A high yielding oxidation method for the preparation of substituted 2,3-dihydro-4-pyridones from 4-piperidones

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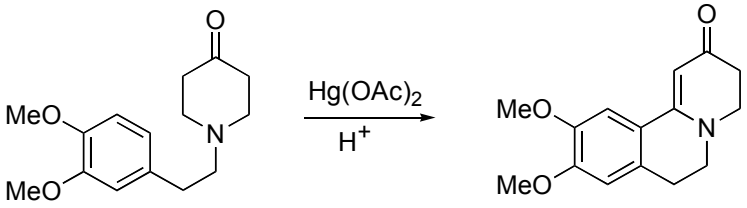
Dedicated to Henk Van der Plas on the occasion of his 80th anniversary

Abstract

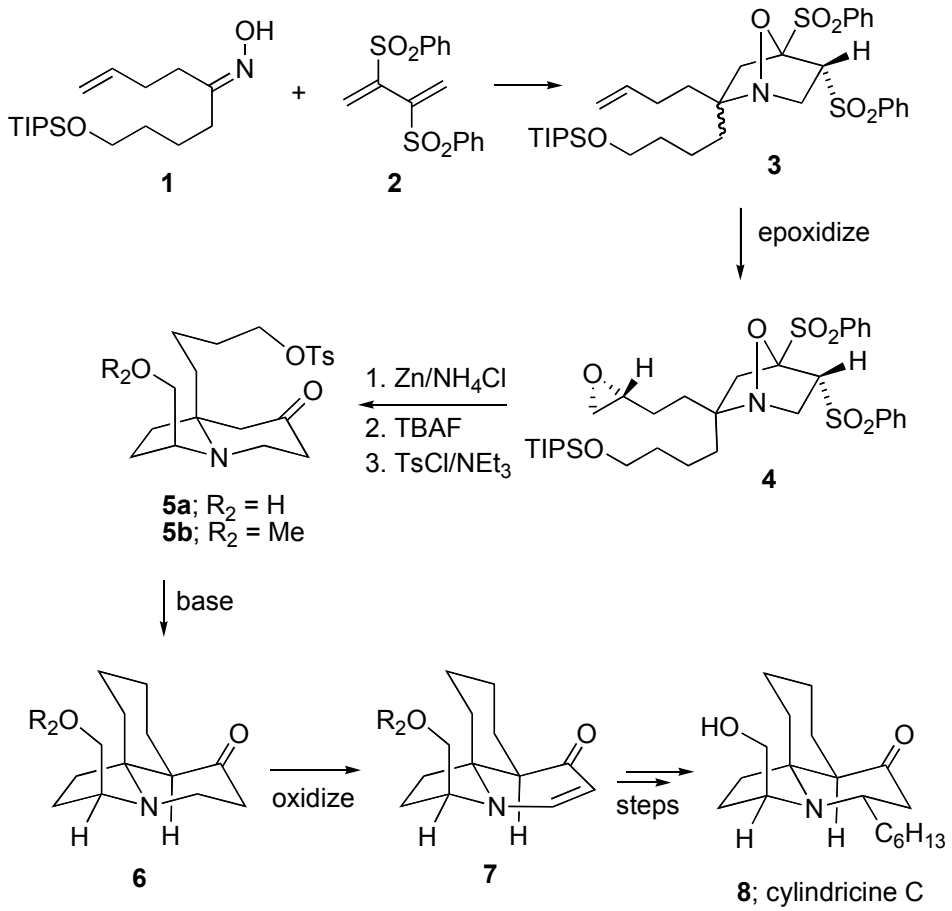


N-Alkyl substituted 4-piperidones readily undergo oxidation in high yield upon reaction with mercuric acetate. Application of the oxidation to the synthesis of the skeletal framework of several alkaloids is described.

Keywords: Mercuric acetate, oxidation, piperidone, dihydropyridone, acid, cyclization

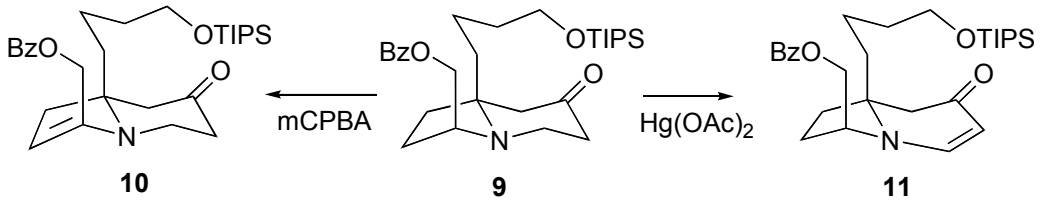
Introduction

We recently reported on the total synthesis of the marine alkaloid cylindricine C (**8**) using a conjugate addition-dipolar cycloaddition cascade of 9-triisopropylsilanyloxy-non-1-en-5-one oxime (**1**) with 2,3-*bis*(phenylsulfonyl)-1,3-butadiene (**2**) as the key strategic element.[1] The cascade sequence proceeds by an initial conjugate addition of the oxime onto the activated diene followed by a proton transfer to create a transient nitrone that then undergoes a 1,3-dipolar cycloaddition with the tethered vinyl sulfone.[2] The resulting cycloadduct **3** was eventually converted into cylindricine C (**8**) by: (1) a reductive-cyclization cascade to set the BC-ring skeleton (*i.e.* **4**→**5**), (2) a base-induced cyclization to construct the tricyclic core (*i.e.* **5**→**6**), and (3) an oxidation-conjugate addition of the *n*-hexyl side chain (*i.e.* **6**→**8**) as indicated in Scheme 1.



Scheme 1

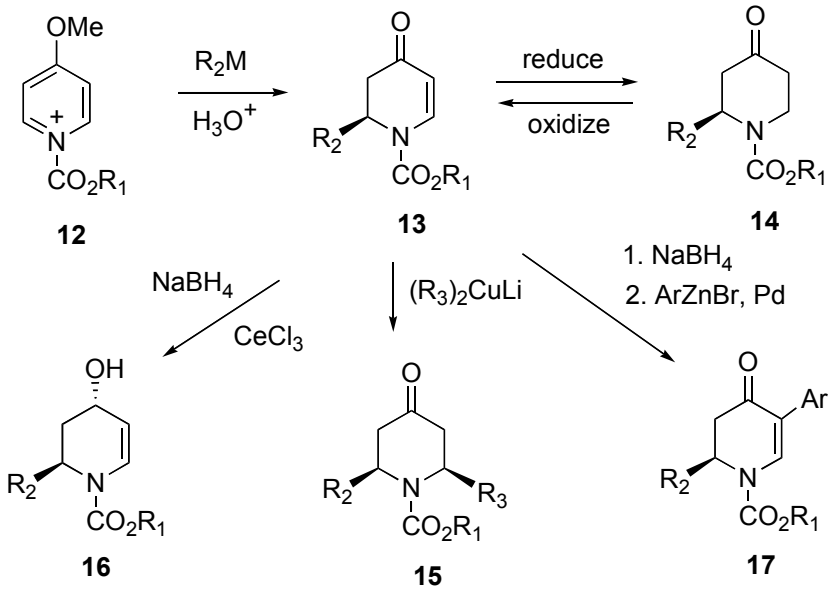
During the course of this study we came to realize that the oxidation of 4-piperidone **6** to the corresponding 2,3-dihydro-4-pyridone **7** was not a trivial transformation. A variety of standard oxidizing agents such as IBX, CAN and $PhSeCl/NaIO_4$ were examined but all failed to produce the dihydropyridone required for the subsequent conjugate addition step. We did have some limited success with the oxidation of 4-piperidone **9** when Polonovski conditions were utilized. Thus, the reaction of **9** with *m*CPBA, trifluoroacetic anhydride and triethyl amine in CH_2Cl_2 brought about an overall oxidation. However, the product isolated in 90% yield corresponded to the undesired enamine **10**. Most interestingly, when mercuric acetate was used as the oxidant,[3] the isomeric 2,3-dihydro-4-pyridone **11** was formed in 95% yield and no signs of **10** could be detected in the crude reaction mixture.



Scheme 2

Since 2,3-dihydro-4-pyridones are important synthetic intermediates,[4] we became interested in developing a method for their synthesis by oxidizing the related 4-piperidone system. The presence of the vinylogous amide in the six-membered azaheterocycle facilitates the introduction of other substituents onto the piperidine ring in a regio and stereocontrolled manner.[5] Due to $A^{1,3}$ strain,[6] the C_2 group of the dihydropyridone **13** is forced into a pseudoaxial position providing a conformational bias in the molecule. This effect allows for control of the stereoselectivity of 1,2- and 1,4-addition to the enone moiety, C_3 enolate alkylation, Luche reduction of the C_4 carbonyl and intramolecular radical cyclization.[7,8] The C_5 position can also be halogenated using NBS and a subsequent palladium-mediated coupling provides various 5-substituted derivatives (Scheme 3).[9] A widely used method for the synthesis of the dihydropyridone system involves the reaction of carbon nucleophiles with various 1-acylpyridinium salts (**12**).[4,10] Because of the abundance of piperidine-containing natural products,[11] this method has been extensively utilized by Comins and coworkers for the asymmetric synthesis of many quinolizidine, indolizidine and perhydroquinoline alkaloids.[7]

Another approach that has been occasionally employed for the preparation of 2,3-dihydro-4-pyridones consists of an oxidation of the related 4-piperidone system (*i.e.*, **14**→**13**).[12] 4-Piperidones are readily available from the Dieckmann cyclization of aminodicarboxylate esters or by the condensation of carbonyl compounds with ammonia *via* a Mannich reaction.[13,14] One general problem associated with this method is that the oxidation only works well when an electron withdrawing group is attached to the nitrogen atom. In addition, the reaction frequently leads to a mixture of 2,3-dihydro-4-pyridone isomers. Oxidation of *N*-acylated 4-piperidones are typically effected by using $PhSeCl/H_2O_2$, Saegusa or IBX methods (carbonyl directed dehydrative protocols).[12] In contrast, the few reported examples of oxidation of *N*-alkyl substituted 4-piperidones almost always involve the use of a peracid induced Polonovski reaction[15] and generally results in meager yields of the corresponding vinylogous amide. Thus, a high yielding oxidation method for the preparation of substituted 2,3-dihydro-4-pyridones from 4-piperidones would be an advance in the area of heterocyclic synthesis.

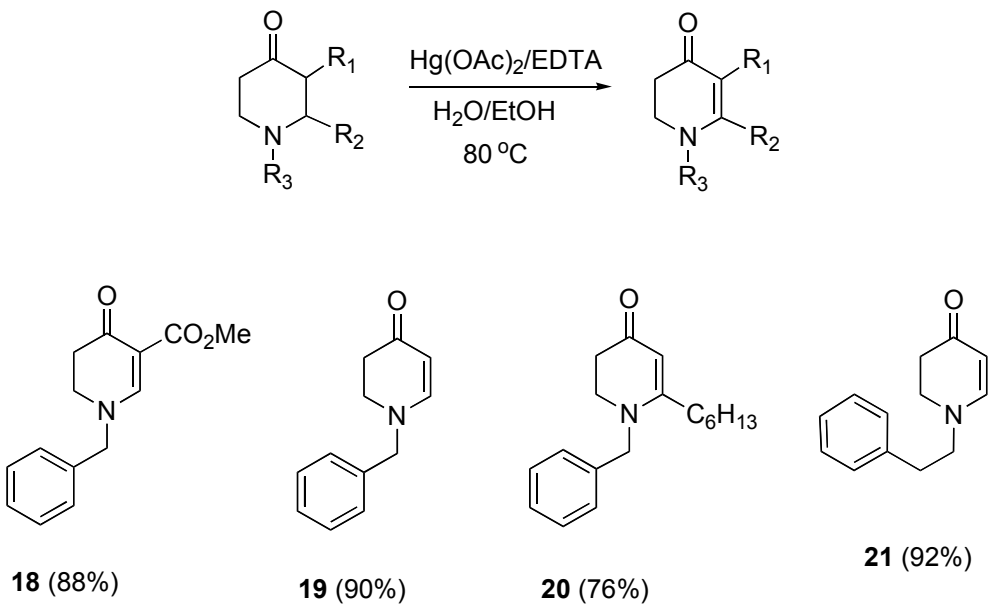


Scheme 3

Results and Discussion

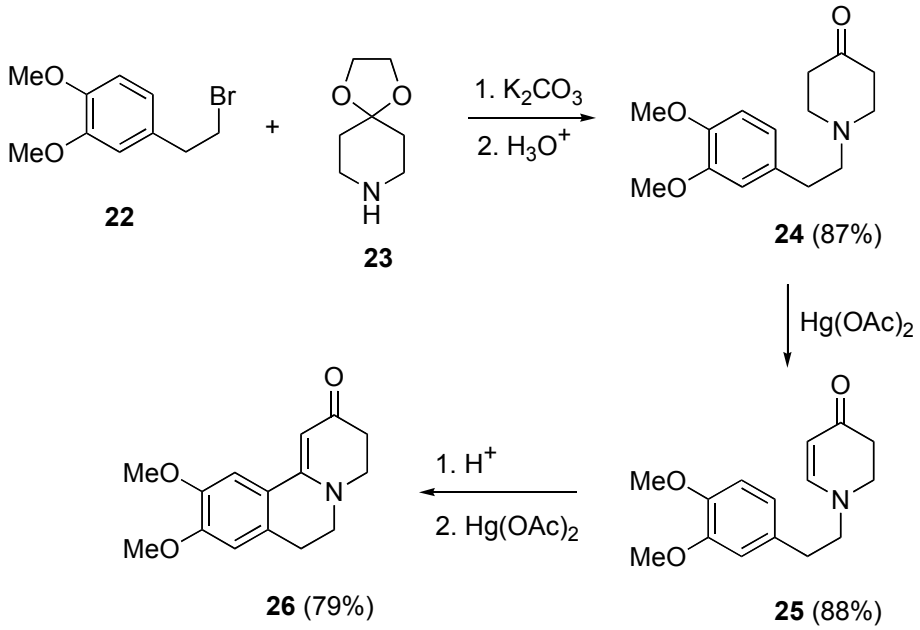
The ubiquity and utility of the dihydropyridone system coupled with the difficulties that are associated with the oxidation of *N*-alkyl substituted 4-piperidones suggested a more detailed investigation. The earlier success of the mercuric acetate oxidation of piperidines by Leonard and coworkers[3] led us to test the utility of this oxidizing agent with various 4-piperidones. Scheme 4 outlines several 2,3-dihydro-4-pyridones that were prepared in good yield from the corresponding *N*-alkyl 4-piperidone precursor using mercuric acetate conditions. It should be noted that only the more substituted dihydropyridone (*i.e.*, **18** and **20**) was obtained from the oxidation thereby indicating a distinct preference for the formation of the thermodynamically most stable product.

We then conducted a brief exploration of the synthetic utility of the reaction to create the skeletal framework of various alkaloids. Reaction of the known bromide **22** with 1,4-dioxa-8-azaspiro[4.5]decane (**23**) in the presence of K_2CO_3 followed by a subsequent hydrolysis of the ketal provided 4-piperidone **24** in 87% yield. Mercuric acetate oxidation of **24** gave **25** in 88% yield. Treatment of **25** with 10% H_2SO_4 at 90 °C induced initial enamide protonation and this was followed by a Pictet-Spengler cyclization. A subsequent mercuric acetate oxidation of the cyclized 4-piperidone intermediate afforded dihydropyridone **26** in 79% yield for the two-step sequence (Scheme 5). Of interest is the fact that only the more heavily substituted enamide **26** was formed in the final oxidation step.



18 (88%) **19** (90%) **20** (76%) **21** (92%)

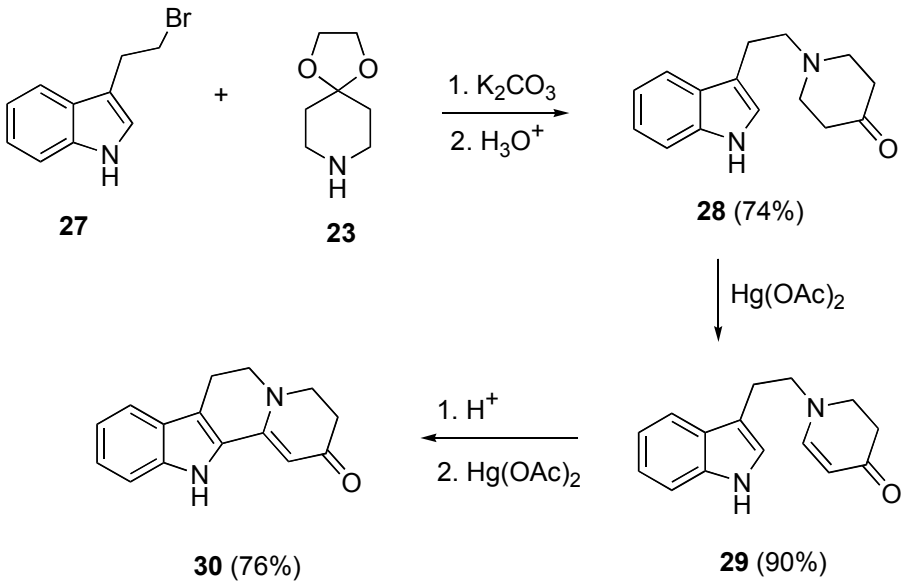
Scheme 4



Scheme 5

We also investigated a similar approach to the core skeleton of the yohimbenone framework. Reaction of 3-(2-bromoethyl)-1*H*-indole (**27**) with 1,4-dioxa-8-azaspiro[4.5]decane (**23**) followed by ketal hydrolysis furnished 4-piperidone **28** in 74% yield. Treatment of **28** with mercuric acetate provided a 90% yield of the corresponding dihydropyridone **29**. This heterocycle represents a useful intermediate for alkaloid synthesis, as is shown by its sequential

acid cyclization/mercuric acetate oxidation to give tetrahydroindolo[2,3-*a*]quinolizinone **30** in 76% yield for the two-step sequence (Scheme 6).



27 **23** **28** (74%) **29** (90%) **30** (76%)

Scheme 6

In summary, we have demonstrated that *N*-alkyl substituted 4-piperidones readily undergo oxidation in high yield upon reaction with mercuric acetate. The resulting 2,3-dihydro-4-pyridones represent useful synthetic intermediates for a host of reactions. Studies concerning the application of the mercuric acetate oxidation to various 4-piperidones prepared by a conjugate addition/dipolar cycloaddition cascade of oximes with 2,3-*bis*(phenylsulfonyl)-1,3-butadiene are in progress and will be reported in due course.

Experimental Section

General procedure for the oxidation of N-alkyl-4-piperidones using mercuric acetate

1-Benzyl-4-oxo-1,4,5,6-tetrahydro-pyridine-3-carboxylic acid methyl ester (18). To a round bottom flask charged with 250 mg (88 mmol) of 1-benzyl-4-oxo-3-piperidine carboxylate was sequentially added 30 mL of a solution of H_2O/EtOH (2:1), 295 mg (92 mmol) of $Hg(OAc)_2$, and 344 mg (92 mmol) of EDTA. The mixture was heated to 80 ^oC for 2 h, cooled to rt and filtered through a pad of Celite. The filtrate was then partitioned between CH_2Cl_2 and aqueous NH_4Cl. The organic layer was extracted with CH_2Cl_2, washed with water, brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give 191 mg (88%) of **18** as a colorless oil which required no further purification: IR (CH_2Cl_2) 1719, 1658, 1601, 1436, 1337, 1155, and 1054 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 2.56 (t, 2H, J = 7.2 Hz), 3.52 (t, 2H,

J = 7.2 Hz), 3.84 (s, 3H), 4.62 (s, 2H), 7.34 (t, 2H, *J* = 6.6 Hz), 7.43-7.48 (m, 3H), 8.41 (s, 1H); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 36.1, 46.3, 51.7, 61.3, 100.5, 128.0, 129.2, 129.5, 134.2, 160.0, 166.4, and 186.6; HRMS Calcd. for [$C_{14}H_{15}NO_3$+ H^+]: 246.1052. Found: 246.1125.

1-Benzyl-2,3-dihydro-1*H*-pyridin-4-one (19) was prepared using the general mercuric acetate oxidation conditions in 90% yield as a pale yellow oil; IR (CH_2Cl_2) 2923, 1716, 1634, 1584, and 1180 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 2.45 (t, *J* = 8.0 Hz, 2H), 3.38 (t, *J* = 8.0 Hz, 2H), 4.36, (s, 2H), 4.99 (d, *J* = 7.6 Hz, 1H), 7.14 (d, *J* = 7.6 Hz, 1H), 7.24-7.26 (m, 2H), and 7.32-7.42 (m, 3H). The spectral data was identical to the values reported in the literature.[16]

1-Benzyl-6-hexyl-2,3-dihydro-1*H*-pyridin-4-one (20). To an oven-dried round bottom flask charged with 15 mg (0.08 mmol) of 1-benzyl-2,3-dihydro-1*H*-pyridin-4-one was added 59 mg (0.28 mmol) of dry copper (I) bromide-dimethylsulfide complex and the atmosphere was flushed with argon. To this mixture was added 0.9 mL of redistilled THF and the solution was cooled to -78 ^{o}C. To this solution was added 40 mL (0.32 mmol) of redistilled BF_3-OEt_2 and the mixture was allowed to stir at -78 ^{o}C for 15 min. This was followed by the dropwise addition of 144 mL (0.28 mmol) of a 2.0 M solution of *n*-hexylmagnesium bromide in THF and the reaction was allowed to stir for 15 min, then warmed to 0 ^{o}C and stirred for an additional 15 min, before being warmed to rt. The reaction mixture was transferred to a separatory funnel and partitioned between ether and water. The organic layer was extracted, washed twice with water, brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified using flash silica chromatography to give 20 mg (91%) of 1-benzyl-2-hexyl-piperidin-4-one as a pale yellow oil: IR (CH_2Cl_2) 2934, 1721, and 1104 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 0.88 (t, *J* = 6.9 Hz, 3H), 1.26-1.48 (m, 8H), 1.59-1.66 (m, 2H), 2.31-2.34 (m, 2H), 2.39-2.43 (m, 1H), 2.57 (dd, *J* = 5.1 and 14.1 Hz, 1H), 2.69-2.73 (m, 1H), 2.95-2.99 (m, 1H), 3.01-3.06 (m, 1H), 3.64 (d, *J* = 13.5 Hz, 1H), 3.90 (d, *J* = 13.5 Hz, 1H), 7.27 (t, *J* = 7.8 Hz, 1H), 7.33 (t, *J* = 7.8 Hz, 2H), and 7.38 (d, *J* = 7.8 Hz, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.3, 22.8, 25.8, 29.5, 31.3, 31.9, 39.7, 44.9, 48.2, 56.2, 60.9, 127.3, 128.6, 128.8, 139.4, and 210.4.

To a round bottom flask charged with 20 mg (0.07 mmol) of the above 4-piperidone was added 2.4 mL of water/ethanol (2:1) at rt. To this solution was added 30 mg (0.09 mmol) of mercuric acetate and 35 mg (0.09 mmol) of EDTA. The mixture was heated to 80 ^{o}C for 2 h, and cooled to rt. The solution was transferred to a separatory funnel and partitioned between CH_2Cl_2 and aqueous NH_4Cl. The organic layer was extracted with ether, washed with aqueous $NaHCO_3$, water, brine, dried over $MgSO_4$, filtered, and then concentrated under reduced pressure. The crude material was purified by silica gel chromatography to give 14 mg (76%) of **20** as a colorless oil: IR (CH_2Cl_2) 2955, 2359, 1639, 1544, and 1458 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.87 (t, *J* = 6.9 Hz, 3H), 1.04-1.06 (m, 2H), 1.25-1.65 (m, 8H), 2.30 (t, *J* = 7.8 Hz, 2H), 2.40 (t, *J* = 7.7 Hz, 2H), 3.45 (t, *J* = 7.7 Hz, 2H), 4.51 (s, 2H), 5.07 (s, 1H), 7.20 (d, *J* = 6.9 Hz, 2H), and 7.32-7.41 (m, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 14.2, 18.2, 22.6, 28.4, 29.9, 33.8, 35.8, 49.1, 54.1, 99.1, 126.7, 128.1, 129.2, 169.3, and 194.7; HRMS Calcd. for [$C_{18}H_{25}NO$+ H^+]: 272.2005. Found: 272.2008.

1-Phenethyl-2,3-dihydro-1*H*-pyridin-4-one (21) was prepared using the general mercuric acetate conditions in 92% yield as a pale yellow oil; IR (CH_2Cl_2) 3060, 1713, 1628, 1585, and 1180 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.43 (t, *J* = 7.9 Hz, 2H), 2.88 (t, *J* = 7.9 Hz, 2H), 3.41-3.48 (m, 4H), 4.85 (d, *J* = 7.5 Hz, 1H), 6.81 (d, *J* = 7.5 Hz, 1H), 7.16-7.19 (m, 2H), and 7.23-7.35 (m, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 35.7, 47.4, 57.9, 98.7, 128.2, 128.7, 130.0, 138.0, 154.4, and 191.6; HRMS Calcd. for [$C_{13}H_{15}NO+H^+$]: 202.1225. Found: 202.1226.

1-[2-(3,4-Dimethoxyphenyl)ethyl]-piperidin-4-one (24). To a solution containing 1.0 g (6.98 mmol) of 4-(2-bromo-ethyl)-1,2-dimethoxybenzene (**22**)[17] in 28 mL of a MeCN/water (6:1) at rt was slowly added 2.41 g (17.5 mmol) of K_2CO_3 and 1.45 mL (6.6 mmol) of 1,4-dioxa-8-aza-spiro[4.5]decane (**23**)[18]. The reaction mixture was transferred to a separatory funnel and partitioned between aqueous $NaHCO_3$ and ethyl acetate. The organic layer was washed twice with water, once with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash silica chromatography to give 1.94 g (90%) of the intermediate acetal[19] as a ple yellow oil which was immediately dissolved in 79 mL of 2 N HCl in AcOH and then subjected to an acid hydrolysis.

A solution of the above acetal in 2N HCl in AcOH was heated to 90 ^{o}C for 16 h. The reaction mixture was cooled to rt, brought to pH 8.0 with dilute NaOH, and extracted twice with toluene. The combined organic layer was washed with water, brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash silica gel chromatography to give 1.1 g (66%) of piperidone **24** as a colorless oil: IR (CH_2Cl_2) 2926, 2359, 1710, 1515, and 1148 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.48 (t, *J* = 6.2 Hz, 4H), 2.68-2.74 (m, 2H), 2.78-2.82 (m, 2H), 2.83 (t, *J* = 6.2 Hz, 4H), 3.86 (s, 3H), 3.88 (s, 3H), 6.75 (dd, *J* = 2.0 and 8.0 Hz, 2H), and 6.81 (d, *J* = 8.0 Hz).

1-[2-(3,4-Dimethoxyphenyl)ethyl]-2,3-dihydro-1*H*-pyridin-4-one (25) was prepared using the general mercuric acetate conditions in 88% as a pale yellow oil: IR (CH_2Cl_2) 2940, 2360, 1841, 1634, 1585, and 731 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 2.42 (t, *J* = 7.4 Hz, 2H), 2.81 (t, *J* = 7.4 Hz, 2H), 3.43 (ddd, *J* = 6.9, 9.6, and 16.5 Hz), 3.85 (s, 6H), 4.84 (d, *J* = 7.5 Hz, 1H), 6.66 (d, *J* = 2.0 Hz, 1H), 6.69 (dd, *J* = 2.1 and 8.1 Hz, 1H), 6.79 (d, *J* = 7.5 Hz, 1H), and 6.81-6.84 (m, 1H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 30.1, 35.4, 36.0, 47.6, 56.2, 56.3, 58.3, 98.1, 111.8, 112.2, 118.5, 121.3, 130.4, 154.4, and 191.7; HRMS Calcd. for [$C_{15}H_{19}NO_3+H^+$]: 262.1436. Found: 262.1437.

9,10-Dimethoxy-3,4,6,7-tetrahydropyrido[2,1-*a*]isoquinolin-2-one (26). To a round bottom flask charged with 11 mg (0.04 mmol) of 1-[2-(3,4-dimethoxy-phenyl)ethyl]-2,3-dihydro-1*H*-pyridin-4-one (**25**) was added 3 mL of 10% H_2SO_4 and the mixture was heated to 90 ^{o}C for 12 h. The reaction mixture was cooled to rt, brought to pH 8.0 with dilute NaOH, and extracted twice with CH_2Cl_2. The combined organic layer was washed with water, brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash silica gel chromatography to give 10 mg (91%) of the intermediate quinolinone which was obtained as a pale yellow oil and was immediately subjected to the following reaction conditions.

To a round bottom flask charged with the above compound was added 6.7 mL of water/ethanol (2:1), 12 mg (0.04 mmol) of mercuric acetate, and 15 mg (0.04 mmol) of EDTA. The mixture was heated to 80 ^{o}C for 2 h, cooled to rt and partitioned between aqueous NH_4Cl and CH_2Cl_2. The organic layer was extracted, washed with aqueous $NaHCO_3$, water, brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash silica gel chromatography to give 6 mg (59%) of **26** as a colorless oil: IR (CH_2Cl_2) 2091, 1644, and 1293 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.58 (t, *J* = 7.6 Hz, 2H), 2.95 (t, *J* = 6.2 Hz), 3.39 (t, *J* = 6.2 Hz, 2H), 3.62 (t, *J* = 7.6 Hz, 2H), 3.87 (s, 3H), 3.92 (s, 3H), 5.69 (s, 1H), 6.66 (s, 1H), and 7.16 (s, 1H). The spectral data was identical to the values reported in the literature.[20]

3,4,7,12-Tetrahydro-6*H*-indolo[2,3-*a*]quinolizin-2-one (30). To a solution of 45 mg (0.18 mmol) of 1-[2-(1*H*-indol-3-yl)-ethyl]-2,3-dihydro-1*H*-pyridin-4-one[21] (**29**) in 3 mL of 20% H_2SO_4 was added 1 mL of water and the mixture was heated to 90 ^{o}C for 12 h. The reaction mixture was cooled to rt, brought to pH 8.0 with dilute NaOH, and extracted twice with CH_2Cl_2. The combined organic layer was washed with water, brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash silica gel chromatography to give 45 mg (90%) of a pale yellow oil which was immediately taken up in 6.7 mL of water/ethanol (2:1) and subjected to the following reaction conditions.

To a solution of the crude oil in 6.7 mL of water/ethanol (2:1) was sequentially added 54 mg (0.18 mmol) of mercuric acetate and 65 mg (0.18 mmol) of EDTA. The mixture was heated to 80 ^{o}C for 2 h, cooled to rt and partitioned between aqueous NH_4Cl and CH_2Cl_2. The organic layer was extracted, washed with aqueous $NaHCO_3$, water, brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash silica gel chromatography to give 34 mg (76%) of **30** as a pale yellow oil: IR (CH_2Cl_2) 2839, 1708, and 1105 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.66 (t, *J* = 7.5 Hz, 2H), 3.12 (t, *J* = 6.8 Hz, 2H), 3.47 (t, *J* = 6.8 Hz, 2H), 3.59 (t, *J* = 7.5 Hz, 2H), 5.60 (s, 1H), 7.13-7.33 (m, 2H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), and 8.90 (brs, 1H). The spectral data was identical to the spectral data reported in the literature.[21]

Acknowledgements

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