

One-Pot, Three-Component Synthesis of 7-Azaindole Derivatives from N-Substituted 2-Amino-4-cyanopyrroles, Various Aldehydes, and Active Methylene Compounds

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Supporting Information

ABSTRACT: An efficient and practical route to 7-azaindole framework has been developed by one-pot, three-component cyclocondensation of N-substituted 2-amino-4-cyanopyrroles, various aldehydes, and active methylene compounds in ethanol or acetic acid at reflux. Reactions involving tetronic acid, indane-1,3-dione, dimedone, and 5-phenylcyclohexane-1,3dione gave carbocyclic fused 7-azaindoles, whereas Meldrum's acid, benzoylacetonitrile, and malononitrile resulted in the highly substituted 7-azaindole derivatives, making this strategy very useful in diversity-oriented synthesis (DOS).



 $R^1 = Ar$, Het, Alk; $R^2 = t$ -Bu, c-C₆H₁₁, m-CF₃C₆H₄, p-MeOC₆H₄CH₂

KEYWORDS: multicomponent reaction, heterocyclisation, 7-azaindoles, 2-aminopyrroles, aromatic aldehydes, active methylene compounds

■ INTRODUCTION

Multicomponent reactions (MCRs) have been used extensively to form carbon-carbon bonds in synthetic chemistry.¹ They provide a powerful tool toward the one-pot synthesis of diverse and complex compounds, as well as small and druglike heterocycles. Such reactions offer a wide range of possibilities for the efficient construction of complex molecules in a single procedural step and are perfectly amenable to automation for combinatorial synthesis. Because of their convergence and productivity, the MCRs have attracted considerable attention from the point of view of combinatorial and medicinal chemistry and are particularly useful for the preparation of polycondensed heterocyclic systems. The synthesis of heterocyclic compounds is a central issue in MCRs research, since heterocycles make up the majority of pharmaceuticals, natural products, and drug-like molecules.

The indole moiety is probably the most well-known heterocycle and is a common and important feature of a variety of natural products and medicinal agents.² Azaindoles have attracted considerable synthetic interest primarily as bioisosteres of the indole nucleus with interesting biological, pharmaceutical, and material properties. Although naturally occurring azaindoles are relatively scarce compared to indoles, a series of such compounds, particularly 7-azaindoles (1Hpyrrolo[2,3-b]pyridines) are very attractive targets for combinatorial library synthesis because of their wide range of valuable biological activities.³ Recently, some 1*H*-pyrrolo[2,3-*b*]pyridine

derivatives were identified as inhibitors of Cdc7 kinase,⁴ Met kinase,⁵ AKT kinase,⁶ and B-Raf kinase.⁷

Given the broad utility of 7-azaindoles in medicinal chemistry, we were interested in developing a simple multicomponent reaction approach, commencing with 2aminopyrrole-based substrates, which would allow access to these interesting heterocyclic compounds. In this paper we detail the successful realization of this goal with an efficient synthesis of 5,6-carbocyclic fused and highly substituted 7azaindole derivatives by a one-pot, three-component reaction.

RESULTS AND DISCUSSION

On the basis of the retrosynthetic analysis and on previous experience of the Iaroshenko's laboratory related to the development of new cyclocondensation reactions of electronrich aminoheterocycles,⁸ we envisioned that 2-aminopyrroles 3 are suitable substrates for the synthesis of 7-azaindole derivatives. It is known that unsubstituted 1H-pyrrol-2-amine is hard to access and it is not stable.⁹ For our current study the stable and easily accessible 1-substituted 5-aminopyrrole-3carbonitriles 3 were used.¹⁰ The N-protective group and the electron-withdrawing cyano functional group maintain the stability of these heterocycles. Previously, methods giving rise

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to pyrrolo[2,3-*b*]pyridines via annulation of the pyridine ring to an aminopyrrole moiety by condensation with 1,3-dicarbonylic compounds have been reported.^{10,11} However, so far 2aminopyrroles have not been used in multicomponent synthesis for the construction of more complex heterocyclic compounds despite their potential interest as building blocks in organic synthesis. On the other hand, various heterocyclic amines such as 5-aminopyrazoles,¹² 6-aminopyrimidin-4-one,¹³ 5-amino-3methylisoxazole,¹⁴ and 6-amino-1,3-dimethyluracil,¹⁵ are widely used as valuable synthetic intermediates in the multicomponent synthesis of pharmacologically relevant products and new heterocyclic systems.

We are reporting now on the formation of 7-azaindole derivatives from active methylene compounds (tetronic acid 1a, indane-1,3-dione 1b, dimedone 1c, 5-phenylcyclohexane-1,3-dione 1d, Meldrum's acid 1e, benzoylacetonitrile 1f, malononi-trile 1g), different aldehydes (aromatic aldehydes 2a-q, heterocyclic aldehydes 2r,s, aliphatic aldehydes 2t-v) (Figure 1) and N-substituted 2-amino-4-cyanopyrroles (Figure 2).



Figure 1. Diversity of active methylene compounds 1 and aldehydes 2.

Thus, seven commercially available active methylene compounds 1a-g, twenty two aldehydes 2a-v, and four easily accessible substituted aminopyrroles 3a-d were chosen for the library validation.

In the initial study, we have developed the synthesis of the hitherto unknown heterocyclic system 4 starting from tetronic acid 1a by a one-pot, three-component reaction depicted in Scheme 1. Different bases and solvents were first briefly examined and the best result was obtained by using L-proline as



Figure 2. Diversity of 2-aminopyrroles 3.

Scheme 1. Reactions of Tetronic Acid 1a with 2 and 3



^aWithout L-proline. ^bFrom 4. ^cFrom 1a.

catalyst and EtOH as the solvent. It was found that treatment of tetronic acid 1a with various aromatic aldehydes 2 and pyrroles 3a, b, and d in refluxing ethanol without catalyst resulted in the formation of furo[3,4-*b*]pyrrolo[3,2-*e*]pyridines 4 with excellent regioselectivity and in moderate to high yields (35-80%). Performing the reaction in the presence of L-proline led to only slightly higher yields (43-82%). In most cases, the reaction was complete after 3-4 h and the products could be isolated by simple filtration of the precipitate formed or by column chromatography over silica gel. The progress of the reaction was monitored by TLC, and the results are summarized in Scheme 1. It is important that a wide range of aldehydes 2 can effectively participate in the reaction with 1a and 3, providing a variety of dihydropyridines 4 with high purity. It can be observed that the process tolerates both electron-donating (hydroxy, methoxy, ethyl) and electron-withdrawing (fluoro, chloro) substituents on the aromatic aldehydes. The structures of all products 4 were characterized by IR, $^1\text{H},\ ^{13}\text{C}$ NMR spectral data as well as HRMS analysis. The regiochemistry of 4ma was unambiguously confirmed by X-ray single crystal analysis (Figure 3, see the Supporting Information).

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It should be noted that under these reaction conditions, the major products are the fused dihydropyridines 4, and only in the case of 5-methylfurfural 2r and octanal 2u the final products were carbocyclic fused 7-azaindoles 5ra and 5ua, indicating that air oxidation of the dihydropyridine ring had occurred. The oxidation of compounds 4 by 4,5-dichloro-3,6-dioxocyclohexa-1,4-diene-1,2-dicarbonitrile (DDQ, 1.2 equiv) in acetonitrile at room temperature for 4 h afforded the corresponding 7azaindoles 5 in good to excellent yields (Scheme 1). Taking into account that the tert-butyl and cyano groups could easily be removed from the pyrrolopyridine derivative,^{11b,16} this is also a method for preparing diverse 7-azaindoles with an unsubstituted pyrrole ring. To the best of our knowledge, this new multicomponent reaction provides the first example of a catalyst-free synthesis of compounds 4 and 5, which can be regarded as heterocyclic analogues of 1-arylnaphthalene lignans and podophyllotoxin.¹⁷

To expand the scope of the present reaction, indane-1,3dione **1b** was examined to replace tetronic acid **1a**. This is particularly attractive because compounds with the indenopyridine framework (4-azafluorenones) exhibit a wide range of biologically activities, for example, cytotoxic¹⁸ and antidepressant activities.¹⁹ These compounds have also been investigated for the treatment of hyperlipoproteinemia and arteriosclerosis²⁰ as well as neurodegenerative diseases.²¹

We found that the reaction of 1b with benzaldehydes 2a-eand o and pyrroles 3a, b, and d under the same condition (ethanol, reflux, 3 h) afforded only 5-oxo-4-aryl-1,5dihydroindeno[1,2-b]pyrrolo[3,2-e]pyridine-3-carbonitriles 6 in variable 44-80% yields. Heteroaromatic and aliphatic aldehydes, such as 5-methylfurfural 2r, thiophene-2-carbaldehyde 2s, acetaldehyde 2t, and decanal 2v, are also reactive in this three-component annulation, producing compounds 6ra, 6sa, 6ta, and 6va in 43%, 37%, 27%, and 80% yields, respectively. In the all cases, the initially formed dihydropyridine 6' is oxidized by air to afford aromatized 7-azaindoles 6. This result and the absence of the nonaromatized products seem to indicate that the indenone fragment activates the intermediate toward formation of the aromatic pyridine ring (Scheme 2).

Our literature survey at this stage revealed that, there is no report yet available on the synthesis of furo[3,4-b]pyrrolo[3,2-e]pyridines 5 and indeno[1,2-b]pyrrolo[3,2-e]pyridines 6 in one-pot via three-component coupling of 2-aminopyrroles, aldehydes, tetronic acid, and indane-1,3-dione. It should be also noted that the catalyst-free reactions carried out in ethanol are considerably safer, nontoxic, environmentally friendly, and inexpensive.

Next we examined the cycloaddition behavior of dimedone **1c** using various reaction conditions. After some optimization, it was found that generally good yields of compounds 7 are obtained when mixtures of the three starting components are refluxed in ethanol with L-proline (10 mol %) or acetic acid (for **2f**, **i**, and **o**) for 6 h. A variety of aromatic aldehydes with electron-donating or electron-withdrawing groups were employed as the reaction substrates; in general, the presence of substituents on aromatic aldehydes appeared to have only a slight influence on the reactivity in most cases. As expected, treatment of dihydropyridine 7 with DDQ in acetonitrile at room temperature provides the aromatized carbofused 7-azaindoles **8** in high yield (Scheme 3). The structures of **8fa** and **8ha** are confirmed by X-ray diffraction analysis (Figures 4 and 5, see the Supporting Information).

Scheme 2. Reactions of Indane-1,3-dione 1b with 2 and 3



Scheme 3. Reactions of Dimedone 1c with 2 and 3



"Using ethanol with L-proline as catalyst (10 mol%). ^bUsing acetic acid.

Furthermore, when dimedone **1c** was replaced by 5phenylcyclohexane-1,3-dione **1d**, target products, 1-substituted 4-aryl-5-oxo-7-phenyl-4,5,6,7,8,9-hexahydro-1*H*-pyrrolo[2,3-*b*]quinoline-3-carbonitriles **9**, were obtained in good yields (45– 81%) in refluxing ethanol in the absence of any catalyst for 6 h. Aromatization of these compounds with DDQ in acetonitrile gave 7-azaindoles **10** in 43–97% yields, the structures of which agree well with the data of elemental analysis, IR, ¹H, and ¹³C NMR spectroscopy and mass spectrometry (Scheme 4).

Next, taking into account the above results and that the pyrrole ring is important structural fragment of many natural and biologically active substances,^{2a} it was of interest to

Scheme 4. Reactions of 5-Phenylcyclohexane-1,3-dione 1d with 2 and 3



evaluate the behavior of 2-aminopyrroles **3** in their reactions with Meldrum's acid **1e** and aldehydes **2**. In this context, two papers are of interest when Meldrum's acid and aromatic aldehydes are reacted with 5-amino-3-methylisoxazole¹⁴ and 5-amino-3-methylpyrazole²² to obtain the corresponding fused dihydropyridinones. We anticipated that aminopyrroles **3** might undergo a similar cycloaddition with **1e** and **2** to give 2,3-heteroannulated pyrroles **11**. In fact, it was found that treatment of **1e** with aromatic aldehydes **2** and pyrroles **3a**–**c** in ethanol at reflux for 5 h resulted in the formation of 6-oxo-4,5,6,7-tetrahydro-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitriles **11** in variable 40–90% yields. As shown in Scheme 5, this protocol

Scheme 5. Reactions of Meldrum's Acid 1e with 2 and 3



can be applied not only to aromatic aldehydes with either electron-donating groups or electron-withdrawing groups, but also to aliphatic aldehydes. In this case, unlike indane-1,3-dione **1b**, the yield of **11ta** from acetaldehyde **2t** was 78%. The exact structure of **11** was established by ¹H and ¹³C NMR spectra, in which we have observed the appearance of the CH₂CH fragment in the partially hydrogenated pyridine ring (ABX-system at δ 2.4–4.9 ppm with J_{AB} = 15.7–16.2 Hz, J_{AX} = 7.0–8.1 Hz, J_{BX} = 2.9–5.4 Hz). Furthermore, the structures of **11aa**, **11ga**, and **11ma** were established by X-ray crystallographic analysis (Figures 6, 7, and 8, see the Supporting Information). Interestingly, although the chemistry of the pyrrole system has been well documented,^{2a} we have found that these simple compounds are hitherto unreported.

Thus, the reaction of cyclic-1,3-dicarbonyls and aldehydes with 2-aminopyrroles 3 makes the latter compounds very useful for a combinatorial approach to the synthesis of various 7azaindole derivatives with potential biological activity. Given the actual interest in these compounds as pharmaceutical intermediates,³⁻⁷ this simple entry to novel 1H-pyrrolo[2,3b]pyridines is useful and will complement the published synthetic methods.³ It is notable that when the reaction of aldehydes 2a and g and aminopyrrole 3a was carried out with acyclic-1,3-dicarbonylic compounds, such as acetylacetone, methyl acetoacetate, ethyl benzoylacetate, N-phenyl acetoacetamide, and (2-thenoyl)trifluoroacetone in various conditions (EtOH, EtOH/base, AcOH, DMF, DMF/TMSCl, CH₂Cl₂) at room temperature or reflux, TLC and ¹H NMR spectra of the reaction mixture showed a complex mixture of products, which was not investigated in detail.

Compounds 4-11 are likely formed via initial condensation of aldehydes 2 with cyclic-1,3-diones 1a-e to afford the Knoevenagel product A,¹⁴ which then undergoes in situ Michael addition with 2-aminopyrroles 3 to yield the intermediate B. Because of the ambident character of heterocyclic amine, a nucleophilic attack of carbon or nitrogen on intermediate A would lead to linear or angular products. The first step of the reaction leading to heterocyclization apparently involves an attack of the internal enamine β -carbon (in general, this atom is more nucleophilic than the primary amino group) at the C=C bond of the initial Knoevenagel product A; the alternative addition including the nitrogen atom to give angular product was not observed at all. In the case of **1a**–**d**, intramolecular attack of the amino group at the carbonyl group (intermediate **B**) with concomitant elimination of water molecule leads to the linear fused dihydropyridine derivatives 4, 7, and 9. When the 1,3-dicarbonyl compound is Meldrum's acid, the intermediate product B subsequently underwent intramolecular cyclization and then released acetone and carbon dioxide to give pyrroles 11 (Scheme 6).

Further experiments were conducted to expand the utility of the reaction and substrate scope with a series of cyano derivatives, such as benzoylacetonitrile, malononitrile, and ethyl cyanoacetate. The results observed for the first two compounds were no exception from the general rule, however, ethyl cyanoacetate did not work under various conditions. As can be seen from Scheme 7, benzoylacetonitrile **1f** underwent pyridine ring annulation with aromatic aldehydes **2** and aminopyrroles **3a**, **b**, and **d**, leading to the formation of highly substituted 7azaindoles **12** in moderate to good yields (37–66%) in boiling acetic acid in the presence of ammonium acetate as catalyst for 6 h. In all cases, conjugated addition at the intermediate Scheme 6. Possible Mechanism for the Formation of Products 4–11



Scheme 7. Reactions of Benzoylacetonitrile 1f with 2 and 3



Knoevenagel product takes place with subsequent annulation and dehydrogenation of the pyridine core.

The reaction of malononitrile **1g** with aromatic aldehydes **2** and aminopyrroles **3a,b**, and **d** under the same conditions gave the expected aromatized 7-azaindoles **13** in 40–63% yields (Scheme 8). The formation of the other regioisomer was not observed in these examples as well. Previously, heteroanalogues of compounds **13** were obtained by the reaction of 5-amino-3-methyl-1-phenylpyrazole with benzylidene derivatives of malononitrile.²³ The structures of all the compounds were deduced from their satisfactory elemental and spectral (IR, ¹H, ¹³C NMR, and MS) studies; their mass spectra displayed molecular ion peaks at the appropriate m/z values.

CONCLUSION

In conclusion, we have developed a rapid route to the synthesis of a wide range of 7-azaindole derivatives by the threecomponent reaction of active methylene compounds, various aldehydes, and 2-aminopyrroles. In this study a total of 81 Scheme 8. Reactions of Malononitrile 1g with 2 and 3



compounds were prepared using this synthesis route. Given the easy access to substituted 2-aminopyrroles and the large number of commercially available aldehydes and cyclic-1,3diones, the present method should be applicable to synthesis of libraries with high diversity. This 2-aminopyrrole-based approach may be of value for constructing highly functionalized biologically and medicinally important products. The biological evaluation of the synthesized compounds is under study in our laboratories.

EXPERIMENTAL PROCEDURES

1. General Procedure for the Synthesis of Compounds 4 and 6. A mixture of tetronic acid 1a or 1,3-indanedione 1b (1 equiv), the corresponding aldehyde 2 (1 equiv), and 5-amino-1-*R*-pyrrole-3-carbonitrile 3 (1 equiv.) was refluxed in ethanol for 3 h. The precipitate was collected and, if necessary, purified by column chromatography (eluent, *n*-heptane/ethylacetate).

1-tert-Butvl-5-oxo-4-phenvl-4.5.7.8-tetrahvdro-1H-furo-[3,4-b]pyrrolo[3,2-e]pyridine-3-carbonitrile (4aa). The product was isolated as a gray solid, yield 43%, mp 238-239 °C. ¹H NMR (250 MHz, DMSO-d₆): δ 1.57 (s, 9H, t-Bu), 4.82-4.94 (m, 3H, CH, CH₂), 7.17-7.19 (m, 3H, Ar), 7.24-7.29 (m, 2H, Ph), 7.36 (s, 1H, H-2), 9.70 (s, 1H, NH). ¹³C NMR (63 MHz, DMSO-*d*₆): δ 29.1 C(CH₃)₃), 36.5 (CH), 57.3 (C(CH₃)₃), 65.7 (CH₂), 88.1 (C), 97.2 (C), 105.9 (C), 116.0 (C), 123.6 (CH), 126.5 (CH), 128.0 (CH), 128.2 (CH), 128.7 (C), 145.0 (C), 157.6 (C), 171.9 (C=O). IR (ATR, cm^{-1}): 3305 (w), 3235 (w), 3153 (w), 3029 (w), 2981 (w), 2943 (w), 2858 (w), 2217 (m), 1711 (m), 1644 (w), 1629 (s), 1536 (s), 1514 (s), 1495 (w), 1433 (w), 1405 (w), 1378 (w), 1355 (w), 1325 (w), 1272 (w), 1222 (w), 1209 (w), 1181 (m), 1078 (w), 1027 (s), 835 (w), 823 (w), 813 (w), 798 (w), 758 (w), 747 (m), 732 (m), 702 (m), 687 (w), 646 (w). MS (EI, 70 eV): *m*/*z* (%) 331 (M⁺, aromatized, 35), 275 (100), 246 (59), 217 (7), 191 (8), 164 (7), 57 (4), 41 (4). MS (EI, 70 eV): *m/z* (%) 333 (M⁺, not aromatized, 36), 318 (100), 277 (60), 259 (25), 233 (26), 221 (9), 204 (9), 193 (6), 164 (6), 140 (4), 57 (8), 41 (7). HRMS (ESI): calcd for $C_{20}H_{18}N_3O_2$ ([M + H]⁺, aromatized) 332.13935, found 332.13872.

1-tert-Butyl-5-oxo-4-phenyl-1,5-dihydroindeno[1,2-b]pyrrolo[3,2-e]pyridine-3-carbonitrile (6aa). The product was isolated as a yellow solid, yield 67%, mp 262-264 °C. ¹H NMR (250 MHz, CDCl₃): δ 1.83 (s, 9H, t-Bu), 7.29-7.34 (m, 1H, Ar), 7.42–7.56 (m, 7H, Ar), 7.72 (s, 1H, H-2), 7.81 (d, J = 8.0 Hz, 1H, Ar). ¹³C NMR (63 MHz, CDCl₃): δ 29.2 (C(CH₃)₃), 59.4 (C(CH₃)₃), 86.3 (C), 114.6 (C), 119.6 (C), 119.9 (C), 120.5 (CH), 123.6 (CH), 127.9 (CH), 129.4 (CH), 129.6 (CH), 130.8 (CH), 131.6 (C), 134.7 (CH), 134.8 (CH), 136.5 (C), 143.1 (C), 143.6 (C), 149.4 (C), 160.7 (C), 190.6 (C= O). IR (ATR, cm⁻¹): 3145 (w), 3062 (w), 3030 (w), 3016 (w), 2981 (w), 2965 (w), 2216 (m), 1709 (m), 1604 (w), 1584 (w), 1561 (m), 1520 (w), 1501 (w), 1467 (w), 1448 (w), 1384 (w), 1368 (w), 1347 (w), 1336 (w), 1295 (m), 1260 (w), 1240 (w), 1204 (m), 1178 (w), 1115 (m), 1086 (w), 1078 (w), 948 (w), 866 (w), 766 (m), 749 (m), 726 (s), 715 (s), 698 (s), 656 (m), 621 (s). MS (EI, 70 eV): m/z (%) 377 (M⁺, 33), 321 (100), 293 (4), 265 (9), 238 (6), 212 (2), 57 (3), 41 (3). Anal. Calcd for C₂₅H₁₉N₃O (377.44): C, 79.55; H, 5.07; N, 11.13. Found: C, 79.31; H, 5.04; N, 11.03.

2. General Procedure for the Synthesis of Compounds 5, 8, and 10. A mixture of the corresponding dihydropyridine (1 equiv.) and 4,5-dichloro-3,6-dioxocyclohexa-1,4-diene-1,2-dicarbonitrile (DDQ) (1.2 equiv.) was stirred in acetonitrile (10 mL) at room temperature for 4 h. The crude product was purified by column chromatography (eluent, *n*-heptane/ethylacetate).

1-tert-Butyl-5-oxo-4-phenyl-5,7-dihydro-1H-furo[3,4-b]pyrrolo[3,2-e]pyridine-3-carbonitrile (5aa). The product was isolated (column chromatography, *n*-heptane/ethylacetate, 1:1) as a white solid, yield 80%, mp 244-246 °C. ¹H NMR (300 MHz, DMSO- d_6): δ 1.84 (s, 9H, t-Bu), 5.48 (s, 2H, CH₂), 7.52-7.57 (m, 5H, Ph), 8.73 (s, 1H, H-2); ¹³C NMR (63 MHz, DMSO-d₆): δ 28.4 (C(CH₃)₃), 59.4 (C(CH₃)₃), 68.9 (CH₂), 83.6 (C), 110.2 (C), 114.3 (C), 119.2 (C), 127.5 (CH), 129.3 (CH), 129.7 (CH), 130.7 (C), 139.7 (CH), 143.4 (C), 149.5 (C), 162.1 (C), 168.0 (C=O); IR (ATR, cm^{-1}): 3130 (w), 3055 (w), 2984 (w), 2939 (w), 2222 (m), 1758 (s), 1587 (m), 1570 (m), 1525 (w), 1506 (w), 1481 (w), 1471 (w), 1394 (m), 1372 (m), 1350 (m), 1324 (w), 1295 (m), 1256 (w), 1209 (s), 1184 (m), 1146 (m), 1103 (w), 1077 (w), 1050 (m), 1022 (m), 990 (w), 929 (w), 871 (m), 851 (m), 806 (w), 799 (w), 758 (s), 745 (w), 708 (s), 660 (s), 624 (m), 605 (w); MS (EI, 70 eV): *m*/*z* (%) 331 (M⁺, 33), 275 (100), 246 (64), 217 (9), 191 (10), 164 (11), 57 (9), 41 (8). Anal. Calcd for C₂₀H₁₇N₃O₂ (331.37): C, 72.49; H, 5.17; N, 12.68. Found: C, 72.30; H, 5.48; N, 12.69.

1-tert-Butyl-4-(4-hydroxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-1H-pyrrolo[2,3-b]quinoline-3-carbonitrile (**8da**). The product was isolated as a white solid, yield 86%, mp 285 °C. ¹H NMR (300 MHz, CDCl₃): δ 1.07 (s, 6H, 2Me), 1.77 (s, 9H, t-Bu), 2.46 (s, 2H, CH₂), 3.11 (s, 2H, CH₂), 5.93 (br s, 1H, OH), 6.82 (d, *J* = 8.5 Hz, 2H), 7.04 (d, *J* = 8.5 Hz, 2H), 7.76 (s, 1H, H-2). ¹³C NMR (62.9 MHz, CDCl₃): δ 27.3 (2C), 28.1 (3C), 31.5, 47.3, 53.2, 57.9, 84.1, 114.1, 119.4, 119.4, 127.2, 128.3, 134.5, 139.1, 145.0, 146.7, 155.3, 157.5, 197.4. MS (GC, 70 eV): m/z (%) 387 (M⁺, 42), 331 (100), 274 (39). HR (EI): calcd for C₂₄H₂₅N₃O₂ (M) 387.19413, found 387.19392. IR (ATR, cm⁻¹): 3266 (w), 2955 (w), 2221 (s), 1663 (s), 1565 (m), 1518 (m), 1463 (m), 1393 (m), 1305 (m), 1233 (m), 1225 (m), 1168 (m), 1119 (m), 830 (m), 811 (m), 794 (m), 633 (m), 565 (m). 1-tert-Butyl-4-(4-hydroxyphenyl)-5-oxo-7-phenyl-5,6,7,8tetrahydro-1H-pyrrolo[2,3-b]quinoline-3-carbonitrile (**10da**). The product was isolated as a white solid, yield 56%, mp 328– 330 °C. ¹H NMR (300 MHz, DMSO-*d*₆): δ 1.85 (s, 9H, *t*-Bu), 2.81 (br s, 1H, CHH), 3.00–3.09 (m, 1H, CHH), 3.50–3.65 (m, 3H, CH, CH₂), 6.86 (d, *J* = 8.3 Hz, 2H), 7.10 (d, *J* = 8.3 Hz, 2H), 7.27–7.53 (m, 5H, Ph), 8.55 (s, 1H, H-2), 9.53 (s, 1H, OH). ¹³C NMR (62.9 MHz, DMSO-*d*₆): δ 28.5 (3C), 38.5, 41.4, 46.9, 58.8, 83.7, 114.3, 114.4, 119.6, 120.5, 126.6, 126.8, 127.0, 128.5, 129.4, 138.3, 143.4, 145.3, 146.7, 156.9, 158.2, 196.3. MS (GC, 70 eV): *m/z* (%) 435 (M⁺, 61), 379 (100), 275 (79). HR (EI): calcd for C₂₈H₂₅N₃O₂ (M) 435.19413, found 435.19443. IR (ATR, cm⁻¹): 3252 (w), 2965 (w), 2218 (s), 1667 (s), 1574 (m), 1511 (m), 1453 (m), 1399 (m), 1266 (m), 1198 (s), 818 (m), 698 (s), 569 (m).

3. General Procedure for the Synthesis of Compounds **7.** A mixture of dimedone 1c (1 equiv), the corresponding aldehyde 2 (1 equiv), and 5-amino-1-*R*-pyrrole-3-carbonitrile 3 (1 equiv) was refluxed in ethanol with L-proline as catalyst or in acetic acid for 6 h. The precipitate was collected and, if necessary, purified by column chromatography (eluent, *n*-heptane/ethylacetate).

1-tert-Butyl-4-(4-hydroxyphenyl)-7,7-dimethyl-5-oxo-4,5,6,7,8,9-hexahydro-1H-pyrrolo[2,3-b]quinoline-3-carbonitrile (7da). The product was isolated as a white solid, yield 69%, mp 247–248 °C. ¹H NMR (300 MHz, DMSO- d_6): δ 0.94 (s, 3H, Me), 1.04 (s, 3H, Me), 1.58 (s, 9H, *t*-Bu), 1.98 (d, *J* = 16.1 Hz, 1H), 2.18 (d, I = 16.1 Hz, 1H), 2.56 (d, I = 17.0 Hz, 1H), 2.69 (d, J = 17.0 Hz, 1H), 4.92 (s, 1H, H-4), 6.59 (d, J = 8.5Hz, 2H), 6.93 (d, I = 8.5 Hz, 2H), 7.29 (s, 1H, H-2), 8.56 (s, 1H, NH), 9.06 (s, 1H, OH). ¹³C NMR (62.9 MHz, DMSO-*d*₆): δ 26.4, 29.1 (3C), 29.3, 31.8, 35.2, 50.3, 56.9, 87.1, 107.9, 108.3, 114.5, 116.2, 122.4, 127.2, 127.9, 138.3, 150.4, 155.2, 193.9. MS (GC, 70 eV): m/z (%) 387 (M⁺, 45), 331 (100) 275 (38). HRMS (ESI): calcd for C₂₄H₂₈N₃O₂ (M + 1) 390.2176, found 390.21842. IR (ATR, cm⁻¹): 3341 (w), 3164 (w), 2956 (w), 2217 (w), 1608 (m), 1524 (s), 1494 (s), 1422 (m), 1343 (m), 1268 (m), 1248 (m), 1226 (m), 1191 (s), 1168 (m), 1153 (m), 766 (m), 596 (m), 546 (m). Anal. Calcd for C₂₄H₂₇N₃O₂: C, 74.01; H, 6.99; N, 10.79. Found: C, 73.80; H, 7.16; N, 10.79.

4. General Procedure for the Synthesis of Compounds 9 and 11. A mixture of 5-phenyl-1,3-cyclohexanedione 1d or Meldrum's acid 1e (1 equiv), the corresponding aldehyde 2 (1 equiv) and 5-amino-1-*R*-pyrrole-3-carbonitrile 3 (1 equiv) was refluxed in ethanol for 5–6 h. The precipitate was collected and, if necessary, purified by column chromatography (eluent, *n*-heptane/ethylacetate).

1-tert-Butyl-4-(4-hydroxyphenyl)-5-oxo-7-phenyl-4,5,6,7,8,9-hexahydro-1H-pyrrolo[2,3-b]quinoline-3-carbonitrile (**9da**). The product was isolated as a white solid, yield 81%, mp 241–242 °C. ¹H NMR (300 MHz, DMSO- d_6): δ 1.55 (s, 9H, t-Bu), 2.52–2.65 (m, 2H, CH₂), 2.93–3.14 (m, 2H, CH₂), 3.36–3.51 (m, 1H, CH), 4.94 (s, 1H, H-4), 6.53 (d, *J* = 8.0 Hz, 2H), 6.85 (d, *J* = 8.2 Hz, 2H), 7.16–7.37 (m, 6H, Ph, H-2), 8.61 (s, 1H, NH), 9.02 (s, 1H, OH). ¹³C NMR (62.9 MHz, DMSO- d_6): δ 29.2 (3C), 34.2, 35.4, 38.4, 43.6, 56.9, 87.1, 108.1, 108.6, 114.4, 116.3, 122.5, 126.4, 126.9, 127.0, 128.1, 128.3, 138.0, 143.6, 151.2, 155.1, 193.2. MS (GC, 70 eV): *m/z* (%) 435 (M⁺, 79), 379 (100), 275 (88). HRMS (ESI): calcd for C₂₈H₂₆N₃O₂ (M + 1) 436.20195, found 436.20257. IR (ATR, cm⁻¹): 3312 (w), 2220 (m), 1603 (m), 1572 (m), 1522 (s), 1495 (s), 1421 (m), 1392 (m), 1374 (w), 1342 (m), 1210 (s),

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1192 (m), 1177 (m), 1157 (m), 981 (m), 883 (m), 855 (m), 819 (m), 758 (m), 698 (m), 548 (m).

1-tert-Butyl-6-oxo-4-phenyl-4,5,6,7-tetrahydro-1Hpyrrolo[2,3-b]pyridine-3-carbonitrile (**11aa**). The product was isolated as a white solid, yield 82%, mp 230–231 °C. ¹H NMR (300 MHz, CDCl₃): δ 1.53 (s, 9H, t-Bu), 2.80 (dd, *J* = 16.0, 5.1 Hz, 1H, H-5"), 2.96 (dd, *J* = 16.0, 7.2 Hz, 1H, H-5'), 4.18 (dd, *J* = 7.2, 5.1 Hz, 1H, H-4), 6.91 (s, 1H, H-2), 7.12–7.27 (m, 5H, Ph), 8.44 (br s, 1H, NH). ¹³C NMR (62.9 MHz, CDCl₃): δ 29.7 (3C), 35.7, 39.6, 57.3, 89.1, 108.2, 115.6, 121.4, 127.0, 127.2, 128.6, 128.9, 141.8, 170.7. MS (GC, 70 eV): *m/z* (%) 293 (M⁺, 77), 237 (100), 194 (87). HRMS (ESI): calcd for C₁₈H₂₀N₃O (M + 1) 294.16009, found 294.15997; IR (ATR, cm⁻¹): 3150 (w), 2217 (m), 1668 (s), 1524 (m), 1492 (m), 1358 (m), 1190 (s), 1031 (w), 983 (w), 767 (s), 685 (s), 631 (s), 561 (s).

5. General Procedure for the Synthesis of Compounds 12 and 13. A mixture of benzoylacetonitrile 1f or malononitrile 1g (1 equiv), the corresponding aldehyde 2 (1 equiv) and 5-amino-1-*R*-pyrrole-3-carbonitrile 3 (1 equiv) was refluxed in acetic acid with 6 equiv of ammonium acetate as a catalyst for 6 h. The product was purified by column chromatography (eluent *n*-heptane/ethylacetate).

1-tert-Butyl-4,6-diphenyl-1H-pyrrolo[2,3-b]pyridine-3,5-dicarbonitrile (12aa). The product was isolated as a brown solid, yield 48%, mp 260–261 °C. ¹H NMR (300 MHz, DMSO- d_6): δ 1.85 (s, 9H, t-Bu), 7.56–7.71 (m, 8H), 7.96–8.01 (m, 2H), 8.80 (s, 1H, H-2). ¹³C NMR (62.9 MHz, DMSO- d_6): δ 28.6 (3C), 59.6, 83.1, 101.2, 114.2, 117.0, 117.7, 128.3, 128.5, 129.3, 129.5, 129.7, 129.9, 133.1, 138.0, 140.2, 146.7, 148.5, 155.2. MS (GC, 70 eV): m/z (%) 376 (M⁺, 24), 320 (100), 319 (85). HRMS (ESI): calcd for C₂₅H₂₁N₄ (M + 1) 377.16070, found 377.17552. IR (ATR, cm⁻¹): 3140 (w), 2986 (w), 2230 (m), 1585 (m), 1571 (m), 1516 (m), 1401 (s), 1371 (m), 1359 (m), 1305 (s), 1209 (s), 756 (s), 707 (s), 697 (s), 644 (m).

6-Amino-1-tert-butyl-4-phenyl-1H-pyrrolo[2,3-b]pyridine-3,5-dicarbonitrile (**13aa**). The product was isolated as a brown solid, yield 60%, mp 194–196 °C. ¹H NMR (300 MHz, CDCl₃): δ 1.69 (s, 9H, t-Bu), 5.12 (s, 2H, NH₂), 7.47 (br s, 5H, Ph), 7.59 (s, 1H, H-2). ¹³C NMR (62.9 MHz, CDCl₃): δ 28.9 (3C), 58.7, 84.5, 88.1, 111.8, 114.8, 117.0, 128.5, 129.2, 130.2, 133.1, 133.6, 147.8, 149.6, 155.8. MS (GC, 70 eV): m/z (%) 315 (M⁺, 19), 259 (100). HRMS (ESI): calcd for C₁₉H₁₈N₅ (M + 1) 316.15567, found 316.15526. IR (ATR, cm⁻¹): 3355 (m), 2216 (m), 2205 (m), 1610 (s), 1592 (m), 1555 (m), 1525 (m), 1484 (m), 1397 (s), 1367 (m), 1305 (s), 1207 (m), 759 (s), 709 (m), 700 (m), 651 (m).

ASSOCIATED CONTENT

S Supporting Information

Experimental procedures, characterization data, and ¹H and ¹³C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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