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Note

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2-Acetylthienopyridines Synthesis via Thiolation and Cu-catalyzed Cyclization of *ortho*-Propynol Fluoropyridine Using Xanthate as a Thiol Surrogate

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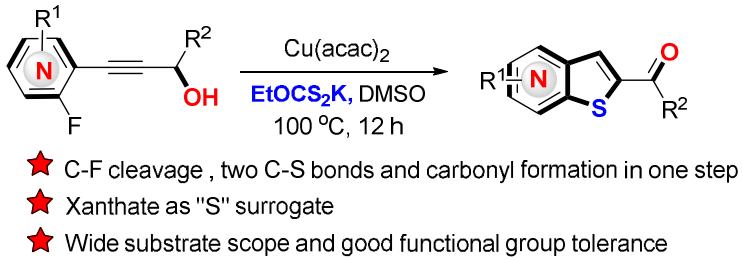
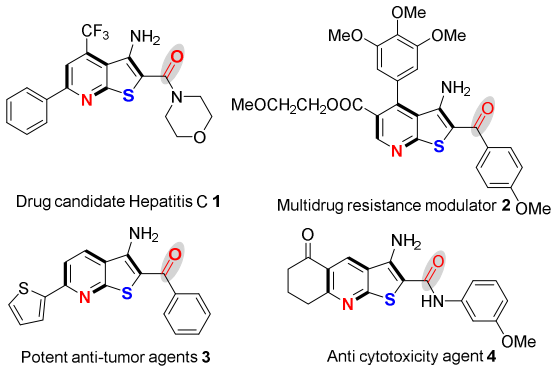


ABSTRACT: 2-Acylthienopyridines and related heterocycles are readily prepared in moderate-to-good yields under mild conditions by a nucleophilic thiolation, copper-catalyzed cyclization and oxidation cascade process using potassium xanthate as the thiol source. Moreover, excellent chemo-selectivity, broad substrate scope and good functional group tolerance are prominent features of this transformation.

The development of efficient and sustainable methodologies for the synthesis of heteroatom-rich heterocycles is crucial in modern organic synthesis. Such compounds are prevalent in natural products, pharmaceuticals and even organic light-emitting materials.[1] The 2-acylthienopyridine scaffold is commonly found in various drug candidates and shows a broad range of bioactivities. This motif appears as the core of many potential small-molecule drugs, as reported by several

research groups (Figure 1). For example, a 2-acylthieno[2,3-*b*]pyridine-based drug has been identified for the treatment of hepatitis C.[2] Krauze and co-workers have also utilized the 2-acylthieno[2,3-*b*]pyridine scaffold as a new class of multidrug resistance modulator **2**.[3] Sugano and co-workers have found that this motif also appears in promising new anti-tumor agents **3**, which are selective against a tumorigenic cell line.[4] Other examples of bioactivity include anti-proliferative activity against the NCI-60 cell lines,[5] binders to dopamine D2 receptor,[6] inhibitors of IκB kinase-*β*,[7] trans activation of HIV-1,[8] and selective inhibition of ICAM-1 and E-selectin expression in human endothelial cells.[9]

Figure 1. Selected 2-acylthieno[2,3-*b*]pyridine derivatives with biological activities



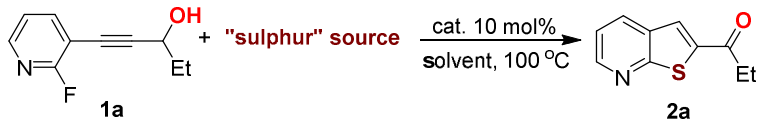
Despite the importance of 2-acylthienopyridines, synthetic methodology to efficiently construct this motif is very limited, which hampers further studies and applications in medicinal chemistry. Sekar and co-workers utilized 2-iodochalcones and xanthate as a sulfur source to synthesize 2-acylbenzothiophene compounds through α-C-H functionalization.[10] Recently, Nguyen and co-workers reported an unusual approach to 2-acylbenzothiophenes by using N,N-Diisopropylethylamine as a sulfur activator to promote the cyclization reaction.[11] Compared with 2-acylbenzothiophene derivatives, 2-acylthienopyridine has broader biological activity;

however, the pyridyl compound is more challenging to synthesize because of the ability of pyridine to coordinate to transition metal catalysts, and the electron-deficient nature of a pyridine ring compared with that of a phenyl ring.[12] In addition to acylation reactions and other traditional synthetic methods, one common approach to the synthesis of 2-acylthienopyridines is the condensation of 2-halobenzaldehyde with 2-mercaptoacetone under basic aqueous conditions.[13] González-Romero and co-workers reported another approach to the synthesis of 2-acylthienopyridines by converting a benzyl azido group to carbonyl group.[14] In these reported methods, the starting materials were either expensive or required several synthetic steps to prepare. During the course of our studies into the development of new reactions involving sulfur-containing heterocycles using Na_2S or potassium xanthate as a thiol source,[15] we observed unusually efficient nucleophilic substitution of aryl fluoride groups by thiol nucleophiles. Herein, we report an efficient and facile approach to 2-acylthienopyridines and 2-acetylbenzothiophenes. We achieved this by employing the well-developed Pd-catalyzed Sonogashira reaction between two commercially available starting materials, followed by nucleophilic thiolation, copper-catalyzed cyclization and oxidation cascade process.

Initially, we examined the reaction of 1-(2-fluoropyridin-3-yl)pent-1-yn-3-ol **1a** and potassium xanthate in DMSO, without a catalyst, and no product was obtained (Table 1, entry 1). Only a trace of the desired product **2a** was obtained when $PdCl_2$ was used as a catalyst (Table 1, entry 2). To our delight, CuCl significantly improved the yield and gave the desired product in 68% yield (Table 1, entry 3). Encouraged by these results, we screened various copper salts to further increase the efficiency of the reaction (Table 1, entries 3-7). The results showed that the $Cu(acac)_2$ was superior to

the other catalysts screened and gave the desired product in 93% yield. Moderate yields (73%) of desired product **2a** were obtained using a decreased amount of $EtOCS_2K$ (1.5 equiv.) (Table 1, entry 8). Subsequently, we investigated various thiol surrogates, such as thiourea, $Na_2S{\cdot}9H_2O$, S_8 and $(NH_4)_2S$ (Table 1, entries 10-13). None of the thiol surrogates promoted the reaction well, only $Na_2S{\cdot}9H_2O$ generated the 1-(thieno[2,3-*b*]pyridin-2-yl)propan-1-one **2a** in 31% yield. Finally, a solvent screen revealed that this transformation works in DMF, DMA and dioxane although they are all less effective than DMSO (Table 1, entries 14-16). It seems that the presence of O_2 (1 atm) does not facilitate the reaction (Table 1 entry 17). Decreased yields were obtained when either lower or elevated reaction temperatures were used (Table 1, entries 18-19).

Table 1. Optimization of Reaction Conditions [a]



entry	catalyst	sulphur source	solvent	Yield (%)[b]
1[c]	-	$EtOCS_2K$	DMSO	n.d.
2	$PdCl_2$	$EtOCS_2K$	DMSO	<5
3	CuCl	$EtOCS_2K$	DMSO	68
4	CuBr	$EtOCS_2K$	DMSO	78
5	CuI	$EtOCS_2K$	DMSO	81
6	$Cu(OTf)_2$	$EtOCS_2K$	DMSO	91
7	$Cu(acac)_2$	$EtOCS_2K$	DMSO	93
8[d]	$Cu(acac)_2$	$EtOCS_2K$	DMSO	73

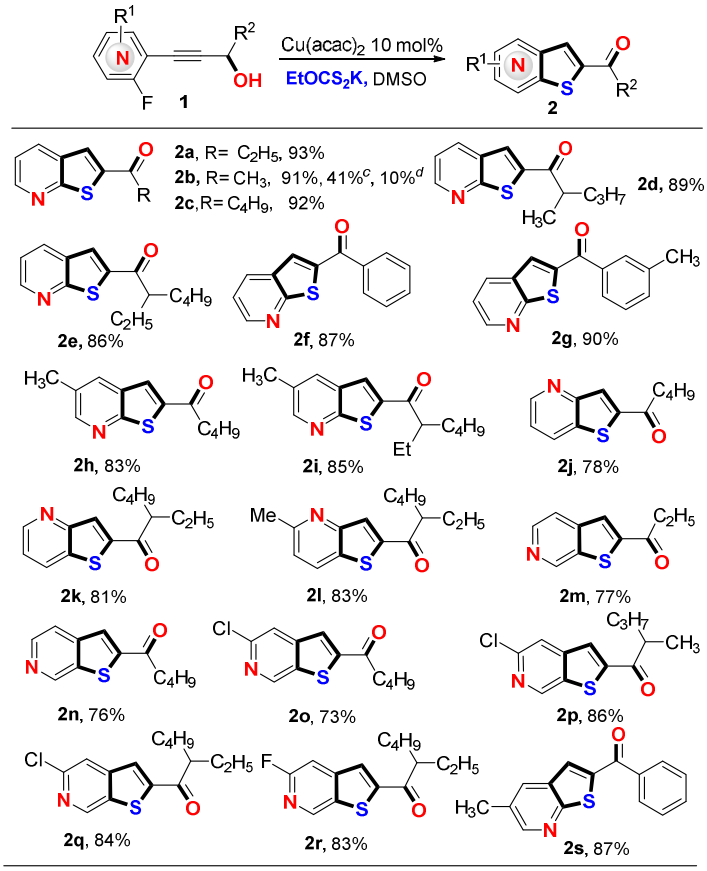
9[e]	$Cu(acac)_2$	$EtOCS_2K$	DMSO	85
10	$Cu(acac)_2$	thiourea	DMSO	n.d.
11	$Cu(acac)_2$	$Na_2S·9H_2O$	DMSO	31
12	$Cu(acac)_2$	S_8	DMSO	<5
13	$Cu(acac)_2$	$(NH_4)_2S$	DMSO	<5
14	$Cu(acac)_2$	$EtOCS_2K$	DMF	83
15	$Cu(acac)_2$	$EtOCS_2K$	DMAc	76
16	$Cu(acac)_2$	$EtOCS_2K$	dioxane	23
17[f]	$Cu(acac)_2$	$EtOCS_2K$	dioxane	19
18[g]	$Cu(acac)_2$	$EtOCS_2K$	DMSO	85
19[h]	$Cu(acac)_2$	$EtOCS_2K$	DMSO	36

[a] Reaction conditions: alkyne **1** (1.0 mmol), catalyst (10 mol%), sulfur source (2.0 mmol) in solvent (3.0 mL) at 100 °C for 12 h; [b] Isolated yields; [c] 1-(thieno[2,3-*b*]pyridin-2-yl)propan-1-ol was obtained as major product; [d] $EtOCS_2K$ (1.5 mmol) was used; [e] under N_2 condition; [f] under O_2 (1 atm) condition; [g] Reaction was carried out at 130 °C; [h] Reaction was carried out at 80 °C.

To verify the practicality of the process, we next explored the scope of the thiolation, cyclization and oxidation cascade, as shown in Scheme 1. The results showed that this approach to 2-acylthienopyridines is quite robust. Initially, R^2 substituents at the propargyglic alcohol moiety of 1-(2-alkynyl)fluoropyridine **1** were evaluated (Scheme 1, **2a**-**e**). The results demonstrated that methyl, ethyl, isopropyl, n-butyl, n-pentyl, sec-pentyl and 3-heptyl groups can be well tolerated and gave the corresponding products in good yields. Cl or Br-substituted 4-(2-halopyridin-3-yl)but-3-yn-2-ol also

afforded 2-acetylthienopyridine products **2b** in 41% and 10% yields, respectively. This result shows that the reactivity of nucleophilic substitution on halogen atoms follows the descending order of F > Cl > Br. Importantly, substrates with an aryl group as the R^2 substituent were compatible with this reaction's conditions, and the corresponding thiolation/cyclization products **2f** and **2g** were obtained in good yields. Next, the R^1 substituents on the pyridyl rings of 1-(2-alkynolyl)fluoropyridine **1** were evaluated. When 1-(2-fluoro-5-methylpyridin-3-yl)hept-1-yn-3-ol was employed as the substrate, the desired product **2h** was obtained in 83% yield. Subsequently, several substituted 2-fluoro alkynylpyridines were examined and the results demonstrated that both electron-deficient and electron-rich pyridines reacted with potassium xanthate to give the corresponding 2-acylthienopyridine products in moderate-to-good yields. Notably, 2-acylthieno[2,3-*b*]pyridines (**2a**-**2i**, **2s**), 2-acylthieno[3,2-*b*]pyridines[16] (**2j**-**2l**) and 2-acylthieno[2,3-*c*]pyridines[17] (**2m**-**2**r) were readily prepared in good yields by employing this process.

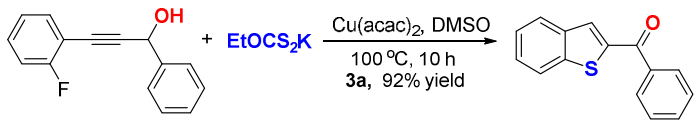
Scheme 1. Synthesis of 2-acylthienopyridines using xanthate as thiol precursor [a]



[a] Reaction conditions: alkyne **1** (1.0 mmol), $Cu(acac)_2$ (10 mol%), $EtOCS_2K$ (2.0 mmol) in DMSO (2.0 mL) at 100 °C for 12 h; [b] Yields are given for isolated; [c] 4-(2-chloropyridin-3-yl)but-3-yn-2-ol was used as substrate; [d] 4-(2-bromopyridin-3-yl)but-3-yn-2-ol was used as substrate.

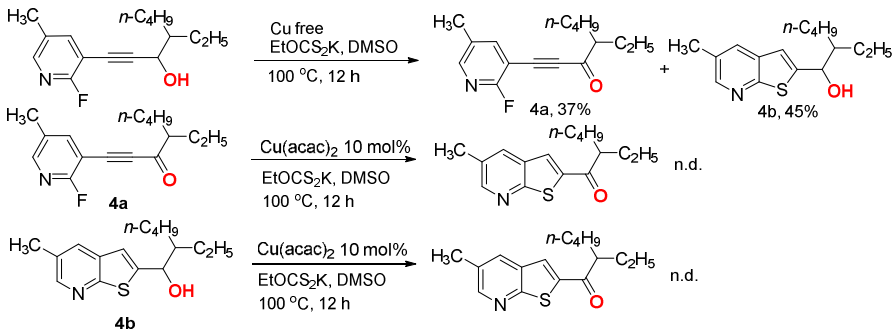
To further broaden the scope of the thiolation, cyclization and oxidation process, a non-pyridyl aryl fluoride was used. Specifically, when 3-(2-fluorophenyl)-1-phenylprop-2-yn-1-ol was used as the substrate, the copper-catalyzed thiolation and *S*-cyclization of 3-(2-fluorophenyl)-1-phenylprop-2-yn-1-ol afforded 2-acylbenzo[*b*]thiophenes **3a** in 92% yield (Scheme 2).

Scheme 2. Synthesis of 2-acylbenzo[*b*]thiophenes



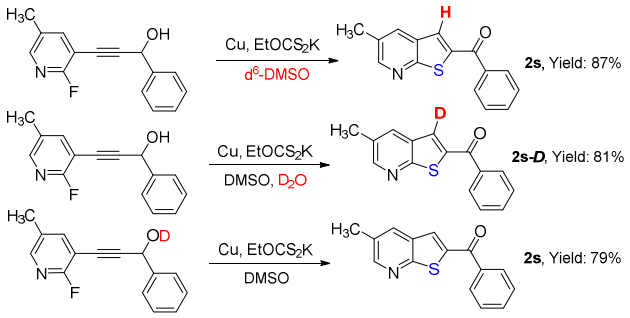
For a clearer understanding of the reaction mechanism, control reactions were performed. When the reaction was performed in the absence of copper, 4-ethyl-1- (2-fluoro-5-methylpyridin-3-one) **4a** and 2-ethyl-1-5-methylthieno[2,3-*b*]pyridin-2-yl) hexan-1-ol **4b** were formed (Scheme 3). When these two products were used as reaction substrates under the standard reaction, no 2-acylthienopyridine product was formed. These results suggest that the reaction occurs through a Cu-catalyzed process rather than a stepwise reaction.

Scheme 3. Control reactions



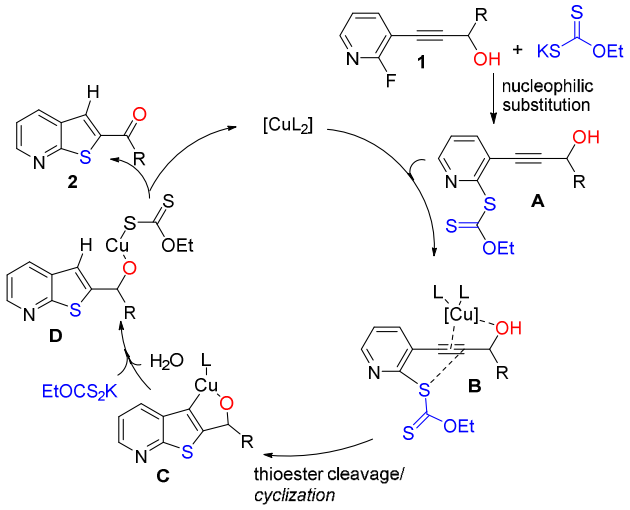
Deuteration experiments revealed further insights into the reaction mechanism. When d_6-DMSO was used as the reaction solvent, deuterium atom-labeled product **2s-D** was not detected. However, when D_2O was used as the solvent, a deuterium at the 3-position of thienopyridine **2s–D** was detected. While using hydroxyl deuterium labeled propargyl alcohol as the substrate, no exchange of deuterium atoms occurred and the normal product **2s** was obtained (Scheme 4). These results indicated that water acted as a proton donor in this transformation.

Scheme 4. Deuteration experiments



The postulated reaction mechanism for the synthesis of 2-acylthienopyridines is proposed in Scheme 5. Initially, a nucleophilic substitution reaction occurs at the *ortho* position of propynol fluoropyridine **1** with $EtOCS_2K$ to provide intermediate **A**.[18] Then, the intermediate **A** may undergoes a thioester cleavage and *5-endo-dig*- cyclization to give the thienylcopper intermediate **C** with the aid of copper salts.[10,15] Next, a copper-catalyzed oxidation of the alcohol through a similar cyclometallation process occurs. Although it is currently difficult to determine the detailed of oxidation mechanism, it seems that the $EtOCS_2K$ may help to facilitate the oxidation process through coordination of potassium xanthate with copper complexes.[20]

Scheme 5. Proposed mechanism



In conclusion, an efficient and practical nucleophilic thiolation and copper-catalyzed cyclization method for preparing functionalized 2-acylthienopyridines and 2-acylbenzothiophenes in

moderate-to-good yields was reported. This thiolation and cyclization method exhibits broad substrate scope and tolerance of various functional groups. This unprecedented cascade thiolation and cyclization reaction provides straightforward access to biologically important 2-acylthienopyridine molecules for pharmaceutical chemistry and materials science. Current efforts are aimed at determining the mechanism in more detail and developing the thiolation and cyclization process for the synthesis of potential small-molecule drugs and materials.

EXPERIMENTAL SECTION

General Information: Unless otherwise noted, all commercial materials and solvents were used without further purification and all the reactions were carried out in a Schlenk tube equipped with magnetic stir bar. ^{1}H NMR spectra were recorded in $CDCl_3$ at 400 MHz and ^{13}C NMR spectra were recorded in $CDCl_3$ at 100 MHz respectively, ^{1}H and ^{13}C NMR were referenced to $CDCl_3$ at δ 7.26 and 77.0 respectively. GC–MS was obtained using electron ionization (Agilent Technologies 7890A/5975C). HRESIMS spectra were acquired using an Agilent 6210 ESI/TOF mass spectrometer. TLC was performed using commercially prepared 100-400 mesh silica gel plates (GF_{254}), and visualization was effected at 254 nm. All the other chemicals were purchased from Aldrich Chemicals. Commercial reagents were used without further purification.

General Procedure for the Preparation of Ethynylpyridines: A mixture of 2-fluoro-3-iodopyridine (1 mmol), but-3-yn-2-ol (1.2 mmol), $PdCl_2(PPh_3)_2$ (5 mol%), CuI (10 mol%), Et_3N (1 mL) and THF (2 mL), was added successively in a 20 mL Schlenk tube. After stirring for 8 h at 30 ^{o}C, the solution was filtered though a small amount of silica gel. Then the residue was concentrated in vacuo and the crude was purified by flash chromatography with

n-hexane/ethyl acetate (10/1, v/v) to afford the 4-(2-fluoropyridin-3-yl)but-3-yn-2-ol as a pale-yellow oil in 90% yield.

General Procedure for the Preparation of 2-Acetylthienopyridines: A mixture of 4-(2-fluoropyridin-3-yl)but-3-yn-2-ol (1 mmol), $Cu(acac)_2$ (10 mol%), $EtOCS_2K$ (2.0 mmol) and DMSO (2 mL), was added successively in a 20 mL Schlenk tube. After stirring for 12 h at 100 ^oC, the solution was filtered though a small amount of silica gel. Then the residue was concentrated in vacuo and the crude was purified by flash chromatography with n-hexane/ethyl acetate (10/1, v/v) to afford the 1-(thieno[2,3-*b*]pyridin-2-yl)ethanones as a pale-yellow solid.

1-(Thieno[2,3-*b*]pyridin-2-yl)propan-1-one (2a): yellow solid (178 mg, 93% yield); mp 155-156 □; R_f = 0.39 (ethyl acetate/petroleum ether = 1:10); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.16 (d, J = 8.1 Hz, 1H), 7.88 (s, 1H), 7.36 (dd, J = 8.0, 4.6 Hz, 1H), 3.04 (q, J = 7.3 Hz, 2H), 1.28 (t, J = 7.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 195.1, 163.3, 149.5, 143.2, 133.4, 132.7, 125.9, 120.2, 32.5, 8.3. **GC-MS** (EI, 70 eV) m/z: 191, 177; **ESI-HRMS** (m/z): $[M+H]^+$ calcd for $C_{10}H_{10}NOS$, 192.0478, found: 192.0482.

1-(Thieno[2,3-*b*]pyridin-2-yl)ethanone (2b)[19]: yellow solid (161 mg, 91% yield); mp 123-125 □; R_f = 0.41 (ethyl acetate/petroleum ether = 1:10); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.17 (d, J = 8.1 Hz, 1H), 7.88 (s, 1H), 7.38 (d, J = 3.1 Hz, 1H), 2.67 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 192.1, 163.4, 149.6, 143.7, 133.4, 132.78, 126.8, 120.4, 26.6; **GC-MS** (EI, 70 eV) m/z: 177, 162, 134; **ESI-HRMS** (m/z): $[M+H]^+$ calcd for C_9H_8NOS, 178.0321, found 178.0322.

1-(Thieno[2,3-*b*]pyridin-2-yl)pentan-1-one (2c): yellow solid (201 mg, 92% yield); mp 105-106 □; R_f = 0.46 (ethyl acetate / petroleum ether = 1:5); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.66 (d, *J* = 3.4 Hz, 1H), 8.15 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.87 (s, 1H), 7.34 (dd, *J* = 8.1, 4.6 Hz, 1H), 2.98 (t, *J* = 7.4 Hz, 2H), 1.84 – 1.67 (m, 2H), 1.42 (dq, *J* = 14.7, 7.4 Hz, 2H), 0.95 (t, *J* = 7.3 Hz, 3H*);* **^{13}C** N**M**R (100 MHz, $CDCl_3$) *δ* 194.8, 163.2, 149.4, 143.5, 133.4, 132.7, 126.0, 120.2, 38.8, 26.6, 22.4, 13.8. **GC-MS** (EI, 70 eV) m/z: 219, 190, 177; **ESI-HRMS** (m/z): $[M+H]^+$ calcd for $C_{12}H_{14}NOS$, 220.0791, found 220.0789.

2-Methyl-1-(thieno[2,3-*b*]pyridin-2-yl)pentan-1-one (2d): yellow liquid (207 mg, 89% yield); R_f = 0.37 (ethyl acetate/petroleum ether = 1:5); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 8.69 (s, 1H), 8.18 (d, *J* = 8.0 Hz, 1H), 7.91 (s, 1H), 7.37 (dd, *J* = 7.9, 4.5 Hz, 1H), 3.41 (dd, *J* = 13.6, 6.8 Hz, 1H), 1.91 – 1.76 (m, 1H), 1.56 – 1.45 (m, 1H), 1.42 – 1.32 (m, 2H), 1.27 (d, *J* = 6.9 Hz, 3H), 0.92 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) *δ* 198.8, 163.3, 149.4, 143.5, 133.6, 132.9, 125.8, 120.3, 42.2, 36.2, 20.7, 17.5, 14.1. **GC-MS** (EI, 70 eV) m/z: 233, 191, 134; **ESI-HRMS** (m/z): $[M+H]^+$ calcd for $C_{13}H_{16}NOS$, 234.0947, found 234.0946

2-Ethyl-1-(thieno[2,3-*b*]pyridin-2-yl)hexan-1-one (2e): yellow liquid (224 mg, 86% yield); R_f = 0.41 (ethyl acetate/petroleum ether = 1:5); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 8.68 (d, *J* = 4.2 Hz, 1H), 8.17 (d, *J* = 8.0 Hz, 1H), 7.90 (s, 1H), 7.35 (dd, *J* = 8.1, 4.6 Hz, 1H), 3.34 – 3.19 (m, 1H), 1.88 – 1.75 (m, 2H), 1.67 – 1.54 (m, 2H), 1.29 – 1.25 (m, 4H), 0.91 (t, *J* = 7.4 Hz, 3H), 0.85 (t, *J* = 6.8 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) *δ* 199.0, 163.5, 149.5, 144.6, 133.5, 132.8, 125.8, 120.2, 49.6, 32.1, 29.8, 25.9, 22.8, 13.9, 12.0. **GC-MS** (EI, 70 eV) m/z: 261, 205, 190; **ESI-HRMS** (m/z): $[M+H]^+$ calcd for $C_{15}H_{20}NOS$, 262.1260, found 262.1259.

Phenyl(thieno[2,3-*b*]pyridin-2-yl)methanone (2f)[21]**:** yellow solid (208 mg, 87% yield); mp 96-98 □; R_f = 0.35 (ethyl acetate/petroleum ether = 1:5); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.71 (dd, *J* = 4.5, 1.4 Hz, 1H), 8.16 (dd, *J* = 8.1, 1.5 Hz, 1H), 8.00 – 7.89 (m, 2H), 7.80 (s, 1H), 7.65 (t, *J* = 7.4 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 2H), 7.38 (dd, *J* = 8.1, 4.6 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 189.5, 163.5, 149.7, 142.9, 137.3, 133.5, 132.8, 132.5, 129.4, 129.3 (2C), 128.6 (2C), 120.3. **GC-MS** (EI, 70 eV) m/z: 239, 211, 162; **ESI-HRMS** (m/z): $[M+H]^+$ calcd for $C_{14}H_{10}NOS$, 240.0478, found 240.0476.

(thieno[2,3-*b*]pyridin-2-yl)(m-tolyl)methanone (2g): yellow solid (228 mg, 90% yield); mp 135-137 □;R_f = 0.44 (ethyl acetate/petroleum ether = 1: 5); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.70 (d, *J* = 4.5 Hz, 1H), 8.16 (d, *J* = 8.1 Hz, 1H), 7.79 (s, 1H), 7.70 (d, *J* = 8.9 Hz, 2H), 7.43 (dt, *J* = 14.8, 7.5 Hz, 2H), 7.37 (dd, *J* = 8.0, 4.6 Hz, 1H), 2.46 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 189.7, 163.5, 149.6, 143.0, 138.6, 137.3, 133.6, 133.5, 132.5, 129.8, 129.4, 128.4, 126.6, 120.3, 21.4. **GC-MS** (EI, 70 eV) m/z: 253, 239, 226; **HRMS ESI** (m/z): calcd for $C_{15}H_{12}NOS$, 254.0634, found: 254.0629.

1-(5-Methylthieno[2,3-*b*]pyridin-2-yl)pentan-1-one (2h): yellow solid (193 mg, 83% yield); mp 113-114□; R_f = 0.41 (ethyl acetate/petroleum ether = 1: 10); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.53 (d, *J* = 1.9 Hz, 1H), 7.94 (d, *J* = 1.0 Hz, 1H), 7.82 (s, 1H), 3.04 – 2.92 (m, 2H), 2.48 (s, 3H), 1.78 (dt, *J* = 20.6, 7.5 Hz, 2H), 1.44 (dq, *J* = 14.7, 7.4 Hz, 2H), 0.97 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 194.9, 160.7, 151.0, 143.6, 133.1, 132.7, 129.9, 125.7, 38.9, 26.7, 22.4, 18.4, 13.9. **GC-MS** (EI, 70 eV) m/z: 233, 204, 176; **ESI-HRMS** (m/z): $[M+H]^+$ calcd for $C_{13}H_{16}NOS$, 234.0947, found 234.0948.

2-Ethyl-1-(5-methylthieno[2,3-*b*]pyridin-2-yl)hexan-1-one (2i): yellow liquid (234 mg, 85% yield); R_f = 0.39 (ethyl acetate/petroleum ether = 1: 10); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.54 (d, J = 1.8 Hz, 1H), 7.97 (d, J = 0.8 Hz, 1H), 7.84 (s, 1H), 3.25 (ddd, J = 8.1, 5.4, 2.7 Hz, 1H), 2.48 (s, 3H), 1.88 – 1.75 (m, 2H), 1.64 – 1.52 (m, 2H), 1.30 – 1.26 (m, 4H), 0.92 (t, J = 7.4 Hz, 3H), 0.86 (t, J = 6.9 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 199.1, 160.8, 151.0, 144.6, 133.2, 132.8, 129.9, 125.6, 49.7, 32.2, 29.8, 25.9, 22.8, 18.4, 13.9, 12.0. **GC-MS** (EI, 70 eV) m/z: 275, 219, 204; **ESI-HRMS** (m/z): $[M+H]^+$ calcd for $C_{16}H_{22}NOS$, 276.1417, found 276.1418.

1-(Thieno[3,2-*b*]pyridin-2-yl)pentan-1-one (2j): yellow liquid (171 mg, 78% yield); R_f = 0.37 (ethyl acetate/petroleum ether = 1: 5); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.76 (dd, J = 4.5, 1.3 Hz, 1H), 8.21 (d, J = 8.3 Hz, 1H), 8.12 (s, 1H), 7.35 (dd, J = 8.3, 4.5 Hz, 1H), 3.05 (t, J = 7.4 Hz, 2H), 1.79 (dt, J = 15.1, 7.5 Hz, 2H), 1.44 (dt, J = 14.7, 7.4 Hz, 2H), 0.97 (t, J = 7.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 195.0, 155.2, 148.6, 147.0, 136.7, 131.1, 129.3, 121.1, 39.0, 26.7, 22.4, 13.9. **GC-MS** (EI, 70 eV) m/z: 219, 177, 134; **ESI-HRMS** (m/z): $[M+H]^+$ calcd for $C_{12}H_{14}NOS$, 220.0791, found 220.0783.

2-Ethyl-1-(thieno[3,2-*b*]pyridin-2-yl)hexan-1-one (2k): yellow liquid (211 mg, 81% yield); R_f = 0.49 (ethyl acetate/petroleum ether = 1:5); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.71 (d, J = 2.9 Hz, 1H), 8.16 (d, J = 8.2 Hz, 1H), 8.11 (s, 1H), 7.30 (dd, J = 8.2, 4.5 Hz, 1H), 3.33 – 3.20 (m, 1H), 1.79 (tt, J = 14.8, 7.5 Hz, 2H), 1.66 – 1.50 (m, 2H), 1.23 (m, 4H), 0.87 (t, J = 7.4 Hz, 3H), 0.79 (t, J = 6.6 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 199.0, 155.1, 148.4, 147.9, 136.8, 130.9, 129.1, 121.0, 49.7, 32.1, 29.7, 25.8, 22.7, 13.8, 11.9. **GC-MS** (EI, 70 eV) m/z: 261, 205, 162; **ESI-HRMS** (m/z): $[M+H]^+$ calcd for $C_{15}H_{20}NOS$, 262.1260, found 262.1258.

2-Ethyl-1-(5-methylthieno[3,2-*b*]pyridin-2-yl)hexan-1-one (2l): yellow liquid (228 mg, 83% yield); R_f = 0.38 (ethyl acetate/petroleum ether = 1:10); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.13 (s, 1H), 8.11 (s, 1H), 7.29 (d, J = 5.5 Hz, 1H), 3.37 – 3.25 (m, 1H), 2.73 (s, 3H), 1.86 (dt, J = 14.7, 7.5 Hz, 2H), 1.72 – 1.57 (m, 2H), 1.31 (m, 4H), 0.94 (t, J = 7.4 Hz, 3H), 0.87 (t, J = 6.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 199.3, 157.5, 154.7, 147.8, 134.4, 131.1, 128.9, 121.8, 49.8, 32.3, 29.9, 26.0, 24.6, 22.8, 13.9, 12.1. **GC-MS** (EI, 70 eV) m/z: 275, 232, 204; **ESI-HRMS** (m/z): $[M+H]^+$ calcd for $C_{16}H_{22}NOS$, 276.1417, found 276.1416.

1-(Thieno[2,3-*c*]pyridin-2-yl)propan-1-one (2m): yellow liquid (147 mg, 77% yield); R_f = 0.45 (ethyl acetate/petroleum ether = 1:5); ^{1}H **NMR** (400 MHz, $CDCl_3$) δ 9.18 (s, 1H), 8.53 (d, J = 5.5 Hz, 1H), 7.92 (s, 1H), 7.74 (d, J = 5.5 Hz, 1H), 3.06 (q, J = 7.3 Hz, 2H), 1.27 (t, J = 7.3 Hz, 3H); ^{13}C **NMR** (100 MHz, $CDCl_3$) δ 195.0, 148.3, 145.6, 144.2, 143.4, 137.8, 126.6, 119.2, 32.9, 8.1. **GC-MS** (EI, 70 eV) m/z: 191, 177; ESI-**HRMS** (m/z): $[M+H]^+$ calcd for $C_{10}H_{10}NOS$, 192.0478, found 192.0477.

1-(thieno[2,3-*c*]pyridin-2-yl)pentan-1-one (2n): yellow liquid (166 mg, 76% yield); R_f = 0.41 (ethyl acetate/petroleum ether = 1:5); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.21 (s, 1H), 8.57 (d, J = 5.4 Hz, 1H), 7.94 (s, 1H), 7.76 (d, J = 5.3 Hz, 1H), 3.04 (t, J = 7.4 Hz, 2H), 1.78 (dt, J = 15.1, 7.5 Hz, 2H), 1.44 (dq, J = 14.7, 7.4 Hz, 2H), 0.97 (t, J = 7.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 194.8, 148.7, 145.7, 144.2, 143.6, 137.7, 126.8, 119.2, 39.4, 26.5, 22.4, 13.9. **GC-MS** (EI, 70 eV) m/z: 219, 190, 107; **ESI-HRMS** (m/z): $[M+H]^+$ calcd for $C_{12}H_{14}NOS$, 220.0791, found 220.0790.

1-(5-Chlorothieno[2,3-*c*]pyridin-2-yl)pentan-1-one (2o): yellow liquid (185 mg, 73% yield); R_f = 0.43 (ethyl acetate/petroleum ether = 1:10); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.96 (s, 1H), 7.86 (s,

1H), 7.79 (s, 1H), 3.02 (t, *J* = 7.4 Hz, 2H), 1.77 (dt, *J* = 15.1, 7.5 Hz, 2H), 1.44 (dd, *J* = 15.0, 7.4 Hz, 2H), 0.97 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 194.5, 150.7, 147.0, 146.3, 145.2, 136.6, 125.6, 119.1, 39.4, 26.3, 22.3, 13.8. **GC-MS** (EI, 70 eV) m/z: 253, 224, 168; **ESI-HRMS** (m/z): $[M+H]^+$ calcd for$C_{12}H_{13}ClNOS$, 254.0401, found: 254.0404.

1-(5-Chlorothieno[2,3-*c*]pyridin-2-yl)-2-methylpentan-1-one (2p): yellow liquid (230 mg, 86% yield); R_f = 0.41 (ethyl acetate/petroleum ether = 1:10); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 8.98 (s, 1H), 7.87 (s, 1H), 7.81 (s, 1H), 3.41 (dd, *J* = 13.5, 6.8 Hz, 1H), 1.90 – 1.79 (m, 1H), 1.56 – 1.47 (m, 1H), 1.39 (dd, *J* = 14.4, 7.3 Hz, 2H), 1.28 (d, *J* = 6.8 Hz, 3H), 0.93 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) *δ* 198.6, 150.6, 147.0, 146.3, 145.2, 136.7, 125.4, 119.1, 42.8, 36.0, 20.6, 17.2, 14.1. **GC-MS** (EI, 70 eV) m/z: 267, 225, 196; **ESI-HRMS** (m/z): $[M+H]^+$ calcd for $C_{13}H_{15}ClNOS$, 268.0558, found: 268.0551.

1-(5-Chlorothieno[2,3-*c*]pyridin-2-yl)-2-ethylhexan-1-one (2q): yellow liquid (248 mg, 84% yield); R_f = 0.41 (ethyl acetate/petroleum ether = 1:10); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 8.95 (s, 1H), 7.86 (s, 1H), 7.79 (s, 1H), 3.32 – 3.14 (m, 1H), 1.91 – 1.77 (m, 2H), 1.69 – 1.55 (m, 2H), 1.25 (dd, *J* = 8.5, 5.3 Hz, 4H), 0.89 (t, *J* = 7.4 Hz, 3H), 0.83 (t, *J* = 6.8 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) *δ* 198.8, 151.6, 147.0, 146.2, 145.1, 136.7, 125.4, 119.2, 50.2, 31.9, 29.7, 25.6, 22.8, 13.8, 11.9. **GC-MS** (EI, 70 eV) m/z: 295, 224, 196; **ESI-HRMS** (m/z): $[M+H]^+$ calcd for $C_{15}H_{19}ClNOS$, 296.0870, found 296.0869.

2-Ethyl-1-(5-fluorothieno[2,3-*c*]pyridin-2-yl)hexan-1-one (2r): yellow liquid (232 mg, 83% yield); R_f = 0.35 (ethyl acetate/petroleum ether = 1:10); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 8.79 (s, 1H),

7.90 (s, 1H), 7.37 (s, 1H), 3.25 (dq, J = 8.0, 5.5 Hz, 1H), 1.89 – 1.75 (m, 2H), 1.70 – 1.54 (m, 2H), 1.31 – 1.24 (m, 4H), 0.91 (t, J = 7.4 Hz, 3H), 0.84 (dd, J = 8.7, 4.9 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 198.8, 161.6 (d, $J_{C\text{-}F}$ = 231.8 Hz, 1C), 152.3, 148.8 (d, $J_{C\text{-}F}$ = 8.4 Hz, 1C), 143.1 (d, $J_{C\text{-}F}$ = 18.18 Hz, 1C), 135.3, 125.8 (d, $J_{C\text{-}F}$ = 5.7 Hz, 1C), 103.4 (d, $J_{C\text{-}F}$ = 39.0 Hz, 1C), 50.3, 31.9, 29.7, 25.7, 22.8, 13.8, 11.9. **GC-MS** (EI, 70 eV) m/z: 279, 223, 208; **ESI-HRMS** (m/z): $[M+H]^+$ calcd for $C_{15}H_{19}FNOS$, 280.1166, found 280.1167.

(5-Methylthieno[2,3-*b*]pyridin-2-yl)(phenyl)methanone (2s): yellow solid (220 mg, 87% yield); mp 168-169 □; R_f = 0.41 (ethyl acetate/petroleum ether = 1:5); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.53 (s, 1H), 7.96 – 7.84 (m, 3H), 7.71 (s, 1H), 7.62 (t, J = 7.4 Hz, 1H), 7.52 (t, J = 7.6 Hz, 2H), 2.46 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 189.5, 160.8, 151.1, 142.9, 137.4, 133.2, 132.6, 132.5, 130.0, 129.2 (2C), 129.2, 128.5(2C), 18.4. **GC-MS** (EI, 70 eV) m/z: 253, 225, 176; **ESI-HRMS** (m/z): $[M+H]^+$ calcd for $C_{15}H_{12}NOS$, 254.0634, found: 254.0636.

(5-methylbenzo[*b*]thiophen-2-yl-3-d)(phenyl)methanone (2s-D): yellow solid (206 mg, 81% yield); mp 170-172 □; R_f = 0.44 (ethyl acetate/petroleum ether = 1:5); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 7.97 – 7.85 (m, 3H), 7.63 (t, J = 7.4 Hz, 1H), 7.53 (t, J = 7.6 Hz, 2H), 2.47 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 189.5, 160.8, 151.1, 142.8, 137.4, 133.2, 132.6, 132.4 (d, $J_{C\text{-}D}$ = 4.3 Hz, 1C), 130.0, 129.3 (2C), 129.2, 128.6 (2C), 18.4. **GC-MS** (EI, 70 eV) m/z: 254, 237, 226; **ESI-HRMS** (m/z): $[M+H]^+$ calcd for $C_{15}H_{11}DNOS$, 255.0697, found: 255.0703.

Benzo[*b*]thiophen-2-yl(phenyl)methanone (3a)[10a]: yellow liquid (219 mg, 92% yield); R_f = 0.42 (ethyl acetate/petroleum ether = 1:5); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.92 (dd, J = 7.6, 4.1 Hz, 3H), 7.88 (d, J = 8.0 Hz, 1H), 7.86 (s, 1H), 7.63 (t, J = 7.2 Hz, 1H), 7.54 (t, J = 7.6 Hz, 2H), 7.49 (t, J =

7.6 Hz, 1H), 7.42 (t, J = 7.6 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 189.6, 143.1, 142.7, 139.0, 137.9, 132.4, 132.2, 129.2 (2C), 128.5 (2C), 127.4, 126.0, 125.0, 122.9. **GC-MS** (EI, 70 eV) m/z: 238, 221, 210.

ASSOCIATED CONTENT

Supporting Information

Copies of NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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