 H); 7.13 (*m*, 3 H); 8.01 (*s*, 1 H). ¹³C-NMR (75 MHz, (D₆)DMSO/D₂O): 22.2; 69.8; 98.6; 102.8; 106.8; 112.4; 116.9; 120.9; 127.3; 128.5; 129.4; 131.7; 137.4; 145.4; 149.8; 156.9; 157.7; 160.2. HR-MS: 384.1319 ([*M* + Na]⁺, C₂₁H₁₉N₃NaO₃⁺; calc. 384.1324).

3-Hydroxy-7-[2-hydroxy-4-(propan-2-yloxy)phenyl]-6-phenyl-1H-[1,2]diazepine-4-carbonitrile (4a). M.p. 248–250°. IR: 3488, 3430, 3337, 3103, 2996, 2222, 1609, 1391, 1145, 988, 856. ¹H-NMR: 1.22 (*d*, *J* = 6.0, 6 H); 4.50 (*sept*, *J* = 6.0, 1 H); 6.24–6.27 (*m*, 2 H); 6.92 (*d*, *J* = 8.2, 1 H); 7.19–7.25 (*m*, 5 H); 7.98 (*s*, 1 H); 9.86 (*s*, 1 H); 10.91 (*s*, 1 H); 12.05 (*s*, 1 H). ¹H-NMR (300 MHz, (D₆)DMSO/D₂O): 1.23 (*d*, *J* = 6.0, 6 H); 4.50 (*septet*, *J* = 6.0, 1 H); 6.27 (*s*, 2 H); 6.92 (*d*, *J* = 8.2, 1 H); 7.21–7.23 (*m*, 5 H); 8.00 (*s*, 1 H). ¹³C-NMR (75 MHz, (D₆)DMSO/D₂O): 21.8; 69.0; 102.7; 103.5; 106.0; 119.3; 126.3; 127.8; 129.0; 129.3; 131.0; 131.8; 140.8; 151.2; 154.3; 156.2; 156.3 158.3. HR-MS: 362.1495 ([*M* + H]⁺, C₂₁H₂₀N₃O₃⁺; calc. 362.1505).

1-Amino-6-(2-hydroxy-4,6-dimethoxyphenyl)-5-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (3b). M.p. 242–243°. IR: 3429, 3229, 3095, 2997, 2225, 1658, 1612, 1507, 1167, 947, 834. ¹H-NMR: 3.51 (*s*, 3 H); 3.69 (*s*, 6 H); 6.01 (*s*, 1 H); 6.03 (*s*, 1 H); 6.75 (*d*, *J* = 7.7, 2 H); 6.97 (*d*, *J* = 7.7, 2 H); 7.98 (*s*, 1 H); 10.03 (*s*, 1 H). ¹³C-NMR: 55.5; 56.1; 56.5; 90.4; 93.9; 98.2; 102.1; 113.7; 114.1; 117.0; 121.8; 129.8; 144.8; 146.9; 156.7; 157.7; 158.5; 162.8. HR-MS: 416.1209 ([*M* + Na]⁺, C₂₁H₁₉N₃NaO₃⁺; calc. 416.1222).

3-Hydroxy-7-(2-hydroxy-4,6-dimethoxyphenyl)-6-(4-methoxyphenyl)-1H-[1,2]diazepine-4-carbonitrile (4b). M.p. 257–258°. IR: 3470, 3396, 3304, 3095, 2961, 2230, 1613, 1509, 1409, 1152, 988, 803. ¹H-NMR: 3.43 (*s*, 3 H); 3.67 (*s*, 3 H); 3.70 (*s*, 3 H); 5.95 (*s*, 1 H); 5.98 (*s*, 1 H); 6.76 (*d*, *J* = 8.1, 2 H); 7.08 (*d*, *J* = 8.1, 2 H); 7.85 (*s*, 1 H); 9.19 (*s*, 1 H); 10.83 (*s*, 1 H); 11.84 (*s*, 1 H). ¹³C-NMR: 55.4; 55.6; 56.1; 90.4; 93.9; 98.2; 102.1; 113.7; 114.2; 117.4; 121.8; 129.9; 144.8; 146.9; 156.7; 157.7; 158.5; 158.7; 162.8. HR-MS: 394.1393 ([*M* + H]⁺, C₂₁H₂₀N₃O₃⁺; calc. 394.1403).

1-Amino-6-(2-hydroxy-4-methoxy-6-methylphenyl)-2-oxo-5-phenyl-1,2-dihydropyridine-3-carbonitrile (3c). M.p. 254–256°. IR: 3425, 3339, 3240, 3058, 2975, 2223, 1618, 1528, 1338, 1155, 1083, 945, 857. ¹H-NMR: 1.74 (*s*, 3 H); 3.66 (*s*, 3 H); 5.98 (*s*, 2 H); 6.17 (*s*, 1 H); 6.30 (*s*, 1 H); 7.13–7.18 (*m*, 5 H); 8.11 (*s*, 1 H); 10.09 (*s*, 1 H). ¹³C-NMR: 19.7; 55.4; 99.0; 99.1; 106.8; 112.7; 116.9; 121.1; 127.7; 128.4; 128.8; 137.1; 137.7; 145.4; 149.2; 156.7; 157.9; 161.4. HR-MS: 370.1153 ([*M* + Na]⁺, C₂₀H₁₇N₃NaO₃⁺; calc. 370.1168).

3-Hydroxy-7-(2-hydroxy-4-methoxy-6-methylphenyl)-6-phenyl-1H-[1,2]diazepine-4-carbonitrile (4c). M.p. 296–298°. IR: 3412, 3343, 3278, 3036, 2965, 2233, 1621, 1368, 1156, 1085, 982, 865. ¹H-NMR: 1.76 (*s*, 3 H); 3.64 (*s*, 3 H); 6.16–6.18 (*m*, 2 H); 7.22 (*s*, 5 H); 7.98 (*s*, 1 H); 9.22 (*s*, 1 H); 10.92 (*s*, 1 H); 11.94 (*s*, 1 H). ¹³C-NMR: 20.2; 55.2; 98.9; 104.3; 106.0; 121.7; 126.9; 128.1; 129.1; 130.5; 130.8; 137.6; 140.7; 152.7; 155.0; 156.2; 156.6; 159.6. HR-MS: 348.1332 ([*M* + H]⁺, C₂₀H₁₈N₃O₃⁺; calc. 348.1348).

1-Amino-6-(2,4-dihydroxyphenyl)-5-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (3d). M.p. 236–237°. IR: 3423, 3282, 3218, 3065, 2965, 2230, 1623, 1506, 1356, 1149, 978, 863. ¹H-NMR: 3.69 (s, 3 H); 6.11 (s, 2 H); 6.38 (s, 1 H); 6.58 (d, *J* = 8.4, 1 H); 6.76 (d, *J* = 7.8, 2 H); 6.96 (d, *J* = 7.8, 2 H); 8.03 (s, 1 H); 9.66 (s, 1 H); 10.23 (s, 1 H). ¹³C-NMR: 55.5; 98.2; 102.7; 107.3; 111.2; 113.9; 117.0; 120.6; 129.8; 130.5; 131.6; 145.2; 149.8; 156.8; 157.5; 158.5; 160.3. HR-MS: 372.0942 ([*M* + Na]⁺, C₁₉H₁₅N₃NaO₄⁺; calc. 372.0960).

7-(2,4-Dihydroxyphenyl)-3-hydroxy-6-(4-methoxyphenyl)-1H-[1,2]diazepine-4-carbonitrile (4d). M.p. 252–254°. IR: 3422, 3333, 3222, 3046, 2960, 2223, 1631, 1360, 1155, 1075, 979, 856. ¹H-NMR: 3.73 (s, 3 H); 6.12 (d, *J* = 8.4, 1 H); 6.19 (s, 1 H); 6.81–6.84 (m, 3 H); 7.12 (d, *J* = 8.2, 2 H); 7.92 (s, 1 H); 9.37 (s, 1 H); 9.78 (s, 1 H); 10.91 (s, 1 H); 11.93 (s, 1 H). ¹³C-NMR: 55.4; 103.0; 104.0; 106.6; 113.9; 118.5; 129.5; 130.6; 131.4; 132.2; 133.7; 151.7; 155.0; 156.7; 157.0; 158.3; 158.9. HR-MS: 372.0952 ([*M* + Na]⁺, C₁₉H₁₅N₃NaO₄⁺; calc. 372.0960).

1-Amino-6-(5-fluoro-2-hydroxyphenyl)-2-oxo-5-phenyl-1,2-dihydropyridine-3-carbonitrile (3e). M.p. 259–260°. IR: 3435, 3312, 3117, 2229, 1724, 1637, 1601, 1498, 1262, 1169, 942, 837. ¹H-NMR: 6.04 (s, 2 H); 6.77–6.85 (m, 2 H); 7.01–7.20 (m, 6 H); 8.15 (m, 1 H); 10.18 (s, 1 H). ¹³C-NMR: 99.7; 108.0; 116.9 (d, ³*J* = 5.5); 117.0 (d, ²*J* = 28.9); 117.8 (d, ²*J* = 22.2); 120.7; 121.0 (d, ³*J* = 8.4); 127.7; 128.5; 129.4; 136.8; 146.1; 148.8; 152.0; 155.1 (d, ¹*J* = 235.1); 158.0. HR-MS: 344.0803 ([*M* + Na]⁺, C₁₈H₁₂FN₃NaO₂⁺; calc. 344.08).

7-(5-Fluoro-2-hydroxyphenyl)-3-hydroxy-6-phenyl-1H-[1,2]diazepine-4-carbonitrile (4e). M.p. 277–278°. IR: 3429, 3255, 3025, 2930, 2230, 1616, 1550, 1488, 1406, 1156, 977, 858. ¹H-NMR: 6.67 (s, 1 H); 6.95–7.22 (m, 5 H); 8.02 (s, 1 H); 9.35 (s, 1 H); 10.98 (s, 1 H); 12.15 (s, 1 H). ¹³C-NMR: 104.5; 112.8; 116.0 (d, ²*J* = 23.1); 116.7 (d, ³*J* = 7.6); 117.2 (d, ²*J* = 22.9); 127.1; 128.3; 129.5; 130.1; 131.2; 140.4; 151.3; 151.8; 154.9; 155.2 (d, ¹*J* = 232.5); 155.7. HR-MS: 344.0800 ([*M* + Na]⁺, C₁₈H₁₂FN₃NaO₂⁺; calc. 344.0811).

1-Amino-6-(5-fluoro-2-hydroxyphenyl)-5-(4-methylphenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (3f). M.p. 264–265°. IR: 3411, 3286, 3211, 3025, 2230, 1635, 1597, 1499, 1416, 1170, 1033, 928, 827. ¹H-NMR: 2.21 (s, 3 H); 6.03 (s, 2 H); 6.87–6.77 (m, 2 H); 7.06–6.96 (m, 5 H); 8.12 (s, 1 H); 10.15 (s, 1 H). ¹³C-NMR: 21.0; 99.7; 108.0; 116.8 (d, ³*J* = 7.5); 117.0 (d, ²*J* = 25.4); 117.8 (d, ²*J* = 22.4); 120.6; 121.0 (d, ³*J* = 8.7); 129.1; 129.2; 133.9; 136.9; 146.1; 148.7; 152.0; 155.1 (d, ¹*J* = 233.2); 158.0. HR-MS: 358.0962 ([*M* + Na]⁺, C₁₉H₁₄FN₃NaO₂⁺; calc. 358.0968).

7-(5-Fluoro-2-hydroxyphenyl)-3-hydroxy-6-(4-methylphenyl)-1H-[1,2]diazepine-4-carbonitrile (4f). M.p. 286–288°. IR: 3407, 3212, 3025, 2924, 2230, 1614, 1558, 1490, 1414, 1235, 1173, 978, 857. ¹H-NMR: 2.26 (s, 3 H); 6.67–6.71 (m, 1 H); 7.12–6.91 (m, 6 H); 7.99 (s, 1 H); 9.34 (s, 1 H); 11.00 (s, 1 H); 12.11 (s, 1 H). ¹³C-NMR: 21.1; 104.5; 112.6; 115.9 (d, ²*J* = 22.4); 116.9 (d, ³*J* = 7.7); 117.3 (d, ²*J* = 23.5); 128.9; 129.4; 129.9; 130.9; 136.0; 137.7; 151.5; 151.8; 154.8; 155.2 (d, ¹*J* = 223.7); 155.5. HR-MS: 336.1143 ([*M* + H]⁺, C₁₉H₁₅FN₃O₂⁺; calc. 336.1148).

1-Amino-6-(5-fluoro-2-hydroxyphenyl)-5-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (3g). M.p. 266–268°. IR: 3300, 3120, 2961, 2230, 1636, 1596, 1502, 1408, 1252, 1177, 928, 832. ¹H-NMR: 3.68 (s, 3 H); 6.03 (s, 2 H); 6.76–6.86 (m, 4 H); 6.99–7.02 (m, 3 H); 8.12 (s, 1 H); 10.16 (s, 1 H). ¹³C-NMR: 55.5; 99.6; 108.4; 113.9; 116.9 (d, ³*J* = 8.9); 117.0 (d, ²*J* = 24.0); 117.8 (d, ²*J* = 22.6); 120.4; 121.1 (d, ³*J* = 8.4); 129.0; 130.6; 146.2; 148.6; 151.9; 155.1 (d, ¹*J* = 233.0); 157.9; 158.8. HR-MS: 374.0906 ([*M* + Na]⁺, C₁₉H₁₄FN₃NaO₃⁺; calc. 374.0917).

7-(5-Fluoro-2-hydroxyphenyl)-3-hydroxy-6-(4-methoxyphenyl)-1H-[1,2]diazepine-4-carbonitrile (4g). M.p. 292–294°. IR: 3439, 3250, 2943, 2233, 1612, 1554, 1491, 1254, 1027, 893. ¹H-NMR: 3.72 (s, 3 H); 7.15–6.71 (m, 7 H); 7.99 (s, 1 H); 9.36 (s, 1 H); 11.02 (s, 1 H); 12.12 (s, 1 H). ¹³C-NMR: 55.4; 104.5; 112.6; 113.7; 115.9 (d, ²*J* = 22.6); 116.8 (d, ³*J* = 7.6); 117.3 (d, ²*J* = 22.4); 129.6; 130.6; 130.8; 132.9; 151.5; 151.8; 154.8; 155.2 (d, ¹*J* = 232.5); 155.5; 158.4. HR-MS: 374.0906 ([*M* + Na]⁺, C₁₉H₁₄FN₃NaO₃⁺; calc. 374.0917).

1-Amino-6-(2-hydroxy-4-methoxyphenyl)-5-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (3h). M.p. 226–227°. IR: 3304, 3250, 3084, 2936, 2226, 1727, 1627, 1600, 1508, 1448, 1419, 1270, 1206, 1024, 917, 831. ¹H-NMR: 3.68 (s, 3 H); 3.69 (s, 3 H); 6.06 (s, 2 H); 6.29 (dd, *J* = 8.4, 2.2, 1 H); 6.46 (d, *J* = 2.2, 1 H); 6.72–6.77 (m, 2 H); 9.97 (d, *J* = 8.7, 2 H); 8.05 (s, 1 H); 10.33 (s, 1 H). ¹³C-NMR: 54.9; 55.0;

98.1; 100.8; 105.0; 112.4; 113.5; 116.5; 120.2; 129.1; 130.0; 131.1; 145.0; 149.0; 156.2; 157.2; 158.1; 161.3. HR-MS: 386.1110 ($[M + Na]^+$, $C_{20}H_{17}N_3NaO_4^+$; calc. 386.1117).

3-Hydroxy-7-(2-hydroxy-4-methoxyphenyl)-6-(4-methoxyphenyl)-1H-[1,2]diazepine-4-carbonitrile (4h). M.p. 241–242°. IR: 3432, 3108, 3043, 2940, 2223, 1607, 1559, 1439, 1368, 1236, 1020, 898. 1H -NMR: 3.73 (s, 3 H); 3.76 (s, 3 H); 6.28–6.32 (m, 2 H); 6.82 (d, $J = 7.4$, 2 H); 6.96 (d, $J = 8.3$, 1 H); 7.14 (d, $J = 7.4$, 2 H); 7.95 (s, 1 H); 9.95 (s, 1 H); 10.95 (s, 1 H); 11.99 (s, 1 H). ^{13}C -NMR: 55.4; 101.7; 104.2; 104.9; 113.7; 120.1; 129.5; 130.6; 131.5; 132.2; 133.5; 151.7; 150.0; 156.6; 156.9; 158.3; 160.6. HR-MS: 386.1109 ($[M + Na]^+$, $C_{20}H_{17}N_3NaO_4^+$; calc. 386.1117).

1-Amino-6-(2-hydroxyphenyl)-5-(4-methylphenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (3i). M.p. 223–224°. IR: 3436, 3297, 3155, 2954, 2227, 1734, 1631, 1600, 1565, 1505, 1453, 1366, 1296, 1025, 922, 821. 1H -NMR: 2.20 (s, 3 H); 6.05 (s, 2 H); 6.64–7.22 (m, 8 H); 8.10 (s, 1 H); 10.28 (s, 1 H). ^{13}C -NMR: 21.0; 99.0; 115.8; 116.9; 119.4; 120.3; 120.6; 129.0; 129.2; 130.6; 131.4; 134.2; 136.7; 145.8; 150.0; 155.6; 157.8. HR-MS: 340.1048 ($[M + Na]^+$, $C_{19}H_{15}N_3NaO_2^+$; calc. 340.1062).

3-Hydroxy-7-(2-hydroxyphenyl)-6-(4-methylphenyl)-1H-[1,2]diazepine-4-carbonitrile (4i). M.p. 232–233°. IR: 3418, 3212, 3051, 2223, 1627, 1602, 1559, 1488, 1445, 1375, 1235, 1159, 954, 838. 1H -NMR: 2.25 (s, 3 H); 6.72 (s, 1 H); 6.74 (s, 1 H); 6.96–7.07 (m, 6 H); 7.98 (s, 1 H); 9.42 (s, 1 H); 11.81 (s, 1 H); 13.56 (s, 1 H). ^{13}C -NMR: 21.1; 104.3; 116.0; 118.8; 128.3; 128.9; 129.4; 129.6; 129.9; 130.9; 131.3; 135.8; 138.1; 152.0; 155.1; 156.9; 159.4. HR-MS: 318.1228 ($[M + H]^+$, $C_{19}H_{16}N_3O_2^+$; calc. 318.1243).

1-Amino-6-[4-(benzyloxy)-2-hydroxyphenyl]-5-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (3j). M.p. 245–246°. IR: 3429, 3311, 3061, 2928, 2227, 1650, 1611, 1506, 1423, 1250, 1175, 1026, 835. 1H -NMR: 3.69 (s, 3 H); 5.02 (s, 2 H); 6.07 (s, 2 H); 6.39 (s, 1 H); 6.53 (s, 1 H); 6.75 (s, 3 H); 6.97 (s, 2 H); 7.41 (s, 5 H); 8.06 (s, 1 H); 10.38 (s, 1 H). ^{13}C -NMR: 55.5; 69.7; 98.6; 102.3; 106.2; 113.2; 114.0; 117.0; 120.7; 128.3; 128.9; 129.6; 130.4; 131.6; 137.2; 145.5; 149.6; 156.8; 157.7; 158.6; 160.9. HR-MS: 462.1410 ($[M + Na]^+$, $C_{26}H_{21}N_3NaO_4^+$; calc. 462.1430).

7-[4-(Benzyloxy)-2-hydroxyphenyl]-3-hydroxy-6-(4-methoxyphenyl)-1H-[1,2]diazepine-4-carbonitrile (4j). M.p. 255–256°. IR: 3393, 3117, 3029, 2926, 2226, 1616, 1515, 1427, 1388, 1243, 1176, 1022, 941, 837. 1H -NMR: 3.73 (s, 3 H); 5.03 (s, 2 H); 6.38 (s, 2 H); 6.82 (d, $J = 8.2$, 2 H); 6.97 (d, $J = 8.8$, 1 H); 7.12 (d, $J = 8.2$, 2 H); 7.33–7.42 (m, 5 H); 7.94 (s, 1 H); 9.94 (s, 1 H); 10.93 (s, 1 H); 12.02 (s, 1 H). ^{13}C -NMR: 69.5; 55.4; 69.5; 102.6; 104.2; 105.7; 113.9; 120.5; 128.2; 128.3; 128.6; 129.5; 130.6; 131.4; 132.2; 133.5; 137.5; 151.6; 154.9; 156.5; 156.8; 158.3; 159.7. HR-MS: 440.1599 ($[M + H]^+$, $C_{26}H_{22}N_3O_4^+$; calc. 440.1610).

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