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Synthesis of New Water-Soluble Bunte Salts Bearing Thieno[2,3-b]Pyridine-3-yl Substituents †

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Abstract: Upon treatment with chloroacetyl chloride, 3-aminothieno[2,3-b]pyridines gave the corresponding chloroacetamides. The latter readily react with sodium thiosulphate to afford water soluble S-alkylthiosulphates with pharmacophoric heterocyclic units.

Keywords: thieno[2,3-b]pyridines; bunte salts; Thorpe-Ziegler reaction; heterocyclization

1. Introduction

The Bunte salts (Figure 1) are easily available and handy reagents that are useful for introduction of sulfur-containing fragments into a molecule [1]. They are practically odorless crystalline solids appear to be water soluble even if they contain highly lipophilic organic fragments [1]. The Bunte salts are useful in organic synthesis as "surrogates of sulfur" [2–4], in the synthesis of metal nanoparticles [5–9] and as complexing agents. In addition, some of these compounds reveal an interesting biological activity [10]. It is known that Bunte salts are stable in aqueous media, while the corresponding alkylthiosulfuric acids, $RSSO_3H$, are usually unstable in aqueous solution [11]. The survey of literature revealed a couple of methods to prepare Bunte salts [12,13]. The most common approach is based on the reaction of alkyl halides with readily available and cheap sodium thiosulfate [13]. Here we propose a new approach towards the synthesis of Bunte salts bearing pharmacophoric aminothieno[2,3-b]pyridine (Figure 1) core. 3-Aminothieno[2,3-b]pyridines are known to exhibit a broad spectrum of biological activity and were recognized as valuable reagents for heterocyclic synthesis [14–17].

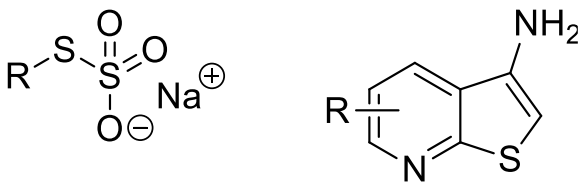
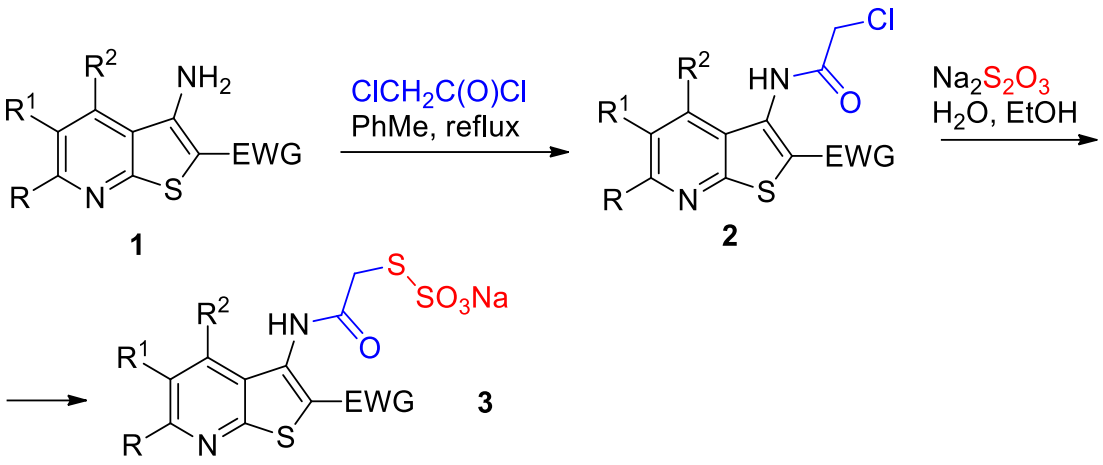


Figure 1. structure of Bunte salts (**left**) and 3-aminothieno[2,3-b]pyridines (**right**).

2. Results and Discussion

3-Aminothienopyridines **1** could be easily N-acylated with $ClCH_2C(O)Cl$ to give corresponding chloroacetamides **2** [18]. The yields are given in the Table 1. The structure of some compounds **2** were proved by means of IR and NMR spectroscopy, including 2D NMR experiments (^1H-^{13}C HSQC, ^1H-^{13}C HMBC, ^1H-^{15}N HMBC) (Figures 2–8). When chloroacetamides **2** were treated with $Na_2S_2O_3$ in aq.

EtOH, corresponding Bunte salts **3** were isolated in good yields. The compounds **3** are colorless solids soluble in alcohol and water, and due to its solubility useful in agrochemistry and pharmacy as perspective bioactive molecules.



Scheme 1. The synthetic pathway to Bunte salts **3**. EWG = COOEt, CONHR, C(O)Ar etc.

Table 1. The prepared *α*-chloro-N-(thienopyridine-3-yl)acetamides **2.**

N	Compound	R	R¹	R²	Yield, %
1	**2a**	Me	Me	OEt	93
2	**2b**	Me	Me	NHPh	84
3	**2c**	Me	Me	2,4-$Me_2C_6H_3NH$	77
4	**2d**	Me	Me	5-Cl-2-MeC_6H_3NH	78
5	**2e**	Me	Me	4-Cl-2-MeC_6H_3NH	82
6	**2f**	Me	Me	4-BrC_6H_4NH	83
7	**2g**	Ph	Ph	NHPh	93
8	**2h**	Ph	4-$MeOC_6H_4$	NHPh	67

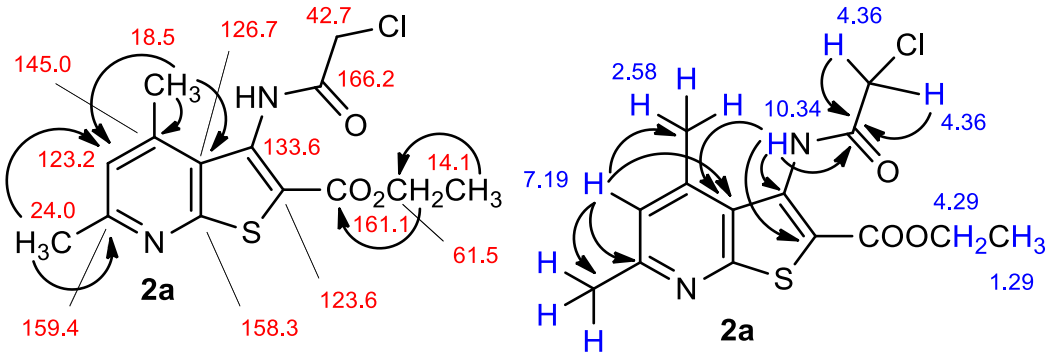


Figure 2. Complete assignments, chemical shifts and key correlations in HSQC and HMBC 2D NMR spectra of the representative compound **2a.**

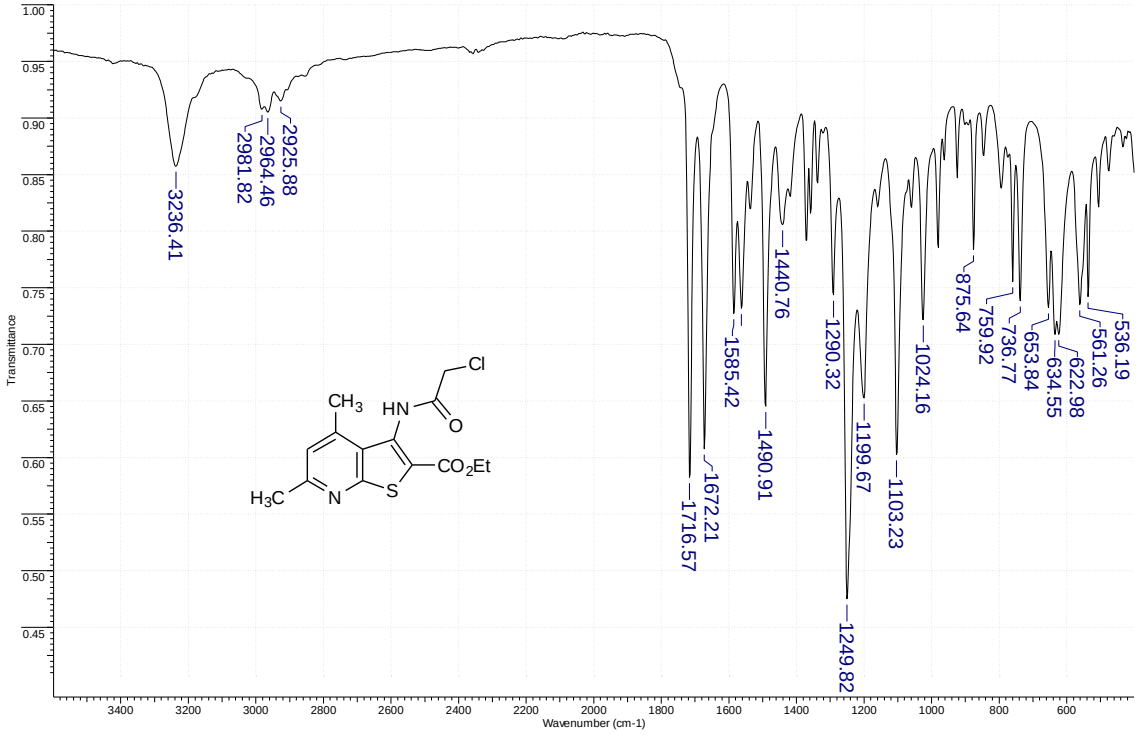


Figure 3. FT-IR (ATR-mode) spectrum of compound **2a.**

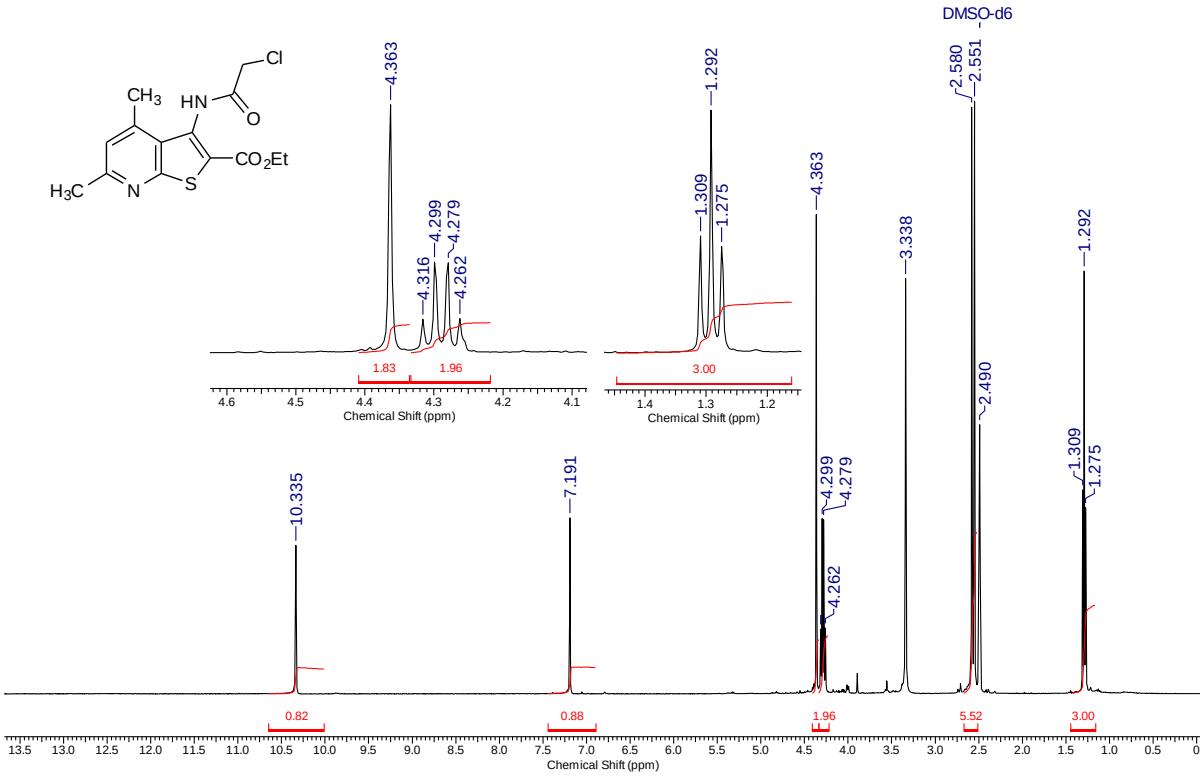


Figure 4. [1]H-NMR spectrum of compound **2a** (400 MHz, DMSO-d_6).

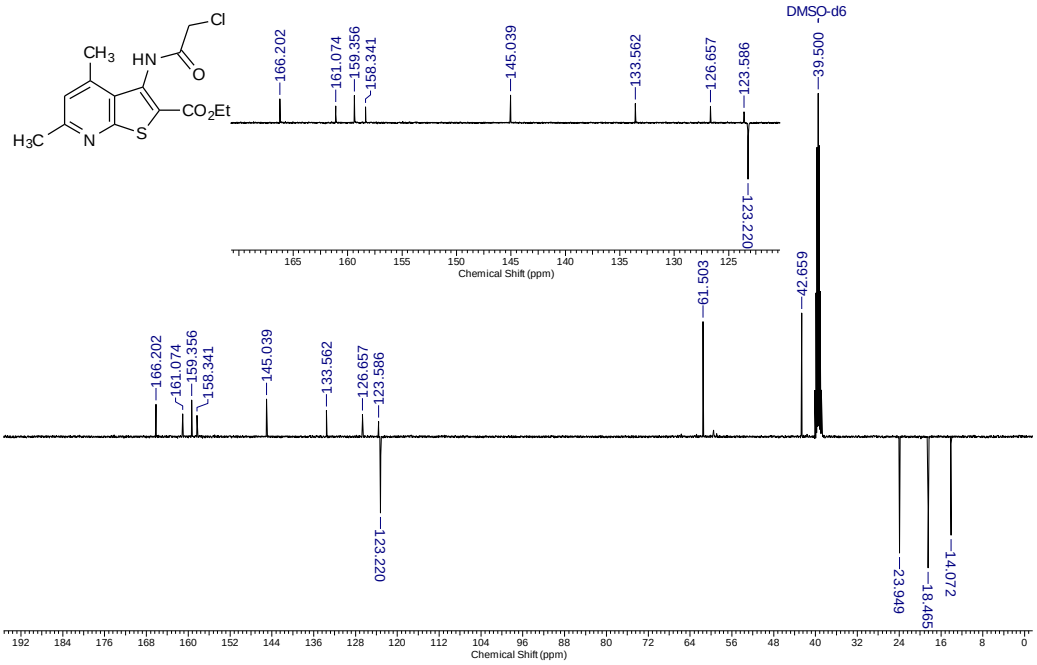


Figure 5. ^{13}C-NMR DEPTQ spectrum of compound **2a** (101 MHz, DMSO-d_6).

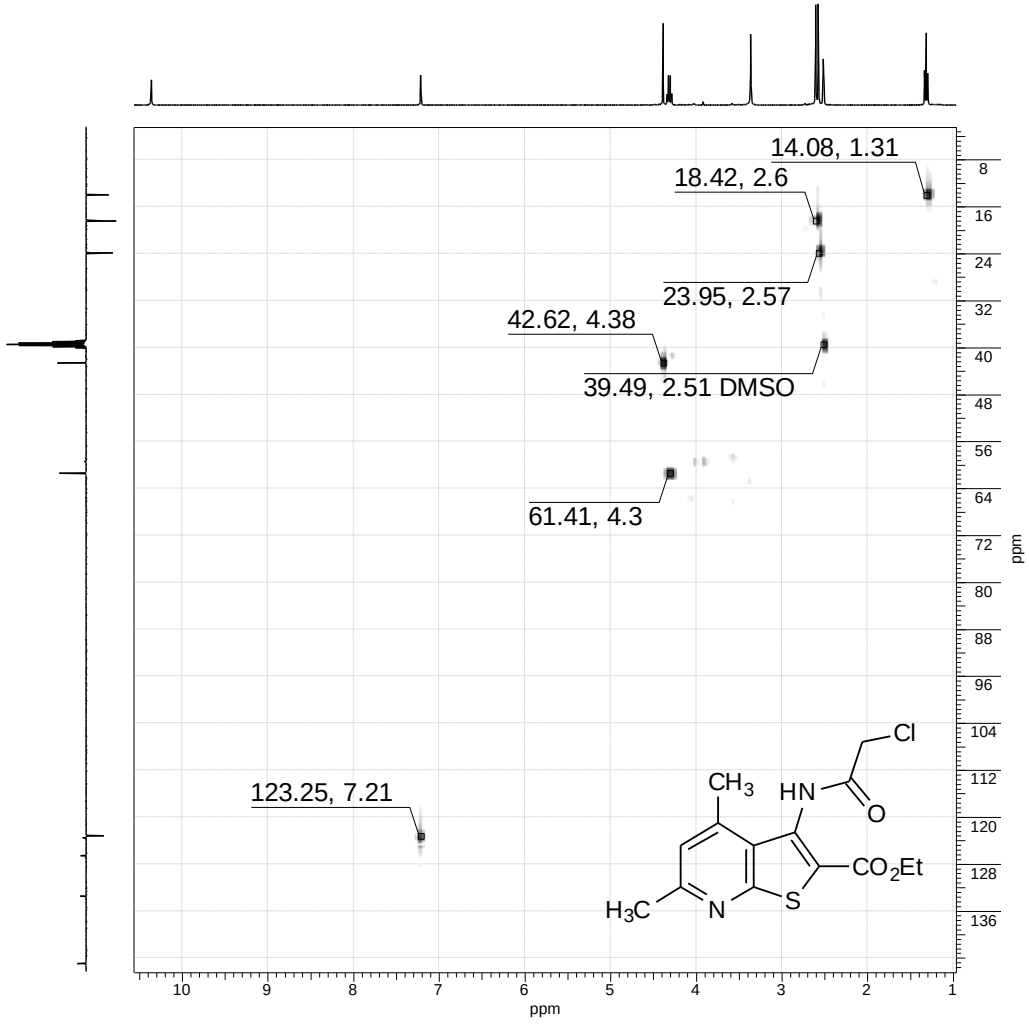


Figure 6. ^{1}H-^{13}C HSQC NMR spectrum of compound **2a** (400/101 MHz, DMSO-d_6).

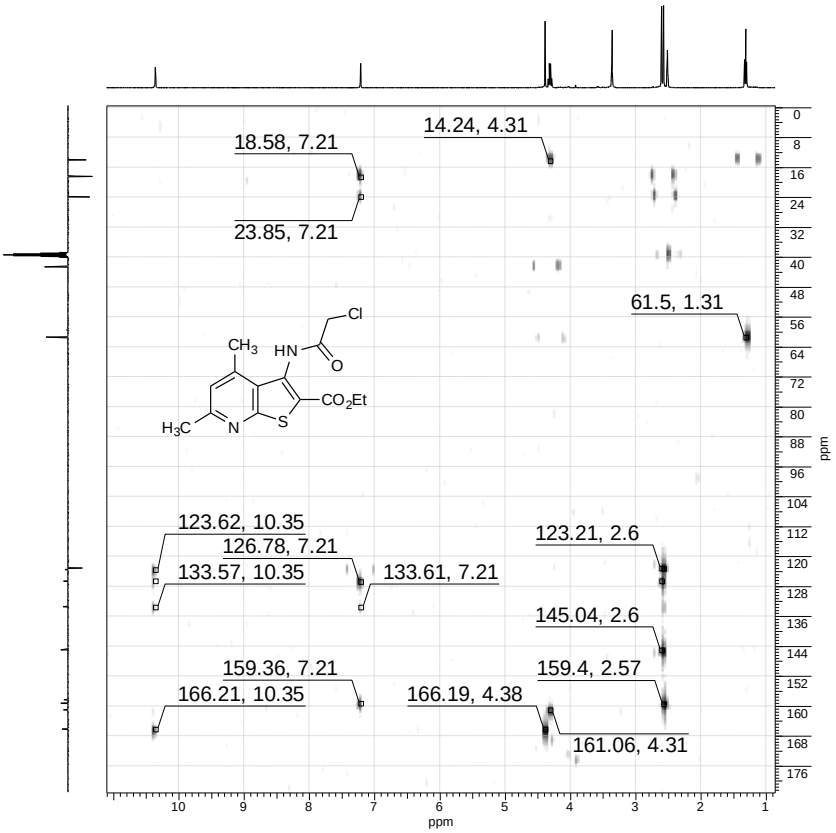


Figure 7. ^{1}H-^{13}C HMBC NMR spectrum of compound **2a** (400/101 MHz, DMSO-d_6).

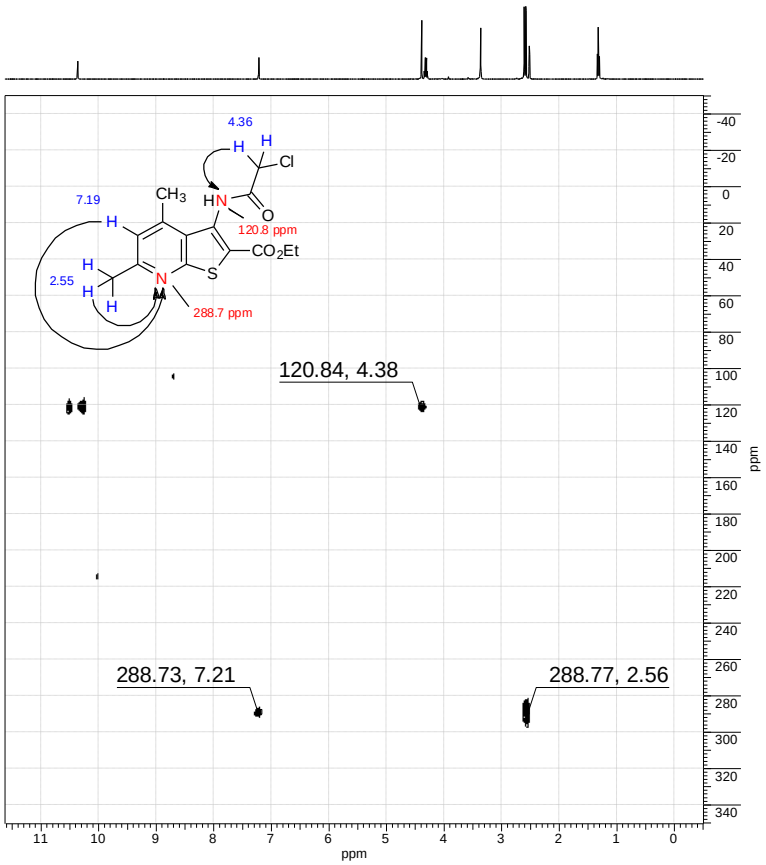


Figure 8. ^{1}H-^{15}N HMBC NMR spectrum of compound **11a** (400/41 MHz, DMSO-d_6).

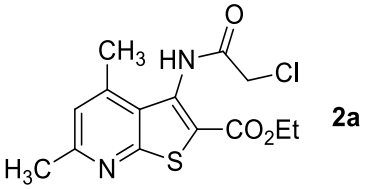
3. Experimental

Solvents and starting reagents were purified according to common procedures. Melting points were determined using Stuart SMP30 device. IR spectra were recorded on a Bruker Vertex 70 instrument in ATR (attenuated total reflection) mode. ^{1}H, ^{13}C DEPTQ, ^{1}H–^{13}C HSQC, ^{1}H–^{13}C HMBC, ^{1}H–^{15}N HSQC, ^{1}H–^{15}N HMBC NMR spectra were recorded on a Bruker Avance III HD spectrometer (400.17 MHz for ^{1}H, 100.63 MHz for ^{13}C, and 40.55 MHz for ^{15}N) in DMSO-d_6 using Me_4Si (δ = 0.0 ppm) as internal standard for ^{1}H and ^{13}C and nitromethane as standard for ^{15}N (δ = +380.23 ppm). Chemical shifts are given in parts per million (ppm), coupling constants are given in Hz, multiplicities are given as s (singlet), d (doublet), dd (doublet of doublets), m (multiplet) and br (broad). The purity of the compounds was checked by TLC (Sorbfil A plates) with hexane:AcOEt (1:1) or hexane:acetone (1:1) mixtures as eluents. The spots were visualized with iodine vapors, $KMnO_4$–H_2SO_4 solution or UV-light. Chloroacetyl chloride is commercially available (ACROS).

3.1. General Procedure for the Synthesis of α-chloro-N-(thienopyridine-3-yl)acetamides 2

A round-bottom 100 cm^3 flask was charged with the corresponding 3-aminothienopyridine **1** (8–10 mmol) and dry toluene (20–40 cm^3). The mixture was warmed until the starting material had dissolved, and chloroacetyl chloride (1.1 eq., 8.8–11 mmol) was added dropwise. The reaction mixture was refluxed until the evolution of HCl had ceased and the starting amine was consumed (TLC control, 3–8 h). Then toluene was evaporated *in vacuo*, and the crude product was recrystallized or purified by boiling with an appropriate solvent.

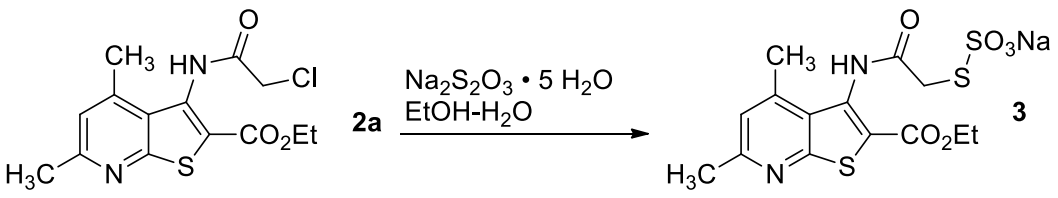
3.2. Ethyl 3-(2-chloroacetamido)-4,6-dimethylthieno[2,3-b]pyridine-2-carboxylate (2a) (EWG = COOEt, R = R^2 = Me, R^1 = H)



2a

Off-white solid, soluble in hot EtOH, yield 93%, m.p. 210 °C; FTIR (ATR): ν = 3236 (N–H), 1716 (C = O_{ester}), 1672 (C=O_{amide}) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.29 (t, 3H, ^{3}J = 6.9 Hz, $OCH_2C\underline{H}_3$), 2.55 (s, 3H, C(6)CH_3), 2.58 (s, 3H, C(4)CH_3), 4.29 (q, 2H, ^{3}J = 6.9 Hz, $OC\underline{H}_2CH_3$), 4.36 (s, 2H, CH_2Cl), 7.19 (s, 1H, H-5), 10.34 (s, 1H, CONH) ppm; ^{13}C DEPTQ NMR (101 MHz, DMSO-d_6): δ 14.1* ($CH_2\underline{C}H_3$), 18.5* (C(4)$\underline{C}H_3$), 24.0* (C(6)$\underline{C}H_3$), 42.7 (CH_2Cl), 61.5 (OCH_2), 123.2* (C-5), 123.6 (C-2), 126.7 (C-3a), 133.6 (C-3), 145.0 (C-4), 158.3 (C-7a), 159.4 (C-6), 161.1 (C = O_{ester}), 166.2 (C = O_{amide}) ppm. *Anti-phase signals. ^{15}N NMR (41 MHz, DMSO-d_6): δ 120.8 (NH), 288.7 (N-7) ppm.

*3.3. Preparation of Compound **3a** (EWG = COOEt, R = R^2 = Me, R^1 = H)*



The starting ethyl 3-(chloroacetamido)-4,6-dimethylthieno[2,3-b]pyridine-2-carboxylate (1) **(0.0**1 mol) was dissolved in hot EtOH (20 mL), and a solution of an excess sodium thiosulfate (0.02 mol) in water (10 mL) was added. Then the reaction mixture was boiled under reflux for 5 h (checked for completion by TLC). To isolate the product, a solvent was distilled off to result in precipitation of white crystalline solid. The resulting crude product **3** was filtered off and washed with a small

amount of acetone to give pure Bunte salt **3** as colorless crystals, yield was 30%. The compound is readily soluble in water, aq. EtOH, sparingly soluble in acetone and diethyl ether.

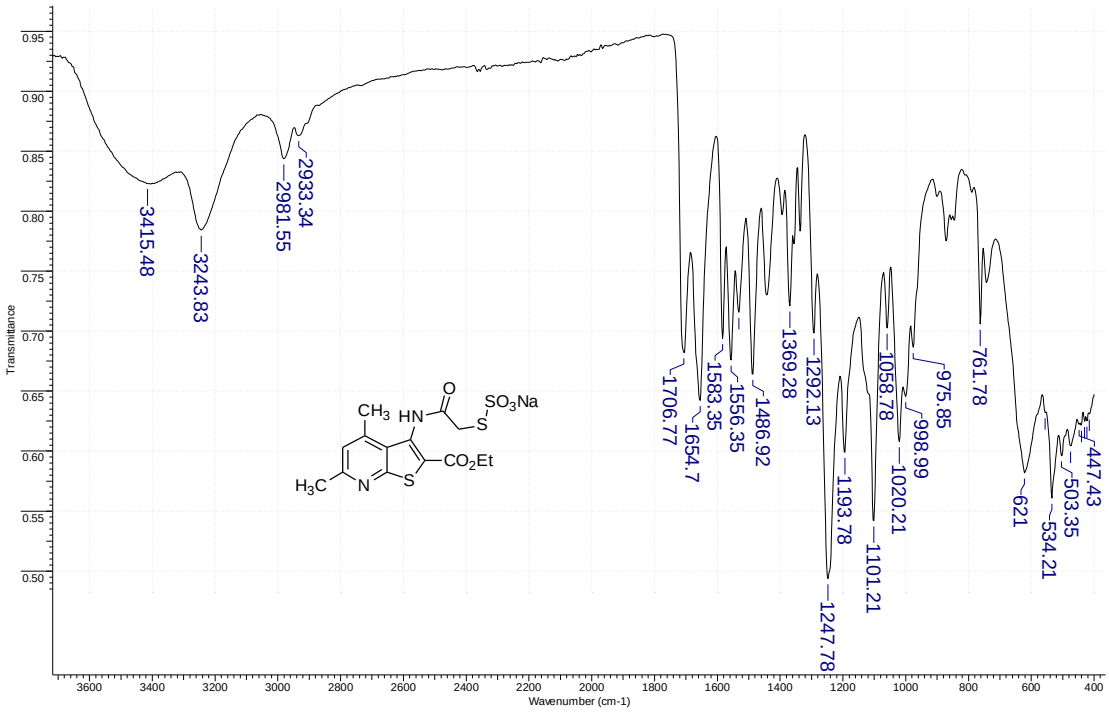


Figure 9. FT-IR (ATR-mode) spectrum of compound **3a.**

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