Synthesis of 1,6-Dihydro-5-hydroxy-6-oxo-3-(trifluoromethyl)-4-pyridazinecarboxylates

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The reaction of 2-(alkylamino)-3-(trifluoroacetyl)butenedioates **2a-b** with alkyl and aryl hydrazines in ether provides 1,6-dihydro-6-oxo-3-(trifluoromethyl)-4-pyridazinecarboxylates as their alkylamine salts **3a-g**. The structures of these products are substantiated using 2D nmr and ^{15}N nmr techniques.

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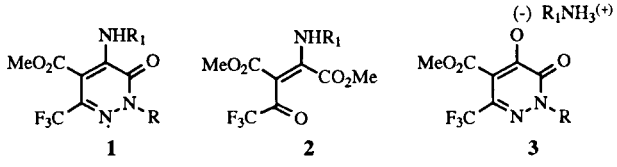
In connection with a program directed toward exploring trifluoromethyl substituted pyridazines as potential agrochemicals, we needed to synthesize 5-(alkylamino)-1,6-dihydro-6-oxo-3-(trifluoromethyl)-4-pyridazinecarboxylates **1**. A convenient method for the preparation of 3-pyridazinones involves the cyclocondensation of β-acyl acrylates with hydrazines [1-4]. We envisioned an extension of this methodology for the preparation of **1** by condensing 2-(alkylamino)-3-(trifluoroacetyl)butenedioates **2** with hydrazines. In this paper we report that the reactions of **2** with hydrazine hydrate and various alkyl and aryl hydrazines assume a slightly anomalous course leading to 1,6-dihydro-5-hydroxy-6-oxo-3-(trifluoromethyl)-4-pyridazinecarboxylate derivatives **3**.



R = H, Alkyl, Aryl
R_1 = $CHMe_2$, CH_2Ph

The butenedioates **2** were synthesized as shown in Scheme 1. Thus, addition of isopropylamine or benzylamine to dimethyl acetylenedicarboxylate (**4**) according to previously reported procedures [5-6] gave the enamines **5a** and **5b**, respectively. Trifluoroacetylation of **5a** and **5b** with trifluoroacetic anhydride in ether afforded **2a** (72%) and **2b** (79%), respectively, as mixtures of *E* and *Z* isomers. Although the separation and stereochemical assignments of individual isomers were not attempted, ^1H nmr and gc analysis of **2a** and **2b** revealed the ratio of geometric isomers to be 1:4 and 1:3, respectively. The reaction of **2a** or **2b** with hydrazine hydrate and various alkyl and aryl hydrazines gave products **3a-g** in isolated yields of 45-70%. These results are summarized in Table 1.

Scheme 1

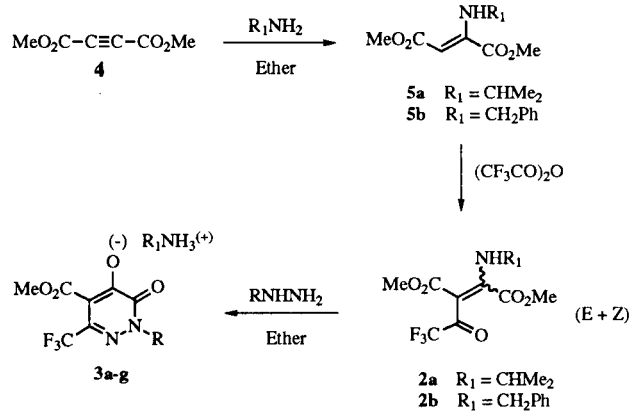


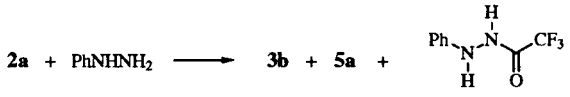
Table 1

Percent Yield and Melting Point Data of **3a-g**

Compound	R	R_1	yield %	mp, °C
3a	H	$CHMe_2$	58	171-172
3b	Ph	$CHMe_2$	64	169-170
3c	Ph	CH_2Ph	57	169-171
3d	4-(OMe)Ph	$CHMe_2$	68	189-191
3e	2-Pyridyl	$CHMe_2$	71	177-179
3f	CH_2Ph	$CHMe_2$	55	146-148
3g	t-C_4H_9	$CHMe_2$	45	154-155

A typical procedure is exemplified by the reaction of **2a** with phenylhydrazine. Thus, stirring equimolar amounts of **2a** and phenylhydrazine in ether at room temperature resulted in the gradual formation of a white precipitate of hydroxypyridazinone salt **3b**. After 12 hours, when the precipitation was apparently complete, the product was isolated by filtration in 64% yield. Analysis of the filtrate by gc-ms indicated several components including unreacted **2a**, phenylhydrazine, compound **5a**, and 1-phenyl-2-(trifluoroacetyl)hydrazine (equation 1).

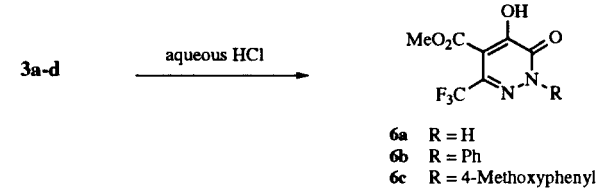
Presumably, the latter two are formed by a simple deacylation of compound **2a** by phenylhydrazine. The expected product, compound **1** (R = Ph, R_1 = *i*-Pr), was not detected in the filtrate.



(equation 1)

Aqueous solutions of compounds **3a-d** were acidified with dilute hydrochloric acid to obtain the parent hydroxypyridazinones **6a-c** (Scheme 2).

Scheme 2

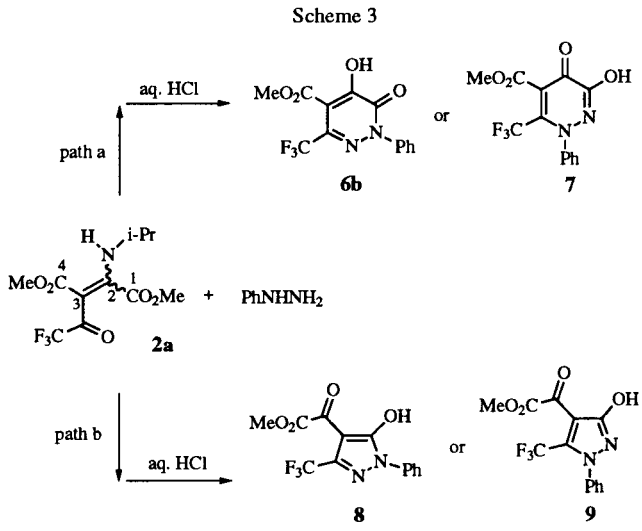


6a R = H
6b R = Ph
6c R = 4-Methoxyphenyl

Structural assignments of compounds **3a-g** and **6a-c** required extensive nmr studies. A summary of these studies is provided below using compound **6b** as an example. Compound **6b** is the acidification product of **3b**, which in turn is derived from the condensation of phenylhydrazine with **2a**. The ^1H and ^{13}C nmr spectra of compound **3b** clearly indicated that the trifluoroacetyl group and one of the two carboxylate ester groups of **2a** had participated in cyclocondensation with phenylhydrazine and that the cyclization was followed by loss of isopropylamine. One can envision four different modes of condensation between compound **2a** and phenylhydrazine that can lead to the formation of four different heterocycles with the same molecular formula (Scheme 3). Cyclization involving the trifluoroacetyl group and the C-1 ester group of butenedioate **2a** (path a) would lead to isomeric pyridazinones **6b** or **7** that differ only in the position of the phenyl group. Alternatively, cyclization involving the trifluoroacetyl group and the C-4 ester group (path b) can result in isomeric pyrazole derivatives **8** or **9**. Thus, the assignment of structure to the product involved resolving two separate issues: (1) distinction between pyridazine and pyrazole ring systems, and (2) identification of the ring nitrogen bearing the phenyl group.

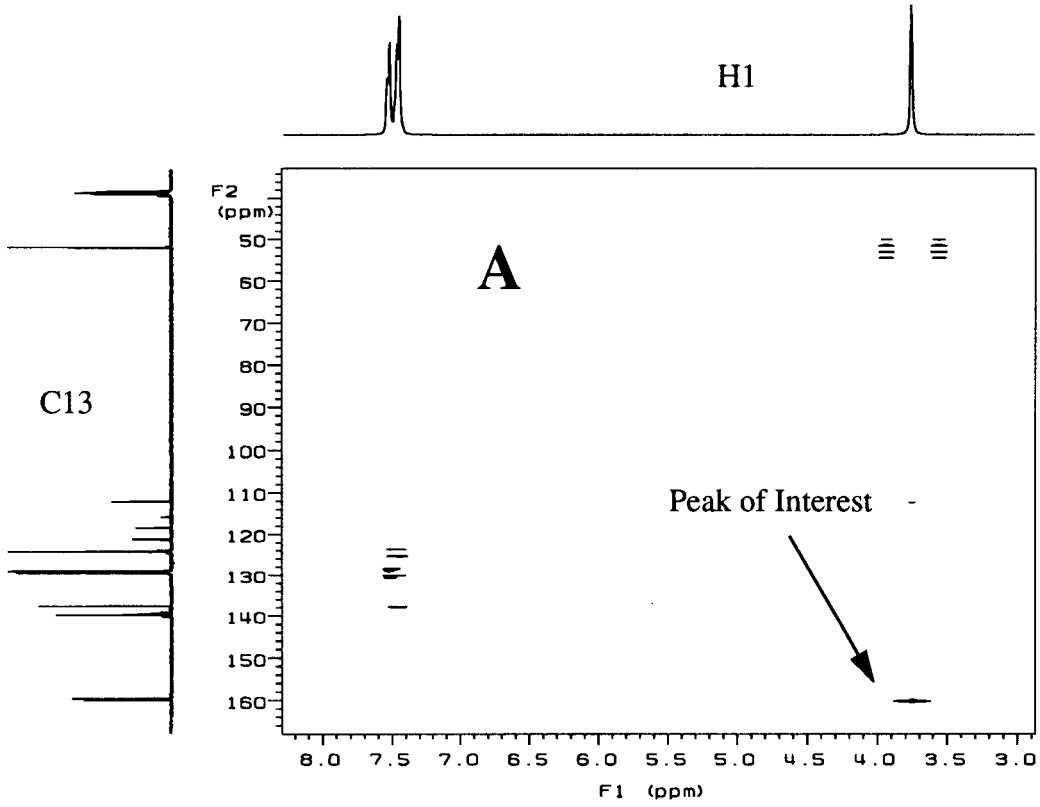
The differentiation between pyridazine and pyrazole ring systems was based upon the carbon-carbon connectivity of the ester carbonyl group. The carbonyl carbon of the ester group in pyridazines **6b** and **7** is bonded to a ring carbon. By contrast, the carbonyl carbon of the ester group in pyrazoles **8** and **9** is bonded to another carbonyl

Scheme 3



carbon. The signal due to the carbonyl carbon of the ester group in **6b** was identified by long-range heteronuclear correlated spectroscopy (LR-HETCOR), a technique used to define molecular structure based on the observation of scalar coupling between specific protons and carbons [7]. The LR-HETCOR spectrum of **6b**, obtained with a pulse sequence optimized to observe typical three bond proton to carbon couplings, is shown in Figure 1. The crosspeak observed between the proton resonance of the methyl group at 3.7 ppm and the carbon resonance at 160 ppm indicated that the latter must be due to the carbonyl carbon of the ester group. The connectivity of the ester carbonyl group was determined by a selective INADEQUATE spectrum shown in Figure 2. This technique is also based on coupling, in this case one bond coupling between two carbons directly bonded to each other [8]. In this experiment a selective pulse is applied to one particular carbon resonance. This results in a very characteristic signal, an antiphase doublet, at the nmr frequency of any carbon or carbons directly bonded to the one which was selectively pulsed. Figures 2A and 2B show that application of a selective pulse to the ring carbon resonance at 112 ppm results in two signals at 140 ppm and 160 ppm. Since the signal at 160 ppm was determined to be due to carbon of the ester carbonyl by LR-HETCOR, the ester group must be bonded to a ring carbon as in structure **6b** or **7**.

The point of attachment of the phenyl group was determined by measuring two ^{15}N spectra; one proton decoupled and one proton coupled (Figure 3). The bottom trace shows the full ^{15}N spectrum and the insets above each resonance show expansions of the respective resonance from the coupled and the decoupled spectra. The resonance at 312 ppm is a quartet in both the coupled and the decoupled spectra indicating that the coupling is due to the trifluoromethyl group. The resonance at 219 ppm is a



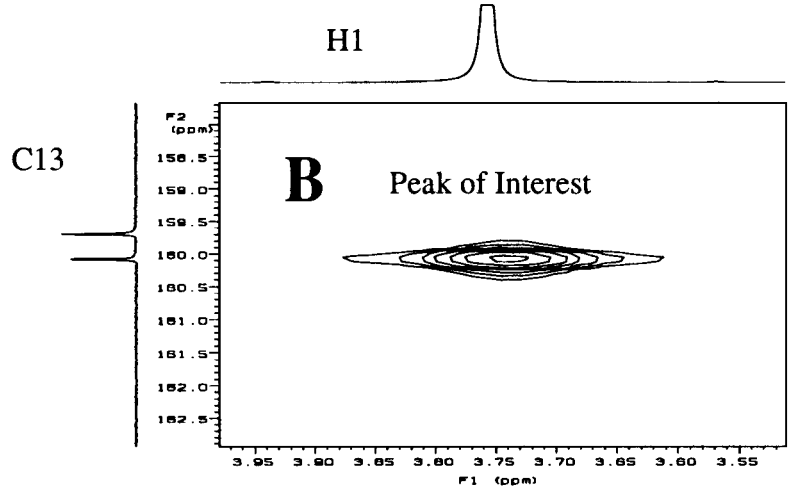


Figure 1A. The LR-HETCOR spectrum of **6b**.
Figure 1B. An expansion of 1A showing the correlation to the carbonyl carbon.

sharp signal in the decoupled spectrum, but is noticeably broadened in the coupled spectrum due to coupling with the protons of the phenyl group. These results show that the ring nitrogen closest to the trifluoromethyl group is not bonded to the phenyl group but the nitrogen furthest from the trifluoromethyl group is directly bonded to the phenyl group, thus confirming structure **6b**.

A reasonable mechanism for the formation of compounds **3a-g** in the reaction of **2a-b** with various hydrazines is illustrated in Scheme 4. We propose that the hydrazines initially add to the trifluoroacetyl carbonyl group to form **10** which undergoes cyclization to the

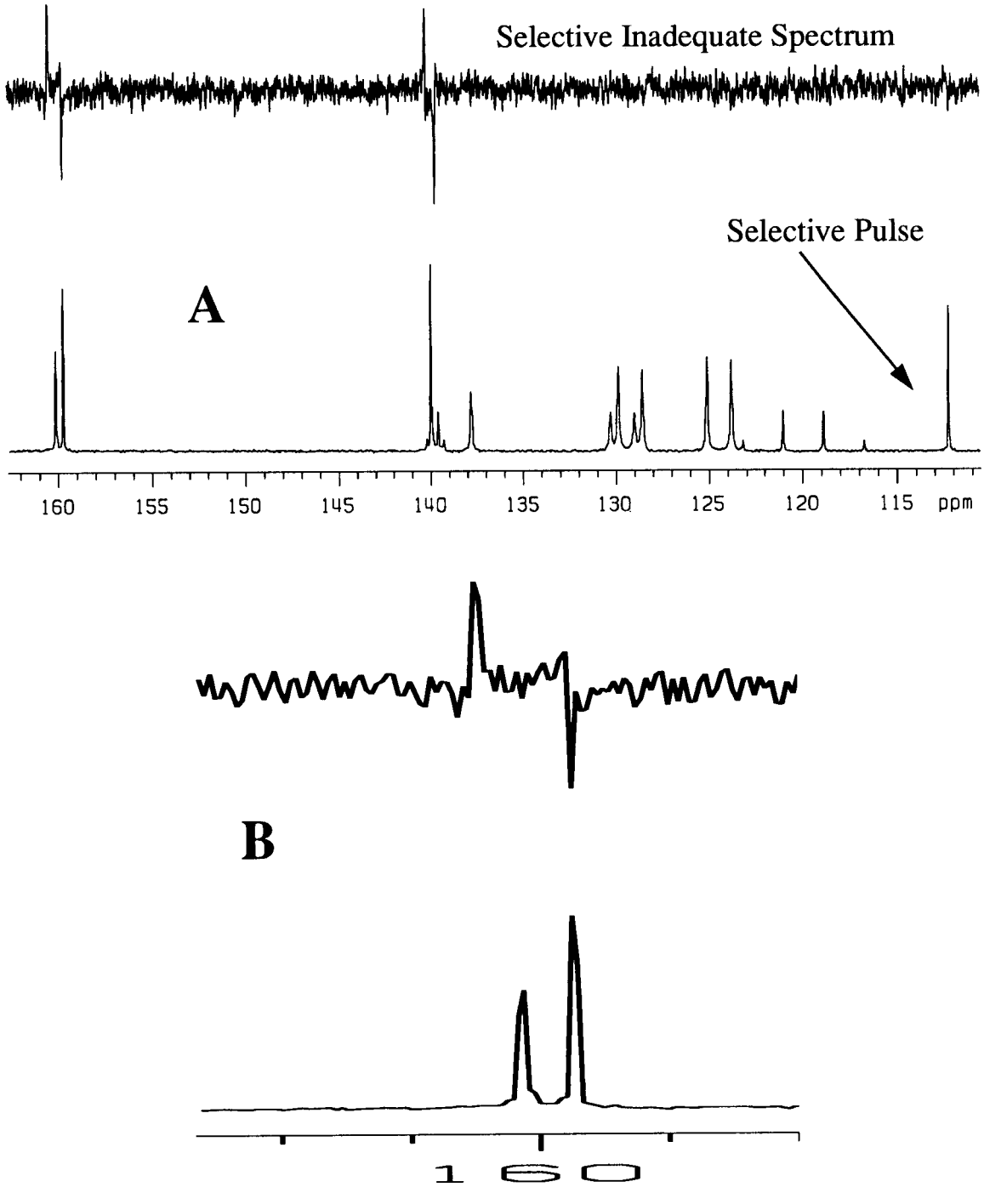


Figure 2A. The selective Inadequate spectrum of **6b**.
Figure 2B. An expansion showing that the affected resonance is the lower field resonance of the two around 160 ppm..

heterocyclic species **11**. Although intermediate **11** can, in theory, eliminate water to give alkylamino pyridazinone **1**, it appears to rearrange instead to an isomeric species **12** and subsequently eliminate the alkylamine group to give **13**. The rearrangement of **11** to **12** can either be stepwise or concerted. A stepwise rearrangement would presumably occur *via* the elimination and readdition of water and, therefore, would invoke the intermediacy of compound **1**. This would also imply that compound **1** is hydrolytically unstable. Alternatively, the addition and

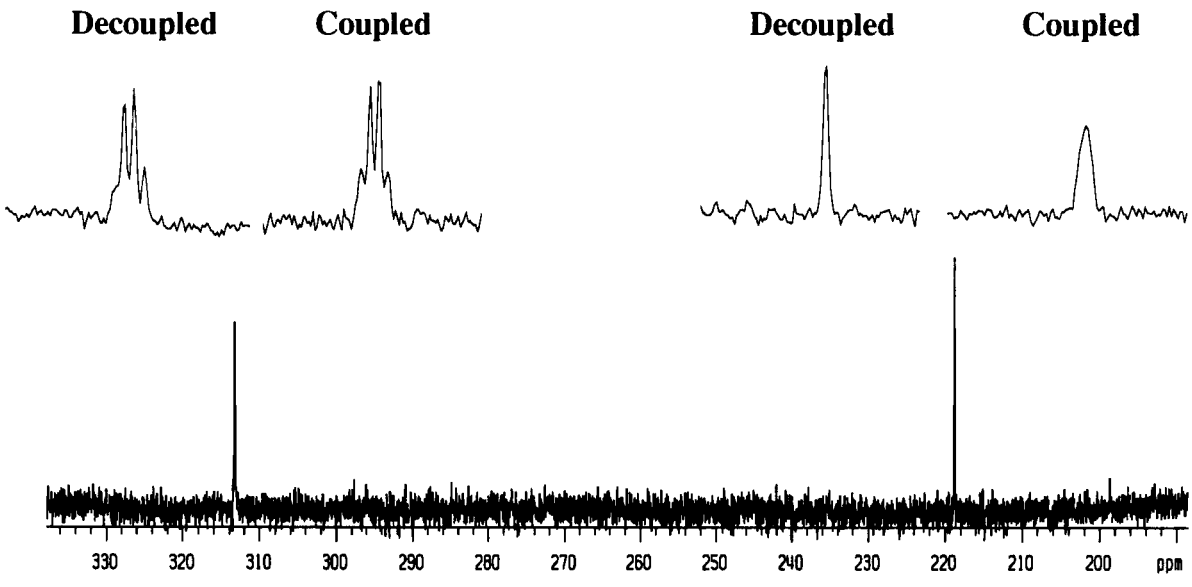
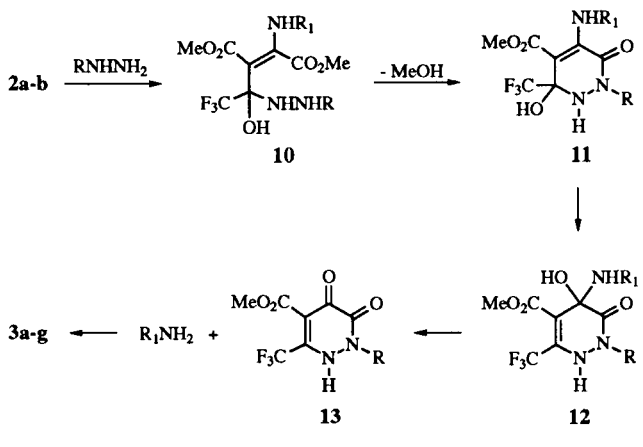


Figure 3. The ^{15}N spectrum of **6b** with insets showing the difference between proton coupled and proton decoupled.

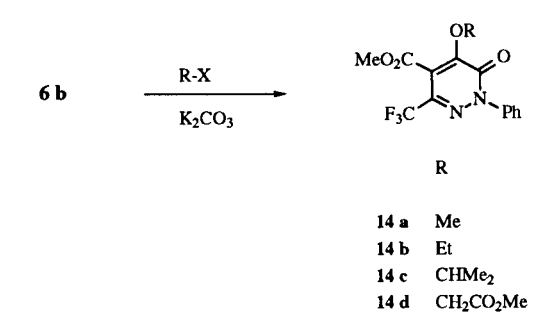
elimination could occur in a synchronous manner amounting to an allylic rearrangement of the hydroxyl group in **11**. In the absence of an alternative synthesis of **1** and a study of its hydrolytic behavior, a clear distinction between the two mechanisms can not be made at this time. Finally, an irreversible acid-base reaction between **13** and the alkylamine results in the formation of compounds **3a-g**. We propose that species **10-12** can exist in equilibrium with each other and that the irreversible formation and precipitation of compounds **3a-g** provide the driving force for the reaction. The deacylation byproducts observed in the reaction of compound **2a** with phenylhydrazine may be explained by an alternative reaction pathway of intermediate **10**. Thus, intermediate **10** can collapse *via* a carbon-carbon bond cleavage to give trifluoroacetyl hydrazine and 2-(alkylamino)butenedioate **5** (equation 1).

Finally, the hydroxypyridazinone **6b** could be converted to the corresponding alkoxy derivatives by alkylation with alkyl halides. Thus, treatment of compound **6b** with methyl iodide, ethyl iodide, isopropyl iodide or methyl bromoacetate in refluxing acetone using potassium carbonate as the base gave **14a-d** as the only products (Scheme 5). The possibility of *N*-alkylated structures for **14a-d** could be ruled out based upon the absence of long-range coupling of the trifluoromethyl fluorines with the alkyl protons or carbons in the ^1H and ^{13}C nmr spectra [9]. Normally, alkylations of hydroxypyridazines with alkyl halides using an alkaline base give *N*-alkylated pyridazinones as major products [10]. In compound **6b**, the sterically bulky and electron-withdrawing trifluoromethyl group as well as the adjacent *N*-phenyl group may hinder the alkylations at nitrogen, resulting in exclusive *O*-alkylation.

Scheme 4



Scheme 5



EXPERIMENTAL

Melting points are uncorrected. The ^1H nmr spectra were

measured at either 400 or 300 MHz; ^{13}C spectra and ^{19}F spectra were measured at 75 and 282 MHz, respectively. The ^{1}H and ^{13}C shifts (δ) are expressed in parts per million (ppm) downfield from tetramethylsilane; the coupling constants are expressed as $_{n}J$, where n is the number of bonds between carbon and fluorine or carbon and hydrogen. The ^{19}F nmr spectra were recorded using benzotrifluoride (δ -63.73) in a sealed capillary as an external standard and are expressed in ppm relative to fluorotrichloromethane, with upfield shifts taken as negative. The ^{15}N spectra were obtained on a Varian XL-400 and ^{15}N shifts are relative to the 113 ppm shift of 90% formamide in dimethyl sulfoxide. The LR-HETCOR spectra were obtained on a Varian XL-400 spectrometer using a simple proton-carbon COSY pulse sequence. The evolution time included a fixed delay of 62 milliseconds. The spectra were obtained with the decoupler off during acquisition. Thus, in Figure 1, while a normal proton decoupled ^{13}C spectrum is shown along the vertical axis, the 2D peaks show full proton coupling. The selective INADEQUATE spectra were obtained on a Varian Unity 500 equipped with waveform generators. It had the unusual feature that the last proton pulse was replaced by a EBURP [11] pulse of 200 Hz bandwidth. Radial preparative tlc was performed on a Chromatotron (Harrison Research) using glass plates coated with 4 mm of E. Merck "Silica gel 60" PF-254 containing a gypsum binder. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, GA. Compounds **5a** and **5b** were prepared according to previously reported procedures [5-6].

Dimethyl 2-[(1-Methylethyl)amino]-3-(trifluoroacetyl)-2-butenedioate (**2a**).

To a solution of 10.0 g (0.05 mole) of **5a** in 100 ml of ether at 0° was added dropwise 10.7 g (0.051 mole) of trifluoroacetic anhydride. The mixture was then warmed to room temperature and stirred for 4 hours. The reaction mixture was washed with water, dried (magnesium sulfate), and evaporated to obtain an oily residue. Trituration of the residue with petroleum ether gave 10.7 g (72%) of **2a** as a pale yellow solid: mp 46-49°; ^{1}H nmr (deuteriochloroform): δ 1.1-1.2 (m, 6H, $(CH_3)_2CH$-N), 3.48-3.56 (m, 1H, $(CH_3)_2CH$-N), 3.58 (s, 2.4 H, CO_2CH_3, major isomer), 3.62 (s, 0.6 H, CO_2CH_3, minor isomer), 3.76 (s, 0.6 H, CO_2CH_3, minor isomer), 3.82 (s, 2.4 H, CO_2CH_3, major isomer); ^{13}C nmr (deuteriochloroform): major isomer: δ 23.26, 50.1, 51.8, 53.27, 95.44, 117.0 (q, $^{1}J_{CF}$ = 286 Hz), 161.9, 162.1, 165.7, 179.0 (q, $^{2}J_{CF}$ = 35.3 Hz), minor isomer: δ 20.46, 44.5, 49.44, 51.32, 93.2, 116.4 (q, $^{1}J_{CF}$ = 280 Hz), 161.6, 162.5, 168.5, 177.6 (q, $^{2}J_{CF}$ = 36.2 Hz); ^{19}F nmr (deuteriochloroform): major isomer δ -74.8 (s, CF_3), minor isomer δ -75.14 (s, CF_3).

Anal. Calcd. for $C_{11}H_{14}F_3NO_5$: C, 44.45; H, 4.75; N, 4.71. Found: C, 44.53; H, 4.77; N, 4.67.

Dimethyl 2-[(Phenylmethyl)amino]-3-(trifluoroacetyl)-2-butenedioate (**2b**).

Treatment of 12.5 g (0.05 mole) of **5b** with 10.7 g (0.051 mole) of trifluoroacetic anhydride as above gave 13.6 g (79%) of **2b** as a colorless solid, mp 60-64°; ^{1}H nmr (deuteriochloroform): δ 3.77 (s, 2.25 H, CO_2CH_3, major isomer), 3.82 (s, 0.75 H, CO_2CH_3, minor isomer), 3.96 (s, 0.75 H, CO_2CH_3, minor isomer), 4.1 (s, 2.25 H, CO_2CH_3, major isomer), 4.55 (m, 2H, phenyl-CH_2), 7.3-7.5 (m, 6H, phenyl protons); ^{13}C nmr (deuteriochloroform): major isomer: δ 44.3, 52.32, 53.27, 94.3, 118.5 (q, $^{1}J_{CF}$ = 286 Hz), 124.2, 130.15, 131.33, 139.7, 160.5, 162.7, 166.4, 180.4 (q, $^{2}J_{CF}$ = 38 Hz), minor isomer: δ 43.15, 51.5, 53.75, 96.2, 117.8 (q, $^{1}J_{CF}$ = 280 Hz), 125.0, 130.15, 131.33, 141.2, 161.3, 162.2, 165.32, 178.6 (q, $^{2}J_{CF}$ = 36.6 Hz); ^{19}F nmr (deuteriochloroform): major isomer δ -74.2 (s, CF_3), minor isomer δ -75.05 (s, CF_3).

Anal. Calcd. for $C_{15}H_{14}F_3NO_5$: C, 52.18; H, 4.09; N, 4.06. Found: C, 51.98; H, 4.13; N, 4.01.

General Procedure for the Preparation of Compounds **3a-g**:

To a solution of **2a** or **2b** (0.01 mole) in 50 ml of ether was added the appropriate hydrazine (0.01 mole) and the mixture was stirred at room temperature overnight. The resulting precipitate was filtered, washed with ether, and air dried to obtain **3a-g** .

Methyl 1,6-Dihydro-5-hydroxy-6-oxo-3-(trifluoromethyl)-4-pyridazinecarboxylate, Isopropylamine Salt (**3a**).

This compound was obtained from **2a** and hydrazine hydrate in 58% yield as a white solid, mp 171-172°; ^{1}H nmr (methanol-d_4): δ 1.28 (d, J = 7.2 Hz, 6H, $(CH_3)_2CH$-N), 3.4 (m, 1H, $(CH_3)_2CH$-N), 3.85 (s, 3H, CO_2CH_3), 5.05 (broad s, 4H); ^{13}C nmr (methanol-d_4): δ 20.3, 44.3, 52.0, 110.06, 122.3 (q, $^{1}J_{CF}$ = 270 Hz), 142.23 (q, $^{2}J_{CF}$ = 38 Hz), 146.0, 163.6, 164.8; ^{19}F nmr (methanol-d_4): δ -60.25 (s, CF_3).

Anal. Calcd. for $C_{10}H_{14}F_3N_3O_4$: C, 40.41; H, 4.75; N, 14.14. Found: C, 40.49; H, 4.78; N, 14.14.

Methyl 1,6-Dihydro-5-hydroxy-6-oxo-1-phenyl-3-(trifluoromethyl)-4-pyridazinecarboxylate, Isopropylamine Salt (**3b**):

This compound was obtained from **2a** and phenylhydrazine in 64% yield as a white solid, mp 169-170°; ^{1}H nmr (methanol-d_4): δ 1.34 (d, J = 7.2 Hz, 6H, $(CH_3)_2CH$-N), 3.38 (m, 1H, $(CH_3)_2CH$-N), 3.94 (s, 3H, CO_2CH_3), 4.87 (br s, 3H, $NH_3^{(+)}$), 7.5 (m, 3H, phenyl protons), 7.7 (m, 2H, phenyl protons); ^{13}C nmr (methanol-d_4): δ 20.88, 45.02, 52.31, 109.7, 122.07 (q, $^{1}J_{CF}$ = 270 Hz), 124.9, 130.12, 130.32, 140.39, 142.54 (q, $^{2}J_{CF}$ = 37.8 Hz), 149.31, 162.74, 166.1; ^{19}F nmr (methanol-d_4): δ -61.2 (s, CF_3).

Anal. Calcd. for $C_{16}H_{18}F_3N_3O_4$: C, 51.48; H, 4.86; N, 11.26. Found: C, 51.50; H, 4.92; N, 11.26.

Methyl 1,6-Dihydro-5-hydroxy-6-oxo-1-phenyl-3-(trifluoromethyl)-4-pyridazinecarboxylate, Benzylamine Salt (**3c**):

This compound was obtained from **2b** and phenylhydrazine in 57% yield as a white solid, mp 169-171°; ^{1}H nmr (methanol-d_4): δ 3.73 (s, 3H, CO_2CH_3), 3.98 (s, 2H, phenyl-CH_2), 4.78 (br s, 3H, $NH_3^{(+)}$), 7.4-7.55 (m, 8H, phenyl protons), 7.72 (m, 2H, phenyl protons); ^{13}C nmr (methanol-d_4): δ 44.3, 52.32, 109.76, 122.07 (q, $^{1}J_{CF}$ = 270 Hz), 124.9, 129.95, 130.1, 130.15, 130.18, 130.31, 134.5, 140.38, 140.39, 142.5 (q, $^{2}J_{CF}$ = 37.8 Hz), 149.25, 162.78, 166.15; ^{19}F nmr (methanol-d_4): δ -60.6 (s, CF_3).

Anal. Calcd. for $C_{20}H_{18}F_3N_3O_4$: C, 57.01; H, 4.31; N, 9.97. Found: C, 57.03; H, 4.35; N, 9.98.

Methyl 1,6-Dihydro-5-hydroxy-1-(4-methoxyphenyl)-6-oxo-3-(trifluoromethyl)-4-pyridazinecarboxylate, Isopropylamine Salt (**3d**).

This compound was obtained from **2a** and 4-methoxyphenylhydrazine in 68% yield as a white solid, mp 189-191°; ^{1}H nmr (methanol-d_4): δ 1.26 (d, J = 7.2 Hz, 6H, $(CH_3)_2$CH-N), 3.37 (m, 1H, $(CH_3)_2CH$-N), 3.82 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.85 (br s, 3H, $NH_3^{(+)}$), 7.0 (d, J = 8.2 Hz, 2H, phenyl protons), 7.6 (d, J =8.2 Hz, 2H, phenyl protons); ^{13}C nmr (methanol-d_4): δ 20.8, 45.05, 52.27, 56.13, 115.33, 122.1 (q, $^1J_{CF}$ = 270 Hz), 126.6, 133.36, 142.6 (q, $^2J_{CF}$ = 37.9 Hz), 148.7, 161.6, 162.8, 166.18; ^{19}F nmr (methanol-d_4): δ -61.02 (s, CF_3).

Anal. Calcd. for $C_{17}H_{20}F_3N_3O_5$: C, 50.62; H, 5.00; N, 10.42. Found: C, 50.63; H, 5.01; N, 10.40.

Methyl 1,6-Dihydro-5-hydroxy-6-oxo-1-(2-pyridinyl)-3-(trifluoromethyl)-4-pyridazinecarboxylate, Isopropylamine Salt (**3e**):

This compound was obtained from **2a** and 2-pyridylhydrazine in 71% yield as a pale yellow solid, mp 177-179°; ^{1}H nmr (methanol-d_4): δ 1.28 (d, J = 7.2 Hz, 6H, $(CH_3)_2$CH-N), 3.39 (m, 1H, $(CH_3)_2CH$-N), 3.84 (s, 3H, CO_2CH_3), 4.87 (br s, 3H, $NH_3^{(+)}$), 7.41 (m, 1H, pyridine ring *H*), 7.9 (m, 1H, pyridine ring *H*), 8.0 (m, 1H, pyridine ring *H*), 8.5 (m, 1H, pyridine ring *H*); ^{13}C nmr (methanol-d_4): δ 20.9, 44.9, 52.36, 116.74, 122.2 (q, $^1J_{CF}$ = 270 Hz), 124.9, 140.4, 142.7 (q, $^2J_{CF}$ = 38 Hz), 148.1, 149.26, 152.2, 162.63, 166.4; ^{19}F nmr (methanol-d_4): δ -61.75 (s, CF_3).

Anal. Calcd. for $C_{15}H_{17}F_3N_4O_4$: C, 48.13; H, 4.58; N, 14.97. Found: C, 48.22; H, 4.63; N, 14.91.

Methyl 1,6-Dihydro-5-hydroxy-6-oxo-1-(phenylmethyl)-3-(trifluoromethyl)-4-pyridazinecarboxylate, Isopropylamine Salt (**3f**).

This compound was obtained from **2a** and benzylhydrazine in 55% yield as a white solid, mp 146-148°; ^{1}H nmr (methanol-d_4): δ 1.28 (d, J = 7.2 Hz, 6H, $(CH_3)_2$CH-N), 3.48 (m, 1H, $(CH_3)_2CH$-N), 3.8 (s, 3H, CO_2CH_3), 4.88 (br s, 3H, $NH_3^{(+)}$), 5.5 (s, 2H, phenyl-CH_2), 7.34-7.4 (m, 5H, phenyl protons); ^{13}C nmr (methanol-d_4): δ 20.7, 44.83, 52.32, 55.67, 110.05, 122.07 (q, $^1J_{CF}$ = 270 Hz), 129.46, 129.8, 133.32, 137.13, 141.2 (q, $^2J_{CF}$ = 38 Hz), 150.85, 163.38, 165.54; ^{19}F nmr (methanol-d_4): δ -61.1 (s, CF_3).

Anal. Calcd. for $C_{17}H_{20}F_3N_3O_4$: C, 52.71; H, 5.20; N, 10.85. Found: C, 52.80; H, 5.22; N, 10.82.

Methyl 1-(1,1-Dimethylethyl)-1,6-dihydro-5-hydroxy-6-oxo-3-(trifluoromethyl)-4-pyridazinecarboxylate, Isopropylamine Salt (**3g**):

This compound was obtained from **2a** and *t*-butylhydrazine in 45% yield as a white solid, mp 154-155°; ^{1}H nmr (methanol-d_4): δ 1.3 (d, J = 7.2 Hz, 6H, $(CH_3)_2$CH-N), 1.7 (s, 9H, *t*-C_4H_9), 3.41 (m, 1H, $(CH_3)_2CH$-N), 3.79 (s, 3H, CO_2CH_3), 4.9 (br s, 3H, $NH_3^{(+)}$); ^{13}C nmr (methanol-d_4): δ 20.32, 30.6, 45.07, 52.0, 108.9, 122.35 (q, $^1J_{CF}$ = 270 Hz), 140.0 (q, $^2J_{CF}$ = 39 Hz), 148.7, 163.2, 168.37; ^{19}F nmr (methanol-d_4): δ -61.08 (s, CF_3).

Anal. Calcd. for $C_{14}H_{22}F_3N_3O_4$: C, 47.59; H, 6.28; N, 11.89. Found: C, 47.51; H, 6.32; N, 11.83.

General Procedure for the Preparation of Compounds **6a-c**:

A solution of **3a-d** (0.01 mole) in 100 ml of water was acidified with 50 ml of 10% hydrochloric acid. The resulting precipitate was filtered, washed with water, air dried, and recrystallized from ether-hexane to obtain **6a-c** .

Methyl 1,6-Dihydro-5-hydroxy-6-oxo-3-(trifluoromethyl)-4-pyridazinecarboxylate (**6a**):

This compound was obtained from **3a** in 90% yield as a white solid, mp 102-104°; ^{1}H nmr (methanol-d_4): δ 3.94 (s, 3H, CO_2CH_3), 4.92 (broad s, 3H, exchangeable N*H* and O*H*); ^{13}C nmr (methanol-d_4): δ 52.5, 115.14, 121.78 (q, $^1J_{CF}$ = 267 Hz), 137.74, 142.26 (q, $^2J_{CF}$ = 38.2 Hz), 159.8, 164.5; ^{19}F nmr (methanol-d_4): δ -61.05 (s, CF_3).

Anal. Calcd. for $C_7H_5F_3N_2O_4 \cdot 0.5H_2O$: C, 34.02; H, 2.45; N, 11.34. Found: C, 34.06; H, 2.44; N, 11.37.

Methyl 1,6-Dihydro-5-hydroxy-6-oxo-1-phenyl-3-(trifluoromethyl)-4-pyridazinecarboxylate (**6b**).

This compound was obtained in 87% yield from **3b** and in 93% yield from **3c** as a white solid, mp 127-128°; ^{1}H nmr (methanol-d_4): δ 3.76 (s, 3H, CO_2CH_3), 5.0 (s, 1H, O*H*), 7.41 (m, 5H, phenyl protons); ^{13}C nmr (methanol-d_4): δ 52.96, 114.5, 121.63 (q, $^1J_{CF}$ = 267.6 Hz), 125.81, 130.43, 130.94, 139.78, 141.05, 142.22 (q, $^2J_{CF}$ = 38.5 Hz), 161.52, 162.21; ^{19}F nmr (methanol-d_4): δ -60.81 (s, CF_3).

Anal. Calcd. for $C_{13}H_9F_3N_2O_4$: C, 49.69; H, 2.89; N, 8.92. Found: C, 49.78; H, 2.92; N, 8.93.

Methyl 1,6-Dihydro-5-hydroxy-6-oxo-1-(4-methoxyphenyl)-3-(trifluoromethyl)-4-pyridazinecarboxylate (**6c**).

This compound was obtained from **3d** in 86% yield as a white solid, mp 94-95°; ^{1}H nmr (methanol-d_4): δ 3.91 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 5.25 (s, 1H, O*H*), 7.13 (d, J = 8.2 Hz, 2H, phenyl protons), 7.54 (d, J = 8.2 Hz, 2H, phenyl protons); ^{13}C nmr (methanol-d_4): δ 52.92, 56.1, 114.1, 115.39, 121.64 (q, $^1J_{CF}$ = 267.3 Hz), 127.33, 132.58, 141.1, 141.9 (q, $^2J_{CF}$ = 38.7 Hz), 161.57, 162.28; ^{19}F nmr (methanol-d_4): δ -60.57 (s, CF_3).

Anal. Calcd. for $C_{14}H_{11}F_3N_2O_5$: C, 48.85; H, 3.22; N, 8.14. Found: C, 48.94; H, 3.25; N, 8.13.

General Procedure for the Preparation of Compounds **14a-d**:

A solution of 2.2 g (0.007 mole) of compound **6b** and the appropriate alkyl halide (0.01 mole) in 50 ml of acetone was added to 5 g of anhydrous potassium carbonate and the resulting mixture was heated at reflux for 36 hours. The reaction mixture was filtered to remove insoluble salts and the filtrate was evaporated under reduced pressure. The residue was diluted with water and extracted with ethyl acetate. The organic layer was washed with water, dried (magnesium sulfate), and evaporated. Purification of the crude product by radial chromatography (silica gel, 10% ethyl acetate/hexane) gave compounds **14a-d**.

Methyl 1,6-Dihydro-5-methoxy-6-oxo-1-phenyl-3-(trifluoromethyl)-4-pyridazinecarboxylate (**14a**).

This compound was obtained from **6b** and methyl iodide as a

white solid in 79% yield, mp 64-65°; ^{1}H nmr (deuteriochloroform): δ 3.77 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 7.4 (s, 5H, phenyl protons); ^{13}C nmr (deuteriochloroform): δ 52.65, 53.63, 114.14, 120.12 (q, $^1J_{CF}$ = 268.6 Hz), 124.5, 129.54, 129.99, 138.23, 138.52, 141.61 (q, $^2J_{CF}$ = 38.9 Hz), 159.72, 160.72; ^{19}F nmr (deuteriochloroform): δ -63.81 (s, CF_3).

Anal. Calcd. for $C_{14}H_{11}F_3N_2O_4$: C, 51.23; H, 3.38; N, 8.53. Found: C, 51.07; H, 3.55; N, 8.42.

Methyl 1,6-Dihydro-5-ethoxy-6-oxo-1-phenyl-3-(trifluoromethyl)-4-pyridazinecarboxylate (**14b**).

This compound was obtained from **6b** and ethyl iodide as a colorless oil in 83% yield, mp 64-65°; ^{1}H nmr (deuteriochloroform): δ 1.13 (t, J = 6.8 Hz, 3H, OCH_2CH_3), 3.8 (s, 3H, CO_2CH_3), 4.22 (q, J = 6.8 Hz, 2H, OCH_2CH_3), 7.4 (s, 5H, phenyl protons); ^{13}C nmr (deuteriochloroform): δ 13.55, 52.4, 62.93, 113.84, 120.0 (q, $^1J_{CF}$ = 268.5 Hz), 124.5, 129.3, 129.8, 138.12, 138.6, 141.4 (q, $^2J_{CF}$ = 38.9 Hz), 158.92, 160.59; ^{19}F nmr (deuteriochloroform): δ -63.93 (s, CF_3).

Anal. Calcd. for $C_{15}H_{13}F_3N_2O_4$: C, 52.64; H, 3.83; N, 8.18. Found: C, 52.47; H, 3.52; N, 8.10.

Methyl 1,6-Dihydro-5-(1-methylethoxy)-6-oxo-1-phenyl-3-(trifluoromethyl)-4-pyridazinecarboxylate (**14c**).

This compound was obtained from **6b** and isopropyl iodide as a white solid in 72% yield, mp 64-65°; ^{1}H nmr (deuteriochloroform): δ 1.22 (d, J = 6.2 Hz, 6H, $(CH_3)_2CH$), 3.9 (s, 3H, CO_2CH_3), 5.18 (m, 1H, $OCH(CH_3)_2$), 7.5 (s, 5H, phenyl protons); ^{13}C nmr (deuteriochloroform): δ 21.1, 52.25, 71.18, 119.8, 120.02 (q, $^1J_{CF}$ = 270 Hz), 124.5, 129.2, 129.6, 138.06, 139.0, 141.36 (q, $^2J_{CF}$ = 38.8 Hz), 158.4, 160.5; ^{19}F nmr (deuteriochloroform): δ -64.19 (s, CF_3).

Anal. Calcd. for $C_{16}H_{15}F_3N_2O_4$: C, 53.94; H, 4.24; N, 7.86. Found: C, 54.06; H, 4.29; N, 7.84.

Methyl 1,6-Dihydro-5-[(2-methoxy-2-oxo)ethoxy]-6-oxo-1-phenyl-3-(trifluoromethyl)-4-pyridazinecarboxylate (**14d**).

This compound was obtained from **6b** and methyl bromoacetate as a white solid in 76% yield, mp 85-86°; ^{1}H nmr (deuteriochloroform): δ 3.78 (s, 3H, CO_2CH_3), 3.95 (s, 3H, CO_2CH_3), 4.8 (s, 2H, OCH_2), 7.52 (m, 3H, phenyl protons), 7.6 (m, 2H, phenyl protons); ^{13}C nmr (deuteriochloroform): δ 52.34, 52.58, 62.02, 118.4, 119.86 (q, $^1J_{CF}$ = 270 Hz), 124.63, 129.26, 129.81, 136.68, 137.85, 140.66 (q, $^2J_{CF}$ = 37.9 Hz), 158.3, 160.53, 166.54; ^{19}F nmr (deuteriochloroform): δ -63.21 (s, CF_3)

Anal. Calcd. for $C_{16}H_{13}F_3N_2O_6$: C, 49.75; H, 3.39; N, 7.25. Found: C, 49.85; H, 3.44; N, 7.21.

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