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A CONVENIENT SYNTHESIS OF 9*H*-THIOXANTHEN-9-ONES AND THEIR AZA-ANALOGUES

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Abstract – An efficient method for the preparation of 9*H*-thioxanthen-9-ones and their three aza-analogues has been developed. The reaction of (2-fluorophenyl)(2-halophenyl)methanones, derived from 1-bromo-2-fluorobenzenes and 2-halobenzaldehydes by an easy two-step sequence, with $Na_2S·9H_2O$ in DMF at 60 ˚C gives 9*H*-thioxanthen-9-ones. This procedure can be applied to the synthesis of 5*H*-[1]benzothiopyrano[2,3-*b*](or [2,3-*c*])pyridin-5-ones or 10*H*-[1]-benzothiopyrano[3,2-*c*]pyridin-10-ones starting from 2-, 3- or 4-chloropyridines, respectively.

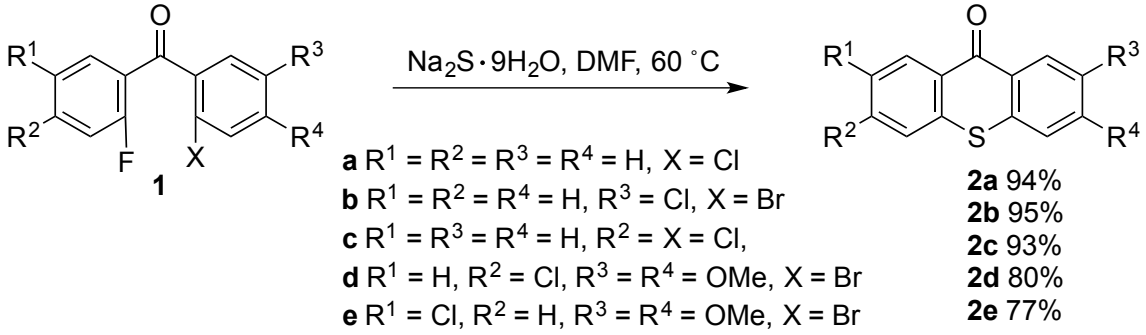
INTRODUCTION

A literature survey of the utility of 9*H*-thioxanthen-9-one derivatives indicated that a number of compounds having this skeleton exhibit a variety of biological activities,[1] and that some compounds are useful for photosensitive materials.[2] While 9*H*-thioxanthen-9-ones have been commonly prepared by the intramolecular Friedel-Crafts acylation of 2-(arylsulfanyl)benzoic acids under harsh conditions,[2,3] few other general methods have been developed. We envisioned that the reaction of (2-fluorophenyl)(2-halophenyl)methanones, which have been easily prepared from 1-bromo-2-fluorobenzenes and 2-halobenzaldehydes and used for the preparation of 10-substituted acridin-9(10*H*)-ones,[4] with $Na_2S·9H_2O$ under mild conditions would provide 9*H*-thioxanthen-9-ones.[5] In this paper, we wish to describe the results of our investigation, which show that 9*H*-thioxanthen-9-ones (**2**) can be prepared by the reaction of (2-fluorophenyl)(2-halophenyl)methanones (**1**) with $Na_2S·9H_2O$ in DMF at 60 °C. We also report that this method is applicable to the synthesis of three types of their aza-analogues,

5*H*-[1]benzothiopyrano[2,3-*b*](or [2,3-*c*])pyridin-5-ones (**6**) (or **10**) or 10*H*-[1]benzothiopyrano[3,2-*c*]-pyridin-10-ones (**14**). These [1]benzothiopyranopyridinone derivatives are also of biological,[6] material scientific,[7] and synthetic interests.[8]

RESULTS AND DISCUSSION

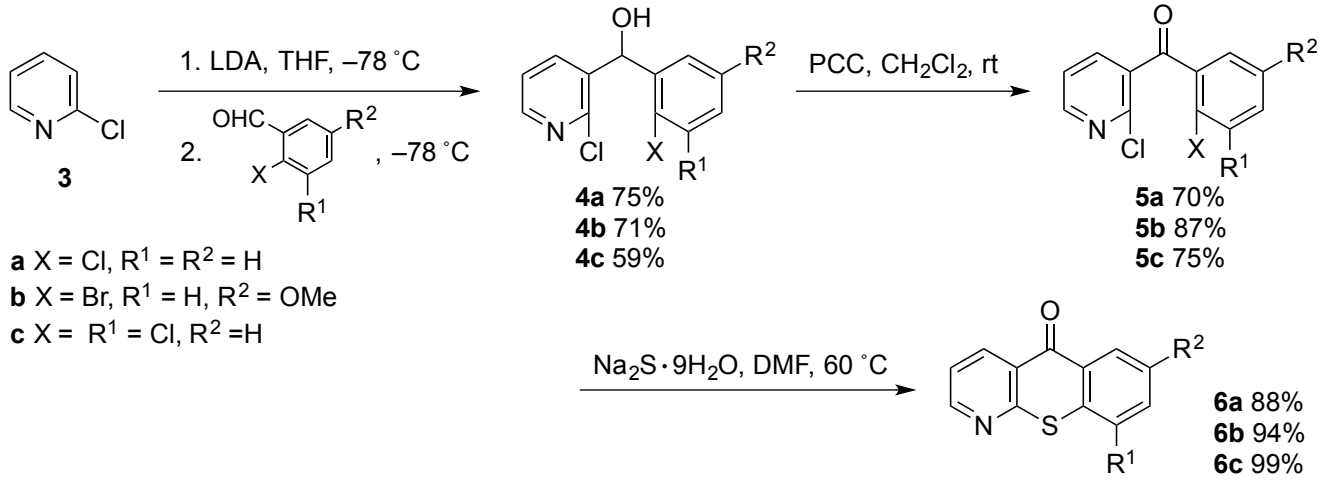
The precursor (2-fluorophenyl)(2-halophenyl)methanones (**1**) were prepared by the reaction of 1-fluoro-2-lithiobenzenes, generated from 1-bromo-2-fluorobenzenes according to the previously reported method,[9] with 2-halobenzaldehydes, followed by the PCC oxidation of the resulting alcohols, as described previously.[4] When these compounds (**1**) were treated with $Na_2S{\cdot}9H_2O$ in DMF at 60 °C, substitution of the two halogens with the sulfur atom proceeded smoothly and cleanly to afford, after addition of water followed by recrystallization of the precipitated crude products, the corresponding 9*H*-thioxanthen-9-ones (**2**) in good to excellent yields, as shown in Scheme 1.



Scheme 1

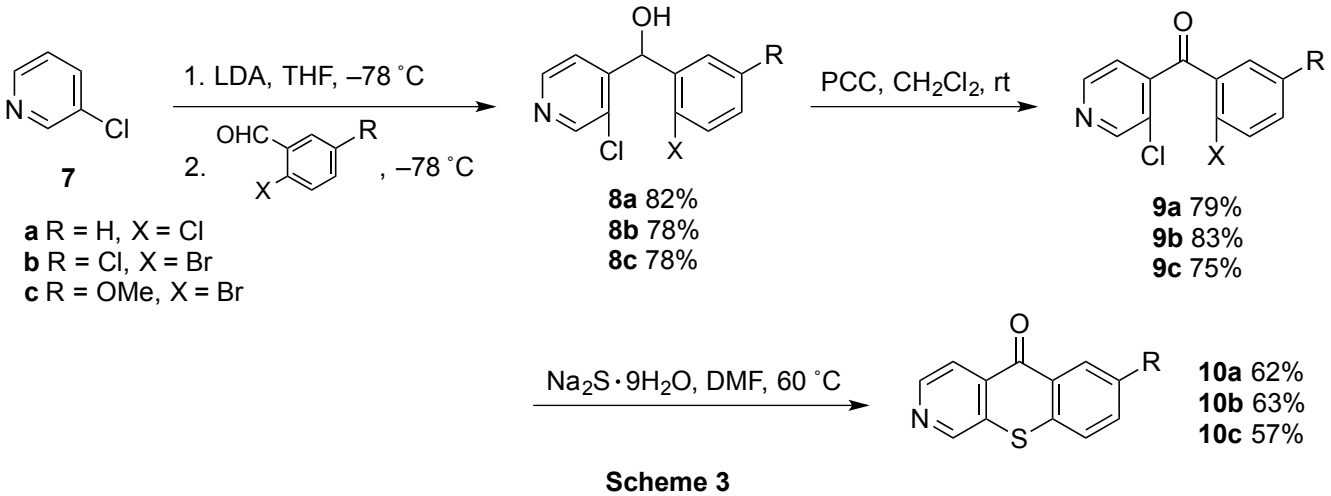
Encouraged by the above results we applied this method to the synthesis of three aza-analogues of 9*H*-thioxanthen-9-ones, 5*H*-[1]benzothiopyrano[2,3-*b*](or [2,3-*c*])pyridin-5-ones (**6**) (or **10**) or 10*H*-[1]-benzothiopyrano[3,2-*c*]pyridine-10-ones (**14**) from 2-, 3- or 4-chloropyridines (**3**, **7**, or **11**), respectively. We first conducted the synthesis of 5*H*-[1]benzothiopyrano[2,3-*b*]pyridin-5-ones (**6**) as illustrated in Scheme 2. Thus, commercially available 2-chloropyridine (**3**) was treated with LDA in THF at –78 °C according to the reported procedure[10] to generate 2-chloro-3-lithiopyridine, which was allowed to react with 2-halobenzaldehydes to give (2-chloropyridin-3-yl)(2-halophenyl)methanols (**4**) in fair to good yields. The lower yield of **4c** is likely due to the steric encumbrance of the two adjacent chloro groups. Then, these alcohols were oxidized with PCC in CH_2Cl_2 at room temperature to give (2-chloropyridin-3-yl)(2-halophenyl)methanones (**5**) in satisfactory yields. The final step, treatment of **5** with $Na_2S{\cdot}9H_2O$, was carried out applying the same conditions described above to afford the desired products (**6**) in excellent yields.

Next, the synthesis of 5*H*-[1]benzothiopyrano[2,3-*c*]pyridin-5-ones (**10**) from commercially available 3-chloropyridine (**7**) was similarly carried out under the same conditions, as depicted in Scheme 3. The precursor (3-chloropyridin-4-yl)(2-halophenyl)methanones (**9**) were also prepared in good yields from **7**, *via* the corresponding alcohols (**8**), by the same sequence used for the preparation of **5**. However, when compounds (**9**) were treated with $Na_2S{\cdot}9H_2O$ in the same way as described above, the expected products (**10**) were obtained in somewhat diminished yields compared to those of **6** as summarized in Scheme 3 as well. These disappointing results are presumably due to the low reactivity of the 3-chloro substituent of the pyridine ring of **9** compared to the 2-chloro substituent of the pyridine ring of **5**.



a X = Cl, R^1 = R^2 = H
b X = Br, R^1 = H, R^2 = OMe
c X = R^1 = Cl, R^2 = H

Scheme 2

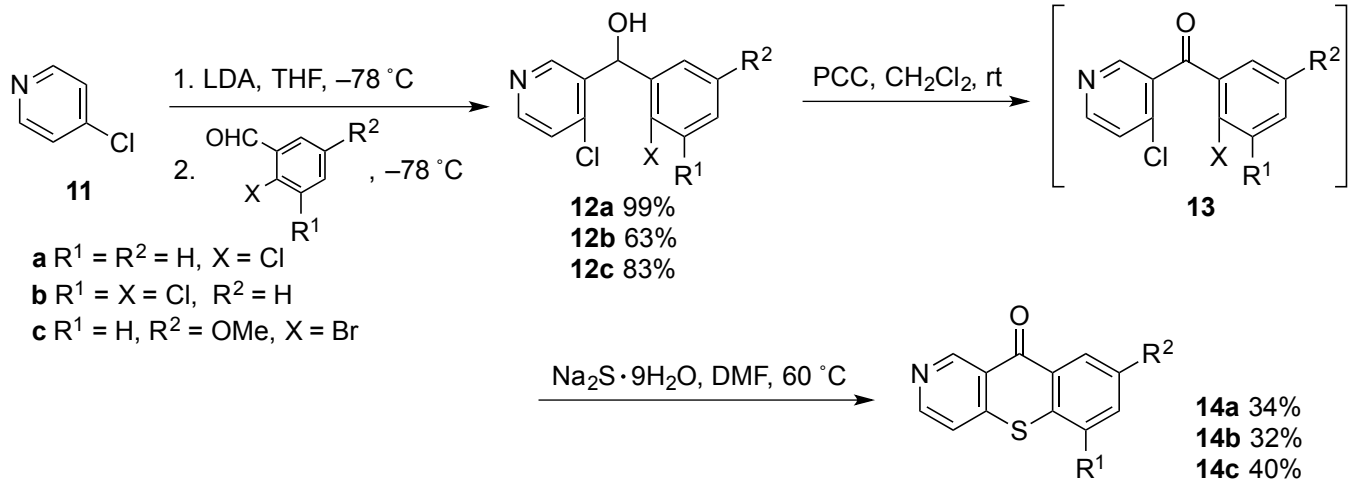


a R = H, X = Cl
b R = Cl, X = Br
c R = OMe, X = Br

Scheme 3

Finally, the preparation of 10*H*-[1]benzothiopyrano[3,2-*c*]pyridin-10-ones (**14**) was also similarly achieved as illustrated in Scheme 4. The reaction of 3-chloro-4-lithiopyridine,[10] generated from 4-chloropyridine (**11**), with 2-halobenzaldehydes to furnish the corresponding alcohols (**12**) in good yields, the PCC oxidation of which gave (4-chloropyridin-3-yl)(2-halophenyl)methanones (**13**). However,

these ketones proved to be rather unstable under isolation conditions by SiO_2 chromatography. So, these compounds were not isolated and were subjected, after filtration through a small pad of SiO_2, to the treatment with $Na_2S{\cdot}9H_2O$ under the same reaction conditions described above to afford the desired products (**14**) in moderate overall yields from **12**.



Scheme 4

In conclusion, we have developed an efficient synthetic approach for the construction of 9*H*-thioxanthen-9-ones *via* the reaction of (2-fluorophenyl)(2-halophenyl)methanones with $Na_2S{\cdot}9H_2O$ under mild conditions. Their three aza-analogues were also synthesized starting with the respective chloropyridines by an application of this sequence.

EXPERIMENTAL

All melting points were obtained on a Laboratory Devices MEL-TEMP II melting apparatus and are uncorrected. IR spectra were recorded with a Perkin–Elmer Spectrum65 FTIR spectrophotometer. ^{1}H NMR spectra were recorded in $CDCl_3$ using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 500 MHz or JEOL LA400 FT NMR spectrometer operating at 400 MHz. ^{13}C NMR spectra were recorded in $CDCl_3$ using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 125 MHz. Low-resolution MS spectra (EI, 70 eV) were measured by a JEOL JMS AX505 HA spectrometer. High-resolution MS spectra (DART, positive) were measured by a Thermo Scientific Exactive spectrometer. TLC was carried out on Merck Kieselgel 60 PF_{254}. Column chromatography was performed using WAKO GEL C-200E. All of the organic solvents used in this study were dried over appropriate drying agents and distilled prior to use.

Starting Materials. (2-Fluorophenyl)(2-halophenyl)methanones (**1a-1d**) were prepared as described previously.[4] *n*-BuLi was supplied by Asia Lithium Corporation. All other chemicals used in this study

were commercially available.

(2-Bromo-4,5-dimethoxyphenyl)(5-chloro-2-fluorophenyl)methanone (1e): prepared from 1-bromo-5-chloro-2-fluorobenzene and 2-bromo-4,5-dimethoxybenzaldehyde, *via* (2-bromo-4,5-dimethoxyphenyl)-(5-chloro-2-fluorophenyl)methanol, under the conditions reported for the preparation of **1a-1d**.[4]

(2-Bromo-4,5-dimethoxyphenyl)(5-chloro-2-fluorophenyl)methanol: yield: 62%; a colorless oil; R_f 0.20 (AcOEt/hexane 1:5); IR (neat) 3469, 1604 cm^{-1}; ^1H NMR (500 MHz) δ 2.42 (d, J = 3.4 Hz, 1H), 3.85 (s, 3H), 3.88 (s, 3H), 6.32 (d, J = 3.4 Hz, 1H), 7.02 (s, 1H), 7.05 (s, 1H), 7.09–7.12 (m, 2H), 7.20 (dd, J = 8.6, 8.0 Hz, 1H). Anal. Calcd for $C_{15}H_{13}BrClFO_3$: C, 47.96; H, 3.49. Found: C, 47.81; H, 3.74.

1e: yield: 62%; a colorless oil; R_f 0.29 (AcOEt/hexane 1:5); IR (neat) 1669, 1604 cm^{-1}; ^1H NMR (500 MHz) δ 3.88 (s, 3H), 3.94 (s, 3H), 7.01 (s, 1H), 7.05 (s, 1H), 7.15 (dd, J = 9.7, 1.1 Hz, 1H), 7.25 (d, J = 8.0 Hz, 1H), 7.65 (t, J = 8.0 Hz, 1H). Anal. Calcd for $C_{15}H_{11}BrClFO_3$: C, 48.22; H, 2.97. Found: C, 48.34; H, 2.87.

Typical Procedure for the Preparation of 9*H*-Thioxanthen-9-ones (2). 9*H*-Thioxanthen-9-one (2a).[11] A mixture of **1a** (0.12 g, 0.49 mmol) in DMF (4 mL) containing $Na_2S{\cdot}9H_2O$ (0.12 g, 0.49 mmol) was heated at 60 °C until TLC analyses (SiO_2; AcOEt/hexane 1:8) had revealed complete consumption of **1a** (*ca*. 1 h). The mixture was cooled to rt and H_2O (20 mL) was added. The precipitate was collected by filtration and recrystallized to give **2a** (0.10 g, 94%); a white solid; mp 219–221 °C (hexane/$CHCl_3$) (lit.,[3] mp 219–220 °C). The spectral (IR and ^1H-NMR) data for this compound were identical to those reported previously.[3]

2-Chloro-9*H*-thioxanthen-9-one (2b);[12] a white solid; mp 150–151 °C (hexane/CH_2Cl_2) (lit.,[12b] mp 150–151.5 °C); IR (KBr) 1635 cm^{-1}; ^1H NMR (400 MHz) δ 7.49–7.55 (m, 2H), 7.58–7.61 (m, 2H), 7.65 (ddd, J = 8.3, 6.8, 1.4 Hz, 1H), 8.60 (d, J = 2.4 Hz, 1H), 8.62 (dd, J = 7.3, 1.4 Hz, 1H).

3-Chloro-9*H*-thioxanthen-9-one (2c): a white solid; mp 171–173 °C (hexane/CH_2Cl_2) (lit.,[13] 168–172 °C); IR (KBr) 1645 cm^{-1}; ^1H NMR (500 MHz) δ 7.43 (ddd, J = 8.7, 1.8, 0.9 Hz, 1H), 7.50 (td, J = 7.3, 0.9 Hz, 1H), 7.56–7.58 (m, 2H), 7.64 (dd, J = 8.7, 6.9 Hz, 1H), 8.54 (d, J = 8.7 Hz, 1H), 8.60 (d, J = 7.3 Hz, 1H).

3-Chloro-6,7-dimethoxy-9*H*-thioxanthen-9-one (2d); a white solid; mp 218–220 °C (hexane/CH_2Cl_2). IR (KBr) 1626 cm^{-1}; ^1H NMR (500 MHz) δ 4.01 (s, 3H), 4.02 (s, 3H), 6.92 (s, 1H), 7.42 (dd, J = 8.7, 2.3 Hz, 1H), 7.57 (d, J = 2.3 Hz, 1H), 8.03 (s, 1H), 8.55 (d, J = 8.7 Hz, 1H); ^{13}C NMR δ 56.18, 56.35, 106.54, 110.06, 122.98, 125.00, 126.78, 127.03, 130.66, 131.25, 138.25, 138.37, 148.87, 153.59, 177.85; MS *m*/*z* 306 (M^+, 100). Anal. Calcd for $C_{15}H_{11}ClO_3S$: C, 58.73; H, 3.61. Found: C, 58.80; H, 3.69.

2-Chloro-6,7-dimethoxy-9*H*-thioxanthen-9-one (2e): a white solid; mp 218–220 °C (hexane/CH_2Cl_2). IR (KBr) 1626 cm^{-1}; ^1H NMR (500 MHz) δ 4.015 and 4.022 (2s, combined 6H), 6.93 (s, 1H), 7.43 (dd, J = 8.6, 2.3 Hz, 1H), 7.57 (d, J = 2.3 Hz, 1H), 8.04 (s, 1H), 8.56 (d, J = 8.6 Hz, 1H); ^{13}C NMR δ 56.22,

56.38, 106.54, 110.07, 122.99, 125.03, 126.77, 127.04, 130.66, 131.25, 138.26, 138.37, 148.88, 153.59, 177.86; MS *m/z* 306 (M^+, 100). Anal. Calcd for $C_{15}H_{11}ClO_3S$: C, 58.73; H, 3.61. Found: C, 58.64; H, 3.85.

Typical Procedure for the Preparation of Compounds (4, 8, and 12). (2-Chlorophenyl)(2-chloropyridin-3-yl)methanol (4a). To a stirred solution of 2-chloro-3-lithiopyridine (10 mmol), generated according to the reported method,[10] in THF (30 mL) at –78 °C was added dropwise 2-ClC_6H_4CHO (1.7 g, 12 mmol). After 5 min, water (20 mL) was added, and the mixture was extracted with AcOEt (3 × 20 mL). The combined extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated by evaporation. The residue was purified by column chromatography on SiO_2 to give **4a** (1.9 g, 75%); a yellow oil; R_f 0.30 (AcOEt/hexane 1:3); IR (neat) 3345 cm^{-1}; ^1H NMR (500 MHz) δ 2.82 (d, *J* = 4.1 Hz, 1H), 6.48 (d, *J* = 4.1 Hz, 1H), 7.26–7.33 (m, 4H), 7.39 (m, 1H), 7.76 (dd, *J* = 7.8, 1.8 Hz, 1H), 8.34 (dd, *J* = 4.6, 1.8 Hz, 1H). Anal. Calcd for $C_{12}H_9Cl_2NO$: C, 56.72; H, 3.57; N, 5.51. Found: C, 56.70; H, 3.78; N, 5.70.

(2-Bromo-5-methoxyphenyl)(2-chloropyridin-3-yl)methanol (4b): a white solid; mp 135–137 °C (hexane/CH_2Cl_2); IR (KBr) 3185 cm^{-1}; ^1H NMR (500 MHz) δ 2.74 (d, *J* = 4.1 Hz, 1H), 3.77 (s, 3H), 6.37 (d, *J* = 4.1 Hz, 1H), 6.77 (dd, *J* = 8.7, 2.8 Hz, 1H), 6.92 (d, *J* = 2.8 Hz, 1H), 7.25 (dd, *J* = 7.8, 4.6 Hz, 1H), 7.47 (d, *J* = 8.7 Hz, 1H), 7.67 (dd, *J* = 7.8, 1.8 Hz, 1H), 8.35 (dd, *J* = 4.6, 1.8 Hz, 1H). Anal. Calcd for $C_{13}H_{11}BrClNO_2$: C, 47.52; H, 3.37; N, 4.26. Found: C, 57.58; H, 3.60; N 4.10.

(2-Chloropyridin-3-yl)(2,3-dichlorophenyl)methanol (4c): a pale-yellow solid; mp 157–158 °C (hexane/Et_2O); IR (KBr) 3213 cm^{-1}; ^1H NMR (500 MHz) δ 2.22 (s, 1H), 6.48 (s, 1H), 7.23–7.31 (m, 3H), 7.47 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.68 (dd, *J* = 7.4, 1.7 Hz, 1H), 8.36 (dd, *J* = 4.6, 1.7 Hz, 1H). Anal. Calcd for $C_{12}H_8Cl_3NO$: C, 49.95; H, 2.79; N, 4.85. Found: C, 59.83; H, 2.83; N, 4.71.

(2-Chlorophenyl)(3-chloropyridin-4-yl)methanol (8a): a white solid; mp 140–141 °C (hexane/Et_2O); IR (KBr) 3104 cm^{-1}; ^1H NMR (500 MHz) δ 2.75 (d, *J* = 4.0 Hz, 1H), 6.48 (d, *J* = 4.0 Hz, 1H), 7.19 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.24–7.31 (m, 2H), 7.42 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.48 (d, *J* = 5.2 Hz, 1H), 8.53 (d, *J* = 5.2 Hz, 1H), 8.55 (s, 1H). Anal. Calcd for $C_{12}H_9Cl_2NO$: C, 56.72; H, 3.57; N, 5.51. Found: C, 56.78; H, 3.60; N, 5.32.

(2-Bromo-5-chlorophenyl)(3-chloropyridin-4-yl)methanol (8b): a white solid; mp 164.5–165 °C (hexane/Et_2O); IR (KBr) 3153 cm^{-1}; ^1H NMR (500 MHz) δ 2.99 (d, *J* = 4.0 Hz, 1H), 6.37 (d, *J* = 4.0 Hz, 1H), 7.20 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.25 (d, *J* = 2.3 Hz, 1H), 7.38 (d, *J* = 5.2 Hz, 1H), 7.53 (d, *J* = 8.6 Hz, 1H), 8.53 (d, *J* = 2.3 Hz, 1H), 8.58 (s, 1H). Anal. Calcd for $C_{12}H_8BrCl_2NO$: C, 43.28; H, 2.42; N, 4.21. Found: C, 43.37; H, 2.66; N, 4.08.

(2-Bromo-5-methoxyphenyl)(3-chloropyridin-4-yl)methanol (8c): a white solid; mp 128–129 °C (hexane/CH_2Cl_2); IR (KBr) 3186 cm^{-1}; ^1H NMR (500 MHz) δ 3.03 (d, *J* = 4.0 Hz, 1H), 3.74 (s, 3H), 6.37 (d, *J* = 4.0 Hz, 1H), 6.76–6.78 (m, 2H), 7.41 (d, *J* = 5.2 Hz, 1H), 7.48 (d, *J* = 9.2 Hz, 1H), 8.49 (d, *J* = 5.2

Hz, 1H), 8.54 (s, 1H). Anal. Calcd for $C_{13}H_{11}BrClNO_2$: C, 47.52; H, 3.37; N, 4.26. Found: C, 47.37; H, 3.50; N, 4.19.

(2-Chlorophenyl)(4-chloropyridin-2-yl)methanol (12a): a pale-yellow solid; mp 147–149 °C (hexane/CH_2Cl_2) (lit.,[14] mp 151 °C); IR (KBr) 3089 cm^{-1}; ^1H NMR (400 MHz) δ 2.80 (s, 1H), 6.54 (s, 1H), 7.29–7.34 (m, 3H), 7.39–7.43 (m, 2H), 8.45 (*d*, *J* = 5.4 Hz, 1H), 8.57 (s, 1H).

(4-Chloropyridin-2-yl)(2,3-dichlorophenyl)methanol (12b): a pale-yellow solid; mp 161–163 °C (hexane/CH_2Cl_2); IR (KBr) 3091 cm^{-1}; ^1H NMR (400 MHz) δ 2.85 (br, 1H), 6.54 (s, 1H), 7.27 (t, *J* = 7.8 Hz, 1H), 7.35 (d, *J* = 4.9 Hz, 1H), 7.41 (d, *J* = 7.8 Hz, 1H), 7.47 (dd, *J* = 7.8, 2.0 Hz, 1H), 8.46 (d, *J* = 4.9 Hz, 1H), 8.49 (s, 1H). Anal. Calcd for $C_{12}H_8Cl_3NO$: C, 49.95; H, 2.79; N, 4.85. Found: C, 49.90; H, 2.88; N, 4.73.

(2-Bromo-5-methoxyphenyl)(4-chloropyridin-2-yl)methanol (12c): a pale-yellow solid; mp 162–163 °C (hexane/CH_2Cl_2); IR (KBr) 3100 cm^{-1}; ^1H NMR (500 MHz) δ 2.68 (d, *J* = 4.6 Hz, 1H), 3.78 (s, 3H), 6.43 (d, *J* = 4.6 Hz, 1H), 6.78 (dd, *J* = 8.6, 2.9 Hz, 1H), 7.01 (d, *J* = 2.9 Hz, 1H), 7.34 (d, *J* = 5.2 Hz, 1H), 7.46 (d, *J* = 8.6 Hz, 1H), 8.46 (d, *J* = 5.2 Hz, 1H), 8.50 (s, 1H). Anal. Calcd for $C_{13}H_{11}BrClNO_2$: C, 47.52; H, 3.37; N, 4.26. Found: C, 47.40; H, 3.18; N, 4.19.

Aryl(chloropyridinyl)methanones (**5**, **9**, and **13**) were prepared by the oxidation of **4**, **8**, and **12**, respectively, with PCC in CH_2Cl_2 as described previously.[15] For compounds **13**, after evaporation of the solvent the residue was filtered through a small pad of SiO_2 using THF as an eluent. The solution was concentrated under reduced pressure and used in the next step without any other purification.

(2-Chlorophenyl)(2-chloropyridin-3-yl)methanone (5a): a pale-yellow oil; R_f 0.44 (AcOEt/hexane 1:3); IR (neat) 1682 cm^{-1}; ^1H NMR (500 MHz) δ 7.37–7.41 (m, 2H), 7.45 (d, *J* = 7.8 Hz, 1H), 7.50 (ddd, *J* = 7.8, 7.3, 1.4 Hz, 1H), 7.60 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.90 (dd, *J* = 7.8, 1.8 Hz, 1H), 8.54 (dd, *J* = 4.6, 1.8 Hz, 1H). Anal. Calcd for $C_{12}H_7Cl_2NO$: C, 57.17; H, 2.80; N, 5.56. Found: C, 57.10; H, 2.91; N, 5.46.

(2-Bromo-5-methoxyphenyl)(2-chloropyridin-3-yl)methanone (5b): a pale-yellow oil; R_f 0.33 (AcOEt/hexane 1:1); IR (neat) 1682 cm^{-1}; ^1H NMR (500 MHz) δ 3.83 (s, 3H), 6.95 (dd, *J* = 8.7, 3.2 Hz, 1H), 7.07 (d, *J* = 3.2 Hz, 1H), 7.37 (dd, *J* = 7.8, 4.6 Hz, 1H), 7.51 (d, *J* = 8.7 Hz, 1H), 7.90 (dd, *J* = 7.8, 1.8 Hz, 1H), 8.55 (dd, *J* = 4.6, 1.8 Hz, 1H). Anal. Calcd for $C_{13}H_9BrClNO_2$: C, 47.81; H, 2.78; N, 4.29. Found: C, 47.66; H, 2.81; N, 4.25.

(2-Chloropyridin-3-yl)(2,3-dichlorophenyl)methanone (5c): a pale-yellow oil; R_f 0.23 (AcOEt/hexane 1:3); IR (neat) 1687 cm^{-1}; ^1H NMR (500 MHz) δ 7.34 (t, *J* = 8.0 Hz, 1H), 7.40 (dd, *J* = 8.0, 4.6 Hz, 1H), 7.45 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.66 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.94 (dd, *J* = 8.0, 1.7 Hz, 1H), 8.56 (dd, *J* = 4.6, 1.7 Hz, 1H). Anal. Calcd for $C_{12}H_6Cl_3NO$: C, 50.30; H, 2.11; N, 4.89. Found: C, 50.08; H, 2.39; N, 4.85.

(2-Chlorophenyl)(3-chloropyridin-4-yl)methanone (9a): a pale-yellow oil; R_f 0.29 (AcOEt/hexane

1:5); IR (neat) 1687 cm^{-1}; ^1H NMR (500 MHz) δ 7.36–7.42 (m, 2H), 7.45–7.51 (m, 2H), 7.59 (dd, *J* = 7.4, 1.7 Hz, 1H), 8.63 (d, *J* = 5.2 Hz, 1H), 8.70 (s, 1H). Anal. Calcd for $C_{12}H_7Cl_2NO$: C, 57.17; H, 2.80; N, 5.56. Found: C, 57.13; H, 3.01; N, 5.51.

(2-Bromo-5-chlorophenyl)(3-chloropyridin-4-yl)methanone (9b): a colorless oil; R_f 0.31 (AcOEt/hexane 1:5); IR (neat) 1693 cm^{-1}; ^1H NMR (500 MHz) δ 7.38–7.40 (m, 2H), 7.48 (d, *J* = 2.3 Hz, 1H), 7.59 (d, *J* = 8.6 Hz, 1H), 8.65 (d, *J* = 5.2 Hz, 1H), 8.72 (s, 1H). Anal. Calcd for $C_{12}H_6BrCl_2NO$: C 43.54; H, 1.83; N, 4.23. Found: C, 43.47; H, 2.06; N, 4.13.

(2-Bromo-5-methoxyphenyl)(3-chloropyridin-4-yl)methanone (9c): a colorless oil; R_f 0.38 (AcOEt/hexane 1:2); IR (neat) 1686 cm^{-1}; ^1H NMR (400 MHz) δ 3.83 (*s*, 3 H), 6.97 (dd, *J* = 8.8, 2.9 Hz, 1H), 7.06 (d, *J* = 2.9 Hz, 1H), 7.37 (d, *J* = 4.9 Hz, 1H), 7.53 (d, *J* = 8.8 Hz, 1H), 8.62 (d, *J* = 4.9 Hz, 1H), 8.71 (s, 1H). Anal. Calcd for $C_{13}H_9BrClNO_2$: C, 47.81; H, 2.78; N, 4.29. Found: C, 47.63; H, 2.88; N, 4.06.

Typical Procedure for the Preparation of Benzothiopyranopyridinones (6, 10, and 14). 5*H*-[1]Benzothiopyrano[2,3-*b*]pyridin-5-one (6a): A solution of **5a** (0.20 g, 0.79 mmol) and $Na_2S·9H_2O$ (0.19 g, 0.79 mmol) in DMF (4 mL) was heated at 60 ˚C for 1 h under stirring. After cooling to rt, H_2O (20 mL) was added and the precipitate was collected by filtration. Recrystallization of the crude product from hexane/CH_2Cl_2 gave **6a** (0.15 g, 88%); a white solid; mp 232–234 °C (lit.,[16] mp 234 °C); IR (KBr) 1651 cm^{-1}; ^1H NMR (500 MHz) δ 7.46 (dd, *J* = 7.3, 4.6 Hz, 1H), 7.53 (ddd, *J* = 7.8, 7.3, 0.9 Hz, 1H), 7.64–7.70 (m, 2H), 8.60 (dd, *J* = 7.8, 0.9 Hz, 1H), 8.80 (dd, *J* = 4.6, 1.8 Hz, 1H), 8.84 (dd, *J* = 7.8, 1.8 Hz, 1H).

7-Methoxy-5*H*-[1]benzothiopyrano[2,3-*b*]pyridin-5-one (6b): a yellow solid; mp 182–184 °C (hexane/$CHCl_3$); IR (KBr) 1634 cm^{-1}; ^1H NMR (500 MHz) δ 3.95 (s, 3H), 7.31 (dd, *J* = 8.7, 2.8 Hz, 1H), 7.44 (dd, *J* = 8.2, 4.6 Hz, 1H), 7.56 (d, *J* = 8.7 Hz, 1H), 8.04 (d, *J* = 2.8 Hz, 1H), 8.80 (dd, *J* = 4.6, 1.8 Hz, 1H), 8.85 (dd, *J* = 8.2, 1.8 Hz, 1H); ^{13}C NMR δ 55.73, 110.49, 121.41, 123.29, 125.71, 127.71, 129.30, 129.95, 137.84, 153.19, 158.72, 158.89, 180.34; MS *m/z* 243 (M^+, 100). Anal. Calcd for $C_{13}H_9NO_2S$: C, 64.18; H, 3.73; N, 5.76. Found: C, 64.14; H, 3.73; N, 5.71.

9-Chloro-5*H*-[1]benzothiopyrano[2,3-*b*]pyridin-5-one (6c): a pale-yellow solid; mp 194–196 °C (hexane/CH_2Cl_2); IR (KBr) 1645 cm^{-1}; ^1H NMR (500 MHz) δ 7.47–7.51 (m, 2H), 7.78 (dd, *J* = 7.4, 1.1 Hz, 1H), 8.56 (dd, *J* = 8.0, 1.1 Hz, 1H), 8.82 (dd, *J* = 8.0, 1.7 Hz, 1H), 8.85 (dd, *J* = 4.6, 1.7 Hz, 1H); ^{13}C NMR δ 122.09, 125.49, 126.69, 128.42, 130.70, 130.85, 133.36, 136.86, 137.74, 153.67, 158.22, 180.40; MS *m/z* 247 (M^+, 100). Anal. Calcd for $C_{12}H_6ClNOS$: C, 58.19; H, 2.44; N, 5.65. Found: C, 58.17; H, 2.57; N, 5.50.

5*H*-[1]Benzothiopyrano[2,3-c]pyridin-5-one (10a):[16] a pale-yellow solid; mp 172–172.5 °C (hexane/CH_2Cl_2); IR (KBr) 1652 cm^{-1}; ^1H NMR (500 MHz) δ 7.56 (dd, *J* = 8.0, 6.9 Hz, 1H), 7.66 (d, *J* = 8.0 Hz,

1H), 7.71 (dd, *J* = 8.0, 6.9 Hz, 1H), 8.34 (d, *J* = 5.2 Hz, 1H), 8.63 (d, *J* = 8.0 Hz, 1H), 8.70 (d, *J* = 5.1 Hz, 1H), 8.98 (s, 1H).

7-Chloro-5*H*-[1]benzothiopyrano[2,3-*c*]pyridin-5-one (10b): a pale-yellow solid; mp 210–212 °C (hexane/CH_2Cl_2); IR (KBr) 1638 cm^{-1}; ^1H NMR (500 MHz) δ 7.62 (d, *J* = 8.6 Hz, 1H), 7.67 (dd, *J* = 8.6, 2.3 Hz, 1H), 8.33 (d, *J* = 4.6 Hz, 1H), 8.59 (d, *J* = 2.3 Hz, 1H), 8.71 (d, *J* = 5.2 Hz, 1H), 8.98 (s, 1H); ^{13}C NMR δ 121.44, 128.18, 129.39, 130.01, 132.20, 133.33, 133.47, 133.50, 134.76, 146.69, 148.55, 178.12; MS *m/z* 247 (M^+, 100). Anal. Calcd for $C_{12}H_6ClNOS$: C, 58.19; H, 2.44; N, 5.65. Found: C, 58.00; H, 2.69; N, 5.57.

7-Methoxy-5*H*-[1]benzothiopyrano[2,3-*c*]pyridin-5-one (10c): a yellow solid; mp 160–161 °C (hexane/CH_2Cl_2); IR (KBr) 1630, 1604 cm^{-1}; ^1H NMR (500 MHz) δ 3.96 (s, 3H), 7.35 (dd, *J* = 8.8, 2.9 Hz, 1H), 7.58 (d, *J* = 8.8 Hz, 1H), 8.07 (d, *J* = 2.9 Hz, 1H), 8.36 (d, *J* = 4.9 Hz, 1H), 8.69 (d, *J* = 4.9 Hz, 1H), 8.99 (s, 1H); ^{13}C NMR δ 55.74, 110.21, 121.42, 123.72, 128.03, 128.47, 130.13, 132.84, 132.99, 146.02, 148.62, 158.88, 178.81; MS *m/z* 243 (M^+, 100). Anal. Calcd for $C_{13}H_9NO_2S$: C, 64.18; H, 3.73; N, 5.76. Found: C, 64.10; H, 3.79; N, 5.80.

10*H*-[1]Benzothiopyrano[3,2-*c*]pyridin-10-one (14a):[16] a pale-yellow solid; mp 145–147 °C (hexane/CH_2Cl_2); IR (KBr) 1643 cm^{-1}; ^1H NMR (500 MHz) δ 7.46 (d, *J* = 5.2 Hz, 1H), 7.56 (ddd, *J* = 8.0, 7.4, 1.1 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.69 (ddd, *J* = 8.0, 7.4, 1.1 Hz, 1H), 8.63 (dd, *J* = 8.0, 1.1 Hz, 1H), 8.67 (d, *J* = 5.2 Hz, 1H), 9.69 (s, 1H).

6-Chloro-10*H*-[1]benzothiopyrano[3,2-*c*]pyridin-10-one (14b): a pale-yellow solid; mp 194–196 °C (hexane/CH_2Cl_2); IR (KBr) 1642 cm^{-1}; ^1H NMR (500 MHz) δ 7.52 (dd, *J* = 8.0, 7.4 Hz, 1 H), 7.54 (d, *J* = 4.9 Hz, 1H), 7.78 (dd, *J* = 7.4, 1.1 Hz, 1H), 8.58 (dd, *J* = 8.0, 1.1 Hz, 1 H), 8.71 (d, *J* = 4.9 Hz, 1H), 9.67 (s, 1H); ^{13}C NMR δ 120.28, 123.01, 127.23, 128.27, 130.73, 132.04, 133.43, 135.28, 145.67, 150.61, 152.15, 179.01. HR MS. Calcd for $C_{12}H_7ClNOS$ (M+H): 247.9937. Found: *m/z* 247.9927. Anal. Calcd for $C_{12}H_6ClNOS$: C, 58.19; H, 2.44; N, 5.65. Found: C, 58.02; H, 2.49; N, 5.37.

8-Methoxy-10*H*-[1]benzothiopyrano[3,2-*c*]pyridin-10-one (14c): a pale-yellow solid; mp 201–203 °C (hexane/CH_2Cl_2); IR (KBr) 1644, 1602 cm^{-1}; ^1H NMR (500 MHz) δ 3.96 (s, 3H), 7.32 (dd, *J* = 8.6, 2.9 Hz, 1H), 7.46 (d, *J* = 5.2 Hz, 1H), 7.51 (d, *J* = 8.6 Hz, 1H), 8.08 (d, *J* = 2.9 Hz, 1H), 8.64 (d, *J* = 5.2 Hz, 1H), 9.70 (s, 1H); ^{13}C NMR δ 55.78, 110.45, 119.82, 123.27, 127.58, 131.33, 146.29, 146.56, 149.75 (2C), 152.27, 159.16, 179.10. HR MS. Calcd for $C_{13}H_{10}NO_2S$ (M+H): 244.0432. Found: *m/z* 244.0416. Anal. Calcd for $C_{13}H_9NO_2S$: C, 64.18; H, 3.73; N, 5.76. Found: C, 64.15; H, 3.76; N, 5.74.

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