

An Easy Direct Conversion of Pyridine- and Pyrimidine-Thiones into Multi-Fused Heterocyclic Compounds

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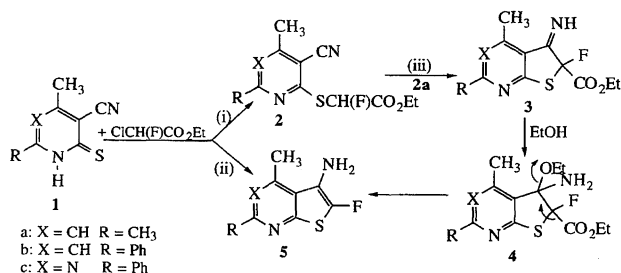
The reaction of azine-thiones with ethyl chlorofluoroacetate afforded 2-fluorothienoazines. The latter underwent self-condensation and gave multi-fused heterocyclic compounds. A wide range of unique heterocycles could be obtained on treatment of 2-fluorothienoazines with nitrogen nucleophilic reagents. The reactivity of the pyrimidine-thiones towards a variety of electrophilic reagents was studied. Chemical and spectroscopic evidence of the newly synthesized compounds are described.

Pyridine- and pyrimidine-thiones and their derivatives¹⁾ constitute an important class of heterocyclic compounds, which are of considerable interest due to their versatility in chemical conversions such as the synthesis of inaccessible annulated heterocyclic systems,²⁾ and their uses as active ingredients in fungicidal and antimicrobial agents.²⁾ The introduction of a fluorine atom into heterocyclic rings often leads to compounds of biological and pharmaceutical importance, such as specific irreversible enzyme inhibitors or paracatalytic inactivators with high specificity.³⁾ Although these heterocycles have been extensively used in organic synthesis,^{4,5)} there is no report in the literature on their utility as reagents for building up fluoroheterocyclic compounds. This paper reports our findings on the reaction of pyridine- and pyrimidine-thiones **1a–c** with ethyl chlorofluoroacetate, in a novel synthesis of fluorothienoazines, which dimerized into multi-fused heterocyclic compounds in a one-pot reaction.

Treatment of **1a–c** with ethyl chlorofluoroacetate in tetrahydrofuran containing a slight excess of triethylamine (TEA) at room temperature afforded the corresponding sulfides **2** in excellent yields (Scheme 1). The structure of **2**^{3e)} was established by elemental analysis and spectroscopic methods

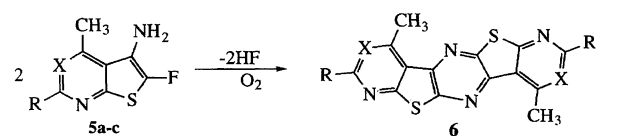
(Table 1). Thus, for example, the mass spectrum of **2a** had a molecular formula of $C_{12}H_{13}FN_2O_2S$ ($m/z = 268$) and its 1H NMR spectrum showed the methyl and ethyl ester groups together with a doublet signal at $\delta = 7.24$ for the methine proton coupled with a fluorine atom with the large coupling constant $J_{HF} = 50.4$ Hz. In addition, the ^{19}F NMR spectrum data supported the proposed structure as it showed a doublet fluorine signal at $\delta = -88.1$ coupled with a hydrogen atom (Table 2).

On the other hand, it was found that the change of solvent from THF to ethanol resulted in the formation of unexpected products **5** in high yields. The structure of **5** was established by various spectroscopic studies and by elemental analysis. For example, the mass spectrum of **5a** showed a molecular ion peak, $m/z = 196$, which corresponds to the molecular formula of $C_9H_9FN_2S$, indicating the loss of a molecule of diethyl carbonate. ^{19}F NMR showed a singlet signal at $\delta = -76.9$. Fluorothienoazines **5** were assumed to be formed via the corresponding cyclized iminothienoazines **3**. Indeed treatment of **2a** with triethylamine in acetonitrile

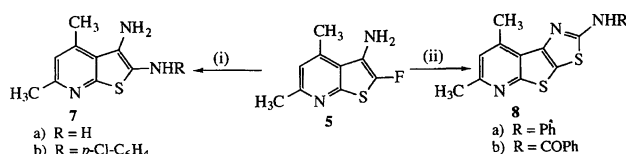


i) TEA, THF ii) TEA, EtOH iii) TEA, MeCN

Scheme 1.



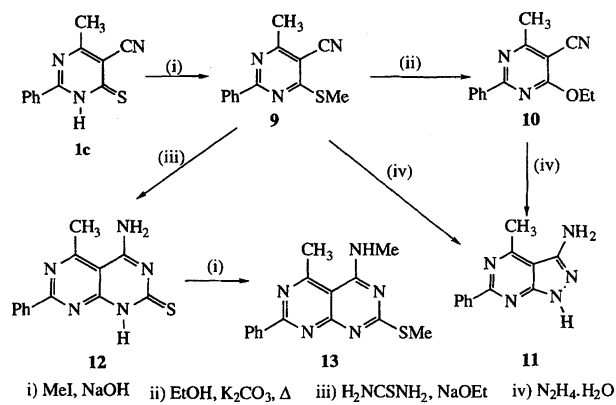
Scheme 2.



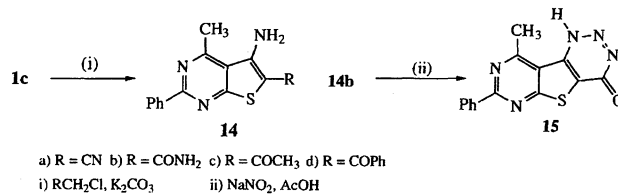
i) RNH_2 , dioxane

ii) $RNCS$, dioxane

Scheme 3.



Scheme 4.



Scheme 5.

gave **3a**, which upon dissolution in ethanol and standing at room temperature gave **5a** directly. Similarly, we could prepare **5b** and **5c**, which were difficult to prepare in our previous anodical fluorination.^{3e)}

At 100 °C, 2-fluorothienoazines **5** undergo self-condensa-

Table 1. Yields, Mps, Color, Mass, and Elemental Analyses for Compounds **2c**, **3a**, **5c**, **6a—c**, **7a,b**, **8a,b**, **9**, **10**, **11**, **12**, **13**, **14a—d**, and **15** (compounds **2a,b** and **5a,b** cited in Ref. 3e)

Compd	Yield %	Mp °C	Color	MS (EI) <i>m/z</i> (M ⁺)	Elemental analysis		
					C	H	N
2c	71	160—161	Yellow	331	58.00 (57.70)	4.22 (4.40)	12.68 (12.70)
3a	65	121—122	Pale Yellow	268	53.72 (53.90)	4.88 (4.60)	10.44 (10.40)
5c	60	171—172	Light green	259	60.23 (60.50)	3.86 (3.80)	16.21 (16.10)
6a	70	270—270	Dark pink	350	61.71 (61.60)	4.00 (3.80)	16.00 (16.40)
6b	80	>290	Dark blue	474	70.88 (70.90)	3.79 (3.80)	11.81 (11.60)
6c	50	>290	Dark green	476	65.54 (65.60)	3.36 (3.40)	17.64 (17.60)
7a	90	92—92	Green	193	55.95 (56.00)	5.69 (5.70)	21.76 (21.70)
7b	88	122—123	Green	303	59.30 (59.10)	4.61 (4.60)	13.38 (13.80)
8a	76	181—182	Golden yellow	311	61.73 (61.70)	4.18 (4.20)	13.50 (13.50)
8b	75	210—211	Golden yellow	339	60.17 (60.20)	3.83 (3.80)	12.38 (12.40)
9	92	133—135	Colorless	241	64.73 (64.63)	4.56 (4.67)	17.42 (17.33)
10	92	90—92	Colorless	239	70.29 (70.39)	5.43 (5.30)	17.57 (17.45)
11	80	160—162	Pale yellow	225	64.00 (63.85)	4.88 (4.95)	31.11 (31.24)
12	80	>300	Pale yellow	269	57.99 (57.81)	4.08 (4.18)	26.08 (26.15)
13	85	>300	Colorless	297	60.58 (60.73)	5.05 (4.81)	23.55 (23.70)
14a	87	230—231	Pale green	266	63.15 (63.35)	3.75 (3.61)	21.05 (21.44)
14b	89	212—214	Pale green	285	59.15 (58.93)	4.22 (4.35)	19.71 (19.60)
14c	100	170—171	Pale green	284 ^{a)}	63.60 (63.50)	4.59 (4.69)	14.84 (14.71)
14d	85	>300	Pale green	345	69.56 (69.45)	4.34 (4.45)	12.17 (12.01)
15	90	>300	Colorless	295	56.94 (56.82)	3.05 (3.17)	23.64 (23.51)

a) MS(Cl), *m/z* 284 (M⁺ + 1).

Table 2. Spectral Data for Compounds **2c**, **3a**, **5c**, **6a–c**, **7a,b**, **8a,b**, **9**, **10**, **11**, **12**, **13**, **14a–d**, and **15** (IR, ^1H NMR, and ^{19}F NMR) (The spectral data of compounds **2a,b** and **5a,b** cited in Ref. 3e)

Compd	IR (cm^{-1})	^1H NMR (δ_{H})	^{19}F NMR (δ_{F})
2c	2210 (CN); 1785 (C=O)	1.32 (t, 3H, CH_3 , $J=7.5$ Hz), 2.4 (s, 3H, CH_3), 4.21 (q, 2H, CH_2 , $J=7.5$ Hz), 7.21 (d, 1H, CH, $J_{\text{HF}}=50.1$ Hz), 7.32–7.81 (m, 5H, aromatic H)	–89.51
3a	1795 (C=O)	1.34 (t, 3H, CH_3 , $J=7.2$ Hz), 2.45 (s, 3H, CH_3), 2.56 (s, 3H, CH_3), 4.35 (q, 2H, CH_2 , $J=7.2$ Hz), 6.92 (s, 1H, CH), 7.31 (s, 1H)	(d, $J_{\text{FH}}=50.3$ Hz) –65.81 (S)
5c	3400–3200 (NH_2)	2.61 (s, 3H, CH_3), 4.32 (br, exch., 2H, NH_2), 6.92–7.49 (m, 5H, aromatic H)	–70.90 (S)
6a	3000, 2450 (CH_3)	2.51 (s, 6H, 2CH_3), 2.67 (s, 6H, 2CH_3), 6.80 (s, 1H, ring H), 6.91 (s, 1H, ring H)	
6b	1660 (C=N)	(insoluble in DMSO)	
6c	1665 (C=N)	(insoluble in DMSO)	
7a	3400–3250 (NH_2)	2.50 (s, 3H, CH_3), 2.59 (s, 3H), 3.91 (br, exch., 4H, 2NH_2), 6.86 (s, 1H, ring H)	
7b	3400–3250 (NH_2 , NH)	2.51 (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 3.50 (br, exch., 2H, NH_2), 6.71–7.13 (m, 5H, aromatic H), 8.10 (s, 1H, NH)	
8a	3400–3200 (NH_2 , NH)	2.51 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 6.71–7.24 (m, 6H, aromatic protons), 8.40 (s, exch., 1H, NH)	
8b	3400–3200 (NH_2 , NH) 1680 (C=O)	2.51 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 6.85–7.24 (m, 6H, aromatic protons), 10.51 (s, exch., 1H, NH)	
9	2216 (CN)	2.68 (s, 3H, CH_3), 2.9 (s, 3H, SCH_3), 7.44–7.52 (m, 2 H, Ph), 8.41–8.43 (m, 3H, Ph)	
10	2222 (CN)	1.48 (t, 3 H, CH_3 , $J=6.48$ Hz), 2.68 (s, 3H, CH_3), 4.64 (q, 2H, CH_2 , $J=7.07$ Hz), 7.44–7.52 (m, 3H, Ph), 8.41–8.44 (m, 2H, Ph)	
11	3418, 3384, 3181 (NH_2 , NH)	12.62 (s, 3 H, CH_3), 5.4 (br, exch., 2H, NH_2), 7.44–7.51 (m, 3H, Ph), 8.3–8.4 (m, 2H, Ph), 12.03 (br, exch., 1H, NH)	
12	3425, 3015 (NH_2)	The sample is sparingly soluble in DMSO	
13	3180 (NH)	2.64 (s, 3H, CH_3), 3 (s, 3 H, SCH_3), 3.21 (d, 3H, NHCH_3 , $J=4.69$ Hz), 6.08 (br, exch., 1H, NH), 7.48 (m, 3H, Ph), 8.6 (m, 2H, Ph)	
14a	3330, 3232 (NH_2) 2206 (CN)	2.73 (s, 3H, CH_3), 7.04 (br, exch., 2H, NH_2), 7.49–7.78 (m, 3H, Ph), 8.53–8.56 (m, 2H, Ph)	
14b	3420, 3315 (NH_2) 1695 (C=O)	2.70 (s, 3H, CH_3), 6.91 (br, exch., 2H, NH_2), 7.20 (br, exch., 2H, NH_2), 7.45–7.50 (m, 3H, Ph), 8.60–8.62 (m, 2H, Ph)	
14c	3417, 3291 (NH_2), 1651 (C=O)	2.61 (s, 3H, CH_3), 2.78 (s, 3H, COCH_3), 7.44–7.47 (m, 3H, Ph), 8.61–8.63 (m, 2H, Ph)	
14d	3460, 3290 (NH_2), 1687 (C=O)	2.61 (s, 3H, CH_3), 7.11 (s, exch., 2H, NH_2), 7.45–8.61 (m, 10 aromatic H)	
15	3089 (NH), 1667 (C=O)	2.61 (s, 3H, CH_3), 7.44–7.49 (m, 3H, Ph), 8.60–8.62 (m, 2H, Ph), 13.56 (br, exch., 1H, NH)	

tion to the dimeric cyclic compounds **6**. This interesting reaction also occurs slowly during the storage of the monomer **5** even at low temperatures. The very characteristic colors (**6a**: pink, **6b**: blue and **6c**: green color) of these products indicates that they are highly π -conjugated systems (Scheme 2). To our knowledge, this is the first synthesis of multi-fused heterocyclic compounds in an essentially one-pot reaction.

The fluorine atom of **5** is also highly reactive to external amine nucleophiles. Thus, the fluorine atom of **5a** could be replaced by passing NH_3 gas in ether solution to

give the diamino derivative **7a**. Similarly **5a** reacted with *p*-chloroaniline to yield **7b**. Compound **5a** also reacted with isothiocyanates to yield thiazolo[2',3':5,4]thieno[2,3-*b*]pyridine derivatives **8a,b** (Scheme 3).

The pyrimidine-thione **1c** could be converted into the *S*-methyl derivatives **9** by being dissolved in ethanol and sodium hydroxide, and treated with MeI at room temperature. Compound **9** showed high reactivity towards nucleophilic reagents. Thus, it reacted readily with ethanol in the presence of K_2CO_3 to give the ethoxypyrimidine derivative **10**

(Scheme 4). Upon refluxing compound **9** with $\text{N}_2\text{H}_4\cdot\text{H}_2\text{O}$, a product of the condensation via elimination of methane-thiol was formed. This product can be proposed as structure **11**. The pyrazolo[3,4-*d*]pyrimidine **11** was established on the basis of the IR spectrum, which revealed the absence of the cyano group stretching band and the presence of an amino group at 3418 and 3384 cm^{-1} . Similarly, the ethoxypyrimidine derivative **10** could be converted into **11** by refluxing in $\text{N}_2\text{H}_4\cdot\text{H}_2\text{O}$. Compound **9** reacted readily with thiourea to give pyrimidino[4,5-*d*]pyrimidinethione **12**, which underwent *S*-methylation to afford compound **13** on treatment with MeI in the presence of NaOH.

This synthetic methodology of thienopyrimidine could be generalized using a variety of α -haloacyl compounds to yield **14a—d** respectively. A unique multi-fused 1,2,3-triazine species (**15**) was obtained in excellent yield (90%) by treatment of **14b** with nitrous acid (Scheme 5).

Experimental

All melting points are uncorrected. IR spectra were recorded (KBr) on a Pye Unicam SP 1000 spectrophotometer. ^1H NMR and ^{19}F NMR spectra were taken at 270 MHz using CDCl_3 as a solvent. The chemical shifts for ^1H and ^{19}F NMR are given in δ downfield from internal TMS and upfield from external CF_3COOH , respectively. High-resolution mass spectra were taken on a Hitachi M-80B GC-mass spectrometer and with GS/MS INCOS XL Finnigan MAT. Analytical data were obtained from the Microanalytical Data Center at Cairo University, Egypt and at the University of Salford, Salford M5, 4WT, UK. Pyridine- and pyrimidine-thione derivatives^{4,5} **1a—c** were prepared according to procedures in the literature.^{4,5}

Preparation of 2-Pyridyl Sulfides (2a,b) and 4-Pyrimidinyl Sulfides (2c). Ethyl chlorofluoroacetate (0.01 mol) was added to a solution of **1a—c** (0.01 mol) in THF (20 ml) containing triethylamine (0.012 mol). The reaction mixture was stirred at room temperature overnight, then passed through a short column (3 cm) of silica gel to yield almost pure fluorinated sulfides (**2a—c**).

2-(Ethoxycarbonyl)-2-fluoro-3-imino-4,6-dimethyl-2,3-dihydrothieno[2,3-*b*]pyridine (3a). Potassium carbonate (0.2 gm, 0.15 mmol) was added to a solution of **2a** (0.1 mmol) in dry acetonitrile (5 ml). The reaction mixture was stirred at room temperature for 1 h. After filtration of insoluble material, the filtrate was evaporated under vacuum at room temperature, to yield **3a** (170 mg).

General Procedure for 5a—c. A solution of **2** (0.1 mmol) in ethanol (5 ml) containing potassium carbonate (0.15 mmol) was stirred at room temperature for 3 h. After filtration of insoluble material, the filtrate was evaporated under vacuum to yield **5a—c** in pure form.

Dimerization of 5a—c. General Procedure for 6a—c. Compound **5** (0.01 mmol) was refluxed for 1 h in xylene. The solid product was collected and washed three times with hot ethanol.

4,6-Dimethylthieno[2,3-*b*]pyridine-2,3-diamine (7a). A solution of **5a** (0.1 mmol) in dry ether (10 ml) in a conical flask fitted with a bubbler stopper was placed in an ice bath. Dry NH_3 gas was bubbled into the solution (care was taken to remove moisture as much as possible). The passage of NH_3 gas was continued for 30 min. The solution then was filtered by gravity to remove any impurities, and kept in a refrigerator overnight before being evaporated under vacuum to yield pure **7a**.

4,6-Dimethyl-2-*p*-chloroanilinothieno[2,3-*b*]pyridine-3-amine (7b). *p*-Chloroaniline (0.1 mmol) and K_2CO_3 (0.1 mmol) was

added to a solution of **5a** (0.1 mmol) in dry acetonitrile (10 ml). The reaction mixture was stirred at room temperature overnight. After filtration of insoluble material the filtrate was evaporated under vacuum to yield **7b**.

2-Anilino-4,6-dimethylthiazolo[2',3' : 5,4]thieno[2,3-*b*]pyridine (8a). Phenyl isothiocyanate (0.1 mmol) was added to a solution of **5a** (0.1 mmol) in dioxane (10 ml) containing K_2CO_3 (0.2 g, 0.15 mmol). The reaction mixture was stirred for 48 h, then refluxed for an additional 0.5 h. After filtration of insoluble material, the filtrate was evaporated under vacuum to yield **8a**, which was recrystallized from absolute ethanol.

2-Benzamido-4,6-dimethylthiazolo[2',3' : 5,4]thieno[2,3-*b*]pyridine (8b). Benzoyl chloride (0.1 mmol) was added to suspension of ammonium thiocyanate (0.7 g, 0.1 mmol) in dry dioxane (20 ml). The reaction mixture was refluxed for 1 min, then treated with **5a** (0.1 mmol) at room temperature for 2 h. The reaction mixture was refluxed for 10 min. After filtration of insoluble material, the filtrate was evaporated under vacuum to yield **8b** which was recrystallized from absolute ethanol.

4-Methyl-6-methylthio-2-phenylpyrimidine-5-carbonitrile (9). Pyrimidine-2(1*H*)-thione (**1**) (0.01 mol) was dissolved in ethanol (25 ml) and sodium hydroxide (10%, 10 ml), then treated with methyl iodide (2 ml) dropwise, with stirring, at room temperature. The reaction mixture was left being stirred at room temperature for 2 h. The solid obtained was recrystallized from ethanol to give pure **9** as colorless crystals.

4-Ethoxy-5-methyl-2-phenylpyrimidine-5-carbonitrile (10). Pyrimidine-5-carbonitrile (**9**) (0.01 mol) was dissolved in ethanol (20 ml) containing anhydrous potassium carbonate (1.5 g), and left under reflux for 3 h. The solid obtained was recovered by filtration and washed several times with water.

3-Amino-4-methyl-6-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (11). A mixture of pyrimidine-5-carbonitrile (**9**) (0.01 mol) or (**10**) (0.01 ml) and hydrazine hydrate (2 ml) in ethanol (20 ml) was left under reflux for 3 h. The solid obtained after evaporation was collected and recrystallized from ethanol.

4-Amino-5-methyl-7-phenylpyrimidino[4,5-*d*]pyrimidine-2(1*H*)-thione (12). A mixture of pyrimidine-5-carbonitrile (**9**) (0.01 mol) and thiourea (0.01 mol) in ethanol (20 ml) and sodium ethoxide (sodium metal 0.46 g, 0.02 mol in 10 ml EtOH) was left under reflux for 4 h. The solid obtained after acidification with concd HCl was recrystallized from DMF/ethanol.

5-Methyl-4-methylamino-2-methylthio-7-phenylpyrimidino[4,5-*d*]pyrimidine (13). Pyrimidino[4,5-*d*]pyrimidine (**12**) (0.01 mol) was dissolved in ethanol (20 ml) containing sodium hydroxide (10 ml, 10%) by warming, and methyl iodide (2 ml excess) was added with stirring for 2 h. The solid obtained was recrystallized from ethanol.

Reaction of 1c with Alkyl Halides: General Procedure: Equimolar amounts of pyrimidine-2(1*H*)-thione (**1c**) (0.01 mol) and α -halo acyl compounds (0.01 mol) in absolute ethanol containing anhydrous potassium carbonate (2 g, 15 mol) were refluxed for 3 h. The reaction mixture was diluted by water and the solid formed was collected by filtration and recrystallized from ethanol.

9-Methyl-7-phenylpyrimidino[4',5' : 5,4]thieno[3,2-*d*]-1,2,3-triazin-4(1*H*)-one (15). 3-Amino-4-methylthieno[2,3-*d*]pyrimidine-2-carboxamide (**14b**) (0.01 mol) in acetic acid (25 ml) was treated with sodium nitrite (0.14 g, 0.02 mol) portionwise with stirring at room temperature, and left being stirred for 1 h. The solid was collected and purified by recrystallization from acetic acid.

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