JOC Article

A Novel Redox Reaction between 8-Aza-5,7-dimethyl-2-trifluoromethylchromone and Alkyl Mercaptoacetates. Facile Synthesis of CF_3-Containing 2-Pyridone Derivatives

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8-Aza-5,7-dimethyl-2-trifluoromethylchromone reacts with alkyl mercaptoacetates in the presence of triethylamine to give pyrido derivatives of 2-oxa-7-thiabicyclo[3.2.1]octane, which undergo the reductive ring opening to alkyl 2-{[3-(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)-3-oxo-1-(trifluoromethyl)propyl]sulfanyl}acetates.The latter can be also obtained directly from 8-aza-5,7-dimethyl-2-trifluoromethylchromone and behave as the masked α,β-unsaturated ketone, 4,6-dimethyl-3-(4,4,4-trifluorobut-2-enoyl)pyridin-2(1*H*)-one. This compound was independently synthesized from 3-acetyl-4,6-dimethyl-2-pyridone, and its synthetic potential was studied. A wide variety of 2-pyridone derivatives containing the CF_3 group have been prepared in good to moderate yields.

Introduction

Trifluoromethylated heterocycles continue to be of great academic and industrial interest, because the replacement of hydrogen by the fluorine atom sometimes brings about a dramatic change in the physical properties, chemical reactivity, and biological activity of the compounds arising as a result of the highest electronegativity of fluorine and high C−F bond energy.[1] In connection with this, the development of new methods to incorporate the CF_3 group into organic compounds remains an important area of research, and remarkable progress has been made in the development of efficient methods for synthesis of polyfluoroalkylated compounds using fluorinated building blocks.[2]

It is well-known that the insertion of polyfluoroalkyl substituents into position 2 of chromones activates molecules of these compounds and reveals significant differences in the reactivity of 2-alkyl- and 2-polyfluoroalkylchromones with respect to nucleophilic reagents.[3] Among the diverse transformations of 2-trifluoromethylchromones **1**, one of the more interesting reactions that has been encountered is the redox conversion of these compounds, on heating with 3 equiv of ethyl mercaptoacetate in the presence of triethylamine, to dihydrothienocoumarin derivatives **2** in high yields.[4]

The ready accessibility of compounds **2** has made them useful substrates for constructing highly functionalized biologically and medicinally important products. Thus, dihydrothienocoumarins **2** are the key intermediate in a novel synthesis of 3-hydrazinopyridazine derivatives,[5] which are widely used for the preparation of triazolo- and tetrazolopyridazines[6] and exhibit different types of biological activity as chemotherapeutics, antiinflammatory agents, CNS depressants and stimulants, and antihypertensives[7] (Scheme 1).

The mechanism for the redox formation of coumarins **2** is not obvious, but it is most likely that, as in the cases with 3,3-dialkyl-6-trifluoromethyl-2,3-dihydro-4-pyrones[8] and 7-polyfluoroalkylnorkhellins,[9] in which esters of thioglycolic acid act as *S*,*C*-dinucleophiles, the reaction initially gives benzo derivatives of 2-oxa-7-thiabicyclo-[3.2.1]octane **3**, which undergo the reductive ring opening to esters **4** under the action of ethyl mercaptoacetate. The

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(1) (a) *Fluorine in Bioorganic Chemistry*; Welch, J. T., Eswarakrishnan, S., Eds.; Wiley and Sons: New York, 1991. (b) *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*; Filler, R., Kobayashi, Y., Yagupolskii, L. M., Eds.; Elsevier: Amsterdam, 1993. (c) Hiyama, T. *Organofluorine Compounds. Chemistry and Application*; Springer-Verlag: Berlin, 2000.

(2) (a) McClinton, M. A.; McClinton, D. A. *Tetrahedron* **1992**, *48*, 6555. (b) Lin, P.; Jiang, J. *Tetrahedron* **2000**, *56*, 3635. (c) Nenaidenko, V. G.; Sanin, A. V.; Balenkova, E. S. *Russ. Chem. Rev.* **1999**, *68*, 437. (d) Sosnovskikh, V. Ya. *Russ. Chem. Rev.* **2003**, *72*, 489.

(3) (a) Sosnovskikh, V. Ya.; Usachev, B. I. *Izv. Acad. Nauk, Ser. Khim.* **2001**, 434; *Russ. Chem. Bull.* **2001**, *50*, 453. (b) Sosnovskikh, V. Ya.; Vorontsov, I. I.; Kutsenko, V. A. *Izv. Acad. Nauk, Ser. Khim.* **2001**, 1360; *Russ. Chem. Bull.* **2001**, *50*, 1430. (e) Sosnovskikh, V. Ya.; Sevenard, D. V.; Usachev, B. I.; Röschenthaler, G.-V. *Tetrahedron Lett.* **2003**, *44*, 2097. (f) Sosnovskikh, V. Ya.; Usachev, B. I.; Sevenard, D. V.; Röschenthaler, G.-V. *J. Org. Chem.* **2003**, *68*, 7747.

(4) (a) Sosnovskikh, V. Ya.; Usachev, B. I.; Sevenard, D. V.; Lork, E.; Röschenthaler, G.-V. *Tetrahedron Lett.* **2001**, *42*, 5117. (b) Sosnovskikh, V. Ya.; Usachev, B. I.; Sevenard, D. V.; Röschenthaler, G.-V. *Tetrahedron* **2003**, *59*, 2625.

(5) Sosnovskikh, V. Ya.; Usachev, B. I.; Vorontsov, I. I. *J. Org. Chem.* **2002**, *67*, 6738.

(6) (a) Katrusiak, A. A.; Baloniak, S.; Katrusiak, A. S. *Polish J. Chem.* **1996**, *70*, 1279. (b) Baloniak, S.; Katrusiak, A. *Polish J. Chem.* **1994**, *68*, 683. (c) Wasfy, A. A. F. *Indian J. Chem.* **1994**, *33B*, 1098.

(7) Pinza, M.; Pifferi, G. *Farmaco* **1994**, *49*, 683.

(8) Sosnovskikh, V. Ya.; Mel'nikov, M. Yu. *Mendeleev Commun.* **1998**, 198.

(9) (a) Sosnovskikh, V. Ya.; Usachev, B. I. *Tetrahedron Lett.* **2001**, *42*, 5121. (b) Sosnovskikh, V. Ya.; Usachev, B. I.; Vorontsov, I. I. *Tetrahedron* **2003**, *59*, 2549.

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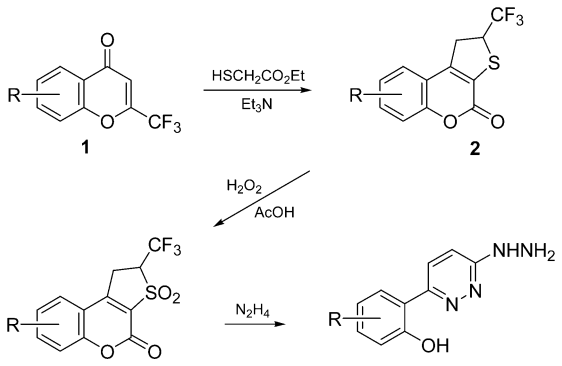
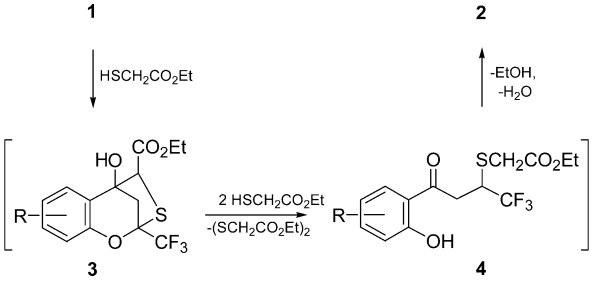
SCHEME 1



latter compound is oxidized to diethyl 3,4-dithiadipate and further two intramolecular cyclizations of the intermediate ester **4** give dihydrothienocoumarins **2**. Unfortunately, we were unable to isolate any intermediates in the transformation **1** → **2** (Scheme 2).

SCHEME 2

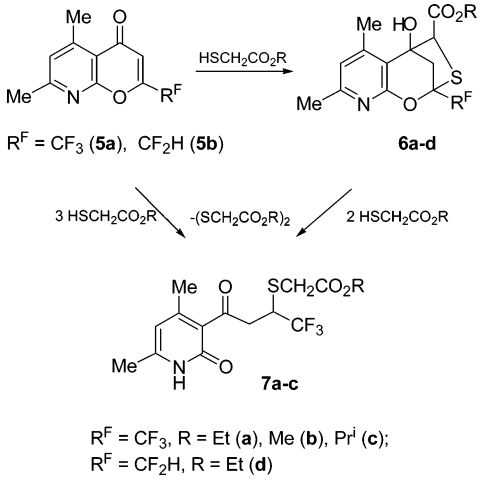


Results and Discussion

To verify the assumption that this useful and unusual redox reaction proceeds through intermediates of type **3** and/or **4** and to reveal the reaction route as a whole, we decided to extend the series of initial chromones. We hoped that drastic changes in their structure (more substantial than the simple variation of substituents in the benzene ring) would allow the process to be stopped at one of the intermediate steps. Because the key step of the transformation **1** → **2** is the formation of the coumarin system, which occurs during the interaction of phenolic hydroxyl with the ester group, it was of interest to introduce 8-azachromones into this reaction. In this case, opening of the pyrone ring results in the appearance of the oxygen atom of the amide type with decreased nucleophilic properties instead of the phenol OH group. This allows us to expect the isolation of open-chained products.

In fact, we found that the reaction of 8-aza-5,7-dimethyl-2-trifluoromethylchromone (**5a**), prepared from 3-acetyl-4,6-dimethyl-2-pyridone and ethyl trifluoroacetate,[10] with an excess of alkyl mercaptoacetates at 80 °C for 4 h in the presence of Et_3N afforded bicycles **6a**−**c** (preliminary communication, see ref 11). When the reaction time and the amount of Et_3N were increased, acyclic trifluoromethylated derivatives **7a**−**c** were isolated instead of compounds **6a**−**c**. Probably, they are the products of reduction of **6** because they were formed from the latter under similar reaction conditions (Scheme 3).

SCHEME 3



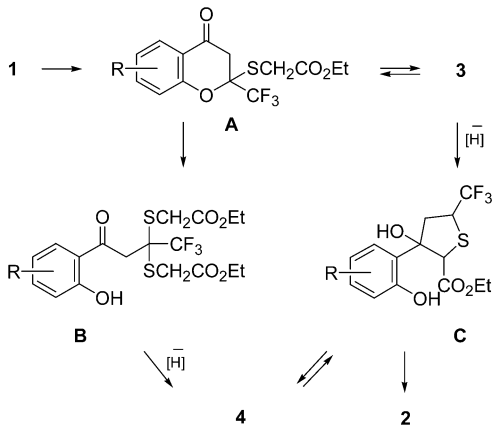
To our knowledge, there are no reports on the analogous ring opening of the chromone system with reducing agents to give acyclic ketones. It is significant that we saw no reaction with known 8-aza-2,5,7-trimethylchromone[12] and ethyl mercaptoacetate under the same reaction conditions as above. This is probably owing to the lack of an R^F group, which enhances the electrophilicity of the substrate and encourages conjugate addition at the initial stage. However, 8-aza-5,7-dimethyl-2-difluoromethylchromone (**5b**) gave only bicycle **6d** in low yield (21%), and the corresponding sulfanyl acetate was not isolated; 8-aza-5,7-dimethyl-2-(1,1,2,2-tetrafluoroethyl)chromone[10] also failed to give useful results. The failure of these reactions might be attributed to the balance between electronic and steric effects.

The IR spectra of compounds **6** showed absorption bands in the two ranges 3120−3150 and 1735−1740 cm^{-1} due to the hydroxyl group and the ester carbonyl; a characteristic feature of the ^1H NMR spectra in $CDCl_3$ is the appearance of two AX doublets (J_{AX} = 11.8 Hz) at δ 2.6 and 3.2 ppm for the CH_2 group and two singlets at δ 4.2 and 4.5 ppm for the OH and CH protons, respectively. The IR spectra of sulfanyl acetates **7** exhibit intense absorption bands at 1720−1730 and 1660−1670 cm^{-1}, corresponding to the ester and ketone carbonyl groups. In the ^1H NMR spectra, the ABX system of the CH_2CH fragment (J_{AB} = 17.8, J_{AX} = 10.0−10.3, J_{BX} = 3.8−4.0 Hz) and the AB system of the CH_2S group (J_{AB} = 14.6−14.8 Hz) due to the chiral center in molecules of **7** are observed.

On the basis of the results obtained by the study of the reaction of azachromones **5** with alkyl mercaptoacetates, we can propose a probable route of the transformation of chromones **1** into dihydrothienocoumarins **2** (Scheme 4). The reaction begins with the addition of the mercapto group to the C(2) atom, and the resulting Michael adduct **A** either undergoes reversible cyclization to form bridged structure **3**, which is stable in the case of **5**, or ring opening to give thioketal **B**, whose reduction by mercapto ester affords diethyl 3,4-dithiadipate and

(10) Sosnovskikh, V. Ya.; Barabanov, M. A. *J. Fluorine Chem.* **2003**, *120*, 25.
(11) Sosnovskikh, V. Ya.; Barabanov, M. A.; Usachev, B. I. *Org. Lett.* **2003**, *5*, 2501.
(12) Bonsall, C.; Hill, J. *J. Chem. Soc. C* **1967**, 1836.

SCHEME 4

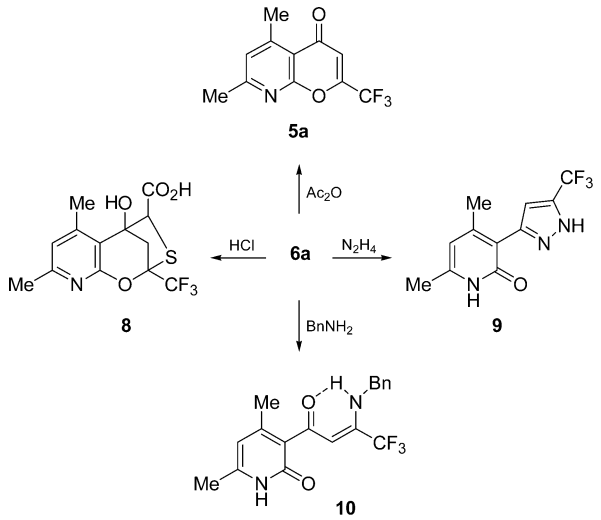


sulfanyl acetate **4**. The latter undergoes two intramolecular cyclizations involving the ketone and ester carbonyl groups to produce coumarin **2**. The second possible direction of the reaction is the reductive opening of bicycle **3** to form intermediate **C**, which undergoes either cyclization to coumarin **2** (in the case of chromones **1**) or retroaldol cleavage to ester **4** (in the case of azachromone **5a**).

Next, we investigated some properties of compounds **6a**, **7a**, and **13** as representative examples, for this, it was anticipated, would give a range of new trifluoromethylated 2-pyridone derivatives with potential biological activity.

Reactions of Compound 6a (Scheme 5). Hydrolysis of bicycle **6a** to the corresponding acid **8** was performed

SCHEME 5



by the action of diluted HCl at reflux for 1 h in 62% yield. This acid was also obtained from **5a** and ethyl mercaptoacetate in the presence of sodium ethoxide in low yield (9%). Acetylation of bicycle **6a** with acetic anhydride in the presence of triethylamine did not yield the expected acetyl derivative but instead gave azachromone **5a** in 87% yield (only starting material **6a** was recovered from similar reaction in the presence of concentrated H_2SO_4). Attempts to prepare some derivatives at the ester group of **6a** were also unsuccessful because reactions with hydrazine hydrate and benzylamine in tetrahydrofuran for 24 h at room temperature proceeded through cleavage of the bridged system and resulted in the formation of pyrazol **9** and aminoenone **10** in 57% and 49% yields, respectively. Previously,[13] these compounds were obtained under similar reaction conditions from **5a**. This result shows that bicycles **6** are rather labile compounds, which revert to the starting azachromones under basic reaction conditions.

Reactions of Compound 7a. Hydrolysis of ester **7a** to the corresponding acid **11** can be easily performed in 87% yield by the action of diluted HCl at reflux for 2 h. However, cyclization of **7a** to dihydrothiophene derivative **12** under basic conditions was unsuccessful because ester **7a** easily eliminates molecule of ethyl mercaptoacetate and behaves as the masked α,β-unsaturated ketone **13**. We found that sulfanyl acetate **7a** acts as an effective in situ source of CF_3-enone **13** in reactions with various *N*- and *O*-nucleophiles, yielding 2-pyridone derivatives **14**−**16** in good to moderate yields (Scheme 6). When ester **7a** was refluxed with aqueous hydrazine hydrate for 30 min, pyrazoline **14a** was obtained in 79% yield after usual workup. The reaction of **7a** with methylhydrazine gave only one regioisomer **14b** in 70% isolated yield (ABX system of the CH_2CH fragment with J_{AB} = 17.4 Hz, J_{AX} = 11.6 Hz, J_{BX} = 11.1 Hz), and the other regioisomer was not detected. It is likely that the interaction of **7a** with hydrazines proceeds in the stepwise formation of enone **13** followed by further cyclocondensation at the activated double bond and the carbonyl group leading to the corresponding pyrazolines **14a**,**b**. In regard to this, a similar reaction with dimethylhydrazine gave *E*-enone **13** ($J_{CH=CH}$ = 15.7 Hz) as the only isolated product in a moderate yield (50%). In a further experiment, we observed that reactions of **7a** with sodium hydroxide, sodium methoxide, and cyclic secondary amines (piperidine, morpholine) were also accomplished by elimination of ethyl mercaptoacetate followed by addition of the nucleophile to give β-hydroxy (**15a**), β-methoxy (**15b**), and β-amino ketones (**16a**,**b**). Interestingly, the reactions of ester **7a** with primary aliphatic amines (cyclohexylamine, benzylamine) occur at the ester group to give amides **17a**,**b** in 29% and 37% yields, respectively (Scheme 6). Diisopropylamine and hydroxylamine did not react with **7a** under our reaction conditions; the use of isopropylamine, diethylamine, and ethylenediamine resulted in the formation of a mixture of products.

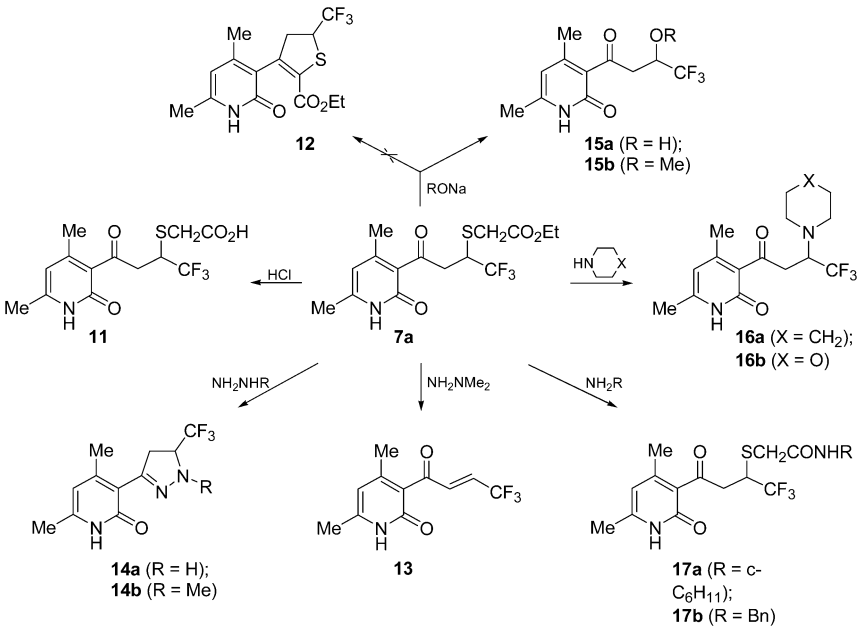
Reactions of Compound 13. Taking into account the above results, it was of interest to evaluate the reactivity of α,β-unsaturated ketone **13**. We anticipated that this compound as a result of the double bond activated by the CF_3 group might undergo nucleophilic addition reactions giving various 2-pyridone derivatives more easily than the masked form **7a**. To demonstrate its ability to undergo A_N reactions, compound **13** was allowed to react with some *N*-, *O*-, *S*-, and *C*-nucleophiles under mild reaction conditions. Previously, trifluoroethylidene derivatives of acetone[14] and acetophenone[15] were prepared

(13) Sosnovskikh, V. Ya.; Barabanov, M. A.; Usachev, B. I. *Izv. Acad. Nauk, Ser. Khim.* **2003**, 1668; *Russ. Chem. Bull.* **2003**, *52*, 1758.

(14) (a) Molines, H.; Wakselman, C. *J. Fluorine Chem.* **1980**, *16*, 97. (b) Ogoshi, H.; Mizushima, H.; Toi, H.; Aoyama, Y. *J. Org. Chem.* **1986**, *51*, 2366.

(15) (a) Norcross, P. E.; Klinedinst, P. E., Jr.; Westheimer, F. H. *J. Am. Chem. Soc.* **1962**, *84*, 797. (b) Xu, Y.; Dolbier, W. R., Jr. *Tetrahedron Lett.* **1998**, *39*, 9151.

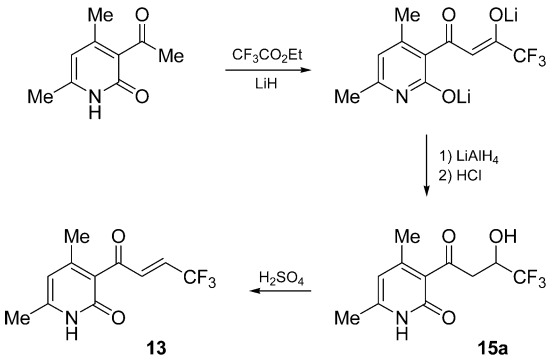
SCHEME 6



from trifluoroacetaldehyde, which is usually generated in situ from its hydrate, hemiacetal, or aminal, sometimes using Lewis acid catalysis.[16] Such fluorinated enones have attracted attention mainly due to the possibility of using them as an excellent building blocks for the preparation of a variety of CF_3-containing compounds.[14,17] On the other hand, the synthesis of 2-pyridone derivatives is a topic area of continuing interest[18] due to the number of biologically active molecules containing this moiety. Over the past decade, natural compounds with this structure have emerged as potent antitumor,[19] antiviral,[20] and psychotherapeutic[21] agents, along with a new antibiotic.[22]

First, enone **13** was independently synthesized from 3-acetyl-4,6-dimethyl-2-pyridone (Scheme 7). We have found that the required α,*β*-unsaturated ketone can be prepared by the Claisen condensation of 3-acetyl-4,6-dimethyl-2-pyridone with ethyl trifluoroacetate in the presence of lithium hydride and subsequent reduction of the dilithium salt with lithium aluminum hydride.[23] The latter reaction gave, after acidic hydrolysis, *β*-hydroxy ketone **15a** in 63% yield, which was dehydrated by concentrated sulfuric acid for 1 h at room temperature to form *E*-enone **13** (yield 79%).

SCHEME 7



It was found that compound **13** readily reacts with both primary and secondary amines under the mild reaction conditions (THF, ~20 °C, 24 h) to give *β*-amino ketones **16a**−**g** in good yields. The reactions with aromatic amines were complex and were not examined more closely. Diisopropylamine and *N*,*N*-dimethylaniline did not react with **13** in THF; only starting materials were recovered. The failure of these addition reactions might be attributed to the steric effect, as well as the lower reactivity of aromatic amines (Scheme 8).

When enone **13** was refluxed with diluted hydrochloric acid or methanolic hydrochloric acid, ketones **15a**,**b** were obtained in good yields. Compound **15a** was also obtained in 70% yield when *β*-morpholino ketone **16b** was heated for 1 h in refluxing 10% HCl. The addition of 2-mercaptoethanol, *p*-thiocresol, and ethyl mercaptoacetate in the presence of triethylamine afforded sulfanyl derivatives **18a**,**b** and **7a** in high to moderate yields. The reaction of

(16) (a) Xu, Y.; Dolbier, W. R., Jr. *J. Org. Chem.* **2000**, *65*, 2134. (b) Funabiki, K.; Nojiri, M.; Matsui, M.; Shibata, K. *Chem. Commun.* **1998**, 2051. (c) Funabiki, K.; Matsunaga, K.; Matsui, M.; Shibata, K. *Synlett* **1999**, 1477. (d) Funabiki, K.; Matsunaga, K.; Nojiri, M.; Hashimoto, W.; Yamamoto, H.; Shibata, K.; Matsui, M. *J. Org. Chem.* **2003**, *68*, 2853. (e) Blond, G.; Billard, T.; Langlois, B. R. *J. Org. Chem.* **2001**, *66*, 4826. (g) Ates, C.; Janousek, Z.; Viehe, H. G. *Tetrahedron Lett.* **1993**, *34*, 5711.

(17) (a) Aoyagi, K.; Haga, T.; Toi, H.; Aoyama, Y.; Mizutani, T.; Ogoshi, H. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 937. (b) Ratner, V. G.; Lork, E.; Pashkevich, K. I.; Röschenthaler, G.-V. *J. Fluorine Chem.* **1997**, *85*, 129. (c) Ratner, V. G.; Lork, E.; Pashkevich, K. I.; Röschenthaler, G.-V. *J. Fluorine Chem.* **2000**, *102*, 73. (d) Khomutov, O. G.; Filyakova, V. I.; Pashkevich, K. I. *Izv. Acad. Nauk, Ser. Khim.* **1994**, 282; *Russ. Chem. Bull.* **1994**, *43*, 261. (e) Takada, E.; Hara, S.; Suzuki, A. *Tetrahedron Lett.* **1993**, *34*, 7067.

(18) Brun, E. M.; Gil, S.; Mestres, R.; Parra, M. *Synthesis* **2000**, 273.

(19) Kelly, T. R.; Bell, S. H.; Ohashi, N.; Armstrong-Chong, R. J. *J. Am. Chem. Soc.* **1988**, *110*, 6471.

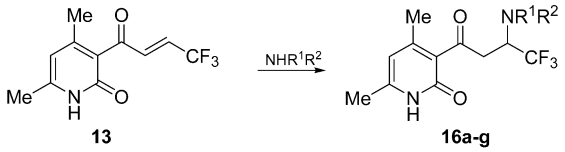
(20) Williams, D. R.; Lowder, P. D.; Gu, Y.-Q. *Tetrahedron Lett.* **1997**, *38*, 327.

(21) Kozikowski, A. P.; Campiani, G.; Sun, L.-Q.; Wang, S.; Saxena, A.; Doctor, B. P. *J. Am. Chem. Soc.* **1996**, *118*, 11357.

(22) Brickner, S. J. *Chem. Ind.* **1997**, 131.

(23) Pashkevich, K. I.; Filyakova, V. I.; Ratner, V. G.; Khomutov, O. G. *Zh. Org. Khim.* **1994**, *30*, 1833.

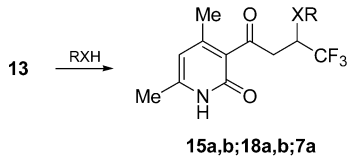
SCHEME 8



	R^1	R^2	Yield (%)
16a	$(CH_2)_5$		78
16b	$(CH_2)_2O(CH_2)_2$		77
16c	$(CH_2)_4$		85
16d	Et	Et	59
16e	H	Bn	55
16f	H	cyclo-C_6H_{11}	42
16g	H	Pr^i	33

ethyl mercaptoacetate is much faster, reaching completion within 5 min (Scheme 9).

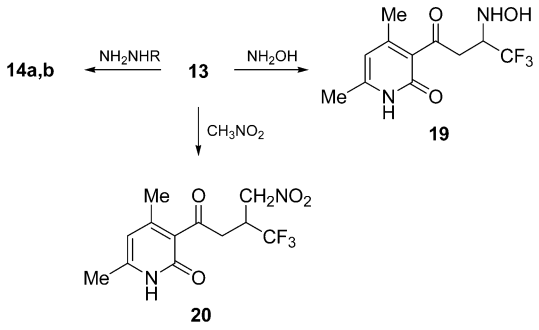
SCHEME 9



	X	R	Yield (%)
15a	O	H	59
15b	O	Me	47
18a	S	$(CH_2)_2OH$	31
18b	S	C_6H_4Me-4	79
7a	S	CH_2CO_2Et	80

Compound **13** smoothly reacts with hydrazine hydrate and methylhydrazine to produce the expected pyrazolines **14a**,**b** in 77% and 68% yields, respectively. Unlike hydrazines, hydroxylamine reacted with **13** in 2-propanol for 30 min at room temperature to give acyclic compound **19** in 51% yield. It is important that the conjugate addition of nitromethane also took place readily under weakly basic conditions (K_2CO_3) to give the nitro derivative **20** in 48% yield (Scheme 10). This result clearly

SCHEME 10



indicates that the β-C atom of α,β-unsaturated ketone **13** is very susceptible to nucleophilic attack and makes enone **13** an attractive building block for the synthesis of various heterocyclic ring assemblies containing the CF_3 group and 2-pyridone moiety. Apparently, the strong electron-withdrawing nature of the trifluoromethyl group plays an important role in the acceleration of each reaction.

In summary, the reaction of 8-azachromone **5a** with alkyl mercaptoacetates is very useful for revealing the route of the transformation **1** → **2** because, depending on the conditions, it stops at the step of product **6** or **7**. Readily available enone **13** may be considered as a new CF_3-containing building block for the preparation of a variety of 2-pyridone derivatives, which are of interest as compounds with potential biological activity.

Experimental Section

General Procedure for Synthesis of Compounds 6. A mixture of azachromone **5a** (1.3 mmol), alkyl mercaptoacetate (4.5 mmol), and 5 drops of Et_3N was heated at 80 °C for 4 h in the case of **6a**−**c** and for 20 h in the case of **6d**. The resulting mixture was diluted with ethanol (2 mL), and the precipitate that formed was isolated by filtration, washed with 50% ethanol, and dried to give **6** as colorless crystals.

Ethyl 5-hydroxy-6,8-dimethyl-2-(trifluoromethyl)-4,5-dihydro-2,5-methano[1,3]oxathiepino[7,6-*b*]pyridine-4-carboxylate (6a): yield 90%; mp 196−197 °C; IR (Nujol) 3120, 1735, 1640, 1615, 1565 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32 (t, 3H, Me, J = 7.1 Hz), 2.42 (s, 3H, Me), 2.54 (s, 3H, Me), 2.63 (dq, 1H, C*H*H, J = 11.8 Hz, $^4J_{H,F}$ = 0.7 Hz), 3.22 (d, 1H, CH*H*, J = 11.8 Hz), 4.18 (s, 1H, OH), 4.29 (m, 2H, CH_2O), 4.45 (s, 1H, CH), 6.73 (s, 1H, pyrid.); ^{13}C NMR ($CDCl_3$) δ 13.8, 21.1, 23.4, 41.3, 54.0, 62.4, 79.3, 90.8 (q, J = 34.9 Hz), 117.9, 122.3 (q, J = 279.9 Hz), 122.4, 149.1, 157.2, 157.6, 171.2. Anal. Calcd for $C_{15}H_{16}F_3NO_4S$: C, 49.58; H, 4.44; N, 3.85. Found: C, 49.55; H, 4.41; N, 3.90.

Methyl 5-hydroxy-6,8-dimethyl-2-(trifluoromethyl)-4,5-dihydro-2,5-methano[1,3]oxathiepino[7,6-*b*]pyridine-4-carboxylate (6b): yield 44%; mp 212−213 °C; IR (Nujol) 3120, 1740, 1610, 1560 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.30 (s, 3H, Me), 2.49 (d, 1H, C*H*H, J = 11.6 Hz), 2.50 (s, 3H, Me), 3.30 (d, 1H, CH*H*, J = 11.6 Hz), 3.71 (s, 3H, MeO), 4.54 (s, 1H, CH), 6.84 (s, 1H, OH), 6.85 (s, 1H, pyrid.). Anal. Calcd for $C_{14}H_{14}F_3NO_4S$: C, 48.14; H, 4.04; N, 4.01. Found: C, 48.08; H, 4.13; N, 3.90.

Isopropyl 5-hydroxy-6,8-dimethyl-2-(trifluoromethyl)-4,5-dihydro-2,5-methano[1,3]oxathiepino[7,6-*b*]pyridine-4-carboxylate (6c): yield 26%; mp 167−168 °C; IR (Nujol) 3150, 1740, 1600, 1555 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (t, 6H, 2Me, J = 6.0 Hz), 2.42 (s, 3H, Me), 2.54 (s, 3H, Me), 2.62 (d, 1H, C*H*H, J = 11.8 Hz), 3.20 (d, 1H, CH*H*, J = 11.8 Hz), 4.14 (s, 1H, OH), 4.49 (s, 1H, CH), 5.14 (sept, 1H, CHO, J = 6.3), 6.73 (s, 1H, pyrid.). Anal. Calcd for $C_{16}H_{18}F_3NO_4S$: C, 50.92; H, 4.81; N, 3.71. Found: C, 50.93; H, 4.96; N, 3.47.

Ethyl 2-(difluoromethyl)-5-hydroxy-6,8-dimethyl-4,5-dihydro-2,5-methano[1,3]oxathiepino[7,6-*b*]pyridine-4-carboxylate (6d): yield 21%; mp 193−194 °C; IR (Nujol) 3100, 1735, 1615, 1570 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.23 (t, 3H, Me, J = 7.1 Hz), 2.29 (s, 3H, Me), 2.37 (d, 1H, C*H*H, J = 11.7 Hz), 2.49 (s, 3H, Me), 3.18 (d, 1H, CH*H*, J = 11.7 Hz), 4.15 (q, 2H, CH_2O, J = 7.1), 4.34 (s, 1H, CH), 6.60 (t, 1H, CF_2H, J = 54.2 Hz), 6.62 (s, 1H, OH), 6.79 (s, 1H, pyrid.). Anal. Calcd for $C_{15}H_{17}F_2NO_4S$: C, 52.17; H, 4.96; N, 4.06. Found: C, 52.21; H, 4.96; N, 4.17.

Ethyl 2-{[3-(4,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)-3-oxo-1-(trifluoromethyl)propyl]sulfanyl}acetate (7a). From Azachromone 5a. A mixture of azachromone **5a** (5.0 g, 20.6 mmol), ethyl mercaptoacetate (11.0 g, 91.2 mmol), and Et_3N (2.1 g, 20.8 mmol) was heated at 80 °C for 8 h and then cooled to room temperature. After dilution with aqueous ethanol (1:1), the crystalline material was isolated by filtration, washed with 50% ethanol, and dried to give **7a** (5.7 g, 76%) as colorless needles: mp 130−131 °C; IR (Nujol) 1730, 1670, 1630, 1540 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (t, 3H, Me, J = 7.1 Hz), 2.31 (s, 3H, Me), 2.32 (s, 3H, Me), 3.37 (d, 1H, C*H*HS, J = 14.6 Hz), 3.38 (dd, 1H, C*H*H, ^2J = 17.8 Hz, ^3J = 10.2 Hz), 3.48 (d, 1H, CH*H*S, J = 14.6 Hz), 3.58 (dd, 1H, CH*H*, ^2J = 17.8 Hz,

^3J = 3.9 Hz), 4.13 (m, 1H, CH), 4.22 (m, 2H, CH_2O), 6.02 (s, 1H, pyrid.), 13.18 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 14.0, 18.6, 21.0, 34.5, 42.7, 42.9 (q, J = 29.9 Hz), 61.7, 110.9, 123.6, 127.0 (q, J = 278.5 Hz), 148.4, 156.7, 164.2, 169.3, 197.7. Anal. Calcd for $C_{15}H_{18}F_3NO_4S$: C, 49.31; H, 4.97; N, 3.83. Found: C, 49.50; H, 4.95; N, 4.04.

From Bicycle 6a. A mixture of **6a** (0.25 g, 0.7 mmol), ethyl mercaptoacetate (0.22 g, 1.8 mmol), and Et_3N (0.14 g, 1.4 mmol) was heated at 80 °C for 8 h. After cooling and dilution with aqueous ethanol (1:1), the crystalline product was isolated by filtration, washed with 50% ethanol, and dried to give **7a** in 80% yield.

From Enone 13. To a mixture of **13** (0.15 g, 0.6 mmol) and ethyl mercaptoacetate (0.22 g, 1.8 mmol) was added Et_3N (0.14 g, 1.4 mmol), causing an immediate exothermic reaction with the formation of a homogeneous solution, which became crystalline during 5 min. The solid was recrystallized from ethanol to give **7a** in 80% yield.

Methyl 2-{[3-(4,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)-3-oxo-1-(trifluoromethyl)propyl]sulfanyl}acetate (7b). This compound was prepared analogously to **7a** from azachromone **5a** and methyl mercaptoacetate in 25% yield as colorless needles: mp 118−119 °C; IR (Nujol) 1725, 1660, 1620, 1530 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.32 (s, 3H, Me), 2.33 (s, 3H, Me), 3.38 (d, 1H, C*H*HS, J = 14.6 Hz), 3.39 (dd, 1H, C*H*H, ^2J = 17.8 Hz, ^3J = 10.3 Hz), 3.49 (d, 1H, CH*H*S, J = 14.6 Hz), 3.57 (dd, 1H, CH*H*, ^2J = 17.8 Hz, ^3J = 3.8 Hz), 3.78 (s, 3H, MeO), 4.11 (m, 1H, CH), 6.03 (s, 1H, pyrid.), 13.35 (s, 1H, NH). Anal. Calcd for $C_{14}H_{16}F_3NO_4S$: C, 47.86; H, 4.59; N, 3.99. Found: C, 47.87; H, 4.59; N, 3.89.

Isopropyl 2-{[3-(4,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)-3-oxo-1-(trifluoromethyl)propyl]sulfanyl}-acetate (7c). This compound was prepared analogously to **7a** from azachromone **5a** and isopropyl mercaptoacetate in 77% yield as colorless needles: mp 119−120 °C; IR (Nujol) 1720, 1660, 1620, 1530 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (d, 3H, Me, J = 6.1 Hz), 1.29 (d, 3H, Me, J = 6.1 Hz), 2.31 (s, 3H, Me), 2.32 (s, 3H, Me), 3.36 (d, 1H, C*H*HS, J = 14.8 Hz), 3.38 (dd, 1H, C*H*H, ^2J = 17.8 Hz, ^3J = 10.0 Hz), 3.46 (d, 1H, CH*H*S, J = 14.8 Hz), 3.59 (dd, 1H, CH*H*, ^2J = 17.8 Hz, ^3J = 4.0 Hz), 4.13 (m, 1H, CH), 5.05 (sept, 1H, CHO, J = 6.3 Hz), 6.02 (s, 1H, pyrid.), 13.02 (s, 1H, NH). Anal. Calcd for $C_{16}H_{20}F_3NO_4S$: C, 50.65; H, 5.31; N, 3.69. Found: C, 50.48; H, 5.03; N, 3.82.

5-Hydroxy-6,8-dimethyl-2-(trifluoromethyl)-4,5-dihydro-2,5-methano[1,3]oxathiepino[7,6-*b*]pyridine-4-carboxylic Acid (8). A mixture of **6a** (1.0 g, 2.8 mmol) and 8% HCl (10 mL) was refluxed for 1 h. After cooling, the crystalline product was filtered off and recrystallized from 50% ethanol to give **8** (0.57 g, 62%) as colorless crystals: mp 245 °C (dec); IR (Nujol) 3430, 1705, 1690, 1610, 1560 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.30 (s, 3H, Me), 2.45 (d, 1H, C*H*H, J = 11.5 Hz), 2.50 (s, 3H, Me), 3.39 (d, 1H, CH*H*, J = 11.5 Hz), 4.35 (s, 1H, CH), 6.0−7.5 (br s, 1H, OH), 6.84 (s, 1H, pyrid.), 12.0−14.0 (br s, 1H, COOH). Anal. Calcd for $C_{13}H_{12}F_3NO_4S$: C, 46.57; H, 3.61; N, 4.18. Found: C, 46.21; H, 3.47; N, 4.29. Acid **8** was also prepared from azachromone **5a** and ethyl mercaptoacetate in the presence of sodium ethylate in low yield (9%).

2-{[3-(4,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)-3-oxo-1-(trifluoromethyl)propyl]sulfanyl}acetic Acid (11). A mixture of **7a** (0.20 g, 0.5 mmol) and 10% HCl (5 mL) was heated under reflux for 2 h. After cooling, the crystalline product was filtered off, washed with water, dried, and recrystallized from toluene/butanol (5:1) to give **11** (0.16 g, 87%) as colorless crystals: mp 165−166 °C; IR (Nujol) 1720, 1675, 1640, 1620 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.16 (s, 3H, Me), 2.19 (s, 3H, Me), 3.27 (dd, 1 H, CHH, ^2J = 17.5 Hz, ^3J = 9.3 Hz), 3.45 (dd, 1H, CHH, ^2J = 17.5 Hz, ^3J = 4.5 Hz), 3.48 (AB-system, $\Delta\delta$ = 0.01 ppm, 2H, CH_2S, J_{AB} = 15.3 Hz), 4.14 (quint d, 1H, CH, $J_{H,H}$ = $J_{H,F}$ = 8.9 Hz, $J_{H,H}$ = 4.5 Hz), 6.03 (s, 1H, pyrid.), 12.0 (br s, 1H, OH), 12.8 (br s, 1H, NH). Anal. Calcd for $C_{13}H_{14}F_3NO_4S$: C, 46.29; H, 4.18; N, 4.15. Found: C, 46.12; H, 4.14; N, 4.17.

4,6-Dimethyl-3-(4,4,4-trifluoro-3-hydroxybutanoyl)pyridin-2(1*H*)-one (15a). From 3-Acetyl-4,6-dimethyl-2-pyridone. Anhydrous dioxane (30 mL), 3-acetyl-4,6-dimethyl-2-pyridone (5.0 g, 0.03 mol), CF_3CO_2Et (7.1 g, 0.05 mol), and finely dispersed LiH (0.79 g, 0.01 mol) were placed in a round-bottom flask equipped with a mechanical stirrer and a reflux condenser. After the initial exothermic reaction had subsided (10−15 min), the reaction mixture was refluxed with stirring for 2 h and concentrated to dryness on a water bath under reduced pressure. Anhydrous THF (100 mL) was added to the dilithio salt, and the resulting mixture was refluxed with stirring for 1 h. After cooling, $LiAlH_4$ (1.0 g, 0.026 mol) was added in four portions over a 1 h period, and the reaction mixture was stirred for 2 h at room temperature and allowed to stand overnight with a drying tube. Then the cooled mixture was quenched by addition of water (10 mL), followed by 10% HCl (120 mL). The resulting solution was concentrated under reduced pressure, and the precipitate that formed was filtered off, washed with water, and dried to give β-hydroxy ketone **15a** in 63% yield as a colorless powder: mp 212−214 °C; IR (Nujol) 3150, 1680, 1645, 1630, 1530 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.35 (s, 3H, Me), 2.37 (s, 3H, Me), 2.79 (dd, 1H, C*H*H, ^2J = 14.0 Hz, ^3J = 2.8 Hz), 3.63 (dd, 1H, CH*H*, ^2J = 14.0 Hz, ^3J = 11.1 Hz), 4.55 (m, 1H, CH), 6.03 (d, 1H, OH, J = 5.7 Hz), 6.17 (s, 1H, pyrid.), 12.4 (br s, 1H, NH); ^1H NMR (DMSO-d_6) δ 2.13 (s, 3H, Me), 2.18 (s, 3H, Me), 3.11 (dd, 1H, C*H*H, ^2J = 16.2 Hz, ^3J = 8.5 Hz), 3.17 (dd, 1H, CH*H*, ^2J = 16.2 Hz, ^3J = 4.2 Hz), 4.42 (m, 1H, CH), 6.03 (s, 1H, pyrid.), 6.42 (d, 1H, OH, J = 6.6 Hz), 12.0 (br s, 1H, NH). Anal. Calcd for $C_{11}H_{12}F_3NO_3$: C, 50.20; H, 4.60; N, 5.32. Found: C, 49.98; H, 4.59; N, 5.21.

From Enone 13. A mixture of **13** (0.22 g, 0.9 mmol) and 20% HCl (4 mL) was refluxed for 20 h. After cooling, the resulting solid was filtered off, washed with water, dried, and recrystallized from toluene to give **15a** (0.14 g, 59%).

From β-Morpholino Ketone 16b. A mixture of **16b** (0.20 g, 0.6 mmol) and 10% HCl (5 mL) was refluxed for 1 h. After cooling, the resulting solid was filtered off, washed with water, and dried to give **15a** (0.11 g, 70%).

4,6-Dimethyl-3-(4,4,4-trifluorobut-2-enoyl)pyridin-2(1*H*)-one (13). From β-Hydroxy Ketone 15a. Ketone **15a** (5.0 g) was added to concentrated H_2SO_4 (20 mL), and the mixture was left for 1 h at room temperature. Then the dark reaction mixture was poured over crushed ice (200 g), and the resulting crystalline product was filtered off, washed with water, dried, and recrystallized from toluene to give **13** (3.7 g, 79%) as yellow crystals: mp 202−203 °C; IR (Nujol) 1680, 1645, 1630, 1530 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.22 (s, 6H, 2Me), 6.10 (s, 1H, H arom.), 6.71 (dq, 1H, =CH, $J_{H,H}$ = 15.7 Hz, $J_{H,F}$ = 7.2 Hz), 7.38 (d, 1H, =CH, J = 15.7 Hz), 12.12 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 18.6, 20.4, 109.2, 122.5, 123.4 (q, J = 269.8 Hz), 124.0 (q, J = 33.5 Hz), 137.1 (q, J = 5.9 Hz), 150.1, 156.5, 162.2, 189.9. Anal. Calcd for $C_{11}H_{10}F_3NO_2$: C, 53.88; H, 4.11; N, 5.71. Found: C, 53.67; H, 4.24; N, 5.75.

From Sulfanyl Acetate 7a. A mixture of **7a** (0.15 g, 0.4 mmol) and *N*,*N*-dimethylhydrazine (0.4 g, 6.6 mmol) was left for 12 h at room temperature. It was then diluted with ethanol (2 mL), acetic acid (1 mL), and water (3 mL). After 2 h, the resulting precipitate was filtered off, washed with 50% ethanol, dried, and recrystallized from hexane/toluene (1:1) to give enone **13** in 50% yield.

4,6-Dimethyl-3-[5-(trifluoromethyl)-4,5-dihydro-1*H*-pyrazol-3-yl]pyridin-2(1*H*)-one (14a). A solution of **7a** (0.26 g, 0.7 mmol) and aqueous 25% hydrazine hydrate (0.85 g, 4.3 mmol) in ethanol (3 mL) was heated under reflux for 30 min. It was then cooled, and the resulting solid was washed with 70% ethanol, dried, and recrystallized from toluene/butanol (2:1) to give **14a** (0.14 g, 78%) as colorless needles: mp >250 °C (subl.); IR (Nujol) 3280, 1660, 1630, 1545 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.14 (s, 3H, Me), 2.15 (s, 3H, Me), 3.08 (ddd, 1H, C*H*H, ^2J = 17.5 Hz, ^3J = 9.1 Hz, $^4J_{H,NH}$ = 1.4 Hz), 3.42 (dd, 1H, CH*H*, ^2J = 17.5 Hz, ^3J = 12.0 Hz), 4.35 (m, 1H, CH), 5.94 (s, 1H, pyrid.), 7.48 (dd, 1H, NH, ^3J = 5.4 Hz, ^4J = 1.2 Hz),

11.61 (s, 1H, NHCO); ^{19}F NMR (HFB, $CDCl_3$) δ 84.82 (d, CF_3, J = 7.3 Hz). Anal. Calcd for $C_{11}H_{12}F_3N_3O$: C, 50.97; H, 4.67; N, 16.21. Found: C, 51.00; H, 4.56; N, 16.27. Pyrazoline **14a** was also obtained from **13** in 2-propanol in 76% yield under similar reaction conditions.

4,6-Dimethyl-3-[1-methyl-5-(trifluoromethyl)-4,5-dihydro-1*H*-pyrazol-3-yl]pyridin-2(1*H*)-one (14b). A mixture of **13** (0.25 g, 1.0 mmol) and methylhydrazine, prepared from $MeNHNH_2{\cdot}H_2SO_4$ (0.29 g, 2.0 mmol) in water (0.5 mL) and KOH (0.22 g, 3.9 mmol) in methanol (3 mL), was heated under reflux for 1 h. After cooling, the resulting precipitate was filtered, washed with methanol, and dried to give **14b** (0.19 g, 68%) as colorless needles: mp >250 °C (subl.); IR (Nujol) 1660, 1630, 1540 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.14 (s, 3H, Me), 2.18 (s, 3H, Me), 2.85 (s, 3H, MeN), 3.17 (dd, 1H, C*H*H, ^2J = 17.4 Hz, ^3J = 11.1 Hz), 3.53 (dd, 1H, CH*H*, ^2J = 17.4 Hz, ^3J = 11.6 Hz), 3.94 (tq, 1H, CH, $J_{H,H}$ = 11.4 Hz, $J_{H,CF3}$ = 6.8 Hz), 5.96 (s, 1H, pyrid.), 11.67 (s, 1H, NH); ^{19}F NMR (HFB, $CDCl_3$) δ 88.21 (d, CF_3, J = 6.1 Hz). Anal. Calcd for $C_{12}H_{14}F_3N_3O$: C, 52.75; H, 5.16; N, 15.38. Found: C, 52.30; H, 5.22; N, 15.13. Pyrazoline **14b** was also obtained from **7a** in 70% yield under similar reaction conditions.

4,6-Dimethyl-3-(4,4,4-trifluoro-3-methoxybutanoyl)pyridin-2(1*H*)-one (15b). From Enone 13. A solution of **13** (0.25 g, 1.0 mmol) in methanol (5 mL), saturated with HCl, was heated at reflux for 5 h. After the removal of solvent under reduced pressure, the residue was washed with aqueous methanol and dried to give **15b** (0.13 g, 47%) as colorless needles: mp 154−155 °C; IR (Nujol) 1665, 1625, 1540 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.30 (s, 3H, Me), 2.31 (s, 3H, Me), 3.33 (dd, 1H, C*H*H, ^2J = 17.6 Hz, ^3J = 9.4 Hz), 3.42 (dd, 1H, CH*H*, ^2J = 17.6 Hz, ^3J = 3.2 Hz), 3.56 (s, 3H, MeO), 4.28 (m, 1H, CH), 6.02 (s, 1H, pyrid.), 13.1 (br s, 1H, NH). Anal. Calcd for $C_{12}H_{14}F_3NO_3$: C, 51.99; H, 5.09; N, 5.05. Found: C, 52.03; H, 5.22; N, 4.94.

From Sulfanyl Acetate 7a. To a solution of sodium methoxide, prepared from sodium (0.20 g, 8.7 mmol) and absolute methanol (10 mL), was added **7a** (0.25 g, 0.7 mmol). The mixture was refluxed for 1 h. It was then cooled, diluted with AcOH (1.5 mL), and concentrated under reduced pressure. The resulting solid was filtered off, dried, and recrystallized from hexane/toluene (3:1) to give **15b** (0.05 g, 26%).

Reactions of Enone 13 with Amines. General Procedure. Enone **13** (0.25 g, 1.0 mmol) was dissolved with heating in anhydrous THF (5 mL), and amine (2.0 mmol) was added. The reaction mixture was allowed to stand at room temperature for 24 h and concentrated to dryness under reduce pressure. The residue was triturated with aqueous ethanol (4 mL), and the precipitate that formed was filtered off, washed with 50% ethanol, and dried to afford the compounds **16a**−**g**.

4,6-Dimethyl-3-(4,4,4-trifluoro-3-piperidinobutanoyl)-pyridin-2(1*H*)-one (16a): yield 78% as colorless needles; mp 177−178 °C; IR (Nujol) 1665, 1630, 1530 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.40 (m, 6H, $(CH_2)_3$), 2.31 (s, 3H, Me), 2.32 (s, 3H, Me), 2.50 (m, 2H, CH_2N), 2.84 (m, 2H, CH_2N), 3.31 (dd, 1H, C*H*H, ^2J = 16.0 Hz, ^3J = 10.0 Hz), 3.38 (dd, 1H, CH*H*, ^2J = 16.0 Hz, ^3J = 4.7 Hz), 3.76 (m, 1H, CH), 6.02 (s, 1H, pyrid.), 13.4 (br s, 1H, NH). Anal. Calcd for $C_{16}H_{21}F_3N_2O_2$: C, 58.17; H, 6.41; N, 8.48. Found: C, 58.50; H, 6.46; N, 8.14.

From Sulfanyl Acetate 7a. A solution of **7a** (0.15 g, 0.4 mmol) in piperidine (0.43 g, 5.1 mmol) was allowed to stand at room temperature for 3 days. The reaction mixture was diluted with ethanol (2 mL) and water (10 mL), and the precipitate that formed was filtered off, washed with water, and dried to afford **16a** (0.09 g, 66%).

4,6-Dimethyl-3-(4,4,4-trifluoro-3-morpholinobutanoyl)-pyridin-2(1*H*)-one (16b): yield 77% as colorless crystals; mp 191−192 °C; IR (Nujol) 1665, 1630, 1540 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.31 (s, 3H, Me), 2.34 (s, 3H, Me), 2.65 (m, 2H, CH_2N), 2.87 (m, 2H, CH_2N), 3.35 (dd, 1H, C*H*H, ^2J = 16.5 Hz, ^3J = 5.3 Hz), 3.40 (dd, 1H, CH*H*, ^2J = 16.5 Hz, ^3J = 8.8 Hz), 3.57 (m, 4H, $2CH_2O$), 3.83 (m, 1H, CH), 6.03 (s, 1H, pyrid.), 13.12 (s, 1H, NH). Anal. Calcd for $C_{15}H_{19}F_3N_2O_3$: C, 54.21; H, 5.76; N, 8.43. Found: C, 54.05; H, 5.77; N, 8.63. Compound **16b** was also obtained from **7a** in 85% yield.

4,6-Dimethyl-3-(4,4,4-trifluoro-3-pyrrolidinobutanoyl)-pyridin-2(1*H*)-one (16c): yield 84% as colorless needles; mp 153−154 °C; IR (KBr) 1675, 1660, 1625, 1540 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.67−1.71 (m, 4H, 2 CH_2), 2.24 (s, 3H, Me), 2.31 (s, 3H, Me), 2.68−2.74 (m, 2H, NCH_2), 2.82−2.88 (m, 2H, NCH_2), 3.33 (dd, 1H, C*H*H, ^2J = 16.5 Hz, ^3J = 8.9 Hz), 3.42 (dd, 1H, CH*H*, ^2J = 16.5 Hz, ^3J = 5.0 Hz), 4.18 (quint d, 1H, CH, $J_{H,H}$ = $J_{H,F}$ = 8.5 Hz, $J_{H,H}$ = 5.0 Hz), 6.01 (s, 1H, pyrid.), 13.3 (br s, 1H, NH). Anal. Calcd for $C_{15}H_{19}F_3N_2O_2$: C, 56.96; H, 6.05; N, 8.86. Found: C, 56.98; H, 6.05; N, 8.87.

3-[3-(Diethylamino)-4,4,4-trifluorobutanoyl]-4,6-dimethylpyridin-2(1*H*)-one (16d): yield 59% as colorless crystals; mp 126−127 °C; IR (KBr) 1655, 1625, 1530 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.96 (t, 6H, 2Me, J = 7.1 Hz), 2.28 (s, 3H, Me), 2.31 (s, 3H, Me), 2.62 (dq, 2H, NCH_2, ^2J = 14.0 Hz, ^3J = 7.0 Hz), 2.73 (dq, 2H, NCH_2, ^2J = 14.0 Hz, ^3J = 7.0 Hz), 3.28 (dd, 1H, C*H*H, ^2J = 16.4 Hz, ^3J = 9.1 Hz), 3.43 (dd, 1H, CH*H*, ^2J = 16.4 Hz, ^3J = 4.9 Hz), 4.02 (quint d, 1H, CH, $J_{H,H}$ = $J_{H,F}$ = 8.8 Hz, $J_{H,H}$ = 4.8 Hz), 6.01 (s, 1H, pyrid.), 13.4 (br s, 1H, NH). Anal. Calcd for $C_{15}H_{21}F_3N_2O_2$: C, 56.60; H, 6.65; N, 8.80. Found: C, 56.67; H, 6.71; N, 8.77.

3-[3-(Benzylamino)-4,4,4-trifluorobutanoyl]-4,6-dimethylpyridin-2(1*H*)-one (16e): yield 55% as colorless needles; mp 119−120 °C; IR (KBr) 3325, 1655, 1620, 1540 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.0 (br s, 1H, NH), 2.15 (s, 3H, Me), 2.26 (s, 3H, Me), 3.15 (dd, 1H, C*H*H, ^2J = 16.2 Hz, ^3J = 3.4 Hz), 3.35 (dd, 1H, CH*H*, ^2J = 16.2 Hz, ^3J = 10.3 Hz), 3.82−3.90 (m, 1H, CH), 3.86 (d, 1H, C*H*HN, ^2J = 12.6 Hz), 3.95 (d, 1H, CH*H*N, ^2J = 12.6 Hz), 5.99 (s, 1H, pyrid.), 7.19−7.29 (m, 5H, Ph), 13.3 (br s, 1H, N3H). Anal. Calcd for $C_{18}H_{19}F_3N_2O_2$: C, 61.36; H, 5.44; N, 7.95. Found: C, 61.28; H, 5.60; N, 7.92.

3-[3-(Cyclohexylamino)-4,4,4-trifluorobutanoyl]-4,6-dimethylpyridin-2(1*H*)-one (16f): yield 42% as colorless crystals; mp 134−135 °C; IR (KBr) 3425, 3335, 1685, 1645, 1535 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.8−1.9 (m, 11H, cyclohexyl, NH), 2.29 (s, 3H, Me), 2.34 (s, 3H, Me), 2.54−2.60 (m, 1H, cyclohexyl), 3.11 (dd, 1H, C*H*H, ^2J = 15.8 Hz, ^3J = 3.6 Hz), 3.28 (dd, 1H, CH*H*, ^2J = 15.8 Hz, ^3J = 10.2 Hz), 3.87−3.92 (m, 1H, CH), 6.04 (s, 1H, pyrid.), 13.4 (br s, 1H, NH). Anal. Calcd for $C_{17}H_{23}F_3N_2O_2{\cdot}0.5H_2O$: C, 57.78; H, 6.85; N, 7.93. Found: C, 57.77; H, 6.76; N, 7.87.

4,6-Dimethyl-3-[4,4,4-trifluoro-3-(isopropylamino)butanoyl]pyridin-2(1*H*)-one (16g): yield 33% as colorless needles; mp 126−127 °C; IR (KBr) 1680, 1660, 1625, 1540 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.95 (d, 3H, Me, J = 6.2 Hz), 1.01 (d, 3H, Me, J = 6.2 Hz), 1.6 (br s, 1H, NH), 2.29 (s, 3H, Me), 2.33 (s, 3H, Me), 2.99 (sept, 1H, CH, J = 6.2 Hz), 3.16 (dd, 1H, C*H*H, ^2J = 15.8 Hz, ^3J = 4.1 Hz), 3.24 (dd, 1H, CH*H*, ^2J = 15.8 Hz, ^3J = 9.7 Hz), 3.80−3.90 (m, 1H, CH), 6.04 (s, 1H, pyrid.), 13.4 (br s, 1H, NH). Anal. Calcd for $C_{14}H_{19}F_3N_2O_2$: C, 55.26; H, 6.29; N, 9.21. Found: C, 55.42; H, 6.07; N, 9.18.

***N*-Cyclohexyl-2-{[3-(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)-3-oxo-1-(trifluoromethyl)propyl]sulfanyl}-acetamide (17a).** A solution of **7a** (0.15 g, 0.4 mmol) in cyclohexylamine (0.43 g, 4.3 mmol) was allowed to stand at room temperature for 2 weeks. The reaction mixture was diluted with ethanol (2 mL), and the precipitate that formed was filtered off, washed with ethanol, and dried to afford **17a** (0.05 g, 29%) as a colorless crystals: mp 230−231 °C; IR (Nujol) 3300, 1670, 1645, 1550 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.1−1.8 (m, 10H, cyclohexyl), 2.16 (s, 3H, Me), 2.18 (s, 3H, Me), 3.21 (dd, 1H, C*H*H, ^2J = 17.5 Hz, ^3J = 9.5 Hz), 3.27 (AB-system, $\Delta\delta$ = 0.02 ppm, 2H, CH_2S, J_{AB} = 14.0 Hz), 3.42−3.48 (m, 1H, cyclohexyl), 3.45 (dd, 1H, CH*H*, ^2J = 17.5 Hz, ^3J = 4.5 Hz), 4.18 (quint d, 1H, CH, $J_{H,H}$ = $J_{H,F}$ = 8.9 Hz, $J_{H,H}$ = 4.4 Hz), 6.02 (s, 1H, pyrid.), 7.92 (d, 1H, NH, J = 7.7 Hz), 12.8 (br s, 1H, NH). Anal. Calcd for $C_{19}H_{25}F_3N_2O_3S$: C, 54.53; H, 6.02; N, 6.69. Found: C, 54.43; H, 5.99; N, 6.62.

***N*-Benzyl-2-{[3-(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)-3-oxo-1-(trifluoromethyl)propyl]sulfanyl}-acetamide (17b).** This compound was prepared analogously to **17a** from **7a** and benzylamine in 37% yield as colorless crystals: mp 184−185 °C; IR (Nujol) 3320, 1665, 1640, 1540 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.16 (s, 3H, Me), 2.18 (s, 3H, Me), 3.24 (dd, 1H, C*H*H, ^2J = 17.5 Hz, ^3J = 9.4 Hz), 3.39 (AB-system, $\Delta\delta$ = 0.01 ppm, 2H, CH_2S, J_{AB} = 14.2 Hz), 3.47 (dd, 1H, CH*H*, ^2J = 17.5 Hz, ^3J = 4.6 Hz), 4.26 (t, 2H, CH_2Ph, J = 5.3 Hz), 4.17−4.31 (m, 1H, CH), 6.02 (s, 1H, pyrid.), 7.22−7.34 (m, 5H, Ph); 8.56 (t, 1H, NH, J = 5.6 Hz), 11.9 (br s, 1H, NH). Anal. Calcd for $C_{20}H_{21}F_3N_2O_3S$: C, 56.33; H, 4.96; N, 6.57. Found: C, 56.07; H, 5.07; N, 6.70.

4,6-Dimethyl-3-{4,4,4-trifluoro-3-[(2-hydroxyethyl)-sulfanyl]butanoyl}pyridin-2(1*H*)-one (18a). Enone **13** (0.20 g, 0.8 mmol) was dissolved with heating in THF (5 mL), and 2-mercaptoethanol (0.22 g, 2.8 mmol) and 3 drops of Et_3N were added. The reaction mixture was allowed to stand at room temperature for 24 h and concentrated to dryness under reduce pressure. The residue was treated with water (10 mL), and the precipitate that formed was filtered off, washed with water, dried, and recrystallized from toluene-hexane (3:1) to afford **20a** (0.08 g, 31%) as colorless crystals: mp 132−133 °C; IR (KBr) 3440, 1695, 1630, 1530 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.33 (s, 3H, Me), 2.36 (s, 3H, Me), 2.77 (ddd, 1H, C*H*HS, ^2J = 14.4 Hz, ^3J = 6.4 Hz, ^3J = 4.3 Hz), 3.01 (ddd, 1H, CH*H*S, ^2J = 14.4 Hz, ^3J = 7.0 Hz, ^3J = 4.1 Hz), 3.25 (t, 1H, OH, J = 6.4 Hz), 3.46 (dd, 1H, C*H*H, ^2J = 18.4 Hz, ^3J = 11.1 Hz), 3.59 (dd, 1H, CH*H*, ^2J = 18.4 Hz, ^3J = 3.1 Hz), 3.79−3.87 (m, 1H, CH), 3.89−4.03 (m, 2H, CH_2O), 6.05 (s, 1H, pyrid.), 13.15 (s, 1H, NH). Anal. Calcd for $C_{13}H_{16}F_3NO_3S$: C, 48.29; H, 4.99; N, 4.33. Found: C, 48.35; H, 4.82; N, 4.10.

4,6-Dimethyl-3-{4,4,4-trifluoro-3-[(4-methylphenyl)-sulfanyl]butanoyl}pyridin-2(1*H*)-one (18b). A mixture of **13** (0.25 g, 1.0 mmol), *p*-thiocresol (0.26 g, 2.1 mmol), 3 drops of Et_3N, and toluene (1 mL) was heated at 80 °C for 5 h. After being cooled to the room temperature, the resulting precipitate was filtered, washed with toluene and hexane, and dried to afford **18b** (0.31 g, 79%) as a colorless powder: mp 172−173 °C; IR (KBr) 1675, 1640, 1625, 1530 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.32 (s, 3H, Me), 2.33 (s, 3H, Me), 2.37 (s, 3H, Me), 3.42 (dd, 1H, C*H*H, ^2J = 17.7 Hz, ^3J = 10.5 Hz), 3.57 (dd, 1H, CH*H*, ^2J = 17.7 Hz, ^3J = 3.8 Hz), 4.15 (m, 1H, CH), 6.04 (s, 1H, pyrid.), 7.12 (d, 2H, J = 8.0, arom.), 7.44 (d, 2H, J = 8.0, arom.), 13.3 (br s, 1H, NH). Anal. Calcd for $C_{18}H_{18}F_3NO_2S$: C, 58.53; H, 4.91; N, 3.79. Found: C, 58.29; H, 4.89; N, 3.81.

4,6-Dimethyl-3-[4,4,4-trifluoro-3-(hydroxyamino)butanoyl]pyridin-2(1*H*)-one (19). Enone **13** (0.24 g, 1.0 mmol) was dissolved with heating in 10 mL of 2-propanol, and hydroxylamine, prepared from $NH_2OH{\cdot}HCl$ (0.41 g, 5.9 mmol) and KOH (0.25 g, 4.5 mmol) in EtOH (10 mL), was added. The resulting mixture was allowed to stand for 30 min at room temperature and diluted with water (10 mL). The precipitate was filtered off, washed with water, dried, and recrystallized from toluene to give **19** (0.14 g, 51%) as colorless needles;: mp 177−178 °C; IR (KBr) 3420, 3310, 1660, 1620, 1535 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.14 (s, 3H, Me), 2.18 (s, 3H, Me), 3.14 (dd, 1H, C*H*H, ^2J = 17.5 Hz, ^3J = 4.9 Hz), 3.19 (dd, 1H, CH*H*, ^2J = 17.5 Hz, ^3J = 7.3 Hz), 3.86−3.96 (m, 1H, CH), 6.02 (s, 1H, pyrid.), 6.11 (t, 1H, NH, J = 3.6 Hz), 7.64 (d, 1H, OH, J = 3.0 Hz), 11.95 (s, 1H, NHCO). Anal. Calcd for $C_{11}H_{13}F_3N_2O_3$: C, 47.49; H, 4.71; N, 10.07. Found: C, 47.81; H, 4.97; N, 9.80.

4,6-Dimethyl-3-[4,4,4-trifluoro-3-(nitromethyl)butanoyl]-pyridin-2(1*H*)-one (20). A mixture of **13** (0.25 g, 1.0 mmol) and a mixed solvent of nitromethane (1.2 mL) and water (0.3 mL) containing K_2CO_3 (0.02 g) was heated under reflux for 1 h. After being cooled to room temperature, the resulting precipitate was filtered, washed with water, and dried. The residue was dissolved in toluene (5 mL) and purified by filtration through a silica gel layer and recrystallization from a mixture of toluene/hexane (2:1) to afford **20** (0.15 g, 48%) as colorless crystals: mp 146−147 °C; IR (KBr) 1655, 1625, 1560 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.31 (s, 3H, Me), 2.33 (s, 3H, Me), 3.37 (dd, 1H, C*H*H, ^2J = 18.0 Hz, ^3J = 9.1 Hz), 3.50 (dd, 1H, CH*H*, ^2J = 18.0 Hz, ^3J = 4.4 Hz), 3.89−4.02 (m, 1H, CH), 4.66 (dd, 1H, C*H*HN, ^2J = 14.0 Hz, ^3J = 5.2 Hz), 4.69 (dd, 1H, CH*H*N, ^2J = 14.0 Hz, ^3J = 6.6 Hz), 6.06 (s, 1H, pyrid.), 13.16 (s, 1H, NH). Anal. Calcd for $C_{12}H_{13}F_3N_2O_4$: C, 47.06; H, 4.28; N, 9.15. Found: C, 46.93; H, 4.41; N, 9.24.

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Supporting Information Available: General experimental methods and ^1H NMR spectra for compounds **6a**, **7a**, **11**, and **14b**−**17b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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