Journal of Fluorine Chemistry, 48 (1990) 123–131

Received: August 23, 1989; accepted October 25, 1989

REGIOSELECTIVE SYNTHESIS OF 1-METHYL-3-HYDROXY-5-PERFLUOROALKYLPYRAZOLES BY THE ADDITION OF METHYLHYDRAZINE TO PERFLUOROALKYLACETYLENIC ESTERS

BRUCE C. HAMPER*

Monsanto Agricultural Company, A Unit of Monsanto Company, 800 N. Lindbergh Blvd., St. Louis, Missouri 63167 (U.S.A.)

SUMMARY

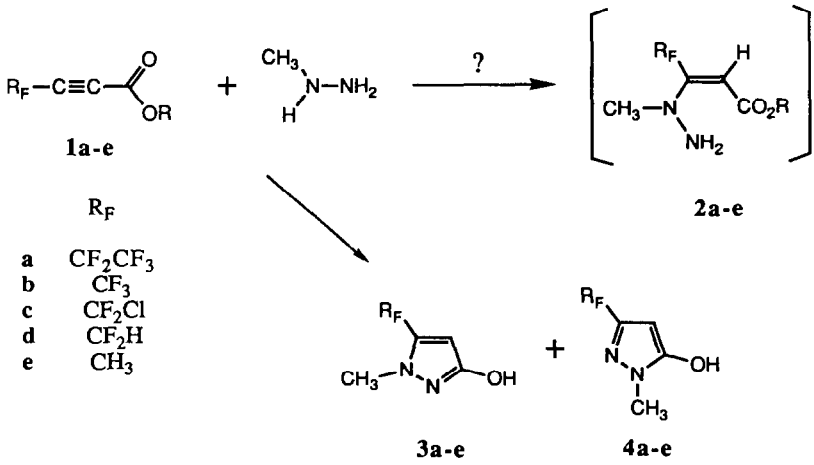
A regioselective route to 1-methyl-3-hydroxy-5-perfluoroalkyl(1H,3H)pyrazoles has been developed. Treatment of perfluoroalkylacetylenic esters with methylhydrazine in methanol-water at 0°C or in methylene chloride at low temperature leads to 1-methyl-3-hydroxy-5-perfluoroalkyl(1H,3H)pyrazoles in a regioselective manner. Structural assignments of the regioisomers are based on ^{13}C nmr chemical shifts, long range carbon-fluorine and carbon-proton coupling. The effect of the acetylene structure on the regioselectivity of the reaction is discussed.

INTRODUCTION

Hydroxypyrazoles or the tautomeric pyrazolinones [1] have been investigated as pharmaceuticals, dyestuffs and intermediates for the preparation of biologically active compounds [2]. Although the addition of alkylhydrazines to β-ketoesters can, in principle, afford two isomeric products, a 1-alkyl-5-hydroxypyrazole **4** is usually the major or sole isomeric product from this condensation reaction [3]. It is also possible to prepare hydroxypyrazoles from acetylenic esters (dimethylacetylene dicarboxylate or ethyl phenylpropiolate) and alkyl- or arylhydrazines, however, these processes require either strongly acidic [4] or strongly basic [5] conditions and frequently afford low yield mixtures of the possible isomeric products [6]. Treatment of alkylacetylenic esters with alkyl hydrazines has been reported to afford only 1-alkyl-5-hydroxypyrazoles **4** [7]. Recently, J. Fabron et al., have

0022-1139/90/$3.50

reported the regioselective preparation of 3-amino(1H,3H)pyrazoles, the amino analog of hydroxypyrazoles **3**, from alkylhydrazines and perfluoroalkylacetylenic nitriles [8].



For our synthetic efforts, we required reasonable quantities of both regioisomeric perfluoro- and perhaloalkylpyrazoles (R_F is a perfluoro- or perhaloalkyl group) **3** and **4**. The 5-hydroxy isomer **4b** ($R_F = CF_3$) had previously been prepared by the condensation of ethyl trifluoroacetoacetate and methyl hydrazine [11] and, more recently, it has been shown that this reaction affords a mixture of regioisomeric **3b** and **4b** [12]. While by careful control of the conditions the minor isomer **3b** can be isolated from this reaction in 25% overall yield, we wished to find a more efficient route to this regioisomer.

RESULTS AND DISCUSSION

In the course of exploring the chemistry of perfluoroalkylacetylenic esters **1** [9], we discovered that addition of methylhydrazine under neutral conditions provided regioselective formation of 1-methyl-3-hydroxypyrazoles **3** . Treatment of **1** ($R_F = CF_3$) with methylhydrazine in methanol-water (1:1) at 0°C resulted in the almost exclusive formation of hydroxypyrazole **3b** ($R_F = CF_3$). The crude reaction contained a 95:5 mixture of regioisomers as determined by ^{19}F NMR and ^{1}H NMR. If the same reaction is carried out in methylene chloride at -78°C, a 70:30 mixture of **3b** and **4b** is obtained. Initially, we expected the reaction to proceed by Michael addition of the hydrazine to the acetylene to afford an isolable enehydrazine **2** or the tautomeric hydrazine imine intermediate, analogous to the addition of

alkyl hydrazines to dimethylacetylene dicarboxylate [10]. If such an intermediate forms, it readily cyclizes under the reaction conditions to afford pyrazoles directly, for even at -78°C we were unable to isolate or detect these intermediates. Trans addition of the hydrazine would give **2** which, due to the cis relationship between the carboxylate and the hydrazine groups, would be expected to readily cyclize to afford hydroxypyrazoles **3**.

TABLE 1

Addition of Methylhydrazine to Acetylenic esters **1**

Entry	R_F	Ratio 3:4[a]	Ratio 3:4[b]	% Yield 3[a]
a	CF_2CF_3	98:2	98:2	98
b	CF_3	90:10	70:30	80
c	CF_2Cl	95:5	95:5	79
d	CF_2H	25:75	55:45	22
e	CH_3	0:100	0:100	85[c]

[a] Reactions were carried out in methanol-water (1:1) at 0°C. [b]Reactions were carried out in methylene chloride at -78°C. [c]Yield of **4e**.

The structure of the acetylene can have a marked effect on the regiochemical result of this reaction as shown in Table 1. In the case of the reaction of pentafluoroacetylenic ester **1a** with methylhydrazine (entry a), only one regioisomer, **3a**, can be detected. As the size and electron withdrawing ability of the R_F group decreases, the amount of isomer **4** increases. Thus, for acetylene **1b** ($R_F = CF_3$) using methylene chloride as the reaction solvent (entry b) a 70:30 mixture of **3b** and **4b** is obtained, for difluoromethylacetylenic ester **1d**, a nearly 1:1 ratio of isomers is obtained and in the case of the non-fluorinated ethyl tetrolate **1e**, only **4e** is obtained. Thus, in order to obtain the 3-hydroxypyrazole isomer **3** as the major product it is desirable to have a sterically large and electron withdrawing group such as CF_3 at the terminal position of the acetylene.

The reaction of methylhydrazine with perfluoroacetylenic esters affords the greatest experimental convience when methanol-water is employed as the solvent. Typically, the desired isomer **3** crystallizes from the reaction mixture and can be collected by filtration. In most cases, the small amount of minor isomer **4** is effectively removed since it is more soluble

in the reaction mixture than **3**. In cases where significant quantities of both isomers were obtained (i.e., entry d), separation was achieved by extraction of an organic solution with aqueous sodium bicarbonate which removes the more acidic isomer **4**. Acidification of the aqueous wash leads to recovery of **4**. The reaction solvent employed can have a pronounced effect on the product ratios (entries b and d). For the trifluoromethyl substituted acetylene **1b**, a greater preference for pyrazole **3b** is observed in water-methanol compared to methylene chloride, however, for the difluoromethyl acetylene, there is a reversal of this trend and less **3d** is obtained in water-methanol. In the case of acetylenes **1a** and **1c**, the change in reaction solvent does not seem to effect product composition.

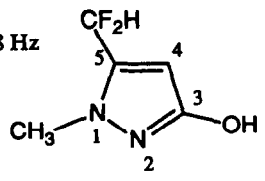
The reaction temperature can also have a profound effect on product composition as shown in Table 2. In these studies, the regioselectivity of the addition of methylhydrazine to acetylenes **1b** and **1d** ($R_F = CF_3$ and CF_2H, respectively) are compared. For reactions carried out in methylene chloride, pyrazoles **3b** and **3d** are preferred at the lower temperatures. Thus, while at room temperature a 48:52 ratio of **3b** and **4b** is obtained (entry 3), at -78°C a ratio of 71:29 in which **3b** is the major product is observed (entry 1). A similar trend is observed for pyrazoles **3d** and **4d**, however, at all temperatures investigated, **4d** is the major product.

TABLE 2

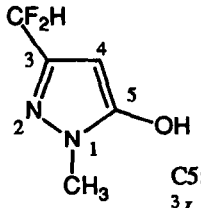
Effect of Reaction Conditions on the Regioisomeric Ratio of **3:4**

Entry	R_F	Solvent Temperature T(°C)	Ratio of **3:4**
1	CF_3	CH_2Cl_2, -78°C	71:29
2	CF_3	CH_2Cl_2, -20°C	63:37
3	CF_3	CH_2Cl_2, 25°C	48:52
4	CF_3	MeOH/H_2O, 0°C	94:6
5	CF_2H	CH_2Cl_2, -78°C	30:70
6	CF_2H	CH_2Cl_2, -20°C	10:90
7	CF_2H	CH_2Cl_2, 25°C	5:95
8	CF_2H	MeOH/H_2O, 0°C	35:65

C5: tm
$^2J_{CF}$ = 28 Hz



3d



4d

C5: qd
$^3J_{CH}$ = 2.5 Hz
$^2J_{CH}$ = 2.5 Hz

Structural assignments of **3b** and regioisomer **4b** have been previously determined by L. Lee et al., by spectral comparison of the long range carbon-proton and carbon-fluorine coupling [11]. For **3b** and **3c** we observed in the ^{13}C nmr four bond carbon-fluorine coupling between the fluorine nuclei and the N-methyl group of 1.0 and 2.3 Hz respectively. The corresponding ^{13}C nmr resonance of the N-methyl group of regioisomer **4b** does exhibit some line broadening (half height line width, 1.5 Hz) however, no coupling to the fluorine nuclei is observed. We were unable, however, to detect this coupling to the N-methyl group for pyrazoles **3a** and **3d** and in these cases the line shape indicates that the coupling must be smaller than 1.0 Hz. Thus long range carbon-fluorine coupling alone is not indicative of regiochemical structure. For the pair of regioisomers **3d** and **4d**, we have compared carbon-proton coupling between the protons of the N-methyl group and the C5 carbon of the pyrazole ring. For the proton coupled spectrum, the C5 resonance of **4d** appears as a quartet of doublets indicating coupling to the ring proton (H4) and to the N-methyl group. Likewise, **3d** exhibits a triplet for C5 in the proton decoupled spectrum due to fluorine coupling to the CF_2H group and a triplet of multiplets in the coupled spectrum. The multiplet must arise from coupling to the ring proton, the CF_2H proton and the N-methyl group. In the absence of coupling to the N-methyl group, this resonance would appear as a much simpler triplet of doublet of doublets. Due to the complexity of this multiplet, it was not possible to measure the carbon-proton coupling constants. None the less, for the **3d** isomer, carbon-proton coupling indicates that the N-methyl group is closest to the pyrazole ring carbon bearing the R_F group (C5) and for **4d**, it is closest to the ring carbon bearing the OH group (C5). (Due to the convention of numbering for the pyrazole ring system, the C5 carbon is different for the two regioisomeric pyrazoles).

We have, thus, developed a straightforward route for the preparation of 1-methyl-3-hydroxy-5-perfluoroalkylpyrazoles **3** from readily available acetylenes and methylhydrazine. This regioisomer is the opposite of that obtained from similar condensation of β-ketoesters with alkylhydrazines, experimental conditions are straightforward and the desired isomers **3** are

obtained by either filtration of the reaction mixture or concentration and separation of the isomers by extraction with aqueous bicarbonate. We are currently exploring the mechanistic details of this reaction.

EXPERIMENTAL

All reactions involving air or moisture-sensitive reagents and all atmospheric distillations were run under a nitrogen atmosphere. The solvents and reactants were reagent grade. Anhydrous solvents were obtained from Aldrich (Sureseal bottles). All melting points were recorded on a capillary melting point apparatus and are uncorrected. Gas chromatographic analysis was preformed using a 30 meter megabore column containing 1.5 μ DB-1. A temperature program was employed which had an initial temperature of 100°C with a hold time of 1 min. followed by an increase of 25°C/min. and a final temperature of 250°C. Proton and ^{13}C NMR resonances were obtained at 400 MHz and 75 MHz, respectively, and are reported relative to the internal tetramethylsilane in ppm. The ^{19}F resonances were obtained at 56.46 MHz and are reported relative to trichlorofluoromethane using trifluorotoluene (-63.763ppm) as an external coaxial standard. Compound **4b** was prepared by the method of L. Lee et al. [12].

General Procedure for the Preparation of 1-Methyl-3-hydroxy-5-perhaloalkylpyrazoles. 1-Methyl-5-(pentafluoroethyl)-1H-pyrazol-3-ol (3a)

To an efficiently stirred solution of methylhydrazine (5.3mL, 100mmol) in 100mL of methanol-water (1:1) cooled in an ice-acetone bath was added dropwise ethyl pentafluoro-2-pentynoate **1a** (25.6 g, 118 mmol) at a rate such that the reaction temperature was maintained between 0°C and 10°C. After addition was complete, the reaction was allowed to stir overnight and subsequently diluted with 100 mL of water. The crystalline product was collected, washed three times with cold water and dried by suction to afford 21.0 g (97%) of **3a** (mp 128-130.5°C, CG t_r = 1.52 min., 97%). An analytical sample was prepared by recrystallization from methylcyclohexane to afford a white, crystalline solid: mp 132.5-133.5°C; ^1H NMR (d^6-acetone) δ 3.80 (t, 3 H), 6.03 (t, 1 H), 9.43 (brs, 1 H); ^{13}C NMR (d^6-acetone) δ 38.5, 94.8 (t, C4), 111.0 (tq, CF_2, $^1J_{CF}$ = 251 Hz, $^2J_{CF}$ = 40 Hz), 119.6 (qt, CF_3, $^1J_{CF}$ = 285 Hz, $^2J_{CF}$ = 38 Hz), 130.2 (t,C5), 161.1 (C3); ^{19}F NMR (d^6-acetone) δ -85.0 (t, 3 F, $^4J_{FF}$ = 2.6 Hz), -111.0 (m, 2 F); MS(EI) 216 (M^+, 96), 147 (-CF_3, 100), MS(CI) 217 (M+1,100). Anal. Calcd. for $C_6H_5N_2OF_5$: C, 33.35; H, 2.33; N, 12.96. Found: C, 33.47; H, 2.37; N, 12.98%.

1-Methyl-5-(trifluoromethyl)-1H-pyrazol-3-ol (3b)

The white precipitate obtained from the reaction mixture (100mmol, carried out in 50 ml of 1:1 methanol-water) was collected and washed with water to afford 12.3 g (74.2 %, GC t_r = 1.31 min, 95%) of **3b**. A small sample was recrystallized from methylcyclohexane to afford a white, crystalline solid: mp 130.0-130.5°C; ^{1}H NMR (d^6-acetone) δ 3.83 (q, 3 H), 6.09 (q, 1 H), 9.79 (brs, 1 H); ^{13}C NMR (d^6-acetone) δ 37.6 (q), 93.1 (q, C4), 120.7 (q, CF_3, $^1J_{CF}$ = 268 Hz), 132.7 (q, C5), 161.0 (C3); ^{19}F NMR (d^6-acetone) δ -61.4; MS(EI) 166 (M^+,100), 165 (38); MS(CI) 167 (M+1, 100). Anal. Calcd. for $C_5H_5N_2OF_3$: C, 36.16; H, 3.03; N, 16.87. Found: C, 36.18; H, 3.04; N, 16.86%.

5-(Chlorodifluoromethyl)-1-methyl-1H-pyrazole-3-ol (3c)

The tan solid obtained from the reaction mixture (100mmol, carried out in 50 ml of 1:1 methanol-water) was collected, washed with water and recrystallized from methylene chloride-hexane to afford 9.8 g (53.7%, GC t_r = 2.41 min) of **3c**. Recrystallization from methylcyclohexane afforded a white, crystalline solid: mp 124.0-124.5°C; ^{1}H NMR (d^6-acetone) δ 3.72 (t, 3 H), 5.99 (s, 1 H), 9.60 (brs, 1 H); ^{13}C NMR (d^6-acetone) δ 37.8 (t), 92.6 (t, C4), 121.6 (t, CF_2Cl, $^1J_{CF}$ = 285 Hz), 137.5 (t, C5), 160.6 (C3); ^{19}F NMR (d^6-acetone) δ -48.0; MS(EI) 182 (M^+, 42), 147 (-Cl, 100); MS(CI) 183 (M+1, 100). Anal. Calcd. for $C_5H_5N_2OF_2Cl_1$: C, 32.90; H, 2.76; N, 15.34. Found: C, 32.99; H, 2.78; N, 15.32%.

5-(Difluoromethyl)-1-methyl-1H-pyrazol-3-ol (3d) and 3-(Difluoromethyl)-1-methyl-1H-pyrazol-5-ol (4d)

A stirred solution of methylhydrazine (4.0 mL, 75 mmol) in 80 mL of CH_2Cl_2 was cooled in a dry ice-acetone bath to -78°C and treated dropwise with a solution of acetylene **1d** (10.15 g, 68.5 mmol) in 20 mL of CH_2Cl_2. The resultant reaction mixture was stirred overnight and subsequently concentrated in vacuo to afford 8.63 g (85.1%) of a clear, orange-yellow oil. ^{19}F NMR showed a mixture of two regioisomers: ^{19}F NMR (d^6-acetone) δ -111.9 (d,55%), -114.9 (d,45%). The oil was dissolved in ethyl acetate and washed with 10% aq. $NaHCO_3$. The organic layer was washed with 1N HCl and the acidic wash extracted three times with ethyl acetate. The combined organic extracts were dried and concentrated to afford 2.2 g (21.7%) of **3d**. An analytical sample was prepared by recrystallization from CCl_4 to afford a

white, crystalline solid: mp 115-119°C; ^{19}F NMR (d^6-acetone) δ -114.9 (d,$^2J_{FH}$=54 Hz); ^{1}HNMR (d^6-acetone) δ 3.78 (s,3H), 5.90 (s,1H), 7.03 (t,1H,$^2J_{HF}$=54 Hz), 10.05 (br s,1H); ^{13}CNMR (d^6-acetone) δ 37.1 (CH_3), 92.0 (C3), 109.9 (CF_2H,$^1J_{CF}$=234 Hz), 137.5 (C5,$^2J_{CF}$=28 Hz), 161.4 (C3). Anal. Calcd for $C_5H_6N_2O_1F_2$: C, 40.55; H, 4.08; N, 18.91. Found: C, 40.47; H, 4.11; N, 18.86%.

The aqueous 10% $NaHCO_3$ wash was acidified with conc. HCl and extracted three times with ethyl acetate. The combined organic layers were dried and concentrated in vacuo to afford 3.5 g (34.5%) of a reddish solid, **4d.** An analytical sample was obtained by recrystallization from $CHCl_3$ to afford a pinkish, white solid: mp 139.0-139.5°C; ^{19}F NMR (d^6-acetone) δ -111.9 (d,$^2J_{FH}$=55 Hz); ^{1}H NMR (d^6-acetone) δ 3.65 (s,3H), 5.66 (s,1H), 6.60 (t,1H,$^2J_{HF}$=55 Hz), 10.4 (br s,1H); ^{13}C NMR (d^6-acetone) δ 33.8 (CH_3), 84.2 (C4), 112.9 (CF_2H,$^1J_{CF}$=231 Hz), 145.2 (C3,$^2J_{CF}$=29 Hz), 153.7 (C5). Anal. Calcd for $C_5H_6N_2O_1F_2$: C, 40.55; H, 4.08; N, 18.91. Found: C, 40.39; H, 4.11; N, 18.81%.

1,3-Dimethyl-1H-pyrazol-5-ol (4e)

To a stirred solution of methylhydrazine (5.3 mL, 100mmol) in 25 mL of methylene chloride cooled in an ice water bath was added ethyl 2-butynoate (11.4 g, 102 mmol) dropwise such that the reaction temperature was maintained between 0°C and 10°C. After stirring overnight, the mixture was concentrated in vacuo and the resultant solid recrystallized from methylene chloride-hexanes to afford 9.72 g (85.3%) of a tan solid: mp 113.0-115.0°C (lit. mp 115-116°C); ^{1}H NMR (d^6-DMSO) δ 2.00 (s, 3 H), 3.38 (s, 3 H), 5.11 (s, 1 H), 10.64 (brs, 1 H); ^{13}C NMR (d^6-DMSO) δ 13.6, 32.0 (N-CH_3), 87.0 (C4), 145.5 (C3), 155.3 (C5); MS (EI), *m/z* (relative intensity) 112 (M^+, 100), 69 (36), 41 (51); MS (DP/CI isobutane), *m/z* 113 (M+1).

ACKNOWLEDGEMENTS

We are grateful for the discussions and suggestions provided by G.Srouji, B.Gaede, K.Moedritzer and P.Charimilund, the assistance in obtaining nmr spectral data provided by W. Hutton and G. Leo and the encouragement provided by G.A.Dutra.

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