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Fluorine-containing heterocycles: synthesis and some reactions of new 3-amino-2-functionalized-6-(2′-thienyl)-4-trifluoromethylthieno [2,3-*b*]pyridines

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3-Cyano-6-(2′-thienyl)-4-trifluoromethylpyridine-2(1*H*)-thione (**2**) was prepared and reacted with chloroacetone or phenacyl bromide to yield the 2-acetyl or benzoyl-3-amino-6-(2′-thienyl)-4-trifluoromethylthieno[2,3-*b*]pyridines (**3a**, **b**). In contrast, the reaction of **2** with chloroacetamide or its *N*-aryl derivatives gave the corresponding 2-carbamoylmethyl thiopyridines **4a**–**c**. Upon treatment of these educts with K_2CO_3 or C_2H_5ONa in ethanol, they underwent intramolecular Thorpe-Ziegler cyclization to afford 3-amino-2-carbamoyl-6-(2′-thienyl)-4-trifluoromethyl-thieno[2,3-*b*]pyridine (**5a**) and its *N*-aryl analogs **5b**, **c**. Compounds **5a**–**c** underwent some reactions to yield new pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidines and pyrido[3′,2′: 4,5]thieno[3,2-*d*][1,2,3] triazines.

1. Introduction

Various biological activities have been attributed to thienopyridines [1–8], pyridothienopyrimidines [9–12] and pyridothienotriazines [13, 14]. Investigations have shown that the introduction of fluorine into heterocycles produces compounds showing diverse biological activities [15–21]. In view of the above observations and as a continuation of our previous work on annelated thienopyridines [22, 23], we report herein the synthesis of new fluorine-containing thieno[2,3-*b*] pyridines and their reactions to new pyridothieno-pyrimidines and pyridothienotriazines with anticipated biological activity.

2. Investigations, results and discussion

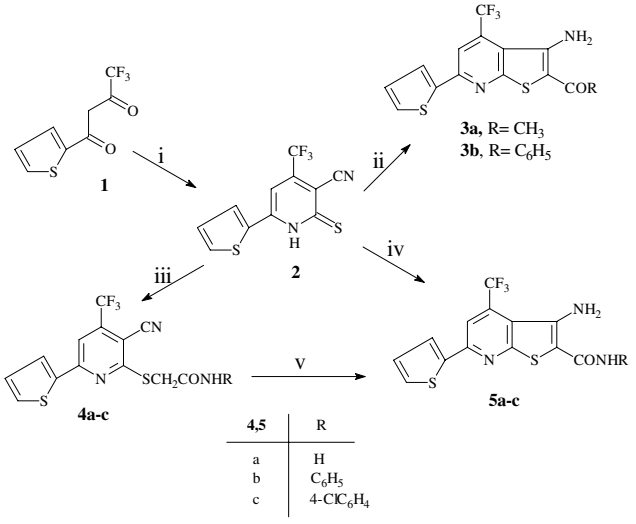
The starting compound, 3-cyano-6-(2′-thienyl)-4-trifluoromethyl-pyridine-2(1*H*)-thione (**2**) was successfully synthesized by cyclocondenstation of (2-thenoyl)-ω,ω,ω-trifluoroacetone (**1**) with cyanothioacetamide in refluxing ethanol containing catalytic amounts of piperidine. The reaction of **2** with chloroacetone or phenacyl bromide in refluxing ethanol in the presence of sodium acetate as a base catalyst afforded 2-acetyl or benzoyl-3-amino-6-(2′-thienyl)-4-trifluoromethylthieno[2,3-*b*] pyridines (**3a** or **3b**) in excellent yields. In contrast, the reaction of **2** with chloroacetamide or its *N*-aryl derivatives under the same (above) conditions gave the corresponding 2-carbamoylmethylthio-pyridines **4a** or its *N*-aryl derivatives **4b**, **c**. When the latter reaction was performed in ethanol in the presence of anh. potassium carbonate or sodium ethoxide, the products were identified as thieno[2,3-*b*] pyridine derivatives **5a** or **5b**, **c**. Upon treatment of **4a**–**c** with anh. potassium carbonate or sodium ethoxide in boiling ethanol, they underwent Thorpe-Ziegler cyclization to yield the compounds **5a**–**c** (Scheme 1).

3-Amino-2-carbamoyl-6-(2′-thienyl)-4-trifluoromethylthieno[2,3-*b*] pyridines and its *N*-aryl derivatives (**5a**–**c**) were used as key intermediates in the synthesis of some new pyridothienopyrimidines and pyridothienotriazines. Thus, the cyclocondensation of **5a**–**c** with triethyl orthoformate by heating in acetic anhydride at reflux temperature led to the formation of pyridothienopyrimidinones **6a**–**c**. The [1,2,3]triazinone analoges **7a**–**c** were obtained by treating **5a**–**c** in AcOH-H_2SO_4 mixture with sodium nitrite solution at low temperature. When compounds **6a** and **7a** were allowed to react with ethyl iodide in *N*,*N*-dimethylformamide containing anh. potassium carbonate, the corresponding *N*-ethylated products **8** and **9** were obtained (Scheme 2).

The reactivity of the amino group of compound **5a** was tested via its condensation with some carbonyl reagents. Thus, the reaction of **5a** with aromatic aldehydes by refluxing in acetic acid did not give the expected Schiffs bases **10a**–**c** or the dihydropyrimidines **11a**–**c** [24], instead, the tetrahydropyrimidinones **12a**–**c** were formed [22, 23]. Under similar conditions, compound **5a** was condensed with cyclopentanone or cyclohexanone to yield the corresponding spiro compounds **14a**, **b** instead of the expected Schiff's bases **13a**, **b** [25]. The reaction of **5a** with acetophenone under the same conditions did not give the tetrahydro-pyrimidinone **15** and compound **5a** was recovered unchanged.

The structural formulas of all synthesized compounds were confirmed by elemental and spectroscopic analysis (Table).

Scheme 1



i: $CNCH_2CSNH_2$ / TEA; ii: $ClCH_2COCH_3$ or $C_6H_5COCH_2Br$ / AcONa; iii: $ClCH_2CONHR$ / AcONa; iv: $ClCH_2CONHR$ / K_2CO_3 or EtONa; v: K_2CO_3 or EtONa / EtOH

Table: Characterization data of the compounds synthesized

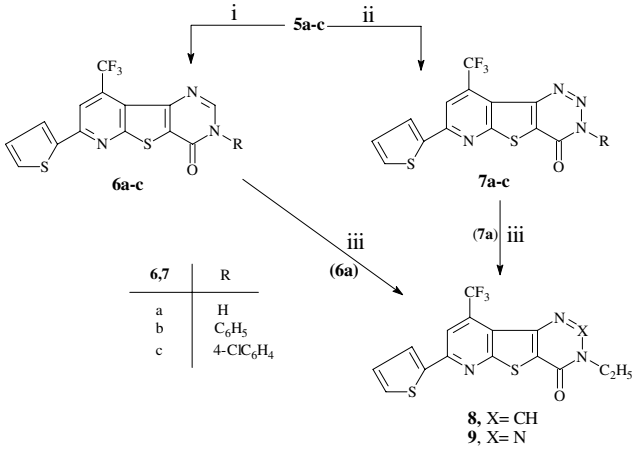
Compd.	M. P. (°C) (yield: %)	Mol. Formula* (M. Wt.)	IR (cm^{-1})	^1H NMR (δ; ppm)
2**	158–160 (87)	$C_{11}H_5F_3N_2S_2$ (286.3)	3190 (NH); 2200 (C≡N)	($CDCl_3$): 14.0 (s, 1 H, NH); 7.8 (d, 1 H, CH thienyl); 7.6 (d, 1 H, CH thienyl); 7.4 (s, 1 H, CH pyridine); 7.0–7.2 (t, 1 H, CH thienyl)
3a	159–161 (82)	$C_{14}H_9F_3N_2OS_2$ (342.3)	3500, 3300 (NH_2); 1620 (CO)	($CDCl_3$): 7.6–7.8 (m, 2 H, CH thienyl and CH pyridine); 7.3–7.5 (m, 1 H, CH thienyl); 6.9–7.1 (m, 3 H, NH_2 and CH thienyl); 2.4 (s, 3 H, CH_3)
3b	190–191 (86)	$C_{19}H_{11}F_3N_2OS_2$ (404.4)	3500, 3300 (NH_2); 1620 (CO)	($CDCl_3$): 7.6–7.9 (m, 3 H, 2CH thienyl and CH pyridine); 7.2–7.4 (m, 4 H, Ar–H); 6.9–7.1 (m, 1 H, CH thienyl); 6.6 (s, 2 H, NH_2)
4a	237–238 (79)	$C_{13}H_8F_3N_3OS_2$ (343.3)	3400, 3150 (NH_2); 2200 (C≡N); 1660 (CO)	(DMSO-d_6): 7.8–8.0 (m, 3 H, 2CH thienyl and CH pyridine), 7.4–7.6 (d, 1 H, CH thienyl), 5.8 (s, 2 H, NH_2), 3.8 (s, 2 H, SCH_2)
4b	240–241 (80)	$C_{19}H_{12}F_3N_3OS_2$ (419.4)	3250 (NH); 2200 (C≡N); 1660 (CO)	(DMSO-d_6): 9.0 (s, 1 H, NH); 8.0 (m, 2 H, CH thienyl and CH pyridine); 7.7–7.8 (d, 1 H, CH thienyl); 7.1–7.5 (m, 6 H, Ar-H and CH thienyl); 4.0 (s, 2 H, SCH_2)
4c**	250–251 (84)	$C_{19}H_{11}F_3ClN_3OS_2$ (453.9)	3250 (NH); 2200 (C≡N); 1660 (CO)	(DMSO-d_6): 9.6 (s, 1 H, NH); 7.8–8.0 (m, 3 H, 2CH thienyl and CH pyridine); 7.1–7.5 (m, 5 H, Ar–H and CH thienyl); 4.0 (s, 2 H, SCH_2)
5a	253–254 (95)***	$C_{13}H_8F_3N_3OS_2$ (343.3)	3500, 3450, 3300, 3250 ($2NH_2$); 1650 (CO)	(DMSO-d_6): 7.8–8.0 (m, 2 H, CH thienyl and CH pyridine); 7.6–7.7 (d, 1 H, CH thienyl); 6.9–7.3 (m, 3 H, NH_2 and CH thienyl); 6.4 (s, 2 H, NH_2)
5b**	260–261 (90)***	$C_{19}H_{12}F_3N_3OS_2$ (419.4)	3500, 3300 (NH_2); 3400 (NH); 1640 (CO)	(DMSO-d_6): 8.7 (s, 1 H, NH); 8.0–8.2 (m, 2 H, CH thienyl and CH pyridine); 7.7–7.8 (d, 1 H, CH thienyl); 7.1–7.5 (m, 6 H, Ar-H and CH thienyl); 5.8 (s, 2 H, NH_2)
5c	245–246 (90)***	$C_{19}H_{11}F_3ClN_3OS_2$ (453.9)	3500, 3300 (NH_2); 3400 (NH); 1640 (CO)	(DMSO-d_6): 9.0 (s, 1 H, NH); 7.9–8.1 (m, 2 H, CH thienyl and CH pyridine); 7.7–7.8 (d, 1 H, CH thienyl); 7.1–7.4 (m, 5 H, Ar-H and CH thienyl); 5.7 (s, 2 H, NH_2)
6a**	>300 (87)	$C_{14}H_6F_3N_3OS_2$ (353.3)	3200–2400 (br, NH); 1660 (CO)	(DMSO-d_6): 9.0 (s, 1 H, CH pyrimidine); 8.3 (s, 1 H, CH pyridine); 8.1 (d, 1 H, CH thienyl); 7.8 (d, 1 H, CH thienyl); 7.2–7.3 (t, 1 H, thienyl)
6b	296–297 (90)	$C_{20}H_{10}F_3N_3OS_2$ (429.4)	1670 (CO)	(DMSO-d_6): 9.1 (s, 1 H, CH pyrimidine); 8.3 (s, 1 H, CH pyridine); 8.0 (d, 1 H, CH thienyl); 7.7 (d, 1 H, CH thienyl); 7.2–7.5 (m, 6 H, Ar-H and CH thienyl)
6c	289–290 (93)	$C_{20}H_9F_3ClN_3OS_2$ (463.9)	1680 (CO)	–
7a	238–240 (83)	$C_{13}H_5F_3N_4OS_2$ (354.3)	3200–2400 (br, NH); 1670 (CO)	(DMSO-d_6): 8.3 (s, 1 H, CH pyridine); 8.1 (d, 1 H, CH thienyl); 7.8 (d, 1 H, CH thienyl); 7.2–7.3 (t, 1 H, CH thienyl)
7b	>300 (80)	$C_{19}H_9F_3N_4OS_2$ (430.4)	1680 (CO)	(DMSO-d_6): 8.2 (s, 1 H, CH pyridine); 8.0 (d, 1 H, CH thienyl); 7.6 (d, 1 H, CH thienyl); 7.1–7.5 (m, 6 H, Ar-H and CH thienyl)
7c**	285–286 (85)	$C_{19}H_8F_3ClN_4OS_2$ (464.9)	1670 (CO)	–
8	290–291 (94)	$C_{16}H_{10}F_3N_3OS_2$ (381.4)	1670 (CO)	(TFA): 9.3 (s, 1 H, CH pyrimidine); 8.3 (s, 1 H, CH pyridine); 8.0–8.1 (d, 1 H, CH thienyl); 7.7–7.8 (d, 1 H, CH thienyl); 7.2–7.3 (t, 1 H, CH thienyl); 4.3–4.7 (q, 2 H, NCH_2); 1.5–1.9 (t, 3 H, CH_3)
9	>300 (91)	$C_{15}H_9F_3N_4OS_2$ (382.4)	1680 (CO)	(TFA): 8.4 (s, 1 H, CH pyridine); 8.1–8.2 (d, 1 H, CH thienyl); 7.8–8.0 (d, 1 H, CH thienyl); 7.3–7.5 (t, 1 H, CH thienyl); 4.6–4.9 (q, 2 H, NCH_2); 1.5–1.8 (t, 3 H, CH_3)
12a	>300 (82)	$C_{20}H_{12}F_3N_3OS_2$ (431.4)	3400, 3200 (2NH); 1650 (CO)	(TFA): 8.2–8.4 (m, 2 H, CH thienyl and CH pyridine); 8.0–8.1 (d, 1 H, CH thienyl); 7.4–7.8 (m, 6 H, Ar-H and CH thienyl); 6.3 (s, 1 H, CH tetrahydropyrimidinone)
12b**	>300 (88)	$C_{21}H_{14}F_3N_3O_2S_2$ (461.4)	3390, 3180 (2NH); 1640 (CO)	(TFA): 8.2–8.4 (m, 2 H, CH thienyl and CH pyridine); 7.9–8.1 (d, 1 H, CH thienyl); 7.5–7.7 (d, 2 H, Ar-H); 7.3–7.4 (t, 1 H, CH thienyl); 6.9–7.1 (d, 2 H, Ar-H); 6.2 (s, 1 H, CH tetrahydropyrimidinone); 3.8 (s, 3 H, OCH_3)
12c	>300 (83)	$C_{20}H_{11}F_3ClN_3OS_2$ (465.9)	3390, 3200 (2NH); 1640 (CO)	(TFA): 8.0–8.4 (m, 3 H, 2CH thienyl and CH pyridine); 7.1–7.7 (m, 5 H, Ar-H and CH thienyl); 6.3 (s, 1 H, CH tetrahydropyrimidinone)

Table (contd.)

Compd.	M. P. (°C) (yield: %)	Mol. Formula* (M. Wt.)	IR (cm^{-1})	^1H NMR (δ; ppm)
14a	>300 (72)	$C_{18}H_{14}F_3N_3OS_2$ (409.4)	3400, 3150 (2NH); 1640 (CO)	(DMSO-d_6): 8.3 (s, 1 H, CONH); 8.0–8.2 (m, 2 H, CH thienyl and CH pyridine); 7.7–7.8 (d, 1 H, CH thienyl); 7.1–7.3 (t, 1 H, CH thienyl); 5.3 (s, 1 H, NH); 1.4–2.0 (2s, 8 H, 4CH_2 of cyclopentylidene ring)
14b**	>300 (77)	$C_{19}H_{16}F_3N_3OS_2$ (423.5)	3400, 3150 (2NH); 1640 (CO)	(TFA): 8.1–8.3 (m, 2 H, CH thienyl and CH pyridine); 8.0–8.1 (d, 1 H, CH thienyl); 7.3–7.5 (t, 1 H, CH thienyl); 1.5–2.5 (m, 10H, 5CH_2 of cyclohexylidene ring)

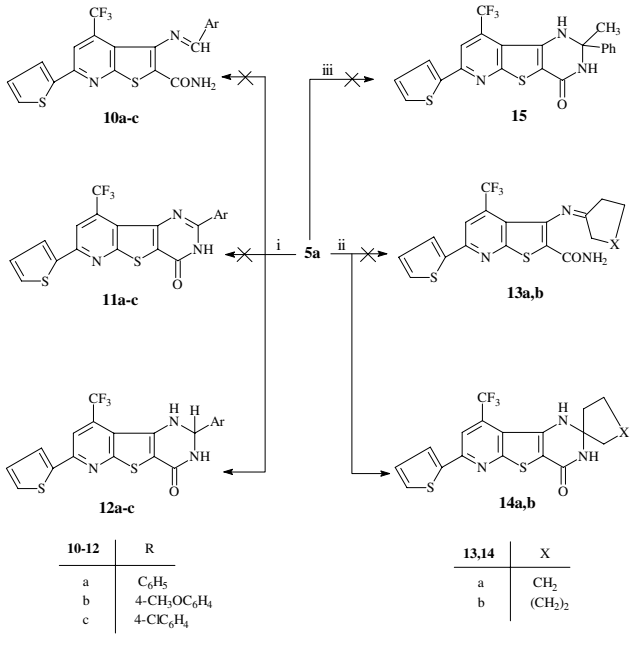
* Satisfactory elemental analyses were obtained for all compounds.**MS of **2**: m/z, fragment, r.i: 286, M^+, 3; 285, M^+-1, 100; 241, M^+-1-CS, 95; .**MS of **4c**: 454, M^+, 20;453, M^+-1, 28; 299, M^+-$CONHC_6H_4Cl$(p); 100; 298, M^+-1-$CONHC_6H_4Cl$(p); **MS of **5b**: 419, M^+, 11; 418, M^+-1, 33; 417, M^+-2, 15; 327, M^+-NHC_6H_5, 34; 326, M^+-1-NHC_6H_5, 78; 325, M^+-2-NHC_6H_5, 39; 93, NHC_5H_5+1, 100; **MS of **6a**: 354, M^++1, 64; 353, M^+, 100; 352; M^+-1, 64; **MS of **7c**: 465, M^+, ;464, M^+-1, ; 372, 100; **MS of **12b**: 462, M^++1, 14; 461, M^+, 12; 460, M^+-1, 100; **MS of **14b**: 423, M^+, 3; 422, M^+-1, 100. ***Yield of method A

Scheme 2



i: $HC(OC_2H_5)_3$ / Ac_2O; ii: $NaNO_2$ / H_2SO_4 / AcOH; iii: C_2H_5I / K_2CO_3 / DMF

Scheme 3



i: ArCHO / AcOH; ii: cycloalkanones / AcOH; iii: $PhCOCH_3$ / AcOH

3. Experimental

Melting points are uncorrected and were measured on a Fisher-John apparatus. IR spectra were recorded on a Shimadzu 470 IR-spectrophotometer using KBr discs, ^1H NMR spectra on a Varian EM 390 90 MHz NMR spectrometer using TMS as internal reference, and MS on a Jeol JMS-600 apparatus. Elemental analyses were determined on a Perkin-Elmer 240C elemental analyzer and the results were in an acceptable range. The characterization data of all synthesized compounds are given in the Table. (2-Thenoyl)-ω,ω,ω,-trifluoroacetone (**1**) was purchased from Aldrich Chemical Co.

3.1. 3-Cyano-6-(2′-thienyl)-4-trifluoromethylpyridine-2(1H)-thione (2)

To a mixture of (2-thenoyl)-ω,ω,ω-trifluoroacetone (**1**) (4.44 g, 0.02 mol) and $CNCH_2CSNH_2$ (2.0 g, 0.02 mol) in abs. C_2H_5OH (70 ml), a few drops of $(C_2H_5)_3N$ were added. The reaction mixture was heated under reflux for 2 h, acidified with CH_2CO_2H and then left to cool. The crystalline product formed was collected and recrystallized from C_2H_5OH to give **2** in the form of yellow plates.

3.2. 2-Acetyl or benzoyl-3-amino-6-(2′-thienyl)-4-trifluoromethylthieno[2,3-b] pyridines 3a, b

A mixture of **2** (1.43 g, 0.005 mol), chloroacetone or phenacyl bromide (0.005 mol) and $CH_3CO_2Na.3H_2O$ (1.36 g, 0.01 mol) in C_2H_5OH (50 ml) was refluxed for 4 h and then allowed to cool. The precipitated product thus formed was collected by filtration, washed with H_2O and recrystallized from C_2H_5OH to give yellow needles of **3a** or **3b**, respectively.

3.3. Reaction of 2 *with chloroacetamide or its N-aryl derivatives; formation of compounds* 4a–c*; general procedure*

To a suspension of **2** (2.86 g, 0.01 mol) and $CH_3CO_2Na.3H_2O$ (2.72 g, 0.02 mol) in C_2H_5OH (100 ml), chloroacetamide, chloro-*N*-phenylacetamide or chloro-*N*-(p-chlorophenyl)acetamide (0.01 mol) was added. The resulting mixture was refluxed for 4 h and then allowed to cool. The precipitated product was collected by filtration, washed with H_2O and recrystallized from C_2H_5OH to give **4a**–**c** in the form of white fine needles.

3.4. 3-Amino-2-carbamoyl-6-(2′-thienyl)-4-trifluoromethylthieno-[2,3-b]pyridines and its N-aryl derivatives 5a–c

3.4.1. Method A

A suspension of **4a**–**c** (0.06 mol) in abs. C_2H_5OH (70 ml) containing anh. K_2CO_3 (2.0 g) or dissolved Na (250 mg) was heated under reflux for 3 h or 10 min, respectively. The product which formed on cooling was collected by filtration, washed thoroughly with H_2O and recrystallized from $C_2H_5OH/CHCl_3$ mixture to give **5a**–**c** in the form of canarian yellow crystals.

3.4.2. Method B

A mixture of **2** (1.43 g, 0.005 mol) and the respective halo-compounds in abs. C_2H_5OH (50 ml) containing anh. K_2CO_3 (3.0 g) or dissolved Na (0.5 g) was refluxed for 4 h or 20 min. respectively. The solid formed after cooling was filtered, washed with H_2O several times and recrystallized from C_2H_5OH to give **5a**–**c** (yields: 70–83%). The products were identical with those reported in method A.

3.5. 7-(2′-Thienyl)-9-trifluoromethylpyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine-4(3H)-one and its 3-aryl derivatives (6a–c)

A suspension of **5a**–**c** (0.002 mol) and $HC(OC_2H_5)_3$ (2 ml) in redistilled $(CH_3CO)_2O$ (25 ml) was heated under reflux for 4 h and then left to cool.

The precipitate was filtered, washed with ethanol and recrystallized form $C_2H_5OH/CHCl_3$ mixture to give **6a-c** in the form of white needles.

3.6. 7-(2′-Thienyl)-9-trifluoromethylpyrido[3′,2′:4,5]thieno[3,2-d][1,2,3]triazine-4(3H)one and its 3-aryl derivatives **7a–c**

To a cold solution of **5a–c** (0.009 mol) in a mixture of conc. H_2SO_4 (5 ml) and glacial CH_3CO_2H (5 ml), sodium nitrite (12 ml, 10%, 0.015 mol) was added dropwise at 0 °C with stirring. The reaction mixture was allowed to stand at room temperature for 1 h whereby a white solid precipitated. It was filtered, washed with H_2O and crystallized from C_2H_5OH to give **7a–c** in the form of white needles.

3.7. Reaction of **6a** *or* **7a** *with ethyliodide; formation of the N-ethylated products* **8** *and* **9***, respectively: general procedure*

To a solution of **6a** or **7a** (0.001 mol) in $HCON(CH_3)_2$ (20 ml), anh. K_2CO_3 (1.0 g) and C_2H_5I (0.32 g, 0.002 mol) were added. The resulting mixture was heated on a water bath for 3 h, then left to cool and diluted with H_2O (20 ml). The precipitate that separated was collected by filtration and crystallized from C_2H_5OH to give **8** or **9**, respectively.

3.8. Reaction of **5a** *with aromatic aldehydes or cycloalkanones; formation of 2-aryl-1,2,3,4-tetrahydro-7-(2′-thienyl)-4-oxo-9-trifluoromethylpyrido[3′,2′:4,3]thieno[3,2-d]pyrimidines (***12a–c***) or spiro compounds* **14a, b** *respectively: general procedure*

A mixture of **5a** (0.69 g, 0.002 mol) and the respective aromatic aldehyde or cycloalkanone (0.002 mol) in glacial CH_3CO_2H (20 ml) was heated under reflux for 4 h. The solid formed after cooling was collected by filtration and recrystallized from CH_3CO_2H to give yellow crystals of **12a–c** or **14a**, **b** respectively.

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