

Selective Instability of Trifluoromethyl Linked to Carbon. A Prerequisite for New Heterocyclizations with Ethyl 4,4,4-Trifluoroacetoacetate Arylhydrazones

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Received August 18, 1986

Highly functionalized pyrazoles, **2**, and 1*H*-pyrazolo[3,4-*d*]pyridazinones **3** have been obtained in moderate yields from ethyl 4,4,4-trifluoroacetoacetate *o*-chlorophenylhydrazones **1** by treatment with sodium hydride in aprotic solvents. Treatment of **2** and **3** with sodium ethoxide in ethanol gave bicyclic 5-(5-oxopyrazol-3-yl)pyrazolones **4** and **5** in high yields. The reactions of **1** with sodium hydride which are accompanied by the loss of fluoride ion from one trifluoromethyl group implicate the anchimeric assistance of an *N*-deprotonated anion of **1** in the initial reaction step.

J. Heterocyclic Chem., **25**, 139 (1988).

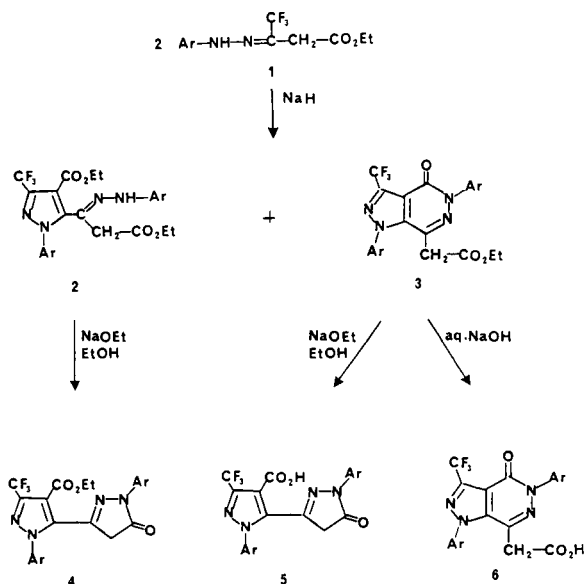
Introduction.

In the reaction of β -ketoesters with a substituted hydrazine the intermediate hydrazones are often isolable and can generally be converted to pyrazolones merely by heating or treatment with base [1].

Aldehyde and ketone 2-phenylsemicarbazones are well known [2,3] and their herbicidal properties have been described [4]. Many of these semicarbazones were prepared by the reaction of an arylhydrazone with sodium hydride in dimethylformamide followed by carbamoylation of the generated anionic species. It was considered that similar 2-arylssemicarbazones might be formed when the ethyl trifluoroacetoacetate phenylhydrazones **1** were allowed to

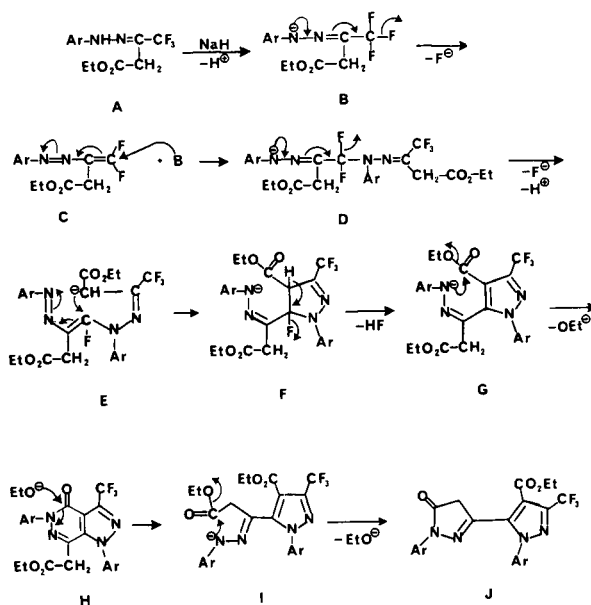
react with sodium hydride in an aprotic solvent followed by treatment of the resulting anionic species, presumed to be **B** (Scheme 2), with a carbomoyl chloride.

The reactions of several of these hydrazones with sodium hydride in dimethylformamide or dimethylacetamide at room temperature gave instead highly functionalized pyrazoles **2** and 1*H*-pyrazolo[3,4-*d*]pyridazinones **3** in low to moderate yields. The reaction is accompanied by the loss of fluoride ion from one trifluoromethyl group and represents a rare case of selective instability of a trifluoromethyl group linked to carbon. In the process, the carbon atom of a trifluoromethyl group becomes the bridgehead atom of the new heterocycle.



a: Ar = 2,4-Cl₂C₆H₃ b: Ar = 2-ClC₆H₄ c: Ar = 2,3-Cl₂C₆H₃

Scheme I



Scheme II. Reaction Mechanism

Results and Discussion.

Entry into the 1*H*-pyrazole-5-propanoic acid and 1*H*-pyrazolo[3,4-*d*]pyridazine ring systems was first obtained when a solution containing **1a** in dimethylacetamide was treated with sodium hydride. During the portionwise addition of one molar equivalent of sodium hydride, which caused the internal temperature to rise to 65°, the rapid disappearance of **1a** with concomitant formation of two new compounds, **2a** (19-23%) and **3a** (9-11%), was observed (Scheme 1).

Elemental analysis and mass spectrometry showed that **2a** and **3a** contained four nitrogen and four chlorine atoms. The positions for methylene groups in their ¹H and ¹³C nmr spectra indicated the presence of an acetic acid moiety, thus eliminating from consideration the bicyclic pyrazolone structure **4a** for **3a**. For example, the signals for methylene protons for **1a** (starting material) and **2a** and **3a** (products) are observed between δ 3.6-3.7 ppm, consistent with the value reported [5a] for methyl 2-pyridylacetate (δ 3.84). Additionally, the corresponding signal in the ¹³C nmr spectrum of **3a** is found at δ CH₂ 37.5, which again is in good agreement with that observed [6a] for methyl 2-pyridylacetate (δ CH₂ 43.6).

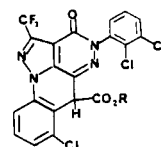
When **2a** was treated with sodium ethoxide in refluxing ethanol (1 hour), the substituted ethyl (5-oxo-1*H*-pyrazolo-3-yl)-1*H*-pyrazole-4-carboxylate **4a** was obtained in 86% yield rather than the 1*H*-pyrazolo[3,4-*d*]pyridazine-7-acetic acid derivative **3a**. The signal at δ 87.8 in the ¹³C nmr

spectrum of **4a** is in excellent agreement with that reported [6b] for 3-phenyl-5-pyrazolone (δ CH₂ 86.9).

Treatment of **3a** with refluxing aqueous ethanolic sodium hydroxide (15 minutes) gave the corresponding substituted acetic acid **6a** in 39% yield. However, treatment of **3a** with sodium ethoxide in refluxing ethanol (2.5 hours) lead to the (5-oxo-1*H*-pyrazolo-3-yl)-1*H*-pyrazole-4-carboxylic acid **5a** in 73% yield. Again, ¹³C nmr spectroscopy was instrumental in assigning structures (see Table 1).

Ethyl 3-(2-chlorophenylhydrazono)-4,4,4-trifluorobutanoate **1b** reacted similarly with sodium hydride in dimethylformamide at ambient temperature. However, the only product isolated in 36% yield was the β-(2-phenylhydrazono)-1*H*-pyrazole-5-propanoic acid derivative **2b** which underwent ready pyrazolone formation when treated with sodium ethoxide in refluxing ethanol (2 hours). An aqueous workup procedure gave the ester **4b** and the corresponding acid **5b** in 15% and 64% yield, respectively.

Treatment of the analogous 2,3-dichlorophenylhydrazono **1c** with sodium hydride in dimethylformamide (18 hours) gave the 1*H*-pyrazolo[3,4-*d*]pyridazinone derivative **3c** albeit in low (3%) yield, along with a very small amount (1%) of the tetraaza-aceanthrylene derivative, **7**.



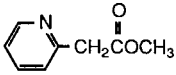
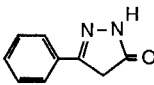
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Correct analytical (C, H, N), ¹³C nmr (δ CH₂ 39.96), and mass spectral data (m/z 580 (M⁺)) are in complete agreement with the proposed structure for **3c**. The structure of the minor co-reaction product **7** follows from (a) the elemental analysis (C, H, Cl, N), (b) the ¹H nmr spectrum which shows the correct proton count and positions for one methyl group (δ 1.3), one methyleneoxy group (δ 4.2), one CH-proton at δ 5.5, and six aromatic protons centered near 7.6 ppm, (c) the electron-impact mass spectrum which shows M⁺ (m/z 544, 3 Cl's), and (d) the field desorption mass spectrum which contains the ions recorded in the Experimental.

With the exception of **6a** which shows m/z = 517 (M⁺-Cl), the parent ions (M⁺) are observed in the mass spectra of all heterocycles. All spectra show fragment peaks involving the loss from the parent ion of either chlorine and fluorine, water or ethanol. Other fragment peaks are the result of decarboxylation, decarbonylation or ethoxydecarbonylation of the parent ion. Other common fragment peaks of significant intensity includes the following: [C₆H₅-x Cl_x N₂]⁺, [C₆H₅-x Cl_x N]⁺, [C₆H₅-x Cl_x]⁺ and [(C₆H₅-x Cl_x)-HCl]⁺.

Table 1.

¹H and ¹³C NMR Positions for CH₂ Groups

Compound	¹ H NMR (in ppm)		¹³ C NMR (in ppm)	
	δ CH ₂ C(=O)	Solvent	δ CH ₂ C(=O)	Solvent
1a	3.6	CDCl ₃	—	—
2a	3.7	CDCl ₃	—	—
2b	3.75	CDCl ₃	—	—
3a	3.6	CDCl ₃	37.5	DMSO-d ₆
3c	—	—	39.96	CDCl ₃
	3.84 [5a]	CDCl ₃	43.6 [6a]	CDCl ₃
4a	—	—	87.8	DMSO-d ₆
5a	—	—	88.36	DMSO-d ₆
	6.06 [5b]	DMSO-d	98.9 [6b]	Polysol

Infrared absorption spectra of compounds of general structure **2**, **3** and **4** gave a very strong broad band around 2600 cm^{-1} indicative of enolizable carbonyl functions. The carbonyl stretching frequency between $1700\text{--}1740\text{ cm}^{-1}$, which is absent in 1-(substituted phenyl)-3-(trifluoromethyl)-5-pyrazolones, is apparent in these heterocycles.

Included in Table 1 are the nmr positions for the methylene groups of selected heterocycles and standards. These data were instrumental in assigning structures as they clearly discriminate between fused pyrazolo[3,4-*d*]pyridazinones (e.g., **6a**) and the isomeric bicyclic 5-(5-oxopyrazol-3-yl)pyrazoles (e.g., **4a**).

Reaction Mechanism.

3-(Phenylhydrazono)-4,4,4-trifluorobutanoates **A** which lack the *ortho*-chloro substituent on phenyl do not undergo heterocyclizations initiated by the elimination of fluoride ion from the trifluoromethyl group. For example, in the three instances investigated, namely, $\text{Ar} = \text{C}_6\text{H}_5$, 3-Cl- C_6H_4 and 2- CH_3 - C_6H_4 , the only products formed and isolated in high yields (85-89%) upon treatment with sodium hydride in dimethylformamide were the corresponding 1-aryl-3-(trifluoromethyl)-5-pyrazolones. This together with the earlier observations that (a) all compounds reacted readily with aqueous alcoholic hydroxide and gave identical pyrazolones and (b) generally higher yields of **2** and **3** obtained with the 2,4-dichlorophenylhydrazones **1a** than with the 2-chloro and 2,3-dichlorophenylhydrazones **1b** and **1c** indicates that both a strongly electron-withdrawing substituent in the *ortho* and/or *para* position on phenyl and a very strong base are required to bring about the conversion of **1** to **2**, **3**, and/or **7**.

While mechanistic studies have not been attempted, the foregoing observations are consistent with the mechanism shown in Scheme 2. The formation of **F** may be rationalized in terms of *N*-deprotonation of **A** by the action of sodium hydride, followed by the elimination of fluoride ion [7,8] from the anionic species **B** to give **C** acting as a powerful Michael acceptor leading to **D** [9]. Loss of fluoride from **D** is followed by internal nucleophilic attack of C-deprotonated species **E** on carbon. Subsequent elimination of hydrogen fluoride gives the observed product **F** which cyclocondenses as indicated in **G** to give **H**.

In ethanol solution, in the presence of sodium ethoxide, the pyrazolo[3,4-*d*]pyridazinone **H** (kinetic product) is readily converted into the bicyclic 5-(5-oxopyrazol-3-yl)pyrazole **J** (thermodynamic product). This isomerization is initiated by attack of ethoxide ion on the ring carbonyl carbon atom as indicated in **H** and **I**.

Thus, the transformations which involve loss of three fluoride ions from one trifluoromethyl group under mild conditions can be explained then in terms of the mechanism proposed in Scheme 2 and the ability of the compounds to form olefinic intermediates necessary for reac-

tions to occur. That this is true can be seen in the stability of compounds incapable of such reactions and provides a strong argument against direct displacement of fluoride ion from the neutral species of **A** in an SN_2 -type displacement.

EXPERIMENTAL

General Methods.

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected, as are boiling points. Routinely, reaction courses and product mixtures were monitored by thin layer chromatography (tlc) or gas-liquid chromatography (glc). Thin layer separations were accomplished on silica gel GF²⁵⁴ plates with visualization by iodine vapor, phosphomolybdic acid spray, or uv light. Infrared (ir) spectra were measured on a Digilab FTS-15E or Beckman Acculab I spectrophotometer, and only pertinent and other strong absorptions are listed. Bruker WM-360 or General Electric QE-300 spectrometers were used to obtain nuclear magnetic resonance (nmr) data. Peak positions are given in ppm downfield from tetramethylsilane as an internal standard. Mass spectra were determined at 70 eV on a Finnigan 4000 spectrometer, either through gas chromatographic (gc/ms) or solid probe (sp/ms) sample introduction, and only the pertinent or more abundant fragment peaks are recorded. In the absence of clearly detectable molecular ions chemical ionization, (ci) using methane was employed on the same instrument.

Ethyl 4,4,4-Trifluoroacetoacetate (ETAA) 2,4-Dichlorophenylhydrazone (**1a**).

A mixture of 46.3 g (0.22 mole) of 2,4-dichlorophenylhydrazine hydrochloride and 36.8 g (0.20 mole) of ETAA in 500 ml of 40% aqueous ethanol was stirred and heated to 60° . The heating resulted in a clear solution. After 2 hours at ambient temperature, the ethanol was removed by rotary evaporation. The aqueous layer was extracted with ether (3 x 200 ml). The combined ether extracts were dried over anhydrous magnesium sulfate, filtered and concentrated to 67 g of an amber oil. Fractional distillation at $135\text{--}140^\circ$ (0.05 mm) gave 63.0 g (95%) of **1a** as an amber liquid; ir (methylene chloride): $3360, 3280\text{ (NH)}\text{ cm}^{-1}$; $^1\text{H nmr}$ (deuteriochloroform): δ 1.4 (3H, CH_3), 3.6 (2H, CH_2), 4.3 (2H, OCH_2), ca. 7.4 (3H, $(\text{CH}=\text{)}_3$), and 9.5 (1H, NH).

Anal. Calcd. for $\text{C}_{12}\text{H}_{11}\text{Cl}_2\text{F}_3\text{N}_2\text{O}_2$ (343.12): C, 42.0; H, 3.2; N, 8.2. Found: C, 42.3; H, 3.2; N, 8.1.

Ethyl β -(2,4-Dichlorophenylhydrazono)-3-[1-(2,4-dichlorophenyl)-3-(trifluoromethyl)-4(ethoxycarbonyl)-1H-pyrazol-5-yl]propanoate (**2a**) and Ethyl 4,5-Dihydro-4-oxo-1,5-bis(2,4-dichlorophenyl)-7-[1H-pyrazolo[3,4-*d*]pyridazinyl]acetate (**3a**).

A solution of 63.0 g (0.184 mole) of **1a** in 200 ml of dimethylacetamide was stirred during the portionwise addition of 4.4 g (0.184 mole) of powdery sodium hydride (nitrogen blanket), causing the internal temperature to increase to 65° . After 1 hour, the reaction mixture was poured into ice water and extracted with methylene chloride (3 x 200 ml). The combined extracts were washed with ice water (3 x 400 ml), dried over magnesium sulfate, filtered, and concentrated to 63 g of dark syrup. Purification by silica chromatography using solvent No. 2 [10], gave 11.0 g (19%) of **2a** as an off-white solid, mp $152\text{--}155^\circ$; nmr (deuteriochloroform): δ 1.3 [6H, $(\text{CH}_3)_2$], 3.7 (2H, CH_2), 4.3 (4H, $(\text{OCH}_2)_2$), 6.3-7.5 [6H, $(\text{CH}=\text{)}_3$], and 9.4 (1H, NH); ci/ms: m/z 625 (MH^+), 4 Cl's), 605 ($\text{MH}^+ - \text{HF}$), 579, 430, 417, 397, 71, 190, 175, 162, 147.

Anal. Calcd. for $\text{C}_{24}\text{H}_{19}\text{Cl}_4\text{F}_3\text{N}_4\text{O}_4$ (626.25): C, 46.0; H, 3.0; N, 8.9. Found: C, 46.1; H, 3.0; N, 8.8.

The second fraction, 6.0 g (11%), consisted of an off-white solid **3a**, mp $155\text{--}156^\circ$; $^1\text{H nmr}$ (deuteriochloroform): δ 1.2 (3H, CH_3), 3.6 (2H, CH_2), 3.95 (2H, OCH_2), and ca. 7.4 [6H, $(\text{CH}=\text{)}_3$]; $^{13}\text{C nmr}$ ($\text{DMSO-}d_6$): δ 37.5 (CH_2); ir (potassium bromide): 1740 and 1695 ($\text{C}=\text{O}$) cm^{-1} ; ei/ms (m/z):

580 (M⁺, 4 Cl⁻), 561 (M⁺-F), 543 (M⁺-Cl), 515 (m/z 543-CO), 471, 435, 297, 173 (C₆H₃Cl₂N₂⁺), 145 (C₆H₃Cl₂⁺), 109 (m/z 145-HCl), 75 (m/z 109-HCl).

Anal. Calcd. for C₂₂H₁₃Cl₄F₃N₄O₂ (580.18): C, 45.5; H, 2.2; N, 9.7; Cl, 24.5. Found: C, 45.5; H, 2.4; N, 9.5; Cl, 25.0.

The chlorine analysis did not change following vacuum drying (100°, 24 hours) of the analytical sample.

In a second experiment under identical reaction conditions and on the same scale **2a** was obtained in 23% yield, mp 152-155° (from ether-hexane); the yield of **3a** was 9%, mp 154-155° (from ether-hexane).

4,5-Dihydro-4-oxo-1,5-bis(2,4-dichlorophenyl)-3-trifluoromethyl-1H-pyrazolo[3,4-d]pyridazine-7-acetic Acid (**6a**).

A mixture of 4.0 g (6.9 mmoles) of **3a** in 20 ml of ethanol and 10 ml of 20% sodium hydroxide was stirred and heated to reflux. After 15 minutes, the ethanol solvent was removed by rotary evaporation from the clear solution. The residual aqueous solution was diluted with 300 ml of water, acidified with dilute hydrochloric acid, and extracted with ether (3 x 100 ml). The combined ether extracts were dried over magnesium sulfate, filtered, and concentrated under rotary evaporation. The residue was purified by silica chromatography using solvent No. 9 [10] to give 1.5 g (39%) of **6a**, a white solid, mp 250-255°. Recrystallization from toluene raised the mp to 254-257°; ir (potassium bromide): 3600-2800 (OH, NH), 1700 (C=O) cm⁻¹; ¹H nmr (deuteriochloroform): δ 3.6 (2H, CH₂) and ca. 7.4 [6H, (CH=)₆]; ei/ms: m/z 517 (M⁺-Cl), 471 (M⁺-CO₂, Cl), 435 (m/z 471-Cl), 218, 200, 187, 174, 162, 145 (C₆H₃Cl₂⁺), 124, 109 (m/z 145-HCl), 75 (m/z 109-HCl), 69 (CF₃⁺), 63, 44 (CO₂⁺).

Anal. Calcd. for C₂₀H₆Cl₄F₃N₄O₃ (552.12): C, 43.5; H, 1.6; N, 10.1; Cl, 25.7. Found: C, 43.6; H, 1.7; N, 10.2; Cl, 25.4.

5-[4,5-Dihydro-5-oxo-1-(2,4-dichlorophenyl)-1H-pyrazol-3-yl]-1-(2,4-dichlorophenyl)-3-(trifluoromethyl)-1H-pyrazole-4-carboxylic Acid (**5a**) and the Corresponding Ethyl Ester (**4a**).

a) Treatment of **2a** with Sodium Ethoxide-Ethanol.

A solution of 6.3 g (0.01 mole) of **2a** in 70 ml of ethanol containing 0.88 g (0.013 mole) of sodium ethoxide was stirred and heated to reflux. After 1 hour, the mixture was diluted with 200 ml of ice water, acidified with dilute hydrochloric acid, and extracted with ether (3 x 200 ml). The combined extracts were washed with cold water (2 x 150 ml), then with 10% sodium hydroxide (300 ml).

The sodium hydroxide solution was acidified with dilute hydrochloric acid and filtered to give 0.7 g (13%) of **5a**, mp 212-215°; ir (potassium bromide): ca. 2600 (OH) and 1700 cm⁻¹ (C=O); ¹³C nmr (DMSO-d₆): δ 88.35 (CH₂); ei/ms: m/z 532 (M⁺-H₂O, 4 Cl⁻), 497 (M⁺-H₂O, Cl), 471 (M⁺-HCOOH, Cl), 365, 284, 173 (C₆H₃Cl₂N₂⁺), 161 (C₆H₃Cl₂NH₂⁺), 145 (C₆H₃Cl₂⁺), 111 (C₆H₃Cl⁺), 75 (m/z 111-HCl), 44 (CO₂⁺, very strong); the field desorption ms indicates a molecular weight of 550 with 4 Cl⁻.

Anal. Calcd. for C₂₀H₆Cl₄F₃N₄O₃ (552.12): C, 43.5; H, 1.6; N, 10.1; Cl, 25.7. Found: C, 43.8; H, 1.7; N, 9.9; Cl, 25.5.

The ether extracts were dried over magnesium sulfate, filtered and concentrated under rotary evaporation to give 5.0 g (86%) of **4a**, an amber glassy material; ir (potassium bromide): ca. 2600 (OH), 1730 (C=O) cm⁻¹; ¹³C nmr (DMSO-d₆): δ 87.8 (CH₂); ei/ms: m/z 580 (M⁺), 545 (M⁺-Cl), 534 (M⁺-C₂H₅OH, 4 Cl⁻), 497 (M⁺-C₂H₅OH, Cl), 471 (m/z 497-CO), 434 (m/z 471-Cl), 173 (C₆H₃Cl₂N₂⁺), 161 (C₆H₃Cl₂NH₂⁺), 124.

Anal. Calcd. for C₂₂H₁₃Cl₄F₃N₄O₃ (580.18): C, 45.5; H, 2.3; N, 9.7. Found: C, 45.7; H, 2.2; N, 9.6.

b) Treatment of **3a** with Sodium Ethoxide-Ethanol.

A solution of 3.5 g (52 mmoles) of sodium ethoxide and 3.6 g (6.2 mmoles) of **3a** in the 150 ml of ethanol was heated to reflux for 2.5 hours. The solvent was removed under rotary evaporation. The residue was dissolved in 150 ml of water and extracted with ether (3 x 150 ml). The aqueous layer was decolorized (charcoal), acidified with dilute hydrochloric acid, and filtered to give 2.5 g (73%) of **5a** as an off-white solid, mp 212-215°; ir (potassium bromide): ca. 2600 (OH) and 1710 cm⁻¹ (C=O); ¹³C nmr (DMSO-d₆): δ 88.36 (CH₂); ei/ms: m/z 550 (M⁺), 532

(M⁺-HCOOH, Cl), 365 (M⁺-HCOOH, CF₃, Cl₂), 284, 173 (C₆H₃Cl₂N₂⁺), 161 (C₆H₃Cl₂NH₂⁺), 145 (C₆H₃Cl₂⁺), 124, 111 (C₆H₃Cl⁺).

Anal. Calcd. for C₂₀H₆Cl₄F₃N₄O₃ (552.12): C, 43.5; H, 1.6; N, 10.1. Found: C, 43.8; H, 1.7; N, 9.9.

Ethyl 4,4,4-Trifluoroacetoacetate 2-chlorophenylhydrazone (**1b**), 1-(2-Chlorophenyl)-3-(trifluoromethyl)-5-pyrazolone and 1,1,1-Trifluoroacetone 2-Chlorophenylhydrazone.

To a warm (60°) solution of 25.0 g (0.14 mole) of 2-chlorophenylhydrazine hydrochloride in 200 ml of water and 200 ml of ethanol was added 25.7 g (0.14 mole) of ethyl trifluoroacetoacetate (ETAA). The mixture was stirred and heated to reflux for one hour. Ethanol was removed by rotary evaporation. The aqueous residue was extracted with ether (3 x 150 ml). The combined ether extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give 40.0 g of an amber oil containing some solid in suspension. Filtration gave 4.5 g (12%) of 1-(2-chlorophenyl)-3-(trifluoromethyl)-5-pyrazolone, a white solid, mp 174-176°; ir (potassium bromide): 3200-2300 cm⁻¹ (NH and/or salt), no C=O; ¹H nmr (DMSO-d₆): δ 5.85 (1H, CH=), ca. 7.5 (4H, (CH=)₄), and 12.1 (1H, NH or OH); ei/ms: m/z 262 (M⁺), 243 (M⁺-F), 277 (M⁺-Cl), 139 (C₆H₄ClN₂⁺), 111 (C₆H₄Cl⁺), 75 (m/z 111-HCl).

Anal. Calcd. for C₁₀H₆ClF₃N₂O₂ (262.63): C, 45.7; H, 2.3; N, 10.7. Found: C, 45.9; H, 2.5; N, 10.5.

The residual oil (filtrate) was distilled under reduced pressure. At 88-98° (0.2 mm), a small fraction consisting of 1.0 g (3%) of 1,1,1-trifluoroacetone 2-chlorophenylhydrazone was collected; colorless solid, mp 42-44° (from hexane); the analytical sample was sublimed, mp 43-44°; ir (potassium bromide): 3370 (NH) cm⁻¹; ¹H nmr (deuteriochloroform): δ 2.04 (3H, CH₃), no OC₂H₅, 6.6-7.5 [4H, (CH=)₄], and 7.8 (1H, NH); ei/ms: m/z 236 (M⁺), 167 (M⁺-CF₃), 126 (C₆H₄ClNH⁺), 99 (m/z 126-HCN), 90, 63.

Anal. Calcd. for C₉H₆ClF₃N₂ (236.62): C, 45.7; H, 3.4; N, 11.8. Found: C, 45.5; H, 3.0; N, 11.9.

The major fraction, 28.6 g (66%), consisted of **1b**, bp 122-125° (0.2 mm), a light yellow liquid; ir (methylene chloride): 3290, 3230 (NH), and 1750, 1720 (C=O) cm⁻¹; ¹H nmr (deuteriochloroform): δ 1.3 (3H, CH₃), 4.2 (2H, OCH₂), 3.5 (2H, CH₂), 6.7-7.7 (4H, (CH=)₄), and 9.25 (1H, NH); ei/ms: m/z 308 (M⁺), 262 (M⁺-C₂H₅OH), 227 (M⁺-Cl, C₆H₅OH), 139 (C₆H₄ClN₂⁺), 111 (C₆H₅Cl⁺).

Anal. Calcd. for C₁₂H₁₂ClF₃N₂O₂ (308.68): C, 46.7; H, 3.9; N, 9.1. Found: C, 46.6; H, 3.8; N, 8.9.

Ethyl β-(2-Chlorophenylhydrazono)-3-[1-(2-chlorophenyl)-3-(trifluoromethyl)-4-(ethoxycarbonyl)-1H-pyrazol-5-yl]propanoate (**2b**).

To a stirred solution of 28.9 g (94 mmoles) of **1b** in 200 ml of dimethylformamide was added portionwise 2.2 g (94 mmoles) of sodium hydride, causing the internal temperature to rise to 60°. After 10 hours at room temperature, the reaction mixture was poured into 750 ml of ice water and extracted with methylene chloride (3 x 150 ml). The combined extracts were washed with ice water (3 x 200 ml), dried over magnesium sulfate, filtered, and concentrated under rotary evaporation. The residual liquid was purified by silica chromatography using solvent No. 1 [10]. The first fraction, 9.4 g (18%), consisted of an amber syrup **2b**; ir (methylene chloride): 3340, 3270 (NH), and 1720 (C=O) cm⁻¹; ¹H nmr (deuteriochloroform): δ 1.3 [6H, (CH₃)₂], 3.75 (2H, CH₂), 4.25 [4H, (OCH₂)₂], 6.4-7.6 [8H, (CH=)₈], and 9.35 (1H, NH); ei/ms: m/z 556 (M⁺) 464 (M⁺-F, CO₂C₂H₅), 429 (M⁺-C₆H₅ClNH₂), 127 (C₆H₄ClNH₂⁺), 111 (C₆H₄Cl⁺), 75 (m/z 111-HCl), 45 (C₂H₅O⁺); field desorption ms supports the structure.

Anal. Calcd. for C₂₄H₂₁Cl₂F₃N₄O₄ (557.36): C, 51.7; H, 3.8; N, 10.1. Found: C, 51.5; H, 3.8; N, 10.1.

The second fraction, 2.0 g (7%), was starting material, **1b**; ei/ms: m/z 308 (M⁺).

5-[4,5-Dihydro-5-oxo-1-(2-chlorophenyl)-1H-pyrazol-3-yl]-1-(2-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazole-4-carboxylic Acid (**5b**) and the Corresponding Ethyl Ester **4b**.

A solution of 7.0 g (13 mmoles) of **2b** in 50 ml of ethanol containing 1.2 g (17 mmoles) of sodium ethoxide was heated to reflux for 2 hours, cool-

ed, poured into 300 ml of ice water, acidified with diluted hydrochloric acid and extracted with ether (3 x 100 ml). The combined extracts were washed with ice water (3 x 100 ml), then with 10% sodium hydroxide (250 ml). Acidification of the basic extract with dilute hydrochloric acid followed by filtration gave 4.0 g (64%) of **5b**, a tan solid, mp 162-165°; ir (potassium bromide): *ca.* 2000 (OH) and 1700 (C=O) cm^{-1} ; ^1H nmr (DMSO- d_6): δ 5.85 (1H, CH=), *ca.* 7.5 [8H, (CH=) $_8$] and *ca.* 12.1 (2H, NH and OH); ei/ms: *m/z* 482 (M $^+$), 464 (M $^+$ -H $_2$ O), 447 (M $^+$ -Cl), 429 (M $^+$ -H $_2$ O, Cl), 401 (*m/z* 429-CO) $^+$, 366 (*m/z* 401-Cl) $^+$, 297 (*m/z* 366 -CF $_3$) $^+$, 125 (C $_6$ H $_4$ ClN $^+$), 111 (C $_6$ H $_3$ Cl $^+$), 75 (*m/z* 111-HCl) $^+$.

Anal. Calcd. for C $_{20}$ H $_{11}$ Cl $_2$ F $_3$ N $_4$ O $_3$ (483.23): C, 49.7; H, 2.3; N, 11.6. Found: C, 49.3; H, 2.4; N, 11.9.

The ethereal extract was washed with water, dried over magnesium sulfate, and concentrated under rotary evaporation to give 1.0 g (15%) of **4b**, a yellow glassy material; ir (potassium bromide) *ca.* 2600 (OH), 1725 (C=O) cm^{-1} ; ei/ms: *m/z* 510 (M $^+$), 475 (M $^+$ -Cl), 464 (M $^+$ -EtOH), 429 (M $^+$ -EtOH, Cl), 366 (*m/z* 429-Cl, CO), 297 (*m/z* 366-CF $_3$), 139 (C $_6$ H $_4$ ClN $_2$) $^+$, 125 (C $_6$ H $_3$ ClN $^+$), 111 (C $_6$ H $_3$ Cl $^+$), 75 (*m/z* 111-CHI).

Anal. Calcd. for C $_{22}$ H $_{13}$ Cl $_2$ F $_3$ N $_4$ O $_3$ (511.29): C, 51.7; H, 3.0; N, 11.0. Found: C, 52.0; H, 3.2; N, 10.6.

Ethyl 4,4,4-Trifluoroacetoacetate 2,3-Dichlorophenylhydrazone (**1c**) and 1-(2,3-Dichlorophenyl)-3-trifluoromethyl-5-pyrazolone.

A mixture of 100.0 g (0.47 mole) of 2,3-dichlorophenylhydrazine hydrochloride and 86.5 g (0.47 mole) of ethyl trifluoroacetoacetate in 350 ml of water and 550 ml of ethanol was heated to reflux (84°) for 1 hour, resulting in a clear solution. The solvent ethanol was removed by rotary evaporation. The aqueous residue was diluted with 1000 ml of ice water and extracted with ether (3 x 300 ml). The combined ether extracts were washed with water (2 x 100 ml), dried over magnesium sulfate, filtered and concentrated to dryness. A small amount of crystalline solid was removed by suction-filtration and identified as 1-(2,3-dichlorophenyl)-3-trifluoro-methyl-5-pyrazolone, yield 2.8 g (2%), mp 209-210° (from ether-hexane); ir (potassium bromide): 3300-2300 cm^{-1} (OH and/or NH), no C=O; ^1H nmr (DMSO- d_6): δ 6.9 (1H, CH=), and 7.7 (3H, aromat CH=); ei/ms, (*m/z*): 296 (M $^+$), 277 (M $^+$ -F), 261 (M $^+$ -Cl), 241 (M $^+$ -Cl, HF), 173 (C $_6$ H $_3$ Cl $_2$ N $_2$) $^+$, 145 (C $_6$ H $_3$ Cl $_2$) $^+$, 124, 111 (C $_6$ H $_3$ Cl $^+$), 75 (*m/z* 111-HCl), 69 (CF $_3$) $^+$.

Anal. Calcd. for C $_{10}$ H $_5$ Cl $_2$ F $_3$ N $_2$ O (297.07): C, 40.4; H, 1.7; N, 9.4. Found: C, 40.4; H, 1.8; N, 9.4.

The filtrate, 143.9 g (89%), was identified as **1c**, an amber liquid; ir (carbon tetrachloride): 3330-3280 (NH), 1750, 1720 (C=O), and 1150 (C-O-) cm^{-1} ; ^1H nmr (deuteriochloroform): δ 1.35 (3H, CH $_3$), 3.5 (2H, CH $_2$), 4.3 (2H, OCH $_2$), 7.0-7.6 (3H, (CH=) $_3$), and 9.4 (1H, NH).

Anal. Calcd. for C $_{12}$ H $_{11}$ Cl $_2$ F $_3$ N $_2$ O $_2$ (343.14): C, 42.0; H, 3.2; N, 8.2. Found: C, 41.8; H, 3.2; N, 7.9.

Ethyl 4,5-Dihydro-4-oxo-1,5-bis(2,3-dichlorophenyl)-7-[1H-pyrazolo[3,4-d]pyridazinyl]acetate (**3c**), and Ethyl 7-Chloro-4-(2,3-dichlorophenyl)-4,6-dihydro-3-oxo-2-(trifluoromethyl)-3H-1,4,5,10b-tetraazaaceanthrylene-6-carboxylate (**7**).

To a solution of 59.0 g (0.172 mole) of **1c** in 200 ml of dimethylacetamide was added portionwise and with stirring 6.7 g (0.28 mole) of

sodium hydride. After eighteen hours at room temperature, the reaction mixture was poured into 750 ml of ice water and extracted with methylene chloride (3 x 300 ml). The combined extracts were dried over magnesium sulfate, filtered and concentrated to 49 g of amber syrup.

Purification by silica chromatography using solvent No. 2 [10] gave 1.0 g (1%) of **7** as a light brown glassy material; ir (potassium bromide): 1740 and 1720 (C=O) cm^{-1} ; ^1H nmr (deuteriochloroform): δ 1.3 (3H, CH $_3$), 4.2 (2H, OCH $_2$), 5.5 (1H, CH), and 7.0-8.2 [6H, (CH=) $_6$]; ei/ms: *m/z* 544 (M $^+$, 3 Cl's), 525 (M $^+$ -F), 507 (M $^+$ -Cl), 469 (M $^+$ -CO $_2$ C $_2$ H $_5$), 450 (*m/z* 469-F), 434 (*m/z* 469-Cl), 365 (*m/z* 434-CF $_3$), 296, 240, 205, 173 (C $_6$ H $_3$ Cl $_2$ N $_2$) $^+$, 145 (C $_6$ H $_3$ Cl $_2$) $^+$, 109 (*m/z* 145-HCl), 69 (CF $_3$) $^+$; field desorption ms at emitter current of 18-19 ma shows the following ions (assignment, chlorine isotope abundance, and relative abundance given): 542 (M $^+$, 3 Cl's, 100%), 507 (M $^+$ -Cl, 2 Cl's, 13%), 469 (M $^+$ -CO $_2$ C $_2$ H $_5$, 3 Cl's, 8%).

Anal. Calcd. for C $_{22}$ H $_{12}$ Cl $_3$ F $_3$ N $_4$ O $_3$ (543.72): C, 48.6; H, 2.2; N, 10.3; Cl, 19.6. Found: C, 48.5; H, 2.3; N, 10.0; Cl, 20.3.

Treatment of **7** in an Abderhalden drying apparatus for 24 hours at 100° had no change on the values of the chlorine analysis.

The second fraction, 2.5 g (3%), consisted of brownish glassy **3c**; ir (potassium bromide): 1730 (C=O) cm^{-1} ; ^{13}C nmr (deuteriochloroform): δ 39.96 (CH $_2$); ei/ms: *m/z* 580 (M $^+$), 534 (M $^+$ -C $_2$ H $_5$ OH), 497 (M $^+$ -C $_2$ H $_5$ Cl $_2$ N $_2$) $^+$, 145 (C $_6$ H $_3$ Cl $_2$) $^+$, 124, 111 (C $_6$ H $_3$ Cl $^+$), 75 (*m/z* 111-HCl), 69 (CF $_3$) $^+$.

Anal. Calcd. for C $_{22}$ H $_{13}$ Cl $_3$ F $_3$ N $_4$ O $_3$ (580.18): C, 45.5; H, 2.3; N, 9.7. Found: C, 45.9; H, 2.2; N, 9.8.

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- [5a] ^1H NMR, Stadler Research Laboratories, 14954 M (Source: Aldrich Chemical Corporation Inc.).
- [5b] ^1H NMR, Stadler Research Laboratories, 18872 M (Source: Eastman Organic Chemicals).
- [6a] Carbon-13 NMR, 1977, Stadler Research Laboratories, 3187C (Source: Aldrich Chemical Corporation Inc.).
- [6b] Carbon-13 NMR, 1977, Stadler Research Laboratories, 7311C (Source: Eastman Organic Chemicals).
- [7] A general mechanism for carbon-fluorine bond labilization has been presented [8].
- [8] T. T. Sakai and D. V. Santi, *J. Med. Chem.*, **16**, 1079 (1973).
- [9] At this point, deprotonation of the CH $_2$ -group is inconsequential. At best, it may prevent internal nucleophilic attack by the N $^-$ species on the ester carbonyl carbon atom to give a pyrazolone.
- [10] Solvent system (by volume) No. 1, THF (4), hexane (96); No. 2, THF (4), ethyl acetate (16), hexane (80); No. 9, THF (25), ethyl acetate (25), hexane (50).