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Synthesis of 2-aryl-4*H*-pyrano[2,3-*b*]pyridin-4-ones by a one-pot deprotection–cyclization reaction

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ABSTRACT

An efficient synthesis of 2-aryl-4*H*-pyrano[2,3-*b*]pyridine-4-ones is reported, using a one-pot, two step process in the presence of pyridinium hydrochloride. The methodology is compatible with a series of functional groups useful for the synthesis of second generation analogs, as part of our SAR program. In addition, the method proved to be scalable (>100 g), allowing for efficient synthesis of material to support animal studies.

1. Introduction

Naturally occurring polyphenols, such as flavonoids, exhibit many biological and pharmacological properties, including anti-cancer, antioxidative, and antiinflammatory activity.[1] In addition, dietary flavonoids, e.g., baicalein[2] (Fig. 1) have been reported to serve a protective role against cardiovascular disease.[3,4] Convenient access to a wide selection of flavonoid analogues would increase the understanding of flavonoid's pharmacological potential and be essential to overcome the poor drug-like properties of natural flavonoids. This could also accelerate the advancement of more flavonoid inspired compounds into drug development.

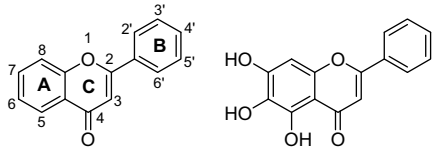

Figure 1. Flavonoid nomenclature and baicalein (right).

Over the years, the synthesis of naturally occurring flavonoids and their synthetic analoges has received widespread attention. Although a number of syntheses for flavonoids exist,[5] the cyclization of substituted dibenzoylmethanes derived from the corresponding esters and ketones is often favored.[6,7] Access to methodology based on readily available building blocks is often essential to maintain a high throughput in a medicinal chemistry program. Since a large number of *O*-methyl protected acetophenones and nicotinic acids are available, we focused heavily on identifying the method that would allow us to deprotect methoxy protected phenols, as well as facilitate cyclization to the final product in one step. However, lack of general reactions conditions for this transformation prompted us to explore new methodology. Herein, we describe an efficient synthesis of flavonoid analogs containing one or more nitrogen atom in the A- and/or B-rings (Fig. 1). The method proved especially efficient for the synthesis of 2-aryl-4*H*-pyrano-[2,3-*b*]pyridin-4-ones, a group of compounds of high interest to us.

2. Results and discussion

2.1. Synthesis of 2-(4-hydroxyphenyl)-4*H*-pyrano[2,3-*b*]pyridin-4-one

Early in the program, we found that the synthesis of 2-aryl-4*H*-pyrano-[2,3-*b*]pyridin-4-ones proceeded with low yields when following conventional methods for cyclization[5] and deprotection of methoxy protected phenols.[8] Especially 2-(4-hydroxyphenyl)-4*H*-pyrano[2,3-*b*]pyridin-4-one (**4**; Scheme 1), a compound of interest for our discovery program, gave very low yield, limiting our capability for scaling-up the synthesis to support animal studies. For example, following the standard conditions by exposing corresponding dibenzoylmethane (**3**) to HBr at 110 °C in order to achieve the cyclization and deprotection in one step, we were able to isolate **4** in only 1.5% yield. Variation of the reactions conditions, including temperature, time, and acid used for the cyclization–deprotection did not lead to any significant improvements in the overall yield of compound **4**. This prompted us to explore alternative methodology that would enable the preparation of the

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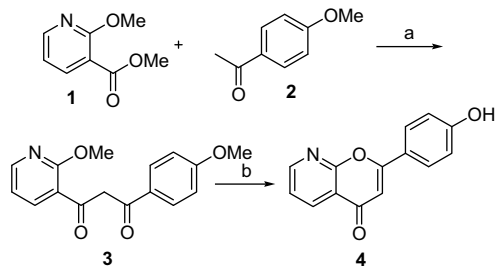
appropriate analogs in a few steps from readily available substituted 2-alkoxynicotinates and substituted acetophenones.



Scheme 1. Synthesis of compound **4**. Yields and conditions: (a) NaH, DMF, rt, 1 h, 92%; (b) pyridinium hydrochloride, 190 °C, 4 h, 73%.

Interestingly, we found that in the presence of pyridinium hydrochloride, compound **3** underwent both deprotection of the two methoxy groups and cyclization to the desired product (**4**) in 73% yield. Exploring the conditions for the cyclization and deprotection reaction, we found that the optimal conditions to be 10 equiv of pyridinium hydrochloride at 190 °C for 1–4 h. Typically, crude **3** was used, simplifying the synthesis. The reactions were followed by TLC and stopped once the starting material was consumed.

2.2. Large scale synthesis of 2-(4-hydroxyphenyl)-4*H*-pyrano[2,3-*b*]pyridin-4-one

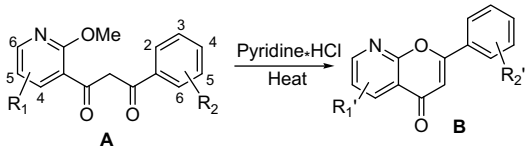
In addition to being an efficient small scale one pot synthesis, we also found the method to be scalable. In particular, compound **4**, required for in vivo animal studies, was synthesized in multi-gram quantities (>100 g) following this methodology. The process only required small modifications to accommodate synthesis on a larger scale (>20 g). For large scale synthesis, the final product was isolated by addition of water to the cooled reaction mixture, whereby the target compound crystallized from the mixture and was isolated by filtration. In addition, we also found that the neutralization step during the work-up could be eliminated.

2.3. Scope and limitations

Encouraged by the outcome of the initial experiments for the synthesis of 2-(4-hydroxyphenyl)-4*H*-pyrano[2,3-*b*]pyridin-4-one, we decided to explore the generality of this one-pot method.[9]

We found that the methodology[10] was appropriate for a wide selection of analogs and functional groups (Table 1). The reaction typically gave 40–80% yields of the isolated product. As observed for the synthesis of compound **4**, the crude dibenzoylmethanes could be used, reducing the need for additional purification steps. Methyl, benzyl, and *tert*-butyldimethylsilyl phenolic ethers were predictably converted to the corresponding phenols. By reducing the reaction time (20–40 min) we were able to isolate cyclized products with the *O*-methyl ethers intact (Entries 6 and 18), but reaction conditions had to be adjusted on a case by case basis, and the reactions needed to be carefully monitored, e.g., by TLC. Isopropyl ethers, on the other hand, were stable under the general reaction conditions (Entry 15). Both nitro (Entry 7) and nitrile (Entry 8) substituents were tolerated, offering a probe for further diversification via amide bond formation.[11] Analogs containing benzylic amines either in the 6-position of the A-ring or the 4′-position of the B-ring were of special interest to us. In all cases (Entries 13→20), we found that the benzylic amines (dimethylamino, pyrrolidino, and morpholino) were stable under the reaction conditions and the target products were isolated in good to excellent yields. Installing the benzylic amine prior to the cyclization–deprotection was the preferred way to these analogs. Use of e.g., benzylic acetates as precurcors for the amines led to displacement of the acetate by the nucleophilic pyridine moiety and the corresponding pyridinium salt was isolated (Fig. 2).

Table 1
Examples of pyridine·HCl mediated reactions.[9] [P]=pyrrolidino; [M]=morpholino



Entry	A→B	R_1	R_2	R_1'	R_2'	Yield (%)
1	3→4	H	4-OMe	H	4-OH	73
2	A1→B1	H	3-F, 4-OMe	H	3-F, 4-OH	59
3	A2→B2	H	3-Cl, 4-OMe	H	3-Cl, 4-OH	33
4	A3→B3	H	3-Br, 4-OMe	H	3-Br, 4-OH	40
5	A4→B4	H	3-Me, 4-OMe	H	3-Me, 4-OH	69
6	A5→B5	H	3-OMe, 4-OBn	H	3-OMe, 4-OH	9
7	A6→B6	H	4-NO_2	H	4-NO_2	43
8	A7→B7	H	4-CN	H	4-CN	52
9	A8→B8	H	4-NHCOOtBu	H	4-NH_2	40
10	A9→B9	H	3,5-DiMe, 4-OTBS	H	3,5-DiMe, 4-OH	40
11	A10→B10	5-Me	4-OMe	5-Me	4-OH	86
12	A11→B11	6-Me	4-OMe	6-Me	4-OH	46
13	A12→B12	5-CH_2[P]	H	5-CH_2[P]	H	42
14	A13→B13	5-CH_2[P]	4-F	5-CH_2[P]	4-F	51
15	A14→B14	5-CH_2[P]	4-OiPr	5-CH_2[P]	4-OiPr	83
16	A15→B15	5-CH_2NMe_2	3,5-diMe, 4-OBn	5-CH_2NMe_2	3,5-diMe, 4-OH	62
17	A16→B16	5-CH_2[P]	3,5-DiMe, 4-OBn	5-CH_2[P]	3,5-DiMe, 4-OH	59
18	A17→B17	5-CH_2[M]	4-OMe	5-CH_2[M]	4-OMe	83
19	A18→B18	5-CH_2[M]	4-F	5-CH_2[M]	4-F	66
20	A19→B19	5-CH_2[M]	4-OBn	5-CH_2[M]	4-OH	57

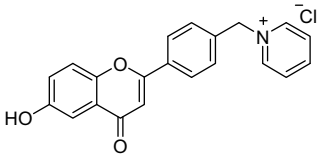
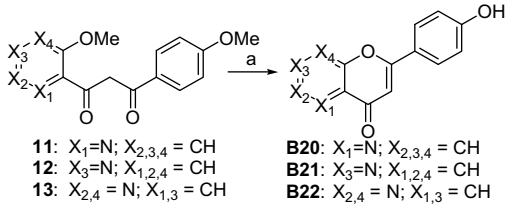


Figure 2. Example of displacement of benzylic acetates by pyridine under the standard reaction conditions.

The method also proved to be useful for the synthesis of compounds with nitrogens in other positions of the A-ring (Scheme 2).



Scheme 2. Deprotection–cyclization with nitrogen in other positions. Yields and conditions: (a) pyridinium hydrochloride, 190 °C, 1–4 h. **B20** (50%), **B21** (86%), **B22** (13%).

Compounds **B20**–**B22** containing 1 or 2 nitrogens in the A-ring were successfully synthesized, following the general methodology, from their dibenzoylmethane precursors **11**-**13**, respectively. The yields were comparable to the yields for the 2-aryl-4*H*-pyrano-[2,3-*b*]pyridin-4-ones.

3. Conclusions

In summary, we have developed an efficient one-pot synthesis of 2-aryl-4*H*-pyrano[2,3-*b*]pyridin-4-ones that facilitates deprotection and cyclization in one step. The methodology proved to tolerate a number of essential functional groups, allowing the synthesis of a broad set of compounds as part of our medicinal chemistry program. In addition, we found the method to be scalable, permitting support of in vivo animal studies.

4. Experimental

4.1. General

Solvents and reagents were used as purchased from commercial suppliers, unless otherwise noted. Dry THF was obtained via distillation over sodium using benzophenone as an indicator. Anhydrous THF was purchased from Sigma–Aldrich. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reported melting points are of materials that have been purified by column chromatography. Reactions were monitored by thin-layer chromatography (TLC) carried out on Macherey-Nagel (MN) Alugram SIL G/UV$_{254}$ silica gel 60 with fluorescent indicator UV$_{254}$ plates (catalogue #818 133) Sigma–Aldrich silica gel plates (catalogue #Z193291-1PAK) using phosphomolybdic acid in absolute EtOH and heat as a developing agent. NMR spectra were recorded on Varian NMR AS400 instrument using residual undeuterated solvent as an internal reference. Low resolution mass spectra (MS) were recorded on a Waters micromass ZQ using electrospray ionization-ion trap (ESI). The following compounds were commercially available and used as supplied: acetophenone, 4′-methoxyacetophenone, 4′-fluoroacetophenone, 4′-aminoacetophenone, 4-acetylbenzonitrile, 4′-nitroacetophenone, 3′-fluoro-4′-methoxyacetophenone, 3′-chloro-4′-methoxyacetophenone, 3′-bromo-4′-methoxyacetophenone, 4′-isopropoxyacetophenone, 4′-benzyloxyacetophenone, and 4′-hydroxy-3,5-dimethylacetophenone.

4.2. The cyclization reaction (A→B)

A mixture of dibenzoylmethane **A** and pyridinium hydrochloride (10 equiv) was heated to 190 °C for 1–4 h. The reaction was followed by TLC, and the reaction mixture was cooled to room temperature once the starting material was consumed. Water was added, and the mixture was neutralized with $NaHCO_3$. The product was extracted with ethyl acetate. The organic layer was washed with water, brine, dried over Na_2SO_4 and concentrated to dryness. The crude product was purified by chromatography to give the desired cyclized product **B**.

4.3. Synthetic details

*4.3.1. 1-(4-Methoxyphenyl)-3-(2-methoxypyridin-3-yl)propane-1,3-dione (**3**)*

To a dry 250 mL round bottom flask was added sodium hydride (5.00 g, 126 mmol, 60% in mineral oil) and methyl 2-methoxynicotinate (**1**)[12] (10.5 g, 62.8 mmol) dissolved in dry DMF (50 mL). A solution of 4′-methoxyacetophenone (**2**) (9.9 g, 66 mmol) in dry DMF (20 mL) was added dropwise over 30 min. The mixture was stirred for 1 h at room temperature. An aqueous solution of NaH_2PO_4 (25.0 g in 400 mL water) was added carefully to adjust the pH to 7. The precipitated solid was filtered off, washed with cold water and dried under vacuum to give crude 1-(4-methoxyphenyl)-3-(2-methoxypyridin-3-yl)propane-1,3-dione (**3**) as a yellow solid (16.4 g, 92%). The crude material was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (dd, J=7.41, 1.95 Hz, 1H), 8.28 (dd, J=4.68, 1.95 Hz, 1H), 7.98 (m, 2H), 7.25 (s, 1H), 7.04 (dd, J=7.61, 4.88 Hz, 1H), 7.00 (m, 2H), 4.12 (s, 3H), 3.89 (s, 3H).

*4.3.2. 2-(4-Hydroxyphenyl)-4H-pyrano[2,3-b]pyridin-4-one (**4**)*

A mixture of the diketone **3** (2 g, 7 mmol) and pyridinium hydrochloride (20 g, 0.17 mol) was heated in a round bottom flask at 190 °C for 4 h. The reaction mixture was cooled to room temperature and diluted with water and neutralized with $NaHCO_3$. The solution was extracted with ethyl acetate. The organic layer was washed with water, brine, dried (Na_2SO_4), and concentrated. The crude product was purified by column chromatography on silica gel using 4% methanol in CH_2Cl_2 to give the title compound **4** as a colorless crystalline solid (1.23 g, 73%); mp 272–274 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.38 (s, 1H), 8.77 (dd, J=4.69, 1.95 Hz, 1H), 8.49 (dd, J=7.82, 1.95 Hz, 1H), 7.97 (d, J=8.99 Hz, 2H), 7.62 (dd, J=7.62, 4.49 Hz, 1H), 7.01–6.93 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 178.2, 164.2, 161.9, 160.8, 153.9, 136.3, 129.2, 123.2, 121.9, 118.7, 116.7, 105.8; MS (ES$^+$) m/z: 240.07. Anal. Calcd for $C_{14}H_9NO_4$ (239.23): C, 70.29; H, 3.79; N, 5.85. Found: C, 70.22; H, 3.73; N, 5.73.

*4.3.3. 1-(3-Fluoro-4-methoxyphenyl)-3-(2-methoxypyridin-3-yl)propane-1,3-dione (**A1**)*

A 50 mL flask was charged with methyl 2-methoxynicotinate (**1**)[12] (2.50 g, 15 mmol), dry DMF (10 mL) and sodium hydride (0.745 g, 19 mmol, 60% in mineral oil). To the mixture was added 3′-fluoro-4′-methoxyacetophenone (2.60 g, 15.5 mmol) in anhydrous DMF (6 mL) over 5–10 min. The reaction mixture was stirred for 30 min. The mixture was poured into an NH_4Cl solution (50 mL). The yellow solid was filtered off and washed with water and purified by column chromatography (*n*-hexane/ethyl acetate 4:1) to give the title compound **A1** (3.0 g, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35–8.28 (m, 2H), 7.82–7.77 (m, 1H), 7.76–7.70 (m, 1H), 7.20 (s, 1H), 7.05 (td, J=7.24, 2.19 Hz, 2H), 4.13 (s, 3H), 3.98 (s, 3H).

*4.3.4. 2-(3-Fluoro-4-hydroxyphenyl)-4H-pyrano[2,3-b]pyridin-4-one (**B1**)*

The title compound was synthesized following general procedure A from A1 (0.8 g, 2.6 mmol). The title compound was isolated as yellow crystalline solid (0.4 g, 59%); mp 267–268 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.25 (br s, 1H), 8.71 (br s, 1H), 8.43 (d, J=7.33 Hz, 1H), 7.86–7.70 (m, 2H), 7.62–7.49 (m, 1H), 7.00–6.81 (m, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 178.2, 162.9, 160.7, 154.0, 153.1, 150.7, 150.2, 150.0, 136.4, 124.4, 123.4, 122.1, 122.0, 118.9, 118.7, 115.2, 115.0, 106.5; ^{19}F NMR (376 MHz, DMSO-d_6) δ −135.5 (t, 1F); MS (ES$^+$) m/z: 257.85. Anal. Calcd for $C_{14}H_8FNO_3$ (257.22): C, 65.37; H, 3.13; N, 5.45. Found: C, 65.51; H, 3.22; N, 5.42.

*4.3.5. 1-(3-Chloro-4-methoxyphenyl)-3-(2-methoxypyridin-3-yl)propane-1,3-dione (**A2**)*

To sodium hydride (0.48 g, 12 mmol, 60% in mineral oil) in anhydrous DMF (10 mL) was added a solution of 3′-chloro-4′-methoxyacetophenone (1.85 g, 10 mmol) in anhydrous DMF (5 mL) at 0 °C under nitrogen. The reaction mixture was stirred at 0 °C for 5 min, then at room temperature for 30 min. The reaction mixture was cooled to 0 °C. A solution of ethyl 2-methoxynicotinate[13] (1.81 g, 10 mmol) in anhydrous DMF (5 mL) was added slowly. The reaction mixture was stirring at room temperature under nitrogen for 20 h. Water (20 mL) was added and the mixture was extracted with ethyl acetate (2×100 mL). The combined organic layers were washed with brine and dried (Na_2SO_4), and concentrated to give a dark colored solid. The solid was triturated with ether to give the title compound **A2** as a yellow amorphous solid (1.64 g, 51% crude). The crude product was used without further purification. MS (ES$^+$) m/z: 319.96 (100%, M) and 321.96 (35%, M+2).

*4.3.6. 2-(3-Chloro-4-hydroxyphenyl)-4H-pyrano[2,3-b]pyridin-4-one (**B2**)*

The title compound was synthesized following general procedure A from **A2** (1.36 g, 4.21 mmol). The title compound was

isolated as a yellow crystalline solid (0.39 g, 33%); mp 259–262 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.20 (s, 1H), 8.78 (dd, J=4.49, 2.15 Hz, 1H), 8.49 (dd, J=7.82, 1.95 Hz, 1H), 8.10 (d, J=2.34 Hz, 1H), 7.94 (dd, J=8.60, 2.34 Hz, 1H), 7.63 (dd, J=7.62, 4.49 Hz, 1H), 7.16 (d, J=8.60 Hz, 1H), 7.06 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 178.3, 162.7, 160.8, 157.3, 154.1, 136.4, 128.9, 127.6, 123.4, 123.2, 121.4, 118.8, 117.7, 106.7; MS (ES$^+$) m/z: 275.94+273.92 (two isotopes). Anal. Calcd for $C_{14}H_8ClNO_3$ (273.68): C, 61.44; H, 2.95; N, 5.12. Found: C, 61.52; H, 3.03; N, 5.13.

4.3.7. 1-(3-Bromo-4-methoxyphenyl)-3-(2-methoxypyridin-3-yl)propane-1,3-dione (**A3**)

To sodium hydride (0.206 g, 5.16 mmol, 60% in mineral oil) and anhydrous DMF (5 mL) was added a solution of 3′-bromo-4′-methoxyacetophenone (0.99 g, 4.3 mmol) in anhydrous DMF (3 mL) at 0 °C under nitrogen. The reaction mixture was stirred at 0 °C for 5 min, then at room temperature for 30 min. The mixture was cooled to 0 °C and a solution of ethyl 2-methoxynicotinate[13] (1.8 g, 10 mmol) in anhydrous DMF (3 mL) was added slowly. The reaction mixture was stirred at room temperature under nitrogen for 20 h. Water (20 mL) was added and the mixture was extracted with ethyl acetate (2×100 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a dark colored solid. The solid was triturated with ether to give the title compound (1.3 g, 84%) as an amorphous yellow solid. The crude product was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35–8.28 (m, 2H), 8.20 (d, J=2.34 Hz, 1H), 7.95 (dd, J=8.60, 2.34 Hz, 1H), 7.22 (s, 1H), 7.08–6.96 (m, 2H), 4.13 (s, 3H), 3.98 (s, 3H); MS (ES$^+$) m/z: 363.91 (M) and 365.91 (two isotopes).

4.3.8. 2-(3-Bromo-4-hydroxyphenyl)-4H-pyrano[2,3-b]pyridin-4-one (**B3**)

The title compound was synthesized following general procedure A from **A3** (1.31 g, 3.6 mmol). The title compound was isolated as a crystalline yellow solid (0.45 g, 40%); mp 267–272 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.25 (s, 1H), 8.78 (dd, J=4.69, 1.95 Hz, 1H), 8.49 (dd, J=7.62, 2.15 Hz, 1H), 8.24 (d, J=2.34 Hz, 1H), 7.98 (dd, J=8.79, 2.15 Hz, 1H), 7.63 (dd, J=7.62, 4.49 Hz, 1H), 7.13 (d, J=8.99 Hz, 1H), 7.06 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 178.2, 162.6, 160.7, 158.3, 154.1, 136.4, 131.8, 128.2, 123.6, 123.4, 118.8, 117.7, 110.9, 106.7; MS (ES$^+$) m/z: 317.84, 239.9. Anal. Calcd for $C_{14}H_8BrNO_3$ (318.12): C, 52.86; H, 2.53; N, 4.40. Found: C, 53.61; H, 2.74; N, 4.72.

4.3.9. 1-(4-Methoxy-3-methylphenyl)-3-(2-methoxypyridin-3-yl)propane-1,3-dione (**A4**)

A 100 mL dry flask was charged with methyl 2-methoxynicotinate[12] (2.5 g, 15 mmol), anhydrous DMF (10 mL) and sodium hydride (0.9 g, 23 mmol, 60% in mineral oil). To the reaction mixture was added 4′-methoxy-3′-methylacetophenone[14] (2.58 g, 15.7 mmol) in anhydrous DMF (3 mL) and the reaction mixture was stirred for 2 h. The mixture was poured into water (120 mL) and acetic acid (3 mL). The yellow solid was isolated by filtration and washed with water and dried. The crude compound was purified by column chromatography (n-hexane/ethyl acetate 3:1) to give the title compound (3.4 g, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34–8.26 (m, 2H), 7.86 (dd, J=8.50, 1.76 Hz, 1H), 7.81 (s, 1H), 7.24 (s, 1H), 7.04 (dd, J=7.62, 5.57 Hz, 1H), 6.90 (d, J=8.50 Hz, 1H), 4.12 (s, 3H), 3.91 (s, 3H), 2.28 (s, 3H).

4.3.10. 2-(4-Hydroxy-3-methylphenyl)-4H-pyrano[2,3-b]pyridin-4-one (**B4**)

The title compound was synthesized following general procedure A from **A4** (1.0 g, 3.3 mmol). The title compound was isolated as a grey crystalline solid (0.58 g, 69%); mp 300–302 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.25 (br s, 1H), 8.71 (br s, 1H), 8.43 (d, J=7.33 Hz, 1H), 7.80 (br s, 1H), 7.74 (d, J=7.91 Hz, 1H), 7.62–7.50 (m, 1H), 6.93 (d, J=8.20 Hz, 1H), 6.87 (s, 1H), 2.18 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 178.1, 164.3, 160.8, 160.1, 153.8, 136.3, 129.7, 126.6, 125.7, 123.2, 121.6, 118.7, 115.8, 105.6, 16.6; MS (ES$^+$) m/z: 253.98. Anal. Calcd for $C_{15}H_{11}NO_3$ (253.22): C, 71.14; H, 4.38; N, 5.53. Found: C, 70.82; H, 4.38; N, 5.68.

4.3.11. 1-(4-(Benzyloxy)-3-methoxyphenyl)-3-(2-methoxypyridin-3-yl)propane-1,3-dione (**A5**)

A 100 mL dry flask was charged with methyl 2-methoxynicotinitate[12] (2.2 g, 13 mmol), 4′-benzyloxy-3′-methoxyacetophenone[15] (3.4 g, 13 mmol) and anhydrous DMF (10 mL). Sodium hydride (0.52 g, 13 mmol, 60% in mineral oil) was added and the reaction mixture was stirred for 2 h at room temperature. The reaction mixture was poured into water and extracted with ethyl acetate (150 mL). The organic layer was washed with water (2×100 mL), brine (100 mL), dried (Na_2SO_4), and concentrated to give the title compound (5.0 g, 98%). The crude product was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (dd, J=7.62, 2.05 Hz, 1H), 7.64–7.59 (m, 1H), 7.64–7.32 (m, 9H), 6.95 (dd, J=8.35, 1.90 Hz, 1H), 5.26 (s, 2H), 4.11 (d, J=2.34 Hz, 3H), 3.99 (d, J=2.05 Hz, 3H).

4.3.12. 2-(4-Hydroxy-3-methoxyphenyl)-4H-pyrano[2,3-b]pyridin-4-one (**B5**)

Compound **A5** (4.0 g, 10 mmol) and pyridine hydrochloride (12.0 g, 10 mmol) were mixed and heated to 170–190 °C for 20 min. The reaction mixture was cooled and poured into water (100 mL). The mixture was extracted with ethyl acetate (3×200 mL). The combined organic layers were washed with brine (3×100 mL), dried (Na_2SO_4), and concentrated. The solid was further purified by refluxing in methanol (40 mL). The solution was cooled and filtered to give the title compound (250 mg, 9%) as a crystalline solid; mp 253–255 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.02 (br s, 1H), 8.77 (br s, 1H), 8.48 (br s, 1H), 7.61 (d, J=8.77 Hz, 3H), 7.08 (br s, 1H), 6.98 (d, J=7.60 Hz, 1H), 3.92 (br s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 178.2, 164.0, 160.8, 153.9, 151.5, 148.7, 136.3, 123.3, 122.2, 121.1, 118.7, 116.5, 110.7, 106.1, 56.6; MS (ES$^+$) m/z: 269.91. Anal. Calcd for $C_{15}H_{11}NO_4$ (269.26): C, 66.91; H, 4.12; N, 5.20. Found: C, 67.29; H, 4.11; N, 5.38.

4.3.13. 1-(2-Methoxypyridin-3-yl)-3-(4-nitrophenyl)propane-1,3-dione (**A6**)

To a stirred solution of 2-methoxynicotinic acid[13] (2.3 g, 15 mmol) in anhydrous THF (75 mL) was added N-methylmorpholine (1.5 g, 15 mmol). The reaction mixture was cooled to −10 °C and ethyl chloroformate (1.6 g, 15 mmol) was added dropwise. The reaction mixture was stirred at −10 °C for 15 min. and then at room temperature for 10 h. Water (50 mL) was added, and the solution was extracted with ethyl acetate. The organic layer was dried (Na_2SO_4), and concentrated to give the acid chloride as a colorless liquid (3.29 g, 97%). To a solution of acid chloride (3.28 g, 14.6 mmol) and 4′-nitroacetophenone (2.5 g, 15 mmol) in anhydrous THF (75 mL) was added lithium bis(trimethylsilyl) amide (18 mL, 1.0 M solution in THF) at −30 °C over a period of 45 min. The reaction mixture was stirred at −30 °C for 30 min. The reaction mixture was stirred for another 15 h at room temperature. The reaction mixture was diluted with ethyl acetate (200 mL), and saturated NH_4Cl solution (50 mL) was added. The organic layer was dried (Na_2SO_4), and concentrated to give the crude product which was triturated with ether to give the title compound (2.79 g, 62%). The crude product was used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47–8.20 (m, 6H), 7.41 (s, 1H), 7.23 (dd, J=7.42, 5.08 Hz, 1H), 4.07 (s, 3H).

4.3.14. 2-(4-Nitrophenyl)-4H-pyrano[2,3-b]pyridin-4-one (**B6**)

The title compound was synthesized following general procedure A from **A6** (2.16 g, 7.19 mmol). The title compound was

isolated as a brown crystalline solid (0.82 g, 43%); mp 261–263 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.84 (dd, J=4.49, 2.15 Hz, 1H), 8.54 (dd, J=7.82, 1.95 Hz, 1H), 8.44–8.36 (m, 4H), 7.68 (dd, J=7.82, 4.69 Hz, 1H), 7.35 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 178.6, 161.3, 160.8, 154.6, 149.9, 137.5, 136.6, 128.6, 124.9, 123.8, 118.9, 110.4; MS (ES$^+$) m/z: 268.88 (M). Anal. Calcd for $C_{14}H_8N_2O_4\cdot 0.25H_2O$ (272.72): C, 61.65; H, 3.14; N, 10.27. Found: C, 61.77; H, 3.31; N, 10.26.

4.3.15. 4-(3-(2-Methoxypyridin-3-yl)-3-oxopropanoyl)-benzonitrile (**A7**)

A dry 50 mL flask was charged with methyl 2-methoxynicotinitate[12] (2.50 g, 14.9 mmol), 4-acetylbenzonitrile (2.25 g, 15.9 mmol) and anhydrous DMF (10 mL). Sodium hydride (0.745 g, 18.6 mmol, 60% in mineral oil) was added and the reaction mixture was stirred for 30 min, then poured into water (100 mL) and acetic acid (2 mL). The yellow solid was washed with water and dissolved into dichloromethane. The organic solution was washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography (n-hexane/ethyl acetate 3:1) to give the title compound (1.7 g, 41%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (m, 2H), 8.06 (d, J=8.19 Hz, 2H), 7.79 (d, J=8.19 Hz, 2H), 7.32 (s, 1H), 7.13–7.02 (m, 1H), 4.13 (s, 3H).

4.3.16. 4-(4-Oxo-4H-pyrano[2,3-b]pyridin-2-yl)benzonitrile (**B7**)

The title compound was synthesized following general procedure A from **A7** (0.7 g, 2.5 mmol). The title compound was isolated as a light yellow crystalline solid (0.32 g, 52%); mp 250–252 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.81 (dd, J=4.69, 2.05 Hz, 1H), 8.51 (dd, J=7.62, 2.05 Hz, 1H), 8.29–8.24 (m, 2H), 8.08–8.03 (m, 2H), 7.65 (dd, J=7.77, 4.54 Hz, 1H), 7.28 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 178.6, 161.7, 160.8, 154.6, 136.6, 135.8, 133.8, 127.9, 123.7, 118.9, 118.9, 114.7, 110.0; MS (ES$^+$) m/z: 248.90. Anal. Calcd for $C_{15}H_8N_2O_2$ (248.27): C, 72.58; H, 3.25; N, 11.27. Found: C, 72.62; H, 3.08; N, 11.31.

4.3.17. tert-Butyl 4-[3-(2-methoxypyridin-3-yl)-3-oxopropanoyl]phenylcarbamate (**A8**)

Di-*tert*-butyl dicarbonate (4.8 g, 22 mmol) was added to a solution of 4′-aminoacetophenone (2.7 g, 20 mmol) in dioxane (50 mL). The reaction mixture was stirred at 60 °C for 15 h. The solvent was removed and the residue was dissolved in ethyl acetate and washed with water (2×50 mL), brine (50 mL), dried (Na_2SO_4), and concentrated to give the crude product, which was purified by column chromatography (15% ethyl acetate in n-hexanes) to give *tert*-butyl 4-acetylphenylcarbamate[16] (**5**) as a white solid (2.7 g, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J=8.97 Hz, 2H), 7.46 (d, J=8.58 Hz, 2H), 6.73 (br s, 1H), 2.57 (s, 3H), 1.53 (s, 9H). To a solution of compound **5** (2.4 g, 10 mmol) in anhydrous THF (50 mL) was added lithium bis(trimethylsilyl) amide solution (22 mL, 1.0 M in THF) at −40 °C over a period of 30 min under nitrogen. The mixture was stirred at −40 °C for 15 min. A solution of ethyl 2-methoxynicotinate in anhydrous THF (10 mL) was added slowly. The reaction mixture was stirred at −40 °C for 10 min, then allowed to warm to room temperature. After 5 h, a saturated aqueous NH_4Cl solution (100 mL) was added. The mixture was extracted with ethyl acetate (300 mL). The organic layer was isolated and dried (Na_2SO_4). The crude compound was purified by column chromatography (15% ethyl acetate in n-hexanes) to give the title compound as a yellow solid (2.9 g, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35–8.27 (m, 2H), 7.95 (d, J=8.97 Hz, 2H), 7.50 (d, J=8.58 Hz, 2H), 7.25 (s, 1H), 7.03 (dd, J=7.42, 4.69 Hz, 1H), 6.80 (br s, 1H), 4.15 (s, 3H), 1.560 (s, 9H).

4.3.18. 2-(4-Aminophenyl)-4H-pyrano[2,3-b]pyridin-4-one (**B8**)

The title compound was synthesized following general procedure A from **A8** (3.0 g, 26 mmol). The title compound was isolated as a yellow crystalline solid (0.25 g, 40%); mp 254–255 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 (d, J=4.69 Hz, 1H), 8.48 (d, J=7.82 Hz, 1H), 7.90 (d, J=8.58 Hz, 2H), 7.61 (dd, J=7.42, 4.69 Hz, 1H), 7.12–6.78 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 177.9, 164.3, 160.8, 153.7, 136.2, 128.8, 123.2, 118.8, 116.8, 104.8; MS (ES$^+$) m/z: 238.89 (M+1). Anal. Calcd for $C_{14}H_{10}N_2O_2\cdot$HCl (274.70): C, 61.21; H, 4.04; N, 10.20. Found: C, 61.23; H, 3.91; N, 9.98.

4.3.19. 1-(4-(tert-Butyldimethylsilyloxy)-3,5-dimethylphenyl)-3-(2-methoxypyridin-3-yl)propane-1,3-dione (**A9**)

To a solution of 3′,5′-dimethyl-4′-hydroxyacetophenone (2.5 g, 15 mmol) in anhydrous DMF (75 mL) was added imidazole (3.3 g, 48 mmol) and *tert*-butyldimethylsilylchloride (2.7 g, 18 mmol). The reaction mixture was stirred at room temperature under nitrogen for 15 h. Water (200 mL) was added, and the mixture was extracted with ethyl acetate (200 mL). The organic layer was washed with water (2×100 mL), brine (100 mL), dried (Na_2SO_4), and concentrated to give 1-(4-(*tert*-butyldimethylsilyloxy)-3,5-dimethylphenyl)ethanone (**6**) as a colorless oil (4.4 g, quantitative yield). The crude product was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (s, 2H), 2.32 (s, 3H), 2.04 (s, 6H), 0.82 (s, 9H), 0.00 (s, 6H). To a stirred solution of compound **6** (1.6 g, 5.6 mmol) in anhydrous THF (15 mL) was added lithium bis(trimethylsilyl) amide (6.8 mL, 1.0 M solution in THF) at −40 °C over a period of 15 min under nitrogen. The mixture was stirred at −40 °C for 15 min. A solution of ethyl 2-methoxynicotinate[13] in anhydrous THF (15 mL) was added slowly. The stirring was continued at −40 °C for 10 min. The mixture was allowed to warm to room temperature and stirred for another 15 h. The reaction mixture was diluted with ethyl acetate (200 mL) and a saturated aqueous NH_4Cl solution (50 mL) was added. The organic layer was isolated, dried (Na_2SO_4), and concentrated to give the desired crude compound (2.4 g). The compound was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35–8.25 (m, 1H), 8.15 (d, J=7.42 Hz, 1H), 7.62 (s, 2H), 7.26 (s, 1H), 6.97–6.90 (m, 1H), 4.05 (s, 3H), 1.03 (s, 9H), 0.22 (s, 6H).

4.3.20. 2-(4-Hydroxy-3,5-dimethylphenyl)-4H-pyrano[2,3-b]pyridin-4-one (**B9**)

The title compound was synthesized following general procedure A from crude **A9** (2.3 g, 5.6 mmol). The title compound was isolated as an off-white crystalline solid (0.60 g, 40% over two steps); mp 295–297 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.19 (s, 1H), 8.76 (d, J=4.69 Hz, 1H), 8.48 (d, J=7.82 Hz, 1H), 7.73 (s, 2H), 7.61 (dd, J=7.42, 4.69 Hz, 1H), 6.95 (s, 1H), 2.27 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 178.1, 164.4, 160.8, 158.0, 153.9, 136.3, 127.6, 125.6, 123.3, 121.7, 118.8, 105.8, 17.3; MS (ES$^+$) m/z: 268.91 (M+1), 267.88 (M). Anal. Calcd for $C_{16}H_{13}NO_3$ (267.28): C, 71.90; H, 4.90; N, 5.24. Found: C, 71.68; H, 4.83; N, 5.29.

4.3.21. 1-(2-Chloro-5-methylpyridin-3-yl)-3-(4-methoxyphenyl)propane-1,3-dione (**A10**)

To a mixture of methyl 2-chloro-5-methylnicotinate[17] (0.90 g, 4.8 mmol) and NaH (0.38 g, 9.6 mmol, 60% in mineral oil) in anhydrous DMF (10 mL) was added 4′-methoxyacetophenone (0.76 g, 5.0 mmol). The reaction mixture was stirred for 2 h at room temperature. The reaction mixture was poured into water and extracted with ethyl acetate (150 mL). The organic layer was washed with water (2×100 mL), brine (100 mL), dried (Na_2SO_4), and concentrated to give the crude product. The crude product was purified by chromatography (n-hexane/ethyl acetate 4:1) to give the title compound (0.36 g, 25%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (br s, 1H), 7.94 (d, J=5.55 Hz, 2H), 7.85 (br s, 1H), 6.97 (d, J=5.26 Hz, 2H), 6.78 (br s, 1H), 3.88 (s, 3H), 2.38 (s, 3H).

*4.3.22. 2-(4-Hydroxyphenyl)-6-methyl-4H-pyrano[2,3-b]pyridin-4-one (**B10**)*

The title compound was synthesized following general procedure A from crude **A10** (0.28 g, 0.92 mmol). The title compound was isolated as a red crystalline solid (0.20 g, 86%); mp 268–270 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.28 (br s, 1H), 8.60 (s, 1H), 8.30 (s, 1H), 7.90 (m, 2H), 6.95 (m, 3H), 2.40(s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 178.1, 164.4, 162.3, 160.8, 154.5, 136.3, 133.4, 129.2, 122.3, 118.8, 117.5, 105.8, 17.3; MS (ES$^+$) *m*/*z*: 253.95. Anal. Calcd for $C_{15}H_{11}NO_3$ (253.26): C, 71.14; H, 4.38; N, 5.53. Found: C, 71.59; H, 4.52; N, 5.68.

*4.3.23. 1-(2-Methoxy-6-methylpyridin-3-yl)-3-(4-methoxyphenyl)propane-1,3-dione (**A11**)*

To a mixture of NaH (637 mg, 26.5 mmol, 60% in mineral oil) in dry DMF (20 mL) at 0 °C was added 4′-methoxyacetophenone (3.62 g, 24.1 mmol) in dry DMF (10 mL) over 30 min. After 1 h, methyl 2-methoxy-6-methylnicotinate[18] (4.37 g, 24.1 mmol) in dry DMF (10 mL) was added slowly on cooling. The mixture was stirred for 16 h at room temperature. The reaction mixture was quenched by addition of a saturated aqueous NH_4Cl solution and diluted with water. The solid was filtered off, washed with water and dried to give the title compound (6.18 g, 86%). The crude product was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J*=7.82 Hz, 1H), 7.97 (d, *J*=8.99 Hz, 2H), 7.20 (s, 1H), 7.00–6.97 (m, 2H), 6.87 (d, *J*=7.82 Hz, 1H), 4.10 (s, 3H), 3.89 (s, 3H), 2.51 (s, 3H).

*4.3.24. 2-(4-Hydroxyphenyl)-7-methyl-4H-pyrano[2,3-b]pyridin-4-one (**B11**)*

The title compound was synthesized following general procedure A from crude **A11** (3.0 g, 10 mmol). The title compound was isolated as a yellow crystalline solid (1.15 g, 46%); mp 303–305 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.36 (s, 1H), 8.35 (d, *J*=7.42 Hz, 1H), 7.95 (d, *J*=8.21 Hz, 2H), 7.48 (d, *J*=7.82 Hz, 1H), 7.02–6.86 (m, 3H), 2.62 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 178.1, 164.1, 163.8, 161.8, 160.4, 136.3, 129.1, 123.1, 122.0, 116.7, 116.3, 105.7, 25.0; MS (ES$^+$) *m*/*z*: 253.88. Anal. Calcd for $C_{15}H_{11}NO_3$ (253.26): C, 71.14; H, 4.38; N, 5.53. Found: C, 71.16; H, 4.37; N, 5.49.

*4.3.25. 1-(2-Methoxy-5-(pyrrolidin-1-ylmethyl)pyridin-3-yl)-3-phenylpropane-1,3-dione (**A12**)*

To a solution of methyl 2-chloro-5-methylnicotinate[17] (14.0 g, 75 mmol) in anhydrous methanol (40 mL) was added sodium methoxide (31 mL, 140 mmol, 25% in methanol) and the reaction was heated at reflux overnight. Acetic acid was added to the mixture until neutral. The mixture was concentrated to remove the methanol. The residue was poured into water and extracted with CH_2Cl_2. The organic layer was washed with water, brine, dried (Na_2SO_4), and concentrated to give methyl 2-methoxy-5-methylnicotinate (13.5 g, 98.0%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (br s, 1H), 7.99 (br s, 1H), 4.02 (s, 3H), 3.90 (s, 3H), 2.29 (s, 3H). To a solution of methyl 2-methoxy-5-methylnicotinate (8.65 g, 48 mmol) in anhydrous carbon tetrachloride (80 mL) was added NBS (8.95 g, 50 mmol). The reaction mixture was heated to reflux under a UV-lamp for 3 h. The mixture was cooled to room temperature and concentrated. The residue was washed with hot water to remove succinimide. The solid was purified by column (dichloromethane/ethyl acetate 30:1) to yield methyl 5-(bromomethyl)-2-methoxynicotinate (**7**) (7.77 g, 62.2%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, *J*=2.34 Hz, 1H), 8.21 (d, *J*=2.63 Hz, 1H), 4.47 (s, 2H), 4.05 (s, 3H), 3.92 (s, 3H). A mixture of compound **7** (4.4 g, 17 mmol), pyrrolidine (4.8 g, 68 mmol) and anhydrous THF (20 mL) was heated to reflux for 2 h, cooled to room temperature, and concentrated. The residue was purified by column chromatography (ethyl acetate to ethyl acetate/MeOH 9:1) to give methyl 2-methoxy-5-(pyrrolidin-1-ylmethyl)nicotinate (**8**) (3.50 g, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1H), 8.15 (s, 1H), 4.04 (s, 3H), 3.90 (s, 3H), 3.58 (s, 2H), 2.50 (br s, 4H), 1.79 (br s, 4H). To a mixture of compound **8** (0.50 g, 2.0 mmol) and acetophenone (0.24 g, 2.0 mmol) in anhydrous DMF (4 mL) was added sodium hydride (0.16 g, 60% in mineral oil), and the reaction mixture was kept overnight at room temperature. The mixture was poured into water (80 mL) and extracted with CH_2Cl_2 (3×80 mL). The combined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated to yield the title compound (0.45 g, 67%). The crude compound was used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70 (s, 1H), 8.60 (s, 1H), 8.10 (m, 2H), 7.50 (m, 3H), 7.20 (s, 1H), 4.20 (s, 2H), 4.10 (s, 3H), 2.20 (br s, 8H).

*4.3.26. 2-Phenyl-6-(pyrrolidin-1-ylmethyl)-4H-pyrano[2,3-b]pyridin-4-one (**B12**)*

The title compound was synthesized following general procedure A from crude **A12** (0.45 g, 1.3 mmol). The hydrochloride of the title compound was isolated as a grey crystalline solid (0.19 g, 42%); mp 294–296 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.00 (br s, 1H), 9.00 (s, 1H), 8.80 (s, 1H), 8.20 (m, 2H), 7.70 (m, 3H), 7.20 (s, 1H), 4.60 (s, 2H), 3.40 (m, 4H), 2.10–1.80 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 178.2, 163.8, 156.0, 138.9, 132.9, 131.3, 129.9, 127.2, 127.1, 118.3, 108.2, 53.6, 53.3, 23.2; MS (ES$^+$) *m*/*z*: 306.94. Anal. Calcd for $C_{19}H_{18}N_2O_2\cdot HCl$ (342.83): C, 66.57; H, 5.59; N, 8.17. Found: C, 66.81; H, 5.31; N, 8.18.

*4.3.27. 1-(4-Fluorophenyl)-3-(2-methoxy-5-(pyrrolidin-1-ylmethyl)pyridin-3-yl)propan-1,3-dione (**A13**)*

To a stirred solution of compound **8** (0.50 g, 2.0 mmol) and 4′-fluoroacetophenone (0.28 g, 2.0 mmol) in anhydrous DMF (3 mL) was added sodium hydride (0.16 g, 2.0 mmol, 60% suspension in mineral oil) in small portions under nitrogen. The reaction mixture was stirred overnight at room temperature. A saturated aqueous solution of NH_4Cl was added. The mixture was extracted with ethyl acetate (100 mL). The organic layer was washed with water (30 mL), brine (30 mL), dried (Na_2SO_4), and concentrated to give a brown solid (0.45 g), which was used in next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (m, 2H), 8.10 (m, 2H), 7.30 (s, 1H), 7.20 (m, 2H), 4.20 (s, 2H), 4.10 (s, 3H), 2.20 (br s, 8H); ^{19}F NMR (376 MHz, DMSO-d_6) δ −107.8.

*4.3.28. 2-(4-Fluorophenyl)-6-(pyrrolidin-1-ylmethyl)-4H-pyrano[2,3-b]pyridin-4-one (**B13**)*

The title compound was synthesized following general procedure A from crude **A13** (0.45 g, 1.3 mmol). The hydrochloride of the title compound was isolated as a yellow crystalline solid (0.21 g, 51%); mp 265–268 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.10 (br s, 1H), 9.00 (s, 1H), 8.80 (s, 1H), 8.20 (m, 2H), 7.50 (m, 2H), 7.20 (s, 1H), 4.50 (s, 2H), 3.3 (m, 2H), 3.0 (m, 2H), 2.0 (m, 2H), 1.8 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 178.2, 162.8, 160.9, 156.1, 138.9, 129.9, 127.1, 118.2, 117.2, 117.0, 108.1, 53.6, 53.2, 23.2; ^{19}F NMR (376 MHz, DMSO-d_6) δ −108; MS (ES$^+$) *m*/*z*: 324.89. Anal. Calcd for $C_{19}H_{17}FN_2O_2\cdot 1.5\ HCl$ (379.36): C, 60.21; H, 4.92; N, 7.39. Found: C, 59.93; H, 4.68; N, 7.35.

*4.3.29. 1-(4-Isopropoxyphenyl)-3-(2-methoxy-5-(pyrrolidin-1-ylmethyl)pyridin-3-yl)propan-1,3-dione (**A14**)*

To a stirred solution of compound **8** (0.50 g, 2.0 mmol) and 4′-isopropoxyacetophenone (0.37 g, 2.1 mmol) in anhydrous DMF (10 mL) was added sodium hydride (96 mg, 2.4 mmol, 60% in mineral oil) in small portions under nitrogen. The reaction mixture was stirred overnight at room temperature. The reaction mixture was stirred at 80 °C for 1 h. Water (30 mL) was added and the pH adjusted to 7 by adding acetic acid. The mixture was extracted with chloroform (150 mL). The organic layer was washed with water (30 mL), brine (30 mL), dried (Na_2SO_4), and concentrated to give the crude title compound as a brown solid (0.66 g), which was used

in next the step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.29 (s, 1H), 8.22 (s, 1H), 7.94 (d, J=7.82 Hz, 2H), 7.22 (s, 1H), 6.94 (d, J=7.42 Hz, 2H), 4.70–4.60 (m, 1H), 4.10 (s, 3H), 3.65 (s, 2H), 2.55 (br s, 4H), 1.80 (br s, 4H), 1.35 (d, J=6.52 Hz, 6H); MS (ES$^+$) m/z: 396.97 (M+1).

4.3.30. 2-(4-Isopropoxyphenyl)-6-(pyrrolidin-1-ylmethyl)-4H-pyrano[2,3-b]pyridin-4-one (**B14**)

The title compound was synthesized following general procedure A from crude **A14** (0.63 g, 1.6 mmol). The hydrochloride of the title compound was isolated as a yellow solid (0.24 g, 41%); mp 261–263 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.25 (br s, 1H), 8.98 (s, 1H), 8.73 (s, 1H), 8.01 (d, J=8.6 Hz, 2H), 7.10 (d, J=9.0 Hz, 2H), 7.03 (s, 1H), 4.76–4.73 (s, 1H), 4.54 (s, 2H), 3.55 (br s, 2H), 3.08 (br s, 2H), 2.05 (br s, 2H), 1.85 (br s, 2H), 1.28 (d, J=5.9 Hz, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 177.9, 163.9, 161.5, 160.9, 155.8, 138.8, 129.1, 122.9, 118.3, 116.6, 106.4, 70.4, 53.6, 53.3, 23.2, 22.3; MS (ES$^+$) m/z: 364.96 (M). Anal. Calcd for $C_{22}H_{24}N_2O_3\cdot HCl\cdot 0.6H_2O$ (414.4): C, 63.99; H, 6.43; N, 6.78. Found: C, 63.97; H, 6.42; N, 6.74.

4.3.31. 1-[4-(Benzyloxy)-3,5-dimethylphenyl]-3-(5-[(dimethylamino)methyl]-2-methoxypyridin-3-yl)propan-1,3-dione (**A15**)

A mixture of compound **7** (1.0 g, 3.8 mmol) and dimethylamine (7.7 mL, 2.0 M in THF) in dry THF (10 mL) was heated to 60 °C for 4 h. The reaction mixture was cooled to room temperature, concentrated and purified by column chromatography (methanol/ethyl acetate 1:3) to give 5-[(dimethylamino)methyl]-2-methoxynicotinate (**9**) (0.82 g, 95%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (d, J=2.05 Hz, 1H), 8.08 (s, 1H), 3.92 (s, 3H), 3.81 (s, 3H), 3.49 (s, 2H), 2.20 (d, 6H). To a mixture of compound **9** (0.82 g, 3.7 mmol) and 1-(4-(benzyloxy)-3,5-dimethylphenyl)ethanone.[19] (0.93 g, 3.7 mmol) in anhydrous DMF (10 mL) was added sodium hydride (0.22 g, 5.5 mmol, 60% in mineral oil). The reaction mixture was stirred overnight at room temperature. The reaction mixture was poured into water (150 mL) and neutralized with acetic acid. Dichloromethane (150 mL) was added and the organic layer was washed with water, brine, dried (Na_2SO_4), concentrated, and purified by column (ethyl acetate: methanol 8:1) to give the title compound (0.90 g, 55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (br s, 1H), 8.24 (br s, 1H), 7.69 (s, 2H), 7.51–7.36 (m, 5H), 7.22 (s, 1H), 4.87 (s, 2H), 4.12 (s, 3H), 3.56 (br s, 2H), 2.96 (s, 3H), 2.89 (s, 3H), 2.36 (s, 6H).

4.3.32. 6-[(Dimethylamino)methyl]-2-(4-hydroxy-3,5-dimethylphenyl)-4H-pyrano[2,3-b]pyridin-4-one (**B15**)

The title compound was synthesized following general procedure A from crude **A15** (0.80 g, 1.8 mmol). The hydrochloride of the title compound was isolated as a yellow crystalline solid (0.40 g, 62%); mp 306–308 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.80 (br s, 1H), 9.30 (s, 1H), 8.90 (s, 1H), 8.70 (s, 1H), 7.75 (s, 2H), 7.0 (s, 1H), 4.50 (s, 2H), 2.75 (s, 6H), 2.25 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 178.1, 164.4, 160.8, 158.0, 156.0, 140.0, 127.6, 125.6, 122.0, 118.5, 105.8, 56.0, 42.0, 17.8; MS (ES$^+$) m/z: 325.02. Anal. Calcd for $C_{19}H_{20}N_2O_3\cdot HCl$ (360.84): C, 63.24; H, 5.87; N, 7.76. Found: C, 63.71; H, 5.76; N, 7.82.

4.3.33. 1-[4-(Benzyloxy)-3,5-dimethylphenyl]-3-(2-methoxy-5-[pyrrolidin-1-ylmethyl]pyridin-3-yl)propane-1,3-dione (**A16**)

To a mixture of compound **8** (0.60 g, 2.4 mmol) and 1-(4-(benzyloxy)-3,5-dimethylphenyl)ethanone[19] (0.61 g, 2.4 mmol) in anhydrous DMF (5 mL) was added sodium hydride (0.2 g, 60% in mineral oil). The reaction mixture was kept overnight at room temperature. The mixture was poured into water (80 mL) and the pH was adjusted to 7 by adding acetic acid. The mixture was extracted with CH_2Cl_2 (3×80 mL). The organic layer was washed with water, brine, dried (Na_2SO_4) and concentrated to give the crude title compound (1.0 g, 88%). The crude product was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (br s, 1H), 8.29 (br s, 1H), 7.69 (s, 2H), 7.51–7.36 (m, 5H), 7.22 (s, 1H), 4.87 (s, 2H), 4.12 (s, 3H), 3.76 (br s, 2H), 2.69 (br s, 4H), 2.36 (s, 6H), 1.87 (br s, 4H).

4.3.34. 2-(4-Hydroxy-3,5-dimethylphenyl)-6-(pyrrolidin-1-ylmethyl)-4H-pyrano[2,3-b]pyridin-4-one (**B16**)

The title compound was synthesized following general procedure A from crude **A16** (1.0 g, 2.1 mmol). The hydrochloride of the title compound was isolated as a yellow crystalline solid (0.50 g, 59%); mp 337–338 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.28 (s, 1H), 9.00 (s, 1H), 8.75 (s, 1H), 7.80 (s, 2H), 7.00 (s, 1H), 4.60 (s, 2H), 3.60–3.40 (m, 2H), 3.10 (br s, 2H), 2.25 (s, 6H), 2.05 (br s, 2H), 1.85 (br s, 2H); MS (ES$^+$) m/z: 351.03. Anal. Calcd for $C_{21}H_{22}N_2O_3\cdot 1.5HCl$ (405.11): C, 62.26; H, 5.85; N, 6.91. Found: C, 61.53; H, 5.56; N, 6.88; HPLC: 95.82%. Due to low solubility it was not possible to record a ^{13}C-NMR.

4.3.35. 1-(2-Methoxy-5-(morpholinomethyl)pyridin-3-yl)-3-(4-methoxyphenyl)propane-1,3-dione (**A17**)

A mixture of compound **7** (3.0 g, 11.5 mmol) and morpholine (4.02 g, 46.1 mmol) in anhydrous THF (15 mL) was heated to reflux for 2 h. The reaction mixture was cooled to room temperature and concentrated. Water and CH_2Cl_2 were added to the residue and the organic layer was washed with brine, dried (Na_2SO_4), and concentrated to give methyl 2-methoxy-5-(morpholinomethyl) nicotinate (**10**) (3.0 g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 8.10 (s, 1H), 4.10 (s, 3H), 3.90 (s, 3H), 3.70 (m, 4H), 3.50 (s, 2H), 2.40 (m, 4H). To a mixture of compound **10** (0.73 g, 2.7 mmol) and 4′-methoxy-acetophenone (0.41 g, 2.7 mmol) in anhydrous DMF was added NaH (0.17 g, 60% in mineral oil). The reaction mixture was kept at room temperature overnight. The mixture was poured into water (80 mL) and the pH was adjusted to 7 by adding acetic acid. The mixture was extracted with CH_2Cl_2 (3×80 mL). The combined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated to give the crude title compound (0.85 g, 81%). The crude compound was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, J=2.34 Hz, 1H), 8.20 (d, J=2.34 Hz, 1H), 7.98 (d, J=9.06 Hz, 2H), 7.00 (d, J=8.77 Hz, 2H), 4.11 (s, 3H), 3.90 (s, 3H), 3.74–3.67 (m, 4H), 3.50 (s, 2H), 2.46 (br s, 4H).

4.3.36. 2-(4-Methoxyphenyl)-6-(morpholinomethyl)-4H-pyrano[2,3-b]pyridin-4-one (**B17**)

The title compound was synthesized following general procedure A from crude **A17** (0.50 g, 1.3 mmol). The reaction time was reduced to 40 min, and the reaction was monitored by TLC. The hydrochloride of the title compound was isolated as a yellow crystalline solid (0.42 g, 83%); mp 307–309 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.50 (br s, 1H), 9.00 (s, 1H), 8.70 (s, 1H), 8.10 (d, J=9.06 Hz, 2H), 7.20 (d, J=8.77 Hz, 2H), 7.10 (s, 1H), 4.55 (br s, 2H), 4.05–3.70 (m, 7H), 3.50–3.00 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 178.2, 164.2, 163.2, 161.1, 139.0, 129.2, 123.0, 118.3, 115.4, 106.4, 63.9, 56.2, 51.6; MS (ES$^+$) m/z: 352.99. Anal. Calcd for $C_{20}H_{20}N_2O_4\cdot HCl$ (388.85): C, 61.78; H, 5.44; N, 7.20. Found: C, 62.14; H, 5.37; N, 7.37.

4.3.37. 1-(4-Fluorophenyl)-3-(2-methoxy-5-(morpholinomethyl)-pyridin-3-yl)propan-1,3-dione (**A18**)

To a mixture of compound **10** (0.51 g, 1.9 mmol) and 4′-fluoro-acetophenone (0.29 g, 2.1 mmol) in anhydrous DMF (3 mL) under N_2 was added sodium hydride (0.13 g, 3.2 mmol, 60% in mineral oil). The mixture was stirred overnight before poured into water (100 mL) and adjusting the pH to 7 by adding acetic acid. The mixture was stirred for an hour and the solid was filtered off, washed with water and hexane to give the crude title compound (0.33 g, 47%), which was used for the next reaction without further

purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.29 (br s, 1H), 8.21 (d, J=1.95 Hz, 1H), 8.17–8.04 (m, 2H), 7.42 (t, J=8.78 Hz, 2H), 4.05 (s, 3H), 3.61–3.52 (m, 4H), 3.50 (s, 2H), 2.37 (br s, 4H).

4.3.38. 2-(4-Fluorophenyl)-6-(morpholinomethyl)-4H-pyrano[2,3-b]pyridin-4-one (**B18**)

The title compound was synthesized following general procedure A from crude **A18** (0.34 g, 0.9 mmol). The hydrochloride of the title compound was isolated as a yellow crystalline solid (0.22 g, 66%); mp 298.2–298.8 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.21 (br s, 1H), 8.98 (br s, 1H), 8.76 (br s, 1H), 8.31–8.16 (m, 2H), 7.48 (t, J=8.80 Hz, 2H), 7.21 (s, 1H), 4.57 (br s, 2H), 3.97 (br s, 2H), 3.74 (br s, 2H), 3.32 (br s, 2H), 3.16 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 178.2, 166.3, 163.8, 162.9, 161.1, 139.9, 130.0, 127.8, 125.0, 118.2, 117.7, 116.7, 107.7, 107.5, 63.7, 55.9; ^{19}F NMR (376 MHz, DMSO-d_6) δ −107.8; MS (ES$^+$) m/z: 364.96 (M). Anal. Calcd for $C_{19}H_{17}FN_2O_3\cdot HCl$ (376.82): C, 60.56; H, 4.81; N, 7.43. Found: C, 60.40; H, 4.31; N, 7.44.

4.3.39. 1-(4-[Benzyloxy)phenyl]-3-(2-methoxy-5-(morpholinomethyl)pyridin-3-yl)propan-1,3-dione (**A19**)

To a mixture of compound **10** (0.81 g, 3.0 mmol) and 4′-benzyloxyacetophenone (0.70 g, 3.0 mmol) in anhydrous DMF (5 mL) was added sodium hydride (0.18 g, 60% in mineral oil). The reaction mixture was kept overnight at room temperature before poured into water (80 mL) and adjusting the pH to 7 by adding acetic acid. The mixture was extracted with CH_2Cl_2 (3×80 mL). The combined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated to give the crude compound (0.13 g, 94%), which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, J=2.35 Hz, 1H), 8.20 (d, J=2.35 Hz, 1H), 7.97 (d, J=9.09 Hz, 2H), 7.49–7.33 (m, 5H), 7.25 (s, 1H), 7.05 (m, 2H), 5.16 (s, 2H), 4.11 (s, 3H), 3.74–3.66 (m, 4H), 3.50 (s, 2H), 2.46 (br s, 4H).

4.3.40. 2-(4-Hydroxyphenyl)-6-(morpholinomethyl)-4H-pyrano[2,3-b]pyridin-4-one (**B19**)

The title compound was synthesized following general procedure A from crude **A19** (1.30 g, 2.8 mmol). The title compound was isolated as a yellow crystalline solid (0.54 g, 57%); mp 232–234 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.39 (s, 1H), 8.69 (d, J=2.34 Hz, 1H), 8.37 (d, J=1.46 Hz, 1H), 7.97 (d, J=8.77 Hz, 2H), 6.96 (m, 3H), 3.66 (s, 2H), 3.59 (t, J=4.24 Hz, 4H), 2.41 (br s, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 178.2, 164.1, 161.9, 160.1, 154.2, 136.1, 133.1, 129.2, 121.8, 118.1, 116.7, 105.7, 66.8, 59.1, 53.6; MS (ES$^+$) m/z 339.15 (M+1). Anal. Calcd for $C_{19}H_{18}N_2O_4$: C, 66.44; H, 5.36; N, 8.28. Found: C, 66.32; H, 5.38; N, 7.49.

4.3.41. 1-(4-Methoxyphenyl)-3-(3-methoxypyridin-2-yl)propan-1,3-dione (**11**)

To a mixture of sodium hydride (1.62 g, 40 mmol, 60% in mineral oil) and methyl 3-methoxypicolinate[20] (3.5 g, 20 mmol) in anhydrous DMF (20 mL) was added a solution of 4′-methoxyacetophenone (3.3 g, 22 mmol) via syringe. The reaction mixture was stirred overnight at room temperature, then a 10% aqueous solution of NaH_2SO_4 was used to adjust the pH to 7. The mixture was extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4), concentrated, and purified by column chromatography using 30% ethyl acetate in hexane to give the title compound (4.68 g, 80%), which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38–8.31 (m, 1H), 8.02–7.96 (m, 2H), 7.44–7.38 (m, 2H), 7.12 (s, 1H), 6.96 (d, J=8.99 Hz, 2H), 3.97 (s, 3H), 3.88 (s, 3H).

4.3.42. 2-(4-Hydroxyphenyl)-4H-pyrano[3,2-b]pyridin-4-one (**B20**)

The title compound was synthesized following general procedure A from crude **11** (0.83 g, 3.5 mmol). The title compound was isolated as a yellow crystalline solid (0.35 g, 50%); mp >310 °C (decomposition). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 (d, J=3.91 Hz, 1H), 8.25 (d, J=8.60 Hz, 1H), 7.98 (d, J=8.60 Hz, 2H), 7.83 (dd, J=8.60, 4.30 Hz, 1H), 7.03 (s, 1H), 6.95 (d, J=8.60 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.7, 163.1, 161.9, 153.8, 148.3, 139.7, 129.2, 129.0, 128.0, 121.7, 116.6, 107.8; MS (ES$^+$) m/z: 239.90. Anal. Calcd for $C_{14}H_9NO_4$ (239.23): C, 70.29; H, 3.79; N, 5.85. Found: C, 69.16; H, 3.83; N, 5.75.

4.3.43. 1-(4-Methoxyphenyl)-3-(3-methoxypyridin-4-yl)propane-1,3-dione (**12**)

To a mixture of methyl 3-fluoroisonicotinitate[21] (3.50 g, 22.7 mmol) and 4′-methoxyacetophenone (3.60 g, 24 mmol) in dry DMF (10 mL) under nitrogen was added sodium hydride (1.82 g, 60% in mineral oil). The reaction mixture was stirred for half hour then poured into an ammonium chloride solution and extracted with ethyl acetate. The organic layer was dried (Na_2SO_4), concentrated, and purified by column chromatography (ethyl acetate/hexane 1:3) to give the title compound (3.5 g, 54%), which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 8.40 (d, J=4.97 Hz, 1H), 7.97 (d, J=9.06 Hz, 2H), 7.77 (d, J=4.97 Hz, 1H), 7.11 (s, 1H), 6.99 (d, J=8.77 Hz, 2H), 4.08 (s, 3H), 3.89 (s, 3H).

4.3.44. 2-(4-Hydroxyphenyl)-4H-pyrano[2,3-c]pyridin-4-one (**B21**)

The title compound was synthesized following general procedure A from crude **12** (0.50 g, 1.8 mmol). The title compound was isolated as a yellow crystalline solid (0.36 g, 86%); mp 294–296 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.42 (br s, 1H), 9.16 (s, 1H), 8.62 (d, J=3.81 Hz, 1H), 7.97 (d, J=7.62 Hz, 2H), 7.85 (d, J=3.81 Hz, 1H), 7.08–6.85 (m, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 176.5, 164.4, 162.1, 151.7, 145.8, 142.9, 129.3, 128.5, 121.7, 117.7, 116.7, 106.4; MS (ES$^+$) m/z: 239.89. Anal. Calcd for $C_{14}H_9NO_4$ (239.23): C, 70.29; H, 3.79; N, 5.85. Found: C, 70.12; H, 3.78; N, 5.88.

4.3.45. 1-[4-(Benzyloxy)phenyl]-3-(4-methoxypyrimidin-5-yl)propane-1,3-dione (**13**)

To a solution of methyl 4-methoxypyrimidine-5-carboxylate[22] (0.41 g, 2.44 mmol) and 4′-benzyloxyacetophenone (0.58 g, 2.6 mmol) in anhydrous DMF (10 mL) was added sodium hydride (117 mg, 2.93 mmol, 60% suspension in mineral oil) in small portions. The reaction mixture was stirred at room temperature under nitrogen for 30 min, then at 80 °C for 3 h. The reaction mixture was cooled to room temperature and a saturated aqueous ammonium chloride solution (100 mL) was added. The mixture was extracted with ethyl acetate (2×100 mL). The combined organic layers were washed with water (100 mL), brine (100 mL), dried (Na_2SO_4), and concentrated. The crude product was purified by column chromatography (Silica Gel 230–400 mesh; 10–20% ethyl acetate in hexanes as eluent) to give the title compound as a yellow solid (0.45 g, 51%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.03 (s, 1H), 8.95 (s, 1H), 8.05 (d, J=8.97 Hz, 2H), 7.53–7.31 (m, 5H), 7.24–7.16 (m, 3H), 5.25 (s, 2H), 4.13 (s, 3H); MS (ES$^+$) m/z: 362.89 (M+1).

4.3.46. 7-(4-Hydroxyphenyl)-5H-pyrano[2,3-d]pyrimidin-5-one (**B22**)

The title compound was synthesized following general procedure A from crude **13** (0.415 g, 1.15 mmol). The title compound was isolated as a yellow crystalline solid (0.035 g, 13%); mp 311–313 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.50 (br s, 1H), 9.35 (s, 1H), 9.30 (s, 1H), 7.95 (d, J=8.95 Hz, 2H), 7.05 (s, 1H), 6.90 (d, J=8.95 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 177.1, 166.1, 164.4, 162.3, 161.8, 158.1, 129.4, 121.2, 116.8, 116.5, 107.6; MS (ES$^+$) m/z: 240.78 (M). Anal. Calcd for $C_{13}H_8N_2O_3$ (240.21): C, 65.00; H, 3.36; N, 11.66. Found: C, 64.24; H, 3.13; N, 11.13.

Supplementary data

NMR spectra for all final products are available. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.06.062.

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