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Cyclizations of phenylethyl-substituted pyridinecarboxaldehydes

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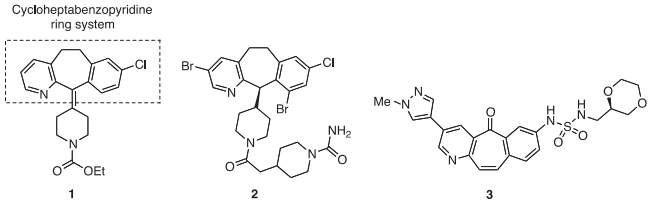
ABSTRACT

Several phenylethyl-substituted pyridinecarboxaldehydes were prepared from 2-bromo-3-pyridinecarboxaldehyde and these substances are found to undergo cyclization reactions in acidic media. In the absence of added nucleophile, acid-promoted cyclization and oxidation (MnO_2) provide an efficient route to 10,11-dihydro-5*H*-benzo[4,5]cyclohepta[1,2-*b*]pyridin-5-ones. Arene nucleophiles may also be added to the acidic mixture to provide good yields of triarylmethane products. Mechanisms are proposed involving dicationic superelectrophilic intermediates.

1. Introduction

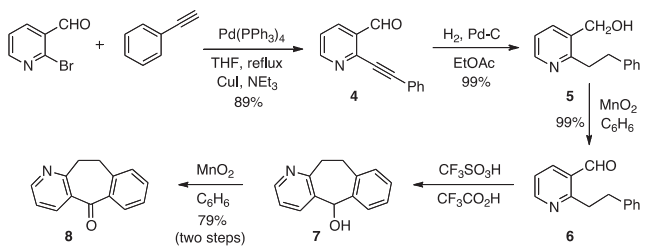
The cycloheptabenzopyridine ring system and related heterocyclic dibenzepinone analogs are useful building blocks for biologically active compounds.[1] Examples of these compounds include *loratadine* (**1**, H_1 histamine antagonist),[1h] SCH 66336 (**2**, anti-cancer agent),[2] and MK-2461 (**3**, anti-cancer agent; Scheme 1).[3] The cycloheptabenzopyridine ring system has been previously prepared by intramolecular cyclizations of carboxylic acids,[4] nitriles,[4b,5] alcohols,[6] ketones,[7] and by other routes.[8] For acid-promoted reactions of carboxylic acids, the cyclization requires extreme conditions (i.e., polyphosphoric acid, 200 °C).[4] Owing to the value of these products, new synthetic methods leading to the cycloheptabenzopyridine ring system are highly desirable. In the following manuscript, we describe the preparation of several phenylethyl-substituted pyridinecarboxaldehydes and their cyclization to cycloheptabenzopyridine products.



Scheme 1.

2. Results

Our approach to the cycloheptabenzopyridines began with the preparation of a suitable electrophilic precursor. We envisaged aldehydes to be particularly useful precursors, as pyridinecarboxaldehydes are known to form exceedingly reactive electrophiles in acidic media. Thus, the cycloheptabenzopyridines could be accessed by intramolecular reactions with a phenethyl group. Preparation of the phenethyl-substituted pyridinecarboxaldehydes was accomplished using readily available 2-bromo-3-pyridinecarboxaldehyde (Scheme 2). Sonogashira coupling provides good yields of the heterocyclic alkynes (i.e., **4**).[9] Although reduction of the triple bond was achieved in quantitative yield, it occurred with reduction of the carboxaldehyde group to give product **5**. Subsequent oxidation to the aldehyde is accomplished readily with MnO_2 providing the desired substrate **6**. We also attempted to



Scheme 2.

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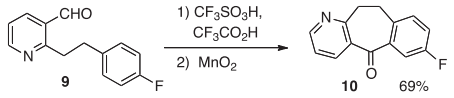
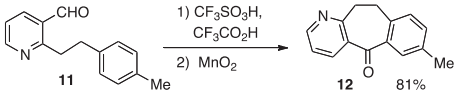
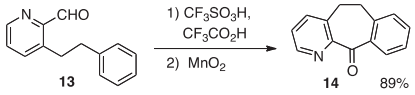
access compound **6** by a complimentary strategy using Pd-catalyzed coupling with styrene (Heck reaction). However, this method did not provide good yields of compound **6**. Cyclization was effected using a mixture of CF_3CO_2H/CF_3SO_3H (4:1 molar ratio) to give the cycloheptabenzopyridine alcohol **7**, which was subsequently oxidized to the heterocyclic ketone **8**. Neither CF_3CO_2H or CF_3SO_3H alone provides the desired alcohol (**7**). Triflic acid gives a complex mixture and trifluoroacetic acid gives only unreacted starting material. Using this approach, substituted ketones **10** and **12** were prepared in good yields from the corresponding aldehydes (Eqs. 1 and 2). Isomeric dihydrobenzocycloheptapyridinones may also be prepared, for example, cyclization of **13** provides ketone **14** in good yield (Eq. 3). Quinoline substrate **15** was also synthesized using Sonagashira coupling and reduction/oxidation, starting from 2-chloro-6-methoxy-3-quinolinecarboxaldehyde. Subsequent reaction with acid and then MnO_2 provides the tetracyclic ketone **16** (Eq. 4).



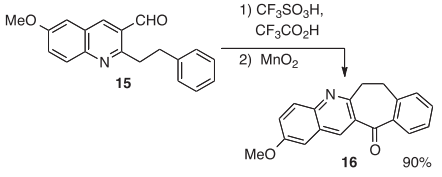
(1)



(2)



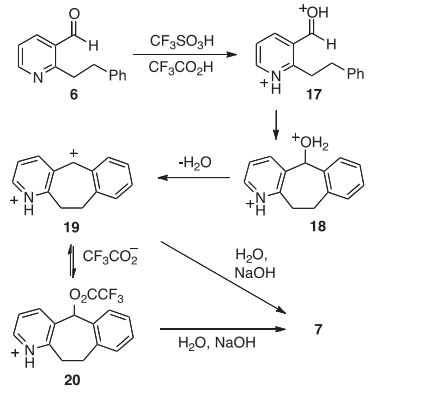
(3)



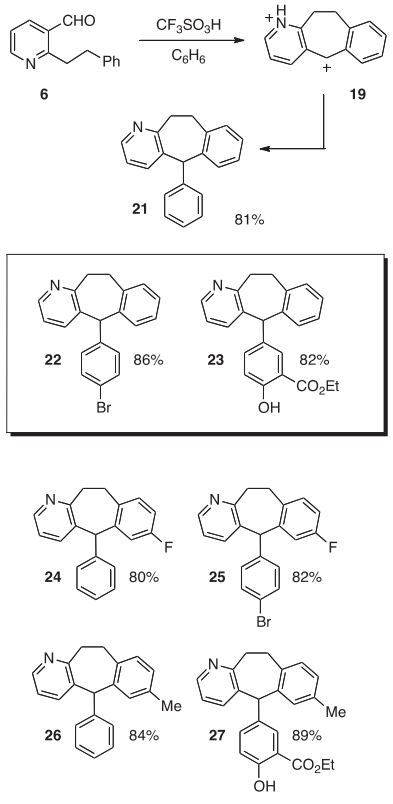
(4)

The key step in this transformation involves formation of dicationic intermediates in the strongly acidic media. The high electrophilic reactivities of dicationic electrophiles have been well documented[10] and pyridinecarboxaldehydes are known to form these types of superelectrophilic species.[11] For example, protonation at the pyridine ring and carbonyl group leads to formation of the superelectrophile **17** (Scheme 3). Upon cyclization, further steps presumably lead to the dicationic oxonium ion (**18**) and carbocation (**19**). With the formation of the carbocation **19**, final aqueous workup of the reaction gives the alcohol product **7**. The proposed mechanism may explain the need for the acid system, CF_3SO_3H/CF_3CO_2H. Trifluoroacetic acid alone is a rather weak acid (H_o −2.7), and thus, it cannot form the requisite superelectrophilic carboxonium ion (**17**). Triflic acid itself is a Brønsted superacid (H_o −14.1) and it should be capable of effecting this type of transformation.[12] Nevertheless, the triflic acid-promoted reactions are found to give complex mixtures of products—possibly due to intermolecular reactions (dimerizations, etc.) involving superelectrophiles **17** and **19**. According to Shudo's analysis of the CF_3SO_3H/CF_3CO_2H acid system,[13] our reaction conditions utilize a mixture having an estimated acidity of ca. H_o −10.8, less than CF_3SO_3H but significantly greater than CF_3CO_2H. This level of acidity enables the reactive dications to form. The results also suggest the trifluoroacetic acid serves the purpose of tempering the reactivity of the carbocation **19**. If the trifluoroacetic acid forms an adduct (i.e., **20**) with the superelectrophilic carbocation **19**, then the overall reactivity of the carbocation should be diminished. Thus, the trifluoroacetic acid would help to compose an 'electrophilic buffer system' in which the overall reactivity of the electrophile is decreased. Although the trifluoroacetate ester was not observed in the product mixture, it would likely hydrolyze during the aqueous workup (made basic with 10 M NaOH) and the alcohol (**7**) would be formed. NMR experiments—designed to detect **19** and **20**—were inconclusive.

We anticipated that ion **19** would be a fairly reactive electrophilic species. This can be seen in its reactions with arene nulceophiles (Scheme 4). When aldehyde **6** is reacted with benzene and triflic acid, the arylated product **21** is isolated in 81% yield. The functionalized cycloheptabenzopyridine (**21**) is the only major product. This result may be contrasted with the simple cyclization in triflic acid that leads to complex product mixtures. As a co-solvent, benzene should react rapidly with the formed



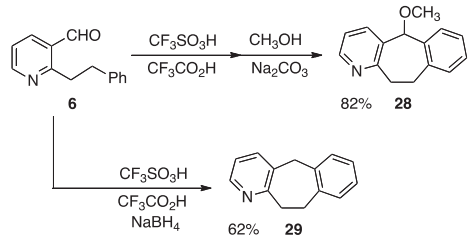
Scheme 3.



Scheme 4.

carbocation (**19**) and this prevents the undesirable side reactions. Two other arene nucleophiles were reacted with aldehyde **6** in superacid and the respective products (**22** and **23**) from bromobenzene and ethyl salicylate were also obtained in good yields. These conversions are accomplished with excellent regioselectivity (*ortho*/*para*, < 1:20). Aldehydes **9** and **11** likewise give condensation products (**24**–**27**) in good yields by reactions with arene nucleophiles and triflic acid.

In addition to arene nucleophiles, carbocation **19** may be trapped with alcohol or hydride nucleophiles. When compound **6** is reacted with CF_3SO_3H/CF_3CO_2H and the solution quenched with a mixture of methanol and Na_2CO_3, the ether product **28** is formed (Scheme 5). The same aldehyde reacts with $NaBH_4$ in CF_3SO_3H/CF_3CO_2H to provide the cycloheptabenzopyridine (**29**) as the exclusive product. Previous reports have described $NaBH_4$ reductions in the presence of neat CF_3SO_3H,[14] however, these reaction conditions only gave an intractable mixture from **6**.



Scheme 5.

3. Conclusion

In summary, we have found that pyridinecarboxaldehydes may be converted to 10,11-dihydro-5*H*-benzo[4,5]cyclohepta-[1,2-*b*] pyridin-5-ones and related cycloheptabenzopyridines. A mechanism is proposed involving reactive dicationic electrophiles. In the reactions leading to 10,11-dihydro-5*H*-benzo[4,5]cyclohepta[1,2-*b*] pyridin-5-ones, a mixture of CF_3CO_2H/CF_3SO_3H is found to work best. It is suggested that the trifluoroacetic acid serves to decrease the electrophilic reactivity of the system and this prevents undesirable oligomerization chemistry. Aryl-substituted cycloheptabenzopyridines are formed in good yields by cyclization of pyridinecarboxaldehydes followed by a Friedel–Crafts reaction with arene nucleophiles.

4. Experimental section

4.1. Materials and methods

Unless otherwise indicated, all reagents and chemical were obtained from commercial suppliers. The trifluoromethanesulfonic acid was distilled from an argon atmosphere prior to its use. All reactions were done in oven dried glassware with an inert atmosphere (Ar). High-resolution mass spectral analyses were done by an off-site analytical laboratory, while low-resolution mass spectra were obtained directly from a gas chromatography instrument equipped with a mass-selective detector.

4.2. Preparation of phenethyl-substituted heterocyclic aldehydes (6, 9, 11, 13, 15)

The respective alkynyl-substituted heterocycles (i.e., **4**) were prepared using a published procedure.[15] A solution is made up containing the heterocyclic alkyne substrate (500 mg, 2.41 mmol), 20 mL EtOAc, and 0.4 g 5% Pd on carbon. The mixture is placed in a 125 mL high-pressure bomb reactor and stirred under a H_2 atmosphere (200 psi, 2 h). The resulting solution is then filtered through Celite and concentrated by rotary evaporation. The crude alcohol (i.e., **5**; 1 mmol) is dissolved in benzene (10 mL) and manganese(IV) oxide (1.5 g, 17.3 mmol) is added. After stirring at room temperature for 12 h, the reaction mixture is filtered through Celite, and concentrated with a rotary evaporator. The resulting phenethyl-substituted heterocyclic aldehyde is sufficiently pure for subsequent reaction steps.

4.3. Preparation of 10,11-dihydro-5*H*-benzo[4,5]cyclohepta [1,2-*b*]pyridin-5-one (8) and related ketones

The *N*-heterocyclic aldehyde (i.e., **6**; 1 mmol) is dissolved in CF_3CO_2H (2 ml, 26 mmol) and then CF_3SO_3H (0.5 ml, 6 mmol) is added slowly. The reaction mixture is stirred for 2 h at 25 °C and subsequently poured over several grams of ice. The resulting solution is then made basic by addition of NaOH (10 M) and the aqueous mixture is extracted twice with chloroform. The organic extract or phase is then washed with water followed by saturated brine (2×). The solution is dried with $MgSO_4$, filtered, and concentrated with a rotary evaporator. The crude product (i.e., **7**) is dissolved in benzene (10 mL) and manganese(IV) oxide (1.5 g, 17 mmol) is added to the solution. Following a reaction period of 12 h at 25 °C, the mixture is filtered through Celite and concentrated with a rotary evaporator. The product is then purified by silica gel chromatography (hexane/ethyl acetate).

4.4. 2-Phenethyl-3-pyridinecarboxaldehyde (6)

Isolated as a yellow crystal (R_f 0.43, 3:2 hexanes/ethyl acetate). Mp 46–47 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.05–3.10 (m, 2H), 3.49–3.54 (m, 2H), 7.19–7.23 (m, 3H), 7.26–7.29 (m, 2H), 7.35 (dd, J=7.8, 4.8 Hz, 1H), 8.10 (dd, J=7.8, 1.9 Hz, 1H), 8.77 (dd, J=4.8, 1.7 Hz, 1H) 10.15 (s, 1H); ^{13}C NMR: δ 36.2, 62.9, 121.9, 126.3, 128.5, 128.6, 129.5, 138.0, 140.8, 153.5, 163.1, 190.7. Low-resolution mass spectrum (EI): 211 (M^+), 210, 182, 167, 91. High-resolution mass spectrum, $C_{14}H_{13}ON$, calcd 211.9972, found 211.10002.

4.5. 10,11-Dihydro-5*H*-benzo[4,5]cyclohepta[1,2-*b*]pyridin-5-one (8)

Isolated as a pale yellow crystal (R_f 0.33, 3:2 hexanes/ethyl acetate). Mp 50–52 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.23–3.27 (m, 2H), 3.46–3.50 (m, 2H), 7.26–7.39 (m, 3H), 7.49 (dt, J=7.4, 1.5 Hz, 1H), 7.94 (dd, J=7.8, 1.4 Hz, 1H), 8.41 (dd, J=7.9, 1.6 Hz, 1H), 8.65 (dd, J=4.7, 1.8 Hz, 1H); ^{13}C NMR: δ 33.0, 38.4, 121.9, 126.9, 129.0, 130.4, 132.9, 133.3, 138.3, 139.0, 141.5, 152.2, 161.7, 193.7. Low-resolution mass spectrum (EI): 209 (M^+), 208, 181, 180, 152, 90. High-resolution mass spectrum, $C_{14}H_{11}ON$, calcd 209.08407, found 209.08504.

4.6. 2-(4-Fluorophenethyl)-3-pyridinecarboxaldehyde (9)

Isolated as a yellow crystal (R_f 0.41, 3:2 hexanes/ethyl acetate). Mp 45–46 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.97–3.03 (m, 2H), 3.43–3.48 (m, 2H), 6.87–6.95 (m, 2H), 7.08–7.14 (m, 2H), 7.31 (dd, J=7.8, 4.8 Hz, 1H) 8.05 (dd, J=7.8, 1.9 Hz, 1H), 8.71 (dd, J=4.8, 1.8 Hz, 1H), 10.12 (s, 1H); ^{13}C NMR: δ 35.1, 37.0, 115.2 (d, J_{C-F}=20.9 Hz), 121.9, 129.4, 129.9 (d, J_{C-F}=7.9 Hz), 136.6 (d, J_{C-F}=3.2 Hz), 1386, 153.4, 159.8, 161.4 (d, J_{C-F}=242.5 Hz), 162.7, 190.8. Low-resolution mass spectrum (EI): 229 (M^+), 212, 200, 109. High-resolution mass spectrum, $C_{14}H_{12}FON$, calcd 229.09029, found 229.09072.

4.7. 7-Fluoro-10,11-dihydro-5*H*-benzo[4,5]cyclohepta[1,2-*b*] pyridin-5-one (10)

Isolated as a yellow oil (R_f 0.31, 3:2 hexanes/ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.19–3.23 (m, 2H), 3.43–3.46 (m, 2H), 7.16 (td, J=7.9, 2.8 Hz, 1H), 7.22–7.28 (m, 1H), 7.32 (dd, J=8.0, 4.7 Hz, 1H), 7.64 (dd, J=9.6, 2.8 Hz, 1H), 8.40 (dd, J=8.0, 1.8 Hz, 1H), 8.65 (dd, J=4.7, 1.8 Hz, 1H); ^{13}C NMR: δ 32.3, 38.4, 116.9 (d, J_{C-F}=22.9hz), 119.8 (d, J_{C-F}=21.3 Hz), 122.0, 131.0 (d, J_{C-F}=7.2 Hz), 132.7, 137.5 (d, J_{C-F}=3.2 Hz), 139.2, 139.6 (d, J_{C-F}=6.4 Hz), 152.4, 161.6 (d, J_{C-F}=244.4 Hz), 161.6, 192.1. Low-resolution mass spectrum (EI): 227 (M^+), 226, 199, 198, 170. High-resolution mass spectrum, $C_{14}H_{10}FON$, calcd 227.07464, found 227.07547.

4.8. 2-(4-Methylphenethyl)-3-pyridinecarboxaldehyde (11)

Isolated as a colorless oil (R_f 0.43, 3:2 hexanes/ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.32 (s, 3H), 3.00–3.06 (m, 2H), 3.46–3.51 (m, 2H), 7.09 (s, 3H), 7.33 (dd, J=7.8, 4.8 Hz, 1H), 8.09 (dd, J=7.8, 1.9 Hz, 1H), 8.76 (dd, J=4.9, 1.9 Hz, 1H), 10.14 (s, 1H); ^{13}C NMR: δ 21.0, 35.8, 37.0, 121.9, 128.4, 129.2, 129.4, 135.7, 137.7, 137.9, 153.5, 136.2, 190.7. Low-resolution mass spectrum (EI): 225 (M^+), 197, 196, 181, 105. High-resolution mass spectrum, $C_{15}H_{15}ON$, calcd 225.11537, found 225.11628.

4.9. 7-Methyl-10,11-dihydro-5*H*-benzo[4,5]cyclohepta[1,2-*b*] pyridin-5-one (12)

Isolated as a pale yellow oil (R_f 0.33, 3:2 hexanes/ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.35 (s, 3H), 3.15–3.19 (m, 2H), 3.40–3.43 (m, 2H), 7.13 (d, J=7.7 Hz, 1H), 8.61 (dd, J=4.7, 1.8 Hz, 1H); ^{13}C NMR: δ 20.8, 32.6, 38.5, 121.8, 129.1, 130.7, 133.3, 133.7, 136.5, 138.0, 138.7, 138.9, 152.1, 161.6, 193.8. Low-resolution mass spectrum (EI): 223 (M^+), 222, 208, 194, 180, 152. High-resolution mass spectrum, $C_{15}H_{13}ON$, calcd 223.09972, found 223.09911.

4.10. 3-Phenethyl-2-pyridinecarboxaldehyde (13)

Isolated as a pale yellow oil (R_f 0.41, 3:2 hexanes/ethyl acetate). Mp 46–47 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.87–2.93 (m, 2H), 3.33–3.38 (m, 2H), 7.18–7.23 (m, 3H), 7.27–7.31 (m, 1H), 7.35 (dd, J=7.8, 4.5 Hz, 1H), 7.51 (d, J=7.8 Hz, 1H), 8.68 (dd, J=4.8, 1.5 Hz, 1H), 10.21 (s, 1H). ^{13}C NMR: δ 34.0, 37.0, 126.2, 126.7, 128.4, 128.6, 139.4, 139.5, 141.0, 147.9, 149.8, 195.2. Low-resolution mass spectrum (EI): 211 (M^+), 194, 183, 182, 120, 91.

4.11. 6-Methoxy-2-phenethylquinoline-3-carboxaldehyde (15)

Isolated as a pale yellow crystal (R_f 0.32, 3:2 hexanes/ethyl acetate). Mp 74–76 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.32–3.35 (m, 2H), 3.56–3.60 (m, 2H), 3.94 (s, 3H), 7.17 (d, J=2.4 Hz, 1H), 7.29 (d, J=8.4 Hz, 1H), 7.35–7.52 (m, 3H), 7.96 (d, J=9 Hz, 1H), 8.10 (d, J=7.8 Hz, 1H), 8.78 (s, 1H). ^{13}C NMR: δ 33.5, 38.5, 55.6, 105.9, 125.1, 126.9, 127.6, 129.6, 129.6, 130.9, 135.4, 133.0, 137.5, 139.4, 142.4, 144.9, 157.6, 157.8, 193.4. Low-resolution mass spectrum (EI): 291 (M^+), 263, 262, 247, 219, 91.

4.12. 6-Methoxy-6*H*-benzo[4,5]cyclohepta[1,2-*b*]quinolin-12(7*H*)-one (16)

Isolated as a pale yellow crystal (R_f 0.32, 3:2 hexanes/ethyl acetate). Mp 74–76 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.32–3.35 (m, 2H), 3.56–3.60 (m, 2H), 3.94 (s, 3H), 7.17 (d, J=2.4 Hz, 1H), 7.29 (d, J=8.4 Hz, 1H), 7.35–7.52 (m, 3H), 7.96 (d, J=9 Hz, 1H), 8.10 (d, J=7.8 Hz, 1H), 8.78 (s, 1H); ^{13}C NMR: δ 33.5, 38.5, 55.6, 105.9, 125.1, 126.9, 127.6, 129.6, 129.6, 130.9, 135.4, 133.0, 137.5, 139.4, 142.4, 144.9, 157.6, 157.8, 193.4. Low-resolution mass spectrum (EI): 289 (M^+), 288, 274, 260, 246, 217, 108.

4.13. 5-Phenyl-10,11-dihydro-5*H*-benzo[4,5]cyclohepta[1,2-*b*] pyridine (21)

Isolated as a brown crystal (R_f 0.43, 3:2 hexanes/ethyl acetate) MP 107–109 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.70–2.77 (m, 1H), 3.08 (dd, J=23.2, 11.3 Hz, 2H), 3.33–3.40 (m, 1H), 5.22 (s, 1H), 6.89–6.92 (m, 2H), 7.14–7.32 (m, 7H), 7.38–7.41 (m, 1H) 7.61 (dd, J=7.6, 1.3 Hz, 1H) 8.53 (d, J=3.8 Hz, 1H); ^{13}C NMR: δ 30.4, 36.2, 56.9, 121.3, 126.1, 126.4, 127.2, 127.9, 128.3, 130.5, 130.9, 135.0, 139.7, 140.0, 140.5, 144.3, 148.0, 159.5. Low-resolution mass spectrum (EI): 271 (M^+), 270, 256, 194, 193, 180. High-resolution mass spectrum, $C_{14}H_{11}ON$, calcd 271.13610, found 271.13625.

4.14. 5-(4-Bromophenyl)-10,11-dihydro-5*H*-benzo[4,5]cyclohepta[1,2-*b*]pyridine (22)

Isolated as a pale yellow crystal (R_f 0.42, 3:2 hexanes/ethyl acetate). Mp 89–90 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.68–2.78 (m, 1H), 2.96–3.11 (m, 2H), 3.26–3.36 (m, 1H), 5.11 (s, 1H), 6.74 (d, J=8.1 Hz, 2H), 7.14–7.35 (m, 7H), 7.58 (d, J=7.6 Hz, 1H), 8.50–8.52 (m, 1H); ^{13}C NMR: δ 30.4, 36.2, 56.4, 120.2, 121.3, 126.5, 128.1, 128.9, 130.6, 130.8, 131.3, 134.4, 139.6, 139.9, 13.9, 143.4, 148.2, 159.4. Low-resolution mass spectrum (EI): 351/349 (M^+), 336/334, 270, 194, 193, 180, 127. High-resolution mass spectrum, $C_{14}H_{11}ON$, calcd 349.04660, found 349.04740.

4.15. Ethyl 5-(10,11-dihydro-5*H*-benzo[4,5]cyclohepta[1,2-*b*] pyridin-5-yl)-2-hydroxybenzoate (23)

Isolated as a pale yellow crystal (R_f 0.3, 3:2 hexanes/ethyl acetate). Mp 131–132 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (t, J=7.1 Hz, 3H), 2.70–2.77 (m, 1H), 3.00–3.12 (m, 2H), 3.30–3.38 (m, 1H), 4.30 (q, J=7.1 Hz, 2H), 5.11 (s, 1H), 6.84 (d, J=8.7 Hz, 1H), 6.98 (ddd, J=6.3, 1.8, 0.6 Hz, 1H), 7.15–7.37 (m, 6H), 7.59 (dd, J=7.8, 1.6 Hz, 1H), 8.51 (dd, J=4.8, 1.6 Hz, 1H), 7.15–7.37 (m, 6H), 7.59 (dd, J=7.7, 1.6 Hz, 1H), 8.51 (dd, J=4.8, 1.6 Hz, 1H), 10.72 (s, 1H); ^{13}C NMR: δ 14.0, 30.4, 36.2, 56.0, 61.4, 112.1, 117.4, 121.3, 126.5, 128.0, 128.1, 130.5, 130.7, 134.2, 134.6, 135.1, 139.1, 139.9, 140.0, 148.0, 159.4, 160.0, 170.0. Low-resolution mass spectrum (EI): 359 (M^+), 256, 193, 180. High-resolution mass spectrum, $C_{23}H_{21}O_3N$, calcd 359.15215, found 359.15300.

4.16. 7-Fluoro-5-phenyl-10,11-dihydro-5*H*-benzo[4,5]cyclohepta [1,2-*b*]pyridine (24)

Isolated as a yellow oil (R_f 0.31, 3:2 hexanes/ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.19–3.23 (m, 2H), 3.43–3.46 (m, 2H), 7.16 (td, J=7.9, 2.8 Hz, 1H), 7.22–7.28 (m, 1H), 7.32 (dd, J=8.0, 4.7 Hz, 1H), 7.64 (dd, J=9.6, 2.8 Hz, 1H), 8.40 (dd, J=8.0, 1.8 Hz, 1H), 8.65 (dd, J=4.7, 1.8 Hz, 1H); ^{13}C NMR: δ 32.3, 38.4, 116.9 (d, J_{C-F}=22.9hz), 119.8 (d, J_{C-F}=21.3 Hz), 122.0, 131.0 (d, J_{C-F}=7.2 Hz), 132.7, 137.5 (d, J_{C-F}=3.2 Hz), 139.2, 139.6 (d, J_{C-F}=6.4 Hz), 152.4, 161.6 (d, J_{C-F}=244.4 Hz), 161.6, 192.1. Low-resolution mass spectrum (EI): 289 (M^+), 288, 274, 212, 211, 198, 183. High-resolution mass spectrum, $C_{20}H_{15}NF$, calcd 288.11885, found 288.11937.

4.17. 5-(4-Bromophenyl)-7-fluoro-10,11-dihydro-5*H*-benzo[4,5] cyclohepta[1,2-*b*]pyridine (25)

Isolated as a yellow oil (R_f 0.41, 3:2 hexanes/ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.64–2.74 (m, 1H), 2.90–3.08 (m, 2H), 3.26–3.33 (m, 1H), 5.04 (s, 1H), 6.73 (d, J=8.3 Hz, 2H), 6.95 (td, J=8.3, 2.5 Hz, 1H), 7.06–7.19 (m, 3H), 7.33 (d, J=8.4 Hz, 2H), 7.56 (d,

J=7.5 Hz, 1H), 8.52 (s, 1H); ^{13}C NMR: δ 29.6, 36.1, 56.1, 114.5(d, J_{C-F}=20.2 Hz), 117.4 (d, J_{C-F}=21.7 Hz), 120.4, 121.5, 128.9, 131.4, 131.9 (d, J_{C-F}=8.2 Hz), 133.8, 135.5 (d, J_{C-F}=3.7 Hz), 139.7, 141.8 (d, J_{C-F}=6.7 Hz), 142.7, 148.4, 159.2, 161.2 (d, J_{C-F}=243.7 Hz). Low-resolution mass spectrum (EI): 369/367 (M^+), 354/352, 288, 272, 212, 211, 198. High-resolution mass spectrum, $C_{20}H_{15}BrFN$, calcd 367.03718, found 367.03680.

4.18. 7-Methyl-5-phenyl-10,11-dihydro-5*H*-benzo[4,5]cyclohepta[1,2-*b*]pyridine (26)

Isolated as a brown oil (R_f 0.44, 3:2 hexanes/ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.41 (s, 3H), 2.67–2.76 (m, 1H), 3.00–3.13 (m, 2H), 3.30–3.40 (m, 1H), 5.18 (s, 1H), 6.93 (d, J=6.9 Hz, 2H), 7.12–7.28 (m, 6H), 7.40 (s, 1H), 7.61 (d, J=7.3 Hz, 1H), 8.52 (d, J=3.4 Hz, 1H). ^{13}C NMR: δ 21.0, 30.0, 36.3, 56.9, 121.2, 126.1, 127.2, 128.3, 128.4, 128.5, 130.5, 131.7, 135.1, 135.9, 136.9, 139.6, 140.2, 144.4, 147.9, 159.7. Low-resolution mass spectrum (EI): 285 (M^+), 270, 254, 208, 207, 194, 193. High-resolution mass spectrum, $C_{21}H_{19}N$, calcd 285.15175, found 285.15260.

4.19. Ethyl 2-hydroxy-5-(7-methyl-10,11-dihydro-5*H*-benzo[4,5]cyclohepta[1,2-*b*]pyridin-5-yl)benzoate (27)

Isolated as a pale yellow crystal (R_f 0.3, 3:2 hexanes/ethyl acetate). Mp 121–122 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 (t, J=7.1 Hz, 3H), 2.37 (s, 3H), 2.66–2.76 (m, 1H), 2.96–3.09 (m 2H), 3.26–3.36 (m, 1H), 4.30 (q, J=7.1 Hz, 2H), 5.05 (s, 1H), 6.84 (d, J=8.7 Hz, 1H), 6.98–7.02 (m, 1H), 7.09 (s, 2H), 7.13–7.17 (m, 2H), 7.29 (dd, J=2.3, 1.1 Hz, 1H), 7.58 (dd, J=7.7, 1.6 Hz, 1H), 8.50 (dd, J=4.8, 1.7 Hz, 1H), 10.73 (s, 1H); ^{13}C NMR: δ 14.0, 20.9, 30.0, 36.3, 56.0, 61.4, 112.1, 117.4, 121.2, 128.0, 128.5, 130.5, 131.5, 134.3, 134.8, 135.1, 136.0, 136.7, 139.4, 139.7, 148.0, 159.5, 160.0, 170.0. Low-resolution mass spectrum (EI): 373 (M^+), 328, 312, 207, 192, 163. High-resolution mass spectrum, $C_{24}H_{23}O_3N$, calcd 373.16780, found 373.16863.

4.20. 5-Methoxy-10,11-dihydro-5*H*-benzo[4,5]cyclohepta[1,2-*b*]pyridine (28)

Isolated as a pale yellow oil (R_f 0.25, 3:2 hexanes/ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.05–3.14 (m, 1H), 3.24–3.34 (m, 1H), 3.40 (s, 3H), 3.49–3.63 (m, 2H), 5.29 (s, 1H), 7.11 (dd, J=7.8, 4.8 Hz, 1H), 7.18–7.28 (m, 3H), 7.35 (d, J=7.2 Hz, 1H), 7.74 (dd, J=7.6, 1.2 Hz, 1H), 8.45 (d, J=3.6 Hz, 1H); ^{13}C NMR: δ 30.1, 36.2, 57.1, 84.6, 121.1, 126.2, 127.4, 128.5, 129.7, 134.2, 136.5, 138.3, 139.3, 148.3, 158.5. Low-resolution mass spectrum (EI): 225 (M+), 224, 210, 194, 193, 180, 165, 152.

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