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(*E*)-AND (*Z*)-3-(4-CHLORO-5*H*-DITHIAZOL-5-YLIDENE)-1,1,1-TRIFLUOROPENTANE-2,4-DIONES AND THEIR ANALOGS: STEREOCHEMISTRY AND THEIR MECHANISMS OF FORMATION

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Abstract: *The reactions of Appel's salt with active methylene compounds such as 1,1,1,5,5,5-hexafluoro-2,4-pentanedione, 1,1,1-trifluoro-2,4-pentanedione, ethyl 4,4,4-trifluoro-3-oxobutanoate, 4,4,4-trifluoro-1-phenyl-1,3-butanedione, and 4,4,4-trifluoro-1-(2-naphthyl)-1,3-butanedione in the presence of pyridine in CH_2Cl_2 at room temperature afforded the corresponding 5-alkyliden-1,2,3-dithiazoles. The ratios of each stereoisomer were determined by ^{19}F NMR spectroscopy.*

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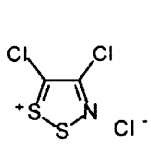
Appel had previously shown that methyl and ethyl cyanoacetates reacted with 4,5-dichloro-1,2,3-dithiazolium chloride (Appel's salt) (**1**) to give methyl and ethyl (4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)cyanoacetates (**2a**) in 68 and 76% yields, respectively.[1] The stereochemistry around the carbon-carbon double bond of **2a** has not been clearly established although the ester carbonyl group and S-1 of dithiazole



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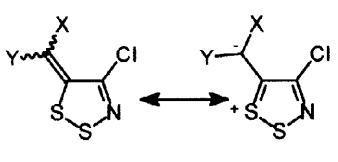

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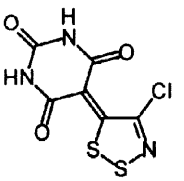
a, X = CN, Y = CO_2R
b, X = Y = CN
c, X = Y = Ph



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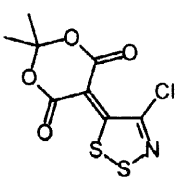

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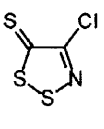

5

moiety are suggested to be *cis* presumably due to the driving force for the strong interaction with an electron-deficient S-1 atom.[2] Recently Rees et al. reported the preparation of dithiazol-5-ylidene derivatives **2b**, **3** and **4** from 4-chloro-1,2,3-dithiazole-5-thione **5** and active methylene compounds such as malonitrile, barbituric acid, and Meldrum's acid, respectively.[3] In addition, treatment of diphenyldiazomethane with **5** in benzene or dichloromethane at room temperature was reported to give the alkene **2c**.[3] All of the dithiazol-5-ylidene derivatives **2b-c**, **3**, and **4** have identical groups at one of the carbons of the carbon-carbon double bond. Consequently the stereoelectronic effects involved in the formation of the carbon-carbon double bond cannot be analyzed with these olefins having two identical groups, in spite of the observation that the ^1H NMR spectrum of **2c** appeared to show that each peak is doubled, indicating that the two phenyl groups of **2c** are in different environments.

In order to understand the stereoelectronic effects involved in the formation of dithiazol-5-ylidene derivatives, we prepared new, unsymmetrically substituted dithiazol-5-ylidene derivatives and determined the ratios of each stereoisomers. We wish to communicate the results herein.

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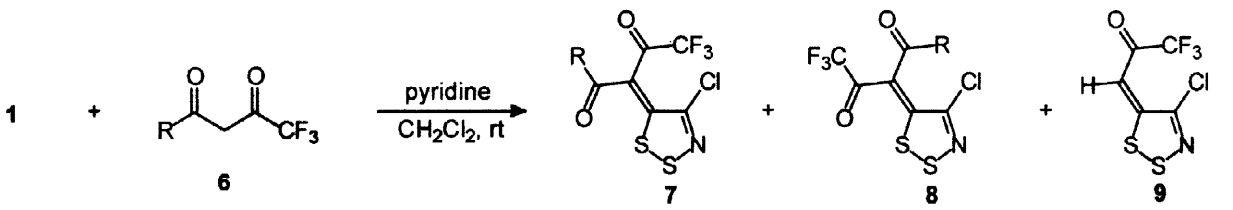
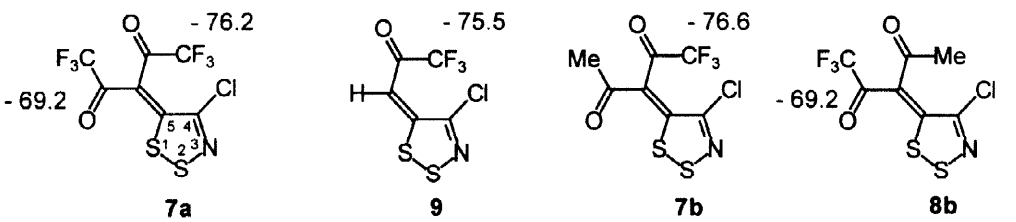
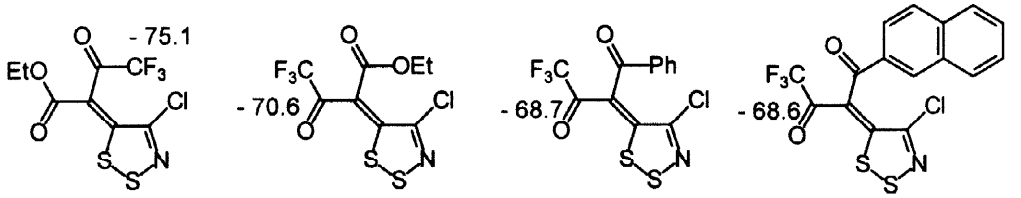


Scheme 1

After some trial, it was found that the reactions of **1** with 1,3-dicarbonyl compounds **6** having at least one trifluoromethyl group bonded to a carbonyl carbon proceeded smoothly to give new 5-alkyliden-1,2,3-dithiazoles **7-9**, albeit in low yields (Scheme 1).[4] When 1,1,1,5,5,5-hexafluoro-2,4-pentanedione (**6a**) (R = CF_3) was used, 3-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-1,1,1,5,5,5-hexafluoro-2,4-pentanedione (**7**) (R = CF_3) and 3-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-1,1,1-trifluoro-2-propanone (**9**) were isolated in 18 and 44% yields, respectively. With 1,1,1-trifluoro-2,4-pentanedione (**6b**) (R = Me), a mixture of stereoisomers **7b** and **8b** (21%; **7b**:**8b** = 85:15), which was inseparable by either column chromatography (silica gel, 230-400 mesh ASTM) or HPLC (μPorasil, 10 μm, 7.8 × 300 mm i.d., CH_2Cl_2, flow rate = 0.8 mL/min) was isolated. With ethyl 4,4,4-trifluoro-3-oxo-butanoate (**6c**) (R = EtO), a mixture of **7c** and **8c** (52%; **7c**:**8c** = 10:90) was isolated. Interestingly, the reactions with aroyl trifluoroacetylmethanes **6d** (R = Ph) and **6e** (R = 2-naphthyl) under the same reaction conditions gave only single stereoisomers **8d** (34%) and **8e** (18%), respectively.

The ratios of each stereoisomer were determined by ^{19}F NMR spectroscopy. Their ^{19}F NMR chemical shifts are shown below:





The ^{19}F NMR spectrum of **7a** exhibited two quartets at -69.2 (J = 5.5 Hz) ppm and -76.2 (J = 5.5 Hz) ppm. The quartets may be attributable to fluorine-fluorine long range coupling through three sp^2 hybridized carbon atoms (2 C=O and 1 C=C) between two CF_3 groups. Since the carbonyl oxygen close to S-1 would be expected to interact with S-1,[2, 3] the carbonyl carbon would be more electron deficient than the other carbonyl carbon. Consequently, the ^{19}F NMR signals of CF_3 bonded to the electron deficient carbonyl carbon would appear more down field (-69.2 ppm). Based on this ^{19}F NMR spectral data, one could determine the ratios of each stereoisomer of other compounds. The structural assignment based on the ^{19}F NMR spectroscopic data was further confirmed by *X*-ray crystallography of **8d**, whose ORTEP drawing is shown in Fig. 1.[5]

Fig. 1 shows that the carbonyl oxygen of the $CF_3C=O$ group is indeed close to the S-1 atom, whereas the carbonyl oxygen of the PhC=O group is oriented toward the opposite direction to that of the $CF_3C=O$ group. The benzoyl phenyl group is oriented to avoid possible repulsive interactions arising from the close proximity between the ortho hydrogens of the phenyl group and the chlorine atom at C-4. On the other hand, if the phenyl group is swapped with a CF_3 group, a severe electronic repulsion as well as unfavorable steric interactions between two electonegative fluorine and chlorine atoms would be expected. Consequently, only **8d** is formed. Compound **8e** was not stable enough to purify by recrystallization. However, ^{13}C NMR spectrum of crude product indicated the formation of the only single isomer **8e**. The stereochemistry of **8e** can be rationalized on the same grounds as for **8d**. The predominant formation of **8c** may be attributable to a less electronic repulsion between the chlorine atom at C-4 and the carboethoxy oxygen which may be an electron deficient center due to delocalization of nonbonding electrons into the ester carbonyl group. In the case of a mixture of **7b** and **8b**, **7b** would be a major isomer if the steric and electronic repulsion effects foregoing were important. However, this is not the case. The electron-donating effect of a methyl group increases the electron density on the oxygen atom of the acetyl group, which results in the strong interaction between S-1 and the acetyl oxygen atoms to give **7b** as a major product.

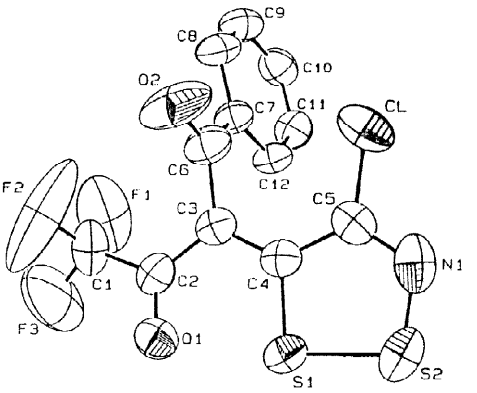
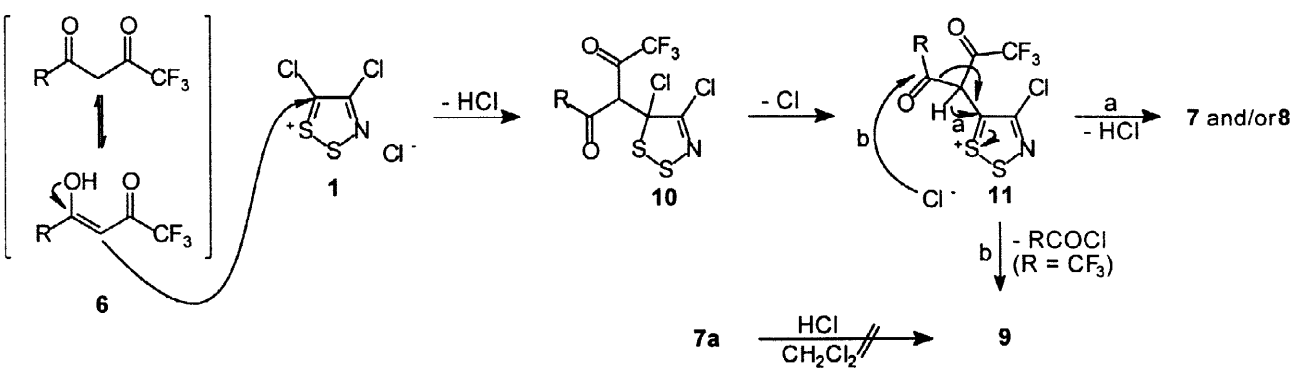


Figure 1. ORTEP drawing of **8d**

Compound **7a** is not likely a precursor of **9** in view of the quantitative recovery of **7a** from the reaction of **7a** with hydrogen chloride gas which is evolved during the reaction in CH_2Cl_2 at room temperature.

The mechanisms for the formation of compounds **7-9** may be rationalized by nucleophilic attack of the enolic carbon of **6** to C-5 of **1** to give an intermediate **10**, which then extrudes a chlorine atom to give a new dithiazolium ion **11**. Deprotonation, followed by electron migration (path a), gives compounds **7** and/or **8**. Alternatively, nucleophilic attack of a chloride to the carbonyl carbon, which would be more electron-deficient than the alternative one because of the interaction with electron deficient S-1 (path b), followed by elimination gives rise to compound **9** (Scheme 2), in which a trifluoroacethyl group and chlorine atom are syn.



Scheme 2

In conclusion, the stereochemistry of dithiazol-5-ylidene derivatives formed from the reactions of Appel's salt with 1,3-dicarbonyl compounds having at least one trifluoromethyl group bonded to a carbonyl carbon is determined by the extent of the attractive interaction between the carbonyl oxygen and an electron-

deficient S-1 atom as well as an electronic and steric repulsion arising from a trifluoromethyl group and a chlorine atom at C-4 of the dithiazole moiety.

Acknowledgment. The authors are grateful to the Basic Sciences Research Institute Program, Ministry of Education (BSRI-97-3417) for financial support.

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2. Rees, C. W. *J. Heterocycl. Chem.* **1992**, *29*, 639-651.
3. Emayan, K.; English, R. F.; Koutentis, P. A.; Rees, C. W. *J. Chem. Soc., Perkin Trans. 1*, **1997**, 3345-3349.
4. **Typical procedure**: To a suspension of **1** (6.70 g, 32.1 mmol) in CH_2Cl_2 (150 mL) was added a solution of 1,1,1,5,5,5-hexafluoro-2,4-pentanedione (6.62 g, 31.8 mmol) in CH_2Cl_2 (20 mL), followed by dropwise addition of pyridine (74.2mmol) in CH_2Cl_2 (30 mL) for 1h. The mixture was stirred for 30 min at room temperature. After removal of the solvent *in vacuo*, the residue was chromatographed on a silica gel (3 x 17 cm, 230-400 mesh) column. Elution with *n*-hexane gave a small amount of **5**. Elution with a mixture of *n*-hexane and CH_2Cl_2 (3:1) gave 3-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-1,1,1-trifluoro-2-propanone (**9**) (3.45 g, 44%): mp 75-77 °C (*n*-hexane-CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.57 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 107.4, 117.7 (q, J_{CF} = 286.5 Hz, CF_3), 144.7 (C-4), 161.6 (C-5), 176.8 (q, J_{CCF} = 37.0 Hz, C=O); ^{19}F NMR ($CDCl_3$, 188 MHz) δ -75.5; IR (KBr) 1600, 1494, 1434, 1356, 1258, 1190, 1149, 1091, 925, and 797 cm^{-1}; MS m/z 247 (M^+, 69), 254 (73), 212 (6.3), 178 (100), 85 (64). *Anal.* Calcd for $C_5HClF_3NOS_2$: C, 24.25; H, 0.41; N, 5.66; S,25.89. Found: C, 24.17; H, 0.39; N, 5.61; S, 25.73. Elution next with the same solvent mixture (2:1) gave 3-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-1,1,1,5,5,5-hexafluoro-2,4-pentanedione (**7a**) (1.96 g, 18%): mp 77-79 °C (*n*-hexane-CH_2Cl_2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 114.8, 115.8 (q, J_{CF} = 292.1 Hz, CF_3), 117.6 (q, J_{CF} = 286.6 Hz, CF_3), 146.2 (C-4), 164.3 (C-5) 172.4 (q, J_{CCF} = 37.5 Hz, C=O), 182.2 (q, J_{CCF} = 38.5 Hz, C=O); ^{19}F NMR ($CDCl_3$, 188 MHz) δ -69.2 (q, J = 5.5 Hz), -76.2 (q, J = 5.5 Hz): IR (KBr) 1731, 1586, 1398, 1285, 1211, 1179, 1152, 1048, and 850 cm^{-1}: MS m/z 343 (M^+, 32), 274 (100), 224 (60). *Anal.* Calcd for $C_7F_6NO_2S_2$: C, 24.47; N, 4.08; S, 18.66. Found: C, 24.42; N, 4.01; S, 18.55.
5. Crystal data for **8d**: $C_{12}H_5ClF_3NO_2S_2$, M = 351.74, T = 293(2) K, Colorless crystal, 0.3 x 0.4 x 0.4 mm, Monoclinic, Space group P_{2_1}/C (No. 14), a = 12.064(2), b = 5.752(4), c = 19.586(3) Å, α = 90.00(2), β = 93.87(2), γ = 90.00(2) °, U = 1355.9(10) Å^3, Z = 4, D_C = 1.723 gcm^{-3}, F(000) = 704, μ = 0.626 mm^{-1}, R = 0.0793, WR^2 = 0.2153 (190 parameters). The data were collected on an Enraf-Nomius CAD 4 diffractometer using graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å). Refinements were carried out by full least-squares techniques. Atomic scattering factors were taken from International Tables for X-ray crystallography, Vol Ⅳ, 1974. All calculations and drawings were performed using a Micro VAX Ⅱ computer with the SPD system.

   Selected Bond lengths [Å] and angles [deg] for **8d**: S(1)-C(4) 1.731 (6), S(1)-S(2) 2.063 (2), S(2)-N(1) 1.618 (7), N(1)-C(5) 1.304 (9), C(4)-C(5) 1.458 (8), C(3)-C(4) 1.383 (8), C(2)-C(3) 1.432 (8), C(3)-C(6) 1.531 (8), O(1)-C(2) 1.232 (7), O(2)-C(6) 1.214 (8), C(4)-S(1)-S(2) 93.9 (2), N(1)-S(2)-S(1) 97.7 (2), C(5)-N(1)-S(2) 116.5 (5), N(1)-C(5)-C(4) 120.9 (6), C(5)-C(4)-S(1) 110.6 (4), C(3)-C(4)-S(1) 120.5 (4), C(4)-C(3)-C(2) 116.2 (5), C(4)-C(3)-C(6) 123.5 (5), O(1)-C(2)-C(3) 121.9 (5), O(2)-C(6)-C(3) 117.2 (5).