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Research Article

Synthesis, Structure, and Cyclocondensation of the 4,4,4-Trifluoro-3,3-dihydroxy-2-methyl-1-(thien-2-yl)-1-butanone with Hydroxylamine and Hydrazine

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The synthesis of 4,4,4-trifluoro-3,3-dihydroxy-2-methyl-1-(thien-2-yl)butan-1-one (3) through acylation of 1,1-dimethoxy-1-(thien-2-yl)propane (1) with trifluoroacetic anhydride and its reactions with hydroxylamine and hydrazine was investigated. X-ray structural analysis of new trifluoromethyl-substituted dielectrophile 3 revealed that this hydrate exists as a racemate with inter- and intramolecular O-H·O bonds. The crystal structure shows alignment along axis *b* of pair molecules with the same configuration of the O_2-H·O1 bond. For 5(3)-trifluoromethyl-4-methyl-3(5)-(thien-2-yl)-1*H*-pyrazole (4), obtained via cyclocondensation of precursor 2 and hydrazine hydrochloride, X-ray structural analysis indicated that its rings are almost planar (torsion angle N2-C5-C6-C7–5.4°) and that S1 at the thienyl moiety is anti-periplanar to N2 (torsion angle N2-C5-C6-S1 176.01); no disorder effect was observed for the thienyl ring.

1. Introduction

The preparation and application of 1,1,1-trifluoro-4-alkoxy-3-alken-2-ones are presently well documented [1, 2]. In the last two decades, *β*-alkoxy-*α*,*β*-unsaturated trifluoromethyl ketones [as 1,1,1-trifluoro-4-alkoxy-3-alken-2-ones (a), 1-methoxy-2-trifluoroacetylcycloalk-1-enes (b), 3-trifluoroacetyl-4,5-dihydrofuran (c), and 3-trifluoroacetyl-5,6-dihydro-4*H*-pyran (d) (Figure 1)], which are formally trifluoroacetylated enol ethers, have proved to be important building blocks for hetero- and carbocyclic compounds [1–3]. In view of the importance of heterocyclic thiophene systems, we have focused our attention on the synthesis of thien-2-yl-substituted dielectrophiles [4]. Thiophenes are abundant in pharmaceuticals and natural products. In addition, they are useful intermediates for preparing novel conducting polymers and nonlinear optical materials as well as for isosteric replacement of phenyl groups in medicinal chemistry [5–7].

In this work, we report the application of an acetal acylation method to 1,1-dimethoxy-1-(thien-2-yl)-propane 1 and the cyclocondensation of dielectrophilic products obtained using the dinucleophiles hydrazine and hydroxylamine.

2. Results and Discussion

2.1. Acylation Methodology. The acetal precursor, 1,1-dimethoxy-1-(thien-2-yl)propane (1), was synthesized by reacting 2-propionylthiophene with trimethyl orthoformate [8]. The acylation process was carried out without solvent, involving only the addition of two molar-equivalent amounts of the acylating agent to a solution of 1 in pyridine (1 : 2) at −5°C, followed by stirring for 10 h at 25°C. The acylated products were isolated by dissolving them with diethyl ether and then were washed with water. The first product of the acylation process was 1,1,1-trifluoro-4-methoxy-3-methyl-4-(thien-2-yl)-3-buten-2-one, which eventually became a

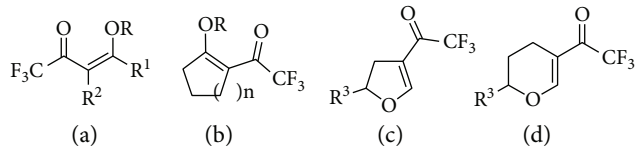


Figure 1: β-Alkoxy-α,β-unsaturated trifluoromethyl ketones or β-alkoxyvinyl trifluoromethyl ketones.

mixture of *E* and *Z* geometric stereoisomers. However, after acid aqueous work-up of the reaction solution, a mixture of 4,4,4-trifluoro-3-methyl-1-(thien-2-yl)butan-1,3-dione (2) and 4,4,4-trifluoro-3,3-dihydroxy-2-methyl-1-(thien-2-yl)butan-1-one (3) at a ratio of approximately 55 : 45 (as calculated by NMR ^{1}H spectroscopy) was obtained. The mixture was stirred with 0.01 M HCl solution for 2 h to convert all dicarbonyl 2 into hydrate 3 (Scheme 1). In a previous study, an analogous 4,4,4-trifluoro-1-(thien-2-yl)butan-1,3-dione was hydrated using various solvents, leading to 4,4,4-trifluoro-3,3-dihydroxy-1-(thien-2-yl)butan-1-one [9]. Our attempts to isolate the product as *E*/*Z*-1,1,1-trifluoro-4-methoxy-3-methyl-5-(thien-2-yl)-3-buten-2-one by vacuum filtration of the resulting reaction mixture were unsuccessful because without the use of ethyl ether as a carrier solvent, the yield was very low and a complex mixture of products including 2 and 3 was obtained. When ethyl ether was used as a carrier solvent, the yield of products increased and the mixture consisted predominantly 2 and 3. The crystallinity and high stability of product 2 and 3 mixtures gave us incentive to isolate them.

In the ^{1}H NMR spectrum of the mixture obtained after acid work-up, a quartet at 3.75 ppm with J_{HH} 6.8 Hz was assigned to H-2 of product 2, and one at 3.85 ppm with J_{HH} 6.8 Hz was assigned to H-2 of hydrate 3; in addition, multiplet signals from the thien-2-yl ring at δ 7.43 and 7.75 ppm were observed. In the ^{13}C{^{1}H} NMR spectrum, quartet signals at 187.6 ppm with J_{CF} 36 Hz and at 95 ppm with J_{CF} 32 Hz were compatible with a mixture of acylated products 2 and 3.

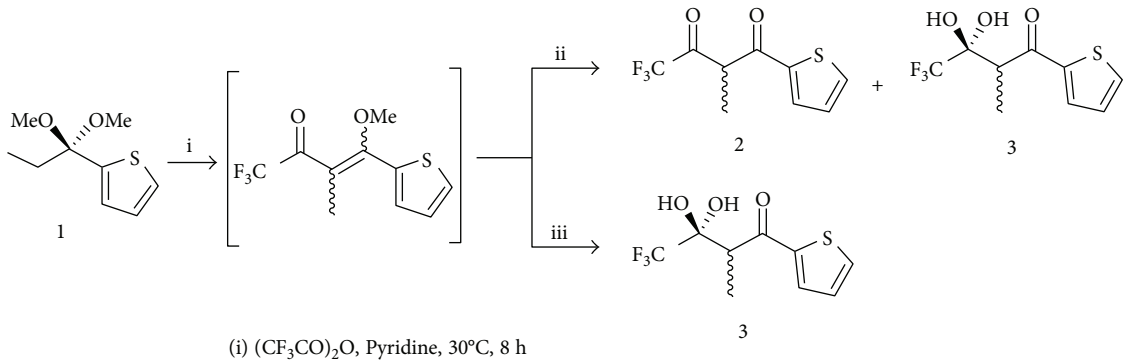
The infrared absorption spectra of compound 3 are presented (Figure 2) and show the O-H stretching at 3383 cm^{-1}, attributable to the linear vibration of O-H bonds; in this region C-H stretching is also observed, 3074 and 3016 cm^{-1}. The C=O stretching is observed at 1662 cm^{-1}, and an intense absorption is observed at 1448 cm^{-1} attributable to bending of CF_3 group. The absorption peaks at the region of 2300–2400 cm^{-1} indicated the carbon dioxide of normal air.

Hydrate compound 3 crystallizes in the $P2_1/n$ space group (Table 1). Figure 1 shows the molecular structure with the atom-numbering scheme, and Figure 2 shows the unit cell packing. Molecule 3 in a solid state consists of a pseudoring with an intramolecular O-H…O hydrogen bond (Figures 2 and 3). The bond distances and angles of the thienyl and trifluoromethyl hydrate moieties in the structure are in an acceptable range. The dihedral angle O3C5C6S1 1.1° indicates coplanarity between the thienyl ring and the carbonyl group, and the refinement indices do not suggest disorder on the thienyl ring. In the crystal structure, the molecules are linked together by pairs of intermolecular O-H…O hydrogen bonds to form dimers (Table 2; Figures 3 and 4); there are also π-π interactions between antiparallel thienyl rings, which yield an infinite 3D arrangement of layers.

2.2. 1,2-Azole Synthesis. The condensation of 3 with hydroxylamine hydrochloride [10] was carried out in ethanol under reflux for 2 h, producing a diastereoisomeric mixture of 4a and 4b with a 7 : 3 ratio at 91% yield. The (4*R*,5*R*)/(4*S*,5*S*)-5-hydroxy-4-methyl-3-(thiophen-2-yl)-5-trifluoromethyl-4,5-dihydroisoxazol (4a), when methyl at position 4 of the isoxazole ring, is *cis* to hydroxyl, and (4*S*,5*R*)/(4*R*,5*S*)-5-hydroxy-4-methyl-3-(thiophen-2-yl)-5-trifluoromethyl-4,5-dihydroisoxazol (4b), when methyl at position 4 of the isoxazole ring, is *cis* to trifluoromethyl group (Scheme 2). There was no evidence of the formation of a regioisomer of the isoxazole derivative. The 4,5-dihydroisoxazol was very stable even in sulfuric acid medium.

The ^{1}H NMR spectra of the mixture 4a/4b in $CDCl_3$ contain two signals assigned to the methyl at position 4 of the isoxazole ring. A doublet at 1.48 ppm with $^3J_{HH}$ 7.6 Hz was attributed to a 4a (4*R*,5*R*)/(4*S*,5*S*) enantiomer pair. And assuming that the spin-spin coupling between the hydrogen from the methyl group and the fluorine from the trifluoromethyl group occurs through space, then the doublet of quartets at 1.45 ppm with $^3J_{HH}$ 8.0 Hz and J_{FH} 2.0 Hz was attributed to a 4b (4*S*,5*R*)/(4*R*,5*S*) enantiomer pair. The quartet at 3.89 ppm with J_{HH} 6.8 Hz was assigned to H-4 of an isoxazole isomer of 4a, and one at 3.78 ppm with J_{HH} 6.8 Hz was assigned to H-4 of a minor isoxazole isomer of 4b. The spectrum also has multiplet signals between δ 7.0 and 7.50 ppm from the thien-2-yl ring. The signals corresponding to OH were assigned to 2.35 (4a) and 2.31 ppm (4b); although the ratio between the integrals of the signal areas corresponding to H-4 and that assigned to OH, for each product 4a or 4b, is not 1 : 1, they maintain the same ratio between these areas in both products, in both 4a and 4b; the ratio between the area of the signal around 3.8–3.9 ppm and the area of the signal around 2.3 is equal to 3.5.

In the ^{13}C{^{1}H} NMR spectra, the quartet signals at 103.8 and 104.1 ppm with J_{CF} 33 Hz were assigned to C-5 of isoxazole rings of 4a/4b, and signals from a CF_3 group were observed at 121.8 and 122.2 ppm with J_{CF} 285 Hz. The signals originating from CH_3 at position 4 of the diastereoisomeric isoxazoles of 4 presented a difference of 2 ppm, a singlet signal at 10.8 ppm was assigned to 4a, and a quartet signal at 12.8 ppm with J_{CF} 2.9 Hz was compatible with 4b; therefore, this coupling between the methyl and the trifluoromethyl groups through space indicates the *cis* relationship [11]. The condensation of 3 with hydrazine hydrochloride was carried out in ethanol under reflux for 6 h, producing 4-methyl-3(5)-(thien-2-yl)-5(3)-trifluoromethyl-1*H*-pyrazole (5) as a crystalline solid at 85–89% yield (Scheme 3). Unlike of the hydroxylamine dinucleophile, [3 + 2] cyclocondensations of unsubstituted hydrazine with trifluoromethyl-



Scheme 1: Acetal acylation process.

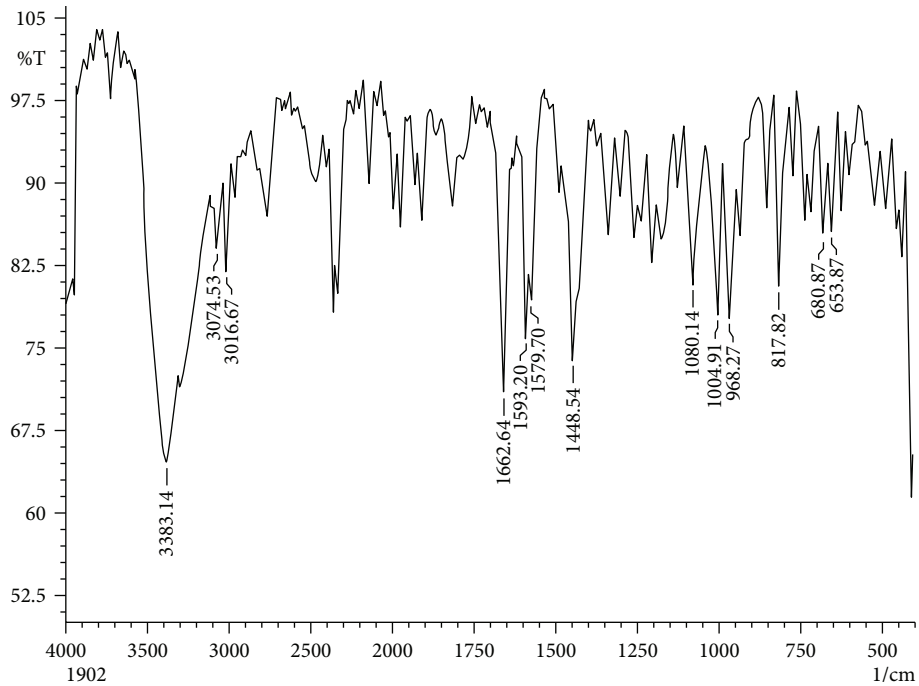


Figure 2: Infrared absorption spectrum of 3,3-dihydroxy-4,4,4-trifluoro-2-methyl-1-(2-thien-2-yl)butan-1-one (3).

substituted dielectrophiles lead to an aromatic 1*H*-pyrazole product [12] without isolating the intermediate 5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazol. The aromatic 1*H*-pyrazole product is isolated as a tautomeric form depending on the substituents and other parameters [13]; here, we attributed the 1,5-tautomer form from NMR CDCl3 solution analysis data and 1,3-tautomer form from the crystal X-ray diffraction data (Tables 3 and 4; Figures 5 and 6).

The ^{1}H NMR spectrum of the 5(3)-trifluoromethyl-4-methyl-3(5)-thien-2-yl-1*H*-pyrazole (5) in $CDCl_3$ contains only one signal set: a singlet at 2.29 ppm assigned to the methyl at position 4 of the 1*H*-pyrazole ring and multiplet signals between δ 7.0 and 7.50 ppm from the thien-2-yl ring. In the ^{13}C{^{1}H} NMR spectra, a quartet signal at 141.2 ppm with J_{CF} 36 Hz corresponded to C-5, a simple signal at 137.4 ppm was assigned to C-3, and a signal from the C-4 of the 1*H*-pyrazole ring was displayed at 112.3 ppm. The signal of the CF_3 group appeared as a characteristically large quartet at 121.6 ppm with J_{CF} 268 Hz.

In conclusion, we report the reaction of dielectrophilic precursor 4,4,4-trifluoro-3,3-dihydroxy-2-methyl-1-(thien-2-yl)-1-butanone with hydroxylamine hydrochloride to regiospecifically produce a diasteroisomeric mixture of 5-trifluoromethyl-5-hydroxy-4-methyl-3-(thien-2-yl)-4,5-dihy droisoxazole, demonstrating a degree of diastereoselectivity through cyclocondensation reactions; we also reacted it with hydrazine hydrochloride to produce aromatic 5-trifluoromethyl-4-methyl-3-(thien-2-yl)-1*H*-pyrazoles. Our results indicate that the dielectrophilic precursor is an efficient building block for the synthesis of 1,2-azoles.

Table 1: Crystallographic data and structure refinement parameters of 3.

Chemical formula	$C_9\ H_9\ F_3\ O_3\ S$
Mass weight	254.22
Temperature	293 K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P 21/n
Unit cell dimensions	$a = 6.4528(4)$ Å, $\alpha = 90.000(0)$ $b = 7.6982(4)$ Å, $\beta = 92.955(3)^\circ$ $c = 21.7838(13)$ Å, $\gamma = 90.000(0)$
Volume	1080.67(11) $Å^3$
Z	4
Density (calculated)	1.563 mg/m^3
$F(000)$	520
Crystal size	$0.45 \times 0.33 \times 0.27\ mm^3$
Theta range for data collection	3.24 to 28.20°
Index ranges	$-8 \le h \le 8$, $-10 \le k \le 10$, $-28 \le l \le 28$
Reflections collected	25372
Independent reflections	2636 [R(int) = 0.0597]
Completeness to theta = 27.27°	98.9%
Refinement method	Full-matrix least-squares on F^2
Computing	COLLECT, HKL Denzo and Scalepack, SHELXS-97, SHELXL-97
Data/restraints/parameters	2636/0/145
Goodness-of-fit on F^2	1.059
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0457$, wR2 = 0.1114
R indices (all data)	$R1 = 0.0634$, wR2 = 0.1216
Largest diff. peak and hole	0.255 and −0.326 e.$Å^{-3}$

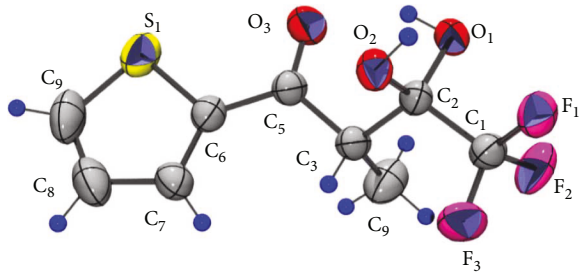


Figure 3: ORTEP-3[5] view of the 4,4,4-trifluoro-3,3-dihydroxy-2-methyl-1-(thien-2-yl)butan-1-one (3) with the corresponding atom numbers. Displacement ellipsoids are drawn at the 50% probability level with hydrogen atoms represented by small spheres of arbitrary radii.

3. Experimental

Unless otherwise indicated, all reagents and solvents were used as obtained from commercial suppliers without further purification. ^1H, ^{13}C, and ^{19}F spectra were acquired at 305 K on a Bruker DPX 400 spectrometer using a 5 mm dual probe. Chemical shifts (δ) are reported in ppm from tetramethylsilane (TMS), and coupling constants (J) are given in Hz. 4000–400 cm^{-1} solid-state infrared (IR) spectrum was recorded on a Shimadzu PRESTIGIE-21 FT-IR spectrophotometer with KBr pellets. Compounds 2–5 were dissolved in acetonitrile (Merck, USA) 50% (v/v) with deionized water and 0.1% formic acid. The dissolved compounds were infused individually into the ESI source using a syringe pump (Harvard Apparatus) at a flow rate of 150 μL min^{-1}. ESI(+)-MS was acquired using a hybrid high-resolution and high-accuracy (5 μL/L) microTof (Q-TOF) mass spectrometer (Bruker® Scientific). Cone voltages were set to +3500 V and +40 V, respectively, at a desolvation temperature of 100°C. Diagnostic ions were identified by comparing experimental to theoretical ESI(+)-MS/MS. Diffraction measurements were made using graphite-monochromatized Mo Kα radiation with $\lambda = 0.71073$ Å on a Bruker SMART CCD diffractometer [14]. The structures were solved by direct methods using the SHELXS-97 program [15] and refined on F^2 using a full-matrix least-squares package by SHELXL97 [16]. Absorption correction was performed using Gaussian methods [17]. Anisotropic displacement parameters for non-hydrogen atoms were applied, and the hydrogen atoms were placed at calculated positions of 0.96 Å (methyl CH3), 0.97 Å (methylene CH_2), 0.98 Å (methine CH), and 0.93 Å (aromatic CH) using a riding model. Hydrogen isotropic thermal parameters were kept equal to $Uiso(H) = xUeq$ (carrier C atom), with $x = 1.5$ for methyl groups and $x = 1.2$ otherwise. The valence angles C-C-H and H-C-H of the methyl groups were set to 109.5°, and H atoms were allowed to rotate around the C-C bond. Molecular graphics were prepared using ORTEP3 for Windows [18].

3.1. Acylation Process of 1,1-Dimethoxy-1-(thien-2-yl)propane. Trifluoroacetic anhydride (60 mmol, 8.5 mL)

Table 2: Hydrogen-bonding geometry for 3 (Å and °).

D-H…A	d(D-H) (Å)	d(H…A) (Å)	d(D…A) (Å)	<(DHA) (°)
O_1-H_1O_1…O_3	0.943(1)	1.847(2)	2.679(2)	145.61(9)
O_2-H_2O_2…O_1	0.945(1)	1.987(1)	2.919(2)	168.17(9)

Symmetry code 1/2 − x, 1/2 + y, 1/2 − z.

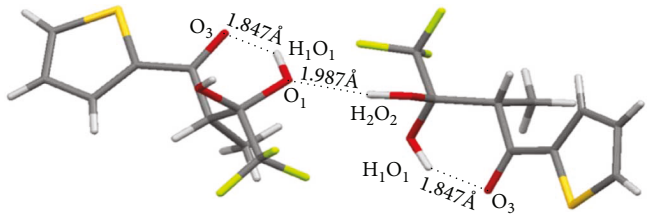
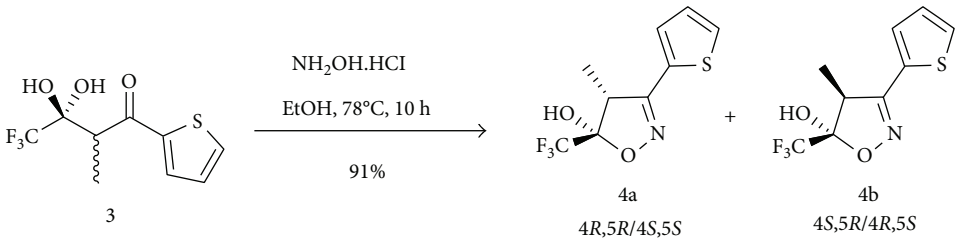
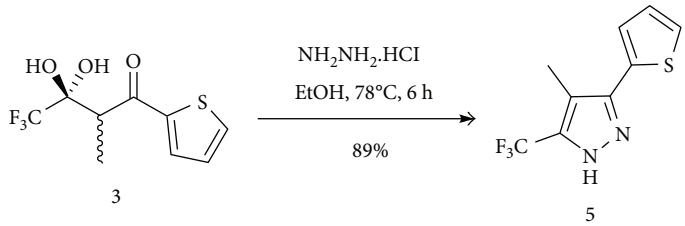


Figure 4: A packing diagram of 4,4,4-trifluoro-3,3-dihydroxy-2-methyl-1-(thien-2-yl)butan-1-one (3) showing the molecules linked by hydrogen bonds. Hydrogen bonds are shown as dashed lines.



Scheme 2: Cyclocondensation between 4,4,4-trifluoro-3,3-dihydroxy-2-methyl-1-(thien-2-yl)butan-1-one (3) and hydroxylamine hydrochloride.



Scheme 3: Cyclocondensation between 4,4,4-trifluoro-3,3-dihydroxy-2-methyl-1-(thien-2-yl)butan-1-one (3) and hydrazine hydrochloride.

Table 3: Crystallographic data and structure refinement parameters of 5.

Empirical formula	$C_9H_7F_3N_2S$
Formula weight	232.23
Temperature	293 K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P 21/c
Unit cell dimensions	$a = 10.0517(3)$ Å $\alpha = 90.000(0)$ $b = 17.1269(5)$ Å $\beta = 87.2780(10)^\circ$ $c = 5.8235(2)$ Å $\gamma = 90.000(0)$
Volume	1001.41(5) Å^3
Z	4
Density (calculated)	1.540 mg/m^3
$F(000)$	472
Crystal size	$0.80 \times 0.31 \times 0.20$ mm^3
Theta range for data collection	3.13 to 28.27°
Index ranges	$-13 \le h \le 13$, $-22 \le k \le 22$, $-7 \le l \le 7$
Reflections collected	30951
Independent reflections	2434 [R(int) = 0.0602]
Completeness to theta = 27.27°	97.9%
Refinement method	Full-matrix least-squares on F^2
Computing	COLLECT, HKL Denzo and Scalepack, SHELXS-97, SHELXL-97
Data/restrains/parameters	2434/0/136
Goodness-of-fit on F^2	1.107
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0726$, wR2 = 0.2332
R indices (all data)	$R1 = 0.0813$, wR2 = 0.2437
Largest diff. peak and hole	0.639 and −0.468 e.Å^{-3}

was added dropwise to a stirred solution of 1,1-dimethoxy-1-(thien-2-yl)propane (30 mmol, 4.75 g) obtained from 1-(thien-2-yl)-1-propanone and pyridine (60 mmol, 5.0 mL) kept at −5 to 0°C, and the resultant mixture was stirred at 30°C for 8 h. To isolate the mixture of 2 and 3, the resultant reaction mixture was cooled until pyridinium trifluoroacetate precipitated; then, it was filtered off and the organic layer was washed with cooled ethyl ether. After solvent evaporation, the residue was a crystalline solid in a brownish oil, identified as a mixture of 4,4,4-trifluoro-2-methyl-1-(thien-2-yl)butan-1,3-dione (2, brownish oil) and 3,3-dihydroxy-4,4,4-trifluoro-2-methyl-1-(2-thien-2-yl)butan-1-one (3, colorless crystalline solid). To isolate the entire acylated product as 3, the reaction mixture was quenched with a 0.01 M hydrochloric acid solution (15 mL) and stirred for 1 h. After adding ethyl ether to extracted insoluble residue, the organic layer was dried over sodium sulfate and the solvent was slowly evaporated to obtain a bright colorless crystalline solid at 92% yield.

Data for 2 are as follows: a brownish oil; ^{1}H NMR ($CDCl_3$) δ 1.43 (d, 6.8 Hz, 3H), 3.74 (q, 6.8 Hz, 1H), 7.11 (m, 1H), and 7.78 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$) δ 196.8 (C1), 187.6 (q, 36 Hz, C3), 128.7, 133.9, 136.5, 142.2 (thienyl), 115.4 (q, 290 Hz, CF_3), 42.6 (C2), and 13.6 (Me) ppm; ^{19}F NMR ($CDCl_3$) −81 (CF_3) ppm; HRMS m/z $C_9H_7F_3O_2SH^+$ requires 237.0197, obsd 237.0203.

Data for 3 are as follows: a crystalline solid that decomposes at 95°C; ^{1}H NMR δ 1.58 (d, 6.8 Hz, 3H), 4.76 (q, 6.4 Hz, 1H), 7.11 (m, 1H), and 7.78 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$) δ 186.9 (C1), 128.5, 133.3, 135.8, 141.5 (thienyl), 122.5 (q, 292 Hz, CF_3), 95.1 (q, 32 Hz, C3) 51.1 (C2), and 13.3 (Me) ppm; ^{19}F NMR ($CDCl_3$)–87.5 (CF_3) ppm; HRMS m/z $C_9H_9F_3O_3SH^+$ requires 255.0203, obsd 255.0297.

3.2. Synthesis of 5-Hydroxy-5-trifluoromethyl-4-methyl-3-(thien-2-yl)-4,5-dihydroisoxazoles 4a/4b. Hydroxylamine

Table 4: Hydrogen-bonding geometry for 5 (Å and °).

D-H…A	d(D-H)	d(H…A)	d(D…A)	<(DHA)
N2-H2…N1	0.8200(0)	2.195(0)	2.872(3)	140.00(0)

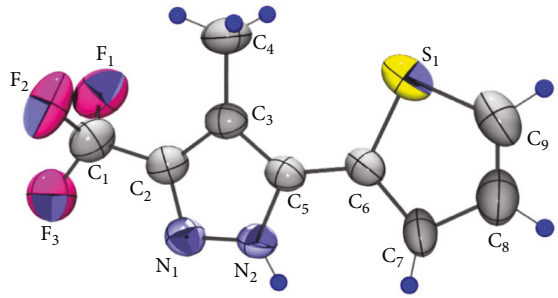


Figure 5: ORTEP view of the 5(3)-trifluoromethyl-4-methyl-3(5)-thien-2-yl-1*H*-pyrazole (5) with the corresponding atom numbers. Displacement ellipsoids are drawn at the 50% probability level with hydrogen atoms represented by small spheres of arbitrary radii.

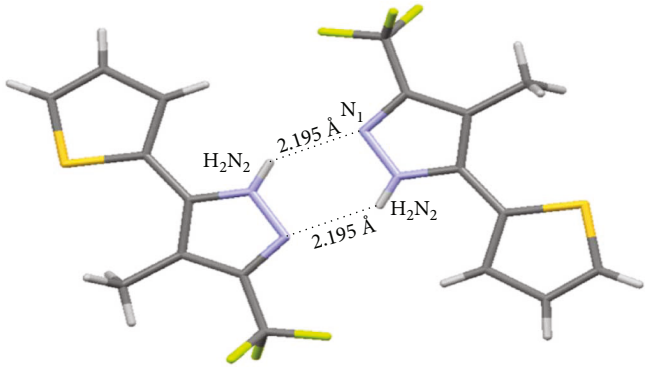


Figure 6: A packing diagram of 5(3)-trifluoromethyl-4-methyl-3(5)-thien-2-yl-1*H*-pyrazole (5) showing the molecules linked by hydrogen bonds. Hydrogen bonds are shown as dashed lines.

hydrochloride (5.1 mmol, ~0.35 g), 3 (5 mmol, 1.27 g), and ethanol (10 mL) were stirred at reflux for 2 h. After the solvent was evaporated, a yellowish waxy residue was obtained. This residue was dissolved in chloroform (10 mL) and washed with water (2 × 10 mL), and then the organic layer was dried over Na_2SO_4. After the chloroform was evaporated, a yellow wax was obtained at 91% yield.

Data for 4a are as follows:^{1}H NMR δ ($CDCl_3$) 1.48 (d, 7.8 Hz, 3H), 3.89 (q, 7.8 Hz, 1H), 7.10 (m, 1H), 7.35 (m, 1H), and 7.45 (m, 1H) ppm; ^{13}C NMR δ ($CDCl_3$) 156.7 (C3), 129.5, 129.1, 128.9, 127.6 (thienyl), 122.2 (q, 286 Hz, CF_3) 103.8 (q, 33 Hz, C5), 47.2 (C4), and 10.8 (Me) ppm; ^{19}F NMR ($CDCl_3$) –74.5 (CF_3) ppm; 4b ^{1}H NMR δ ($CDCl_3$) 1.48 (d, 7.8 Hz, 3H), 3.89 (q, 7.8 Hz, 1H), 7.10 (m, 1H), 7.35 (m, 1H), and 7.45 (m, 1H) ppm; ^{13}C NMR δ ($CDCl_3$) 158.1 (C3), 129.5, 129.1, 128.9, 127.6 (thienyl), 121.8 (q, 292 Hz, CF_3), 104.4 (q, 33 Hz, C5), 52.5 (C4), and 12.8 (q, 2.9 Hz, Me) ppm; ^{19}F NMR ($CDCl_3$) –74.8 (CF_3) ppm; HRMS *m/z* $C_9H_8F_3NO_2SH^+$ requires 252.0206, obsd 252.0209.

3.3. Synthesis of 5(3)-Trifluoromethyl-4-methyl-3(5)-(thien-2-yl)-1H-pyrazole 5. Hydrazine hydrochloride (5.1 mmol, ~0.35 g), 3 (5 mmol, 1.27 g), and ethanol (10 mL) were stirred at 50°C for 2 h. After the solvent was evaporated, a crystalline solid was obtained. This solid was recrystallized in hexane solution, obtaining prismatic crystals at 86% yield (see photograph in Supplementary Material available here).

Data for 5 are as follows: $C_9H_7F_3N_2S$, mp 116-117°C, ^{1}H NMR δ ($CDCl_3$) 2.29 (s, 3H), 7.15 (dd, 4.0 and 4.8 Hz, 1H), 7.25 (d, 4.0 Hz, 1H), and 7.43 (d, 5.0 Hz, 1H); ^{13}C NMR δ ($CDCl_3$) 141.2 (q, 36 Hz, C5), 137.4 (C3), 129.7, 127.7, 126.5126.0 (thienyl), 121.6 (q, 268 Hz, CF_3), 112.3 (C4), 8.5 (Me); HRMS *m/z* (MH^+) $C_9H_7F_3N_2SH^+$ requires 233.0360, obsd 233.0360.

Crystallographic data for the structural analyses have been deposited at the Cambridge Crystallographic Data Centre, CCDC reference numbers 1012599 for 4,4,4-trifluoro-3,3-dihydroxy-2-methyl-1-(thien-2-yl)butan-1-one (3) and 1012597 for 5(3)-trifluoromethyl-4-methyl-3(5)-thien-2-yl-1*H*-pyrazole (5). Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Supplementary Materials

Figure S1. ^{1}H NMR spectrum (400.13 MHz, $CDCl_3$) of the mixture of 4,4,4-trifluoro-2-methyl-1-(thien-2-yl)butan-1,3-dione (2, 55.6%) and 4,4,4-trifluoro-3,3-dihydroxy-2-methyl-1-(thien-2-yl)butan-1-one (3, 44.4%). Figure S2. ^{13}C NMR spectrum (100.62 MHz, $CDCl_3$) of the mixture of 4,4,4-trifluoro-2-methyl-1-(thien-2-yl)butan-1,3-dione (2, 55.6%) and 4,4,4-trifluoro-3,3-dihydroxy-2-methyl-1-(thien-2-yl)butan-1-one (3, 44.4%). Figure S3. ^{1}H NMR spectrum (400.13 MHz, $CDCl_3$) of 4,4,4-trifluoro-3,3-dihydroxy-2-methyl-1-(thien-2-yl)butan-1-one (3). Figure S4. ^{1}H NMR spectrum (100.62 MHz, $CDCl_3$) of 4,4,4-trifluoro-3,3-dihydroxy-2-methyl-1-(thien-2-yl)butan-1-one (3). Figure S5. ^{1}H NMR spectrum (100.62 MHz, $CDCl_3$) of 4,4,4-trifluoro-3,3-dihydroxy-2-methyl-1-(thien-2-yl)butan-1-one (3), expanded between 90 and 140 ppm. Figure S6. ^{1}H NMR spectrum (400.13 MHz, $CDCl_3$) of 5-trifluoromethyl-5-hydroxy-4-methyl-3-(thien-2-yl)-4,5-dihydroisoxazole (4), a diasteroisomeric mixture. Figure S7. ^{1}H NMR spectrum

(400.13 MHz, $CDCl_3$) of 5-trifluoromethyl-5-hydroxy-4-methyl-3-(thien-2-yl)-4,5-dihydroisoxazole (4), a diasteroisomeric mixture, expanded between 1.0 and 4.2 ppm. Figure S8. ^{13}C NMR spectrum (100.62 MHz, $CDCl_3$) of 5-trifluoromethyl-5-hydroxy-4-methyl-3-(thien-2-yl)-4,5-dihydroisoxazole (4), a diasteroisomeric mixture. Figure S9. ^{13}C NMR spectrum (100.62 MHz, $CDCl_3$) of 5-trifluoromethyl-5-hydroxy-4-methyl-3-(thien-2-yl)-4,5-dihydroisoxazole (4), a diasteroisomeric mixture, expanded between 10 and 55 ppm. Figure S10. ^{13}C NMR spectrum (100.62 MHz, $CDCl_3$) of 5-trifluoromethyl-5-hydroxy-4-methyl-3-(thien-2-yl)-4,5-dihydroisoxazole (4), a diasteroisomeric mixture, expanded between 102 and 131 ppm. Figure S11. 2D HSQC NMR spectrum ($CDCl_3$) of the diasteroisomeric mixture 5-trifluoromethyl-5-hydroxy-4-methyl-3-(thien-2-yl)-4,5-dihydroisoxazole (4a/4b). Figure S12. 2D HSQC NMR spectrum ($CDCl_3$) of the diasteroisomeric mixture 5-trifluoromethyl-5-hydroxy-4-methyl-3-(thien-2-yl)-4,5-dihydroisoxazole (4a/4b), expanded in the H-4 region. Figure S13. 2D HSQC NMR spectrum ($CDCl_3$) of the diasteroisomeric mixture 5-trifluoromethyl-5-hydroxy-4-methyl-3-(thien-2-yl)-4,5-dihydroisoxazole (4a/4b), expanded in the thien-2-yl region. Figure S14. 2D HMBC NMR spectrum ($CDCl_3$) of the diasteroisomeric mixture 5-trifluoromethyl-5-hydroxy-4-methyl-3-(thien-2-yl)-4,5-dihydroisoxazole (4a/4b). Figure S15. 2D HMBC NMR spectrum ($CDCl_3$) of the diasteroisomeric mixture 5-trifluoromethyl-5-hydroxy-4-methyl-3-(thien-2-yl)-4,5-dihydroisoxazole (4a/4b), expanded in the methyl-4 region. Figure S16. 2D HMBC NMR spectrum ($CDCl_3$) of the diasteroisomeric mixture 5-trifluoromethyl-5-hydroxy-4-methyl-3-(thien-2-yl)-4,5-dihydroisoxazole (4a/4b), expanded in the H-4 region. Figure S17. High-resolution mass spectrum of diasteroisomeric mixture 5-trifluoromethyl-5-hydroxy-4-methyl-3-(thien-2-yl)-4,5-dihydroisoxazole (4). Figure S18. ^1H NMR spectrum (400.13 MHz, $CDCl_3$) of 5(3)-trifluoromethyl-4-methyl-3(5)-(thien-2-yl)-1*H*-pyrazole (5). Figure S19. ^{13}C NMR spectrum (100.62 MHz, $CDCl_3$) of 5(3)-trifluoromethyl-4-methyl-3(5)-(thien-2-yl)-1*H*-pyrazole (5). Figure S20. ^{13}C NMR spectrum (100.62 MHz, $CDCl_3$) of 5(3)-trifluoromethyl-4-methyl-3(5)-(thien-2-yl)-1*H*-pyrazole (5), expanded between 105 and 150 ppm. Figure S21. High-resolution mass spectrum of 5(3)-trifluoromethyl-4-methyl-3(5)-(thien-2-yl)-1*H*-pyrazole (5). Figure S22. ORTEP drawing of 4,4,4-trifluoro-3,3-dihydroxy-2-methyl-1-(thien-2-yl)-1-butenone (3), showing all nonhydrogen atoms and atom-numbering scheme; 50% probability amplitude displacement ellipsoids are shown. Figure S23. Crystalline supramolecular packing diagram of 4,4,4-trifluoro-3,3-dihydroxy-2-methyl-1-(thien-2-yl)-1-butenone (3), view along the *b*-axis. Figure S24. Crystalline supramolecular packing diagram of 4,4,4-trifluoro-3,3-dihydroxy-2-methyl-1-(thien-2-yl)-1-butenone (3), view along the *a*-axis. Figure S25. Partial view of the infinite 3D-structure formed by the different units of 3, showing intra- and intermolecular hydrogen bonds as dashed lines. Table S1. Crystallographic data and structure refinement parameters for 4,4,4-trifluoro-3,3-dihydroxy-2-methyl-1-(thien-2-yl)butan-1-one (3). Table S2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$). **U**(eq) is defined as one-third of trace of the orthogonalized $\mathbf{U}_{ij}$ tensor. Table S3. Bond lengths (Å) for 3. Table S4. Bond angles (°) for 3. Table S5. Hydrogens coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$). Table S6. Torsion angles [°] for 3. Table S7. Hydrogen-bonding geometry for 3 (Å and °). Table S8. Atomic displacement parameters ($Å^2$) to 3. Figure S26. Prismatic crystalline solid of 3(5)-trifluoromethyl-4-methyl-5(3)-(thien-2-yl)-1*H*-pyrazole (5) obtained from recrystallization in hexane. Figure S27. ORTEP drawing of 3(5)-trifluoromethyl-4-methyl-5(3)-(thien-2-yl)-1*H*-pyrazole (5), showing all nonhydrogen atoms and atom-numbering scheme; 50% probability amplitude displacement ellipsoids are shown. Figure S28. Crystalline supramolecular packing diagram of 3(5)-trifluoromethyl-4-methyl-5(3)-(thien-2-yl)-1*H*-pyrazole (5), view along the *b*-axis. Figure S29. Crystalline supramolecular packing diagram of 3(5)-trifluoromethyl-4-methyl-5(3)-(thien-2-yl)-1*H*-pyrazole (5), view along the *c*-axis. Figure S30. Crystalline supramolecular packing diagram of 3(5)-trifluoromethyl-4-methyl-5(3)-(thien-2-yl)-1*H*-pyrazole (5), view along the *a*-axis. Figure S31. Partial view of the infinite 3D-structure formed by the different units of 5, showing intermolecular hydrogen bonds as dashed lines. Table S9. Crystallographic data and structure refinements for 3(5)-trifluoromethyl-4-methyl-5(3)-(thien-2-yl)-1*H*-pyrazole (5). Table S10. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$). **U**(eq) is defined as one-third of trace of the orthogonalized $\mathbf{U}_{ij}$ tensor. Table S11. Bond lengths (Å) for 5. Table S12. Bond angles [°] for 5. Table S13. Hydrogen-bonding geometry for 5 (Å and °). Table S14. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($Å^2 \times 10^3$) for 5. Table S15. Atomic displacement parameters ($Å^2$) to 5. Table S16. Torsion angles [°] for 5. *(Supplementary Material)*

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