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SYNTHESIS OF 1-AZAXANTHONES AND 1-AZATHIOXANTHONES BY Yb(OTf)$_3$/TfOH CO-CATALYZED INTRAMOLECULAR FRIEDEL-CRAFTS REACTION

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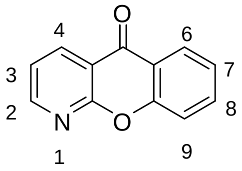
Abstract – Intramolecular Friedel-Crafts cyclization of phenoxypyridine acids (**3a**-**3j**) and phenythiopyridine acids (**4a-4i**) to form 1-azaxanthones (**1a**-**1j**) and 1-azathioxanthones (**2a**-**2i**), respectively, was efficiently promoted by Yb(OTf)$_3$/TfOH as co-catalysts. And a number of substrates could be cyclized in moderate to good yields.

INTRODUCTION

5*H*-[1]Benzopyrano[2,3-*b*]pyridine-5-one (**1**), referred to throughout this series, was commonly called 1-azaxanthone.[1] And 5*H*-[1]benzothiopyrano[2,3-*b*]pyridine-5-one (**2**) was called 1-azathioxanthone.



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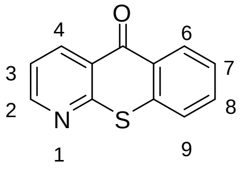


2

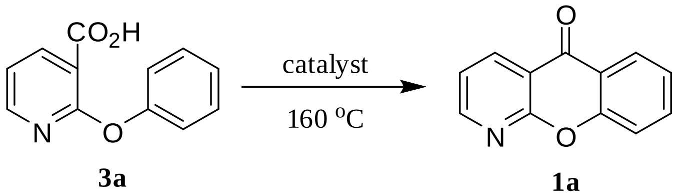
1-Azaxanthones are of considerable pharmacological relevance.[2] For example, benzopyranopyridine derivatives possess antiallergic activity.[3] The photochemical and photophysical properties of 1-azaxanthone have also been studied and it is usefulness as a probe for polarity, reactivity, and/or radical pair dynamics in supramolecular systems.[4] Azaxanthones and azathioxanthones are effective sensitisers for europium and terbium luminescence.[5]

Only a few procedures have been used to prepare 1-azaxanthones and 1-azathioxanthones. Among these methods, the most general one is intramolecular cyclization of the corresponding phenoxypyridine acids[6,7] or nitriles.[2] However, an excess of protic acid (often as solvent) such as sulfuric acid,[8] polyphosphoric acid (PPA)[6] is the reagent of choice for the intramolecular Friedel-Crafts cyclization reaction. Therefore, a large amount of acid wastes were formed after the reaction. Bromine-magnesium exchange has also been used for the synthesis of a series of 1-azaxanthone.[9] However, the materials are expensive and the reactions cause some side reactions. To the best of our knowledge, no report has been made about a simple and clean methodology for the synthesis of 1-azaxanthones and 1-azathioxanthones. In this paper, we first describe the cyclization of phenoxypyridine acids and phenythiopyridine acids to form 1-azaxanthones and 1-azathioxanthones catalyzed by $Yb(OTf)_3$/TfOH under solvent free conditions.

RESULTS AND DISCUSSION

Phenoxypridine acid **3a** was chosen as a model substrate for the intramolecular cyclization reaction. Effects of various types of acids on the intramolecular cyclization of phenoxypridine acid **3a** to 1-azaxanthone **1a** were summarized in Table 1. As indicated, in the presence of a catalytic amount of metal triflate such as $Bi(OTf)_3$, $Zn(OTf)_2$ and $Yb(OTf)_3$, $Yb(OTf)_3$ (5 mol%) afforded **1a** in 62% yield (entry 3). $Bi(OTf)_3$ and $Zn(OTf)_2$ also afforded **1a** but in lower yields (entries 1-2). Yield of the product **1a** was slightly improved when 10 mol% of Brønsted acids such as trifluoromethanesulfonic acid (TfOH), trifluoroacetic acid (TFA) and *p*-toluenesulfonic acid (TsOH) were used (entries 4, 5 and 6). While lower yields were obtained in the presence of 5 mol% of $Yb(OTf)_3$ or 10 mol% of TfOH, a 76% yield of **1a** was obtained when combining 5 mol% of $Yb(OTf)_3$ and 10 mol% of TfOH (entry 7). Further increasing the amount of the catalysts could not improve the yield (entry 8). Change of acid co-catalyst into methanesulfonic acid (MSA) led to a lower yield of **1a** (entry 9). During initial studies, the effects of different solvents were examined. Only trace amount of product was detected in the solvent of $PhNO_2$ or xylene (entries 12 and 13), while the reaction did not proceed in DMF or DMSO (entries 10 and 11). As can be seen in Table 1, 5 mol% of $Yb(OTf)_3$ and 10 mol% of TfOH was favorable and acceptable under solvent free conditions.

Table 1. Optimization of reaction conditions for the synthesis of **1a**



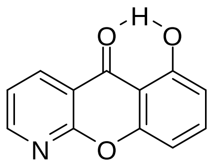
Entry	Catalyst (mol%)	Solvent	Time(h)	Yield[a] (%)
1	$Bi(OTf)_3$ (5)	-----	6	50
2	$Zn(OTf)_2$ (5)	-----	12	50
3	$Yb(OTf)_3$ (5)	-----	5	62
4	TfOH (10)	-----	5	65
5	TFA (10)	-----	5	60
6	p-TsOH (10)	-----	5	58
7	$Yb(OTf)_3$/TfOH (5/10)	-----	5	76
8	$Yb(OTf)_3$/TfOH (10/20)	-----	5	76
9	$Yb(OTf)_3$/MSA (5/10)	-----	5	67
10	$Yb(OTf)_3$/TfOH (5/10)	DMF	12	N.R.[b]
11	$Yb(OTf)_3$/TfOH (5/10)	DMSO	12	N.R.
12	$Yb(OTf)_3$/TfOH (5/10)	$PhNO_2$	12	trace
13	$Yb(OTf)_3$/TfOH (5/10)	xylene	12	trace

[a] yield of isolated product

[b] N.R.= no reaction

The substrate scope of $Yb(OTf)_3$/TfOH catalyzed cyclization of the phenoxypyridine acids **3a**-**3j** was summarized in Table 2. The electronic effect of the substituents on aromatic ring of substrates was not observed (entries 2-8). When a *para*-substituted phenoxypyridine acid was used, the reaction gave a single product in excellent yield. However, in the *meta*-substituted phenoxypyridine acids, both of possible regioisomers 6- and 8-substituted 1-azaxanthones were produced (except for entry 5). In the case of **3f**, the ratio of the two products (**1f** and **1f'**) was 2:3 (entry 6). However, in the case of **3e**, only 6-substituted isomer was obtained and no 8-substituted product was detected (entry 5). This could possibly due to the formation of intramolecular hydrogen bond in **1e** between the hydroxyl protons (OH) with the carbonyl oxygen (CO) (Figure 1). We were very excited to find that the deactivated phenoxypyridine acid with three fluorine atoms on aromatic ring was successfully transformed to **1h** in 69% yield (entry 8). And it was noteworthy that substrates **3i** and **3j** bearing a naphthalene group rather than a phenyl group were transformed into tetracyclic azaxanthones **1i** and **1j** in the yield of 74% and

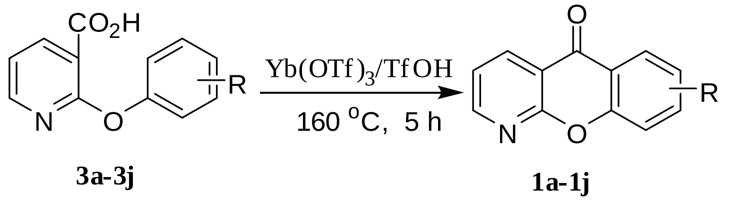
87% respectively (entries 9 and 10).

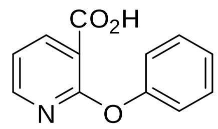
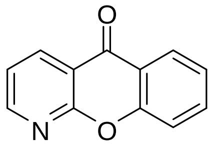
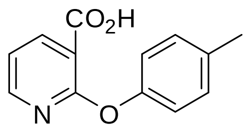
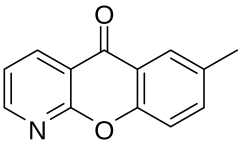
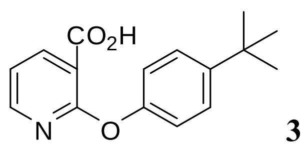
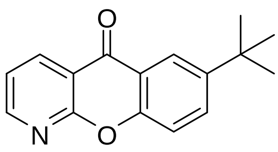
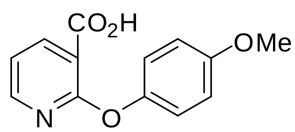
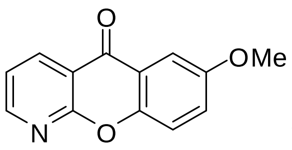
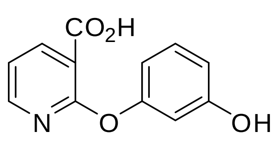
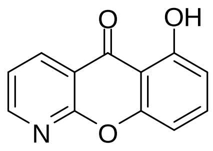


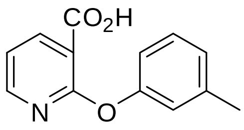
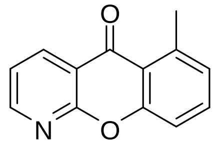
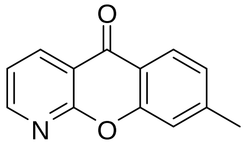
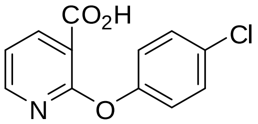
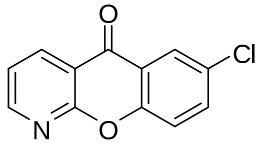
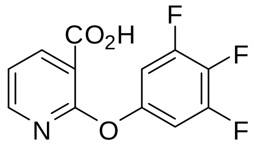
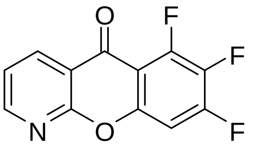
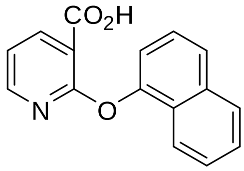
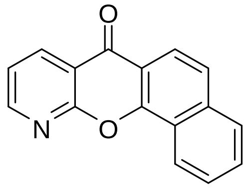
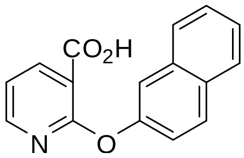
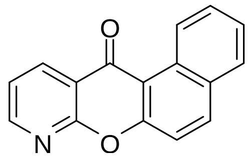
1e

Figure 1. Formation of intramolecular hydrogen bond

Table 2. Extension of substrates for the synthesis of 1-azaxanthones

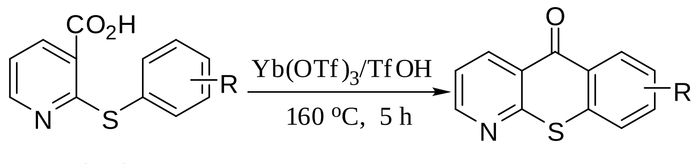


Entry	Substrate	Product	Yield (%)
1	 **3a**	 **1a**	76
2	 **3b**	 **1b**	81
3	 **3c**	 **1c**	80
4	 **3d**	 **1d**	65
5	 **3e**	 **1e**	75

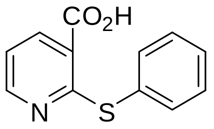
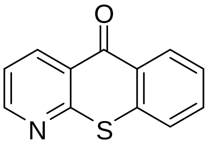
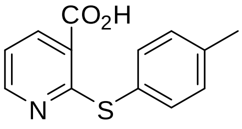
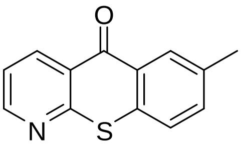
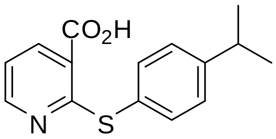
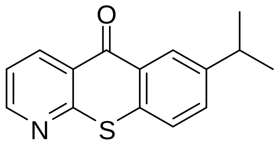
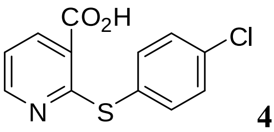
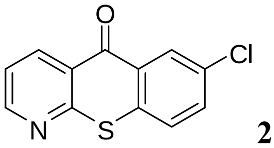
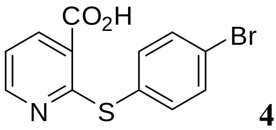
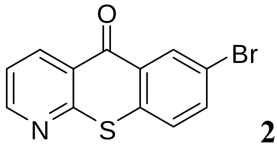
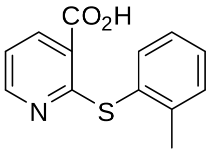
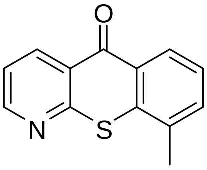
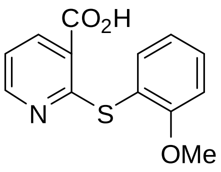
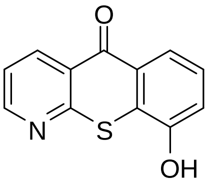
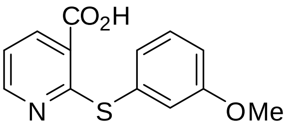
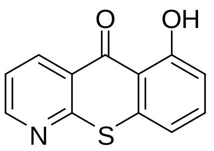
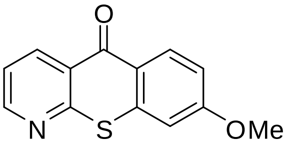
6	 **3f**	 **1f**  **1f'**	33 50
7	 **3g**	 **1g**	73
8	 **3h**	 **1h**	69
9	 **3i**	 **1i**	74
10	 **3j**	 **1j**	87

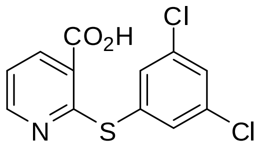
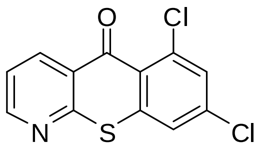
Furthermore, under optimized conditions, a number of substituted phenythiopyridine acids were converted into the corresponding 1-azathioxanthones in respective yields (Table 3). The results clearly show that all the substrates participated very efficiently in the reaction to afford the cyclized products in good yields.

Table 3. Synthesis of 1-azathioxanthones by intramolecular Friedel-Crafts reaction

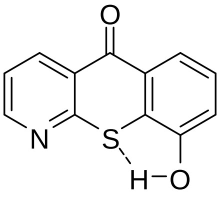


4a-4i **2a-2i**

Entry	Substrate	Product	Yield (%)
1	 **4a**	 **2a**	71
2	 **4b**	 **2b**	84
3	 **4c**	 **2c**	80
4	 **4d**	 **2d**	70
5	 **4e**	 **2e**	65
6	 **4f**	 **2f**	78
7	 **4g**	 **2g**	71
8	 **4h**	 **2h**	26
		 **2h’**	53

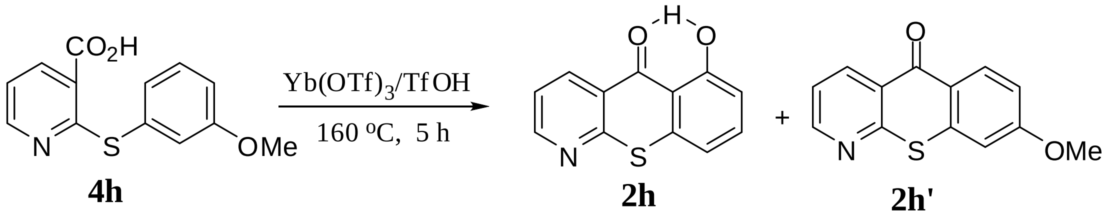
9	 **4i**	 **2i**	62

Phenythiopyridine acids with electron-donating groups on the aromatic ring generally afforded 1-azathioxanthones in good yields (entries 2, 3, 7, 8). The reaction of **4b** and **4c** bearing a methyl and bulky isopropyl group gave the corresponding **2b** and **2c** in 84% and 80% yields (entries 2 and 3). It should be noted that deactivated substrates, which have one or two halogen atoms on the aromatic ring, were successfully cyclized to give 1-azathioxanthones in moderate yields (entries 4, 5, 9).



2g

Figure 2. Formation of intramolecular hydrogen bond



Scheme 1. Synthesis of the pruducts **2h** and **2h'** from **4h**

Ortho- and *para*-substituted phenythiopyridine acids gave rise to a single product whereas a *meta*-substituted phenythiopyridine acid led to formation of 6- and 8-substituted isomers. In the case of **4h**, the reaction afforded a 1:2 mixture of the demethylation product **2h** and the desired product **2h'** in 79% total yield (Scheme 1). The formation of **2g** and **2h** were demethylation products (entries 7 and 8). The product **2g** might form an intramolecular hydrogen bond with the sulfur atom, forming a 5-membered ring as shown in Figure 2 (or 6-membered ring in the case of the product **2h** as shown in Scheme 1).[10] Our group has previously developed a method for the $Yb(OTf)_3$ catalyzed Friedel-Crafts acylation and demethylation of aryl-methyl ethers to produce hydroxyacylphenones.[11]

A possible mechanism is proposed according to literatures and considering Friedel-Crafts acylation.[12] A very active catalyst could be produced by mixing appropriate Lewis and Brønsted acids.[13,14] The synergistic effect might have been formed by combining ytterbium triflate (Yb(OTf)$_3$) with trifluoromethanesulfonic acid (TfOH), leading to active catalytic systems for the intramolecular Friedel-Crafts reaction.

In summary, we have devised an effective protocol for the intramolecular Friedel-Crafts cyclization of phenoxypyridine acids and phenythiopyridine acids to synthesis 1-azaxanthones and 1-azathioxanthones. This approach has some advantages in term of operational simplicity, broad substrate scope and solvent-free conditions. Further research is ongoing to apply this method to other systems.

EXPERIMENTAL

Melting points were determined by Büchi B-540 melting point apparatus and are uncorrected. The IR spectra (KBr pellet) were measured on a Nicolet Avatar-370 spectrometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Varian 400-MHz spectrometer. Mass spectra were obtained on a Thermo Finnigan LCQ-Advantage spectrometer (ESI, APCI) or a Finnigan Trace DSQ spectrometer (EI, CI). HRMS was carried out on an APEX (Bruker) mass III spectrometer.

General Procedure for Synthesis of 1-azaxanthone 1a

A mixture of Yb(OTf)$_3$ (0.12g, 0.2mmol, 5mol%), TfOH (0.06g, 0.4mmol, 10mol%) and phenoxypridine acid **3a** (0.86g, 4.0mmol) in a flask was heated in an oil bath at 160 °C for 5 h. Then the reaction mixture was dissolved in CH$_2$Cl$_2$ (30 mL) and washed with a saturated aqueous NaOH solution (20 mL). The organic layer was separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (2×30 mL). The combined organic layer was dried with anhydrous Na$_2$SO$_4$, filtered and evaporated to give a crude product. The crude product was then charged on a small silica gel column and eluted with a mixture of EtOAc: petroleum ether (1:5) to afford the corresponding pure product 1-azaxanthone **1a** (0.6g, 76% yield).

5*H*-Chromeno[2,3-*b*]pyridin-5-one (1a)

White solid. mp 178-179 °C (Lit.,[6] mp 178-182 °C). IR (KBr): 3069, 1677, 1617, 1597, 1584, 1472, 1415, 1347, 1115, 1100, 760 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$) δ: 8.78-8.77 (m, 1H), 8.74 (dd, *J* = 2.0, 7.6,Hz, 1H), 8.33 (dd, *J* = 2.0, 8.0 Hz, 1H), 7.80 (dt, *J* =1.6, 7.6 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.47 (t, *J* = 4.4, 1H), 7.44 (d, *J* = 6.8 Hz, 1H). ^{13}C NMR (100 MHz, CDCl$_3$) δ: 177.6, 160.3, 155.7, 154.1, 137.3, 135.6, 126.6, 124.6, 121.5, 121.0, 118.5, 116.7. MS (EI): m/z (%) = 197(M$^+$, 28), 169 (47), 113(100), 87(35).

7-Methyl-5*H*-chromeno[2,3-*b*]pyridin-5-one (1b)

White solid. mp 166-167 °C (Lit.,[6] mp 166-168 °C). IR (KBr): 3074, 2920, 1663, 1618, 1600, 1584, 1485, 1420, 1139, 1102, 777 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.77-8.75 (m, 1H), 8.73 (dd, *J* = 2.0, 7.6 Hz, 1H), 8.11 (s, 1H), 7.61 (dd, *J* = 2.0, 8.4 Hz, 1H), 7.53 (d, *J* = 8.8 Hz, 1H), 7.46-7.43 (m, 1H), 2.50 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.2, 160.0, 154.0, 153.9, 137.3, 136.9, 134.5, 125.9, 121.1, 120.8, 118.2, 116.6, 20.6. MS (EI): m/z (%) = 211(M^{+}, 100), 182 (92), 154(41), 127(32).

7-*tert*-Butyl-5*H*-chromeno[2,3-*b*]pyridin-5-one (1c)

White solid. mp 100.3-101.8 °C (Lit.,[6] mp 98-100 °C). IR (KBr): 3073, 2961, 2903, 2868, 1665, 1616, 1599, 1470, 1413, 1133, 1099, 781 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.76-8.73 (m, 2H), 8.30 (s, 1H), 7.86 (dd, *J* = 2.4, 8.8 Hz, 1H), 7.58 (d, *J* = 8.8 Hz, 1H), 7.46-7.43 (m, 1H), 1.41 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.8, 160.3, 153.9, 153.8, 147.9, 137.3, 133.5, 122.3, 121.3(2C), 118.1, 116.6, 34.7, 31.2(3C). MS (EI): m/z (%) = 253(M^{+}, 25), 238 (100), 210(43), 198(32), 115(34), 77(35).

7-Methoxy-5*H*-chromeno[2,3-*b*]pyridin-5-one (1d)

White solid.[15] mp 154-157.7 °C. IR (KBr): 3072, 3019, 2974, 2925, 2831, 1659, 1615, 1588, 1486, 1420, 1026, 781 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.77-8.73 (m, 2H), 7.68 (s, 1H), 7.58 (d, *J* = 8.8 Hz, 1H), 7.47-7.44 (m, 1H), 7.39 (dd, *J* = 3.2, 8.8 Hz, 1H), 3.94 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.4, 160.1, 156.4, 154.0, 150.4, 137.3, 125.5, 121.8, 120.8, 119.9, 116.0, 105.7, 55.9. MS (EI): m/z (%) = 227(M^{+}, 100), 212 (40), 184(42), 156(84), 128(33), 101(31).

6-Hydroxy-5*H*-chromeno[2,3-*b*]pyridin-5-one (1e)

Yellow solid. mp 142.6-143.6 °C. IR (KBr): 3079, 1647, 1622, 1599, 1480, 1417, 1383, 1290, 1230, 1210, 1106, 1033, 782 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.27 (s, 1H), 8.78 (dd, *J* = 2.0, 7.2 Hz, 1H), 8.68 (dd, *J* = 1.6, 7.6 Hz, 1H), 7.66 (t, *J* = 8.4 Hz, 1H), 7.48-7.45 (m, 1H), 7.08 (d, *J* = 8.4 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR (100 MHz, CDCl3) δ: 182.6, 161.7, 160.3, 155.6, 154.9, 137.5, 136.6, 121.1, 115.6, 111.3, 108.7, 107.7. HRMS (ESI): calcd for $C_{12}H_8NO_3$ [M+H]$^{+}$: 214.0504, found: 214.0501.

6-Methyl-5*H*-chromeno[2,3-*b*]pyridin-5-one (1f)

Pale yellow solid. mp 155.5-157 °C. IR (KBr): 2968, 2929, 1664, 1611, 1596, 1565, 1476, 1426, 1411, 1030, 784 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.72 (dd, *J* = 2.0, 4.4 Hz, 1H), 8.67 (dd, *J* = 2.0, 8.0 Hz, 1H), 7.61 (t, *J* = 8.4 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.44-7.40 (m, 1H), 7.18 (d, *J* = 7.6 Hz, 1H), 2.92 (s, 3H). ^{13}C NMR (100 MHz, CDCl3) δ: 179.0, 159.6, 156.9, 153.7, 142.0, 137.2, 134.3, 127.3, 120.7, 119.8, 117.3, 116.4, 22.9. HRMS (ESI): calcd for $C_{13}H_{10}NO_2$ [M+H]$^{+}$: 212.0706, found: 212.0706.

8-Methyl-5*H*-chromeno[2,3-*b*]pyridin-5-one (1f')

Grey solid. mp 149.3-151 °C (Lit.,[6] mp151-152 °C). IR (KBr): 3035, 2908, 1662, 1624, 1601, 1470, 1416, 1115, 775 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.74 (dd, *J* = 2.0, 4.4 Hz, 1H), 8.72 (dd, *J* = 2.0, 7.6 Hz, 1H), 8.20 (d, *J* = 8.0 Hz, 1H), 7.46-7.42 (m, 2H), 7.27 (s, 1H), 2.54 (s, 3H). ^{13}C NMR (100 MHz, CDCl3) δ: 177.1, 160.1, 155.6, 153.7, 147.2, 137.1, 126.2, 126.0, 120.8, 119.1, 118.0, 116.6, 21.9. MS (EI): m/z (%) = 211(M^+, 100), 182(83), 154(52), 127(62), 77(60).

7-Chloro-5*H*-chromeno[2,3-*b*]pyridin-5-one (1g)

White solid. mp 193.7-195.6 °C (Lit.,[6] mp 198-200 °C). IR (KBr): 3098, 3066, 1667, 1596, 1475, 1434, 1417, 1130, 1105, 777 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.78 (dd, *J* = 2.0, 4.8 Hz, 1H), 8.73 (dd, *J* = 2.0, 8.0 Hz, 1H), 8.28 (s, 1H), 7.74 (dd, *J* = 2.8, 8.8 Hz, 1H), 7.60 (d, *J* = 8.8 Hz, 1H), 7.50-7.47 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.5, 160.1, 154.5, 154.0, 137.4, 135.7, 130.5, 125.9, 122.3, 121.2, 120.2, 116.4. MS (EI): m/z (%) = 233 ([M^++2], 34), 231 (M^+, 100), 203(44), 140(43).

6,7,8-Trifluoro-5*H*-chromeno[2,3-*b*]pyridin-5-one (1h)

White solid. mp 207-209 °C. IR (KBr): 3049, 1673, 1645, 1607, 1594, 1508, 1478, 1426, 1324, 1205, 1174, 1129, 1079, 778 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.76 (dd, *J* = 2.0, 4.4 Hz, 1H), 8.69 (dd, *J* = 2.0, 7.6 Hz, 1H), 7.52-7.49 (m, 1H), 7.30-7.26 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.3, 159.3, 154.8(d, *J* = 257.8 Hz, 1C), 154.2, 149.9(d, *J* = 261.7 Hz, 1C), 137.2, 137.1(d, *J* = 250.1 Hz, 1C), 121.8, 116.3, 109.6, 102.4. HRMS (ESI): calcd for $C_{12}H_5F_3NO_2$ $[M+H]^+$: 252.0272, found: 252.0269.

7*H*-Benzo[7,8]chromeno[2,3-*b*]pyridin-7-one (1i)

Light green solid. mp 200-201.8 °C. IR (KBr): 3056, 1652, 1601, 1473, 1412, 1384, 1249, 1223, 1193, 771 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.82-8.78 (m, 3H), 8.23 (d, *J* = 8.4 Hz, 1H), 7.95 (dd, *J* = 2.0, 7.2 Hz, 1H), 7.79 (d, *J* = 8.8 Hz, 1H), 7.76-7.70 (m, 2H), 7.54-7.51 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.1, 159.9, 153.6, 153.4, 137.0, 136.7, 129.9, 127.9, 127.1, 124.7, 123.7, 123.2, 121.4, 120.8, 117.3, 117.21. HRMS (ESI): calcd for $C_{16}H_{10}NO_2$ $[M+H]^+$: 248.0706, found: 248.0703.

12*H*-Benzo[5,6]chromeno[2,3-*b*]pyridin-12-one (1j)

White solid. mp 175-176 °C. IR (KBr): 3009, 1647, 1604, 1577, 1516, 1470, 1424, 1442, 1213, 1153, 1112, 788 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.99 (d, *J* = 8.0 Hz, 1H), 8.81 (dd, *J* = 2.0, 8.0 Hz, 1H), 8.77 (dd, *J* = 1.6, 4.8 Hz, 1H), 8.19 (d, *J* = 8.0 Hz, 1H), 7.93 (d, *J* = 8..4 Hz, 1H), 7.80 (t, *J* = 8.4 Hz, 1H), 7.68 (d, *J* = 8.8 Hz, 1H), 7.63 (t, *J* = 7.6 Hz, 1H), 7.52-7.49 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.1, 158.5, 156.9, 152.9, 136.9, 136.9, 130.2, 129.8, 129.4, 128.0, 126.1, 126.0, 120.9, 117.6, 113.9(2C). HRMS (ESI): calcd for $C_{16}H_{10}NO_2$ $[M+H]^+$: 248.0706, found: 248.0703.

5*H*-Thiochromeno[2,3-*b*]pyridin-5-one (2a)

White solid. mp 233-234 °C (Lit.,[16] mp 234 °C). IR (KBr): 3033, 1650, 1591, 1573, 1446, 1433, 1398, 1322, 1261, 1161, 1091, 739 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.82 (dd, *J* = 2.0, 8.0 Hz, 1H), 8.78 (dd, *J* = 2.0, 6.0 Hz, 1H), 8.58 (d, *J* = 8.0 Hz, 1H), 7.69-7.63 (m, 2H), 7.51 (t, *J* = 6.8 Hz, 1H), 7.45-7.42 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 180.5, 158.7, 153.4, 137.9, 137.6, 135.2, 133.1, 130.0, 128.9, 126.9, 126.6, 121.8. MS (EI): m/z (%) = 213(M^+, 98), 185(100), 158(26), 140(33).

7-Methyl-5*H*-thiochromeno[2,3-*b*]pyridin-5-one (2b)

White solid. mp 147-148 °C (Lit.,[17] mp 153-154 °C). IR (KBr): 3024, 2919, 1640, 1602, 1577, 1470, 1446, 1398, 1323, 1297, 1160, 1139, 1094, 760 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.81 (dd, *J* = 2.0, 8.0 Hz, 1H), 8.76 (dd, *J* = 2.0, 4.8 Hz, 1H), 8.38 (s, 1H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.48 (dd, *J* = 2.0, 8.0 Hz, 1H), 7.43-7.39 (m, 1H), 2.50 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 180.3, 158.5, 152.9, 137.5, 136.7, 135.1, 134.1, 130.4, 129.4, 128.4, 126.1, 121.2, 21.2. MS (EI): m/z (%) = 227(M^+, 100), 198(67), 154(16), 86(16).

7-Isopropyl-5*H*-thiochromeno[2,3-*b*]pyridin-5-one (2c)

Yellow solid. mp 66-67 °C. IR (KBr): 3062, 2954, 2952, 2866, 1643, 1601, 1576, 1474, 1450, 1397, 1319, 1135, 1077, 754 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.82 (dd, *J* = 2.0, 8.0 Hz, 1H), 8.77 (dd, *J* = 2.0, 4.4 Hz, 1H), 8.44 (s, 1H), 7.59-7.54 (m, 2H), 7.44-7.41 (m, 1H), 3.10-3.04 (m, 1H), 1.34 (s, 3H), 1.33 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 180.3, 158.5, 152.8, 147.6, 137.5, 134.4, 131.8, 128.5, 126.9, 126.2, 126.1, 121.2, 33.9, 23.8(2C). HRMS (ESI): calcd for $C_{15}H_{14}NOS$ $[M+H]^+$: 256.0796, found: 256.0793.

7-Chloro-5*H*-thiochromeno[2,3-*b*]pyridin-5-one (2d)

White solid. mp 193.5-194.6 °C (Lit.,[17] mp 194-195 °C). IR (KBr): 3063, 1644, 1578, 1401, 1316, 1289, 1163, 1099, 760 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.82-8.78 (m, 2H), 8.54 (s, 1H), 7.63 (dd, *J* = 2.0, 8.4 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.47-7.44 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 179.2, 158.1, 153.3, 137.6, 135.4, 133.0, 129.7, 129.1, 127.6, 125.8, 121.7(2C). MS (EI): m/z (%) = 249 ($[M^++2]$, 37), 247(M^+, 100), 219(48), 184(30), 140(22), 92(15).

7-Bromo-5*H*-thiochromeno[2,3-*b*]pyridin-5-one (2e)

Grey solid. mp 180-182 °C (Lit.,[17] mp 190-193 °C). IR (KBr): 3061, 1645, 1577, 1398, 1311, 1289, 1127, 1091, 762 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.83-8.78 (m, 2H), 8.69 (s, 1H), 7.75 (dd, *J* = 2.4, 8.4 Hz, 1H), 7.52 (d, *J* = 8.8 Hz, 1H), 7.48-7.44 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 179.5, 158.4, 153.6, 138.0, 136.3, 136.0, 132.6, 130.2, 128.1, 126.2, 122.0, 120.9. MS (EI): m/z (%) = 294($[M^++3]$, 14), 291 (M^+, 100), 265(22), 212(20), 184(60), 140(47).

9-Methyl-5*H*-thiochromeno[2,3-*b*]pyridin-5-one (2f)

Pale yellow solid. mp 160.3-161 °C (Lit.,[5] mp 135-137 °C). IR (KBr): 3024, 2927, 1634, 1584, 1397, 1326, 1131, 1058, 750 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.82-8.78 (m, 2H), 8.47 (d, *J* = 8.0 Hz, 1H), 7.53 (d, *J* = 7.2 Hz, 1H), 7.46-7.44 (m, 1H), 7.43-7.41 (m, 1H), 2.58 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 180.8, 158.0, 153.1, 137.4, 136.6, 134.4, 133.9(2C), 128.9, 127.5, 125.9, 121.6, 19.6. MS (EI): m/z (%) = 227(M$^+$, 100), 198(45), 154(15), 121(10).

9-Hydroxy-5*H*-thiochromeno[2,3-*b*]pyridin-5-one (2g)

Grey solid. mp 177-178.7 °C. IR (KBr): 3438, 2927, 1671, 1615, 1597, 1470, 1417, 1347, 1198, 760 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.74 (dd, *J* = 2.0, 4.8 Hz, 1H), 8.71 (dd, *J* = 2.0, 7.6 Hz, 1H), 8.30 (dd, *J* = 2.0, 8.0 Hz, 1H), 7.78 (dt, *J* = 1.6, 7.2 Hz, 1H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.44 (t, *J* = 4.4 Hz,1H), 7.42 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.3, 160.1, 155.5, 154.0, 137.2, 135.5, 126.5, 124.5, 121.4, 120.9, 118.4, 116.6. HRMS (ESI): calcd for $C_{12}H_8NO_2S$ [M+H]$^+$: 230.0270, found 230.0276.

6-Hydroxy-5*H*-thiochromeno[2,3-*b*]pyridin-5-one (2h)

Orange solid. mp 189.4-191 °C. IR (KBr): 3444, 2925, 2847, 2757, 1621, 1574, 1440, 1399, 1264, 1183, 1127, 1090, 783 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 13.66 (s, 1H), 8.79-8.77 (m, 2H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.45-7.42 (m, 1H), 7.11 (d, *J* = 7.6 Hz, 1H), 6.95 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 186.1, 164.9, 159.0, 153.9, 138.5, 137.4, 135.6, 125.6, 121.7, 116.3, 114.9, 114.5. HRMS (ESI): calcd for $C_{12}H_8NO_2S$ [M+H]$^+$: 230.0270, found: 230.0276.

8-Methoxy-5*H*-thiochromeno[2,3-*b*]pyridin-5-one (2h')

Yellow solid. mp 188-190 °C. IR (KBr): 3075, 3006, 2967, 1636, 1601, 1577, 1399, 1326, 1277, 1070, 1032, 758 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.80 (dd, *J* = 1.6, 8.0 Hz, 1H), 8.74 (dd, *J* = 2.0, 4.8 Hz, 1H), 8.51 (d, *J* = 8.8 Hz, 1H), 7.44-7.41 (m, 1H), 7.05 (dd, *J* = 2.4, 4.8 Hz, 1H), 7.02 (d, *J* = 2.4 Hz, 1H), 3.94 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 179.5, 163.1, 158.5, 152.9, 140.0, 137.7, 132.1, 126.6, 122.7, 121.7, 115.7, 108.7, 56.1. HRMS (ESI): calcd for $C_{13}H_{10}NO_2S$ [M+H]$^+$: 244.0432, found: 244.0431.

6,8-Dichloro-5*H*-thiochromeno[2,3-*b*]pyridin-5-one (2i)

Yellow solid. mp 199-201 °C. IR (KBr): 3067, 3044, 2921, 1650, 1570, 1399, 1376, 1143, 1093, 928, 857 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.74 (dd, *J* = 1.6, 4.4 Hz, 1H), 8.67 (dd, *J* = 2.0, 8.0 Hz, 1H), 7.54 (s, 1H), 7.50 (s, 1H), 7.45-7.42 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 179.3, 155.7, 153.0, 141.0, 137.9, 137.6, 133.6, 130.7, 127.8, 124.6, 122.7, 122.0. HRMS (ESI): calcd for $C_{12}H_6Cl_2NOS$ [M$^+$]: 281.9547, found: 281.9539.

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