SYNTHESIS OF ^{13}C-LABELLED AND DOUBLY LABELLED (^{13}C, ^{2}H) 1,2,3-THIADIAZOLES. PRECURSORS TO ISOTOPICALLY LABELLED THIIRENES.

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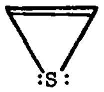
SUMMARY

The incorporation of carbon-13 and deuterium in the 1,2,3-thiadiazole framework is described.

Key Words: Carbon-13, Deuterium, 1,2,3-Thiadiazole.

INTRODUCTION

For characterization of matrix-isolated thiirene **1** and the determination of its mechanism of formation, we required ^{13}C-labelled and doubly labelled (^{13}C and ^{2}H) 1,2,3-thiadiazoles. We have previously shown that 1,2,3-thiadiazoles



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are photochemically converted to thiirenes.[1]

The ^{13}C-labelled molecules were synthesized by the following general scheme involving condensation of the requisite carbonyl compound to form a hydrazone which was then treated with thionyl chloride to give the thiadiazoles.

4-carboxy-4-^{13}C-1,2,3-thiadiazole (**2**) prepared in the above manner could be decarboxylated to yield 4-^{13}C-1,2,3-thiadiazole (**3**). 4-deuterio-4-^{13}C-1,2,3-thiadiazole (**4**) was prepared by decarboxylating the d_1-carboxylic acid obtained from exchange of(**2**)with deuterium oxide.

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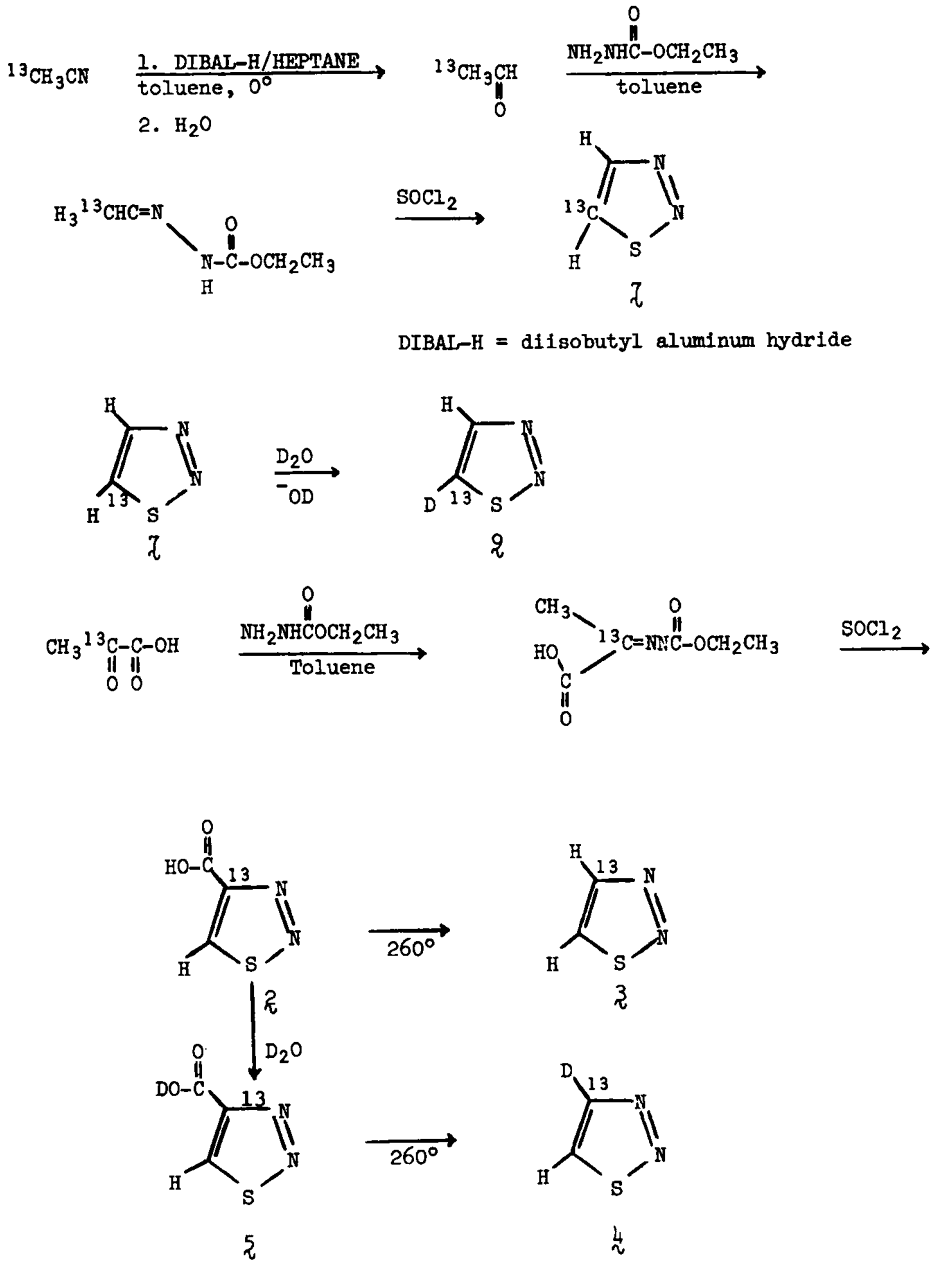
SCHEME



DIBAL-H = diisobutyl aluminum hydride

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EXPERIMENTAL

4-^{13}C-1,2,3-Thiadiazole (**3**)[2]

The sodium salt of pyruvic acid-2-^{13}C (1.0 g, 0.009 mol, Merck, Sharpe and Dohme, 90-Atom % C-13) was placed in a 50 ml round bottom flask with a stirring bar. Two ml of concentrated hydrochloric acid were added with stirring and the resulting solution was extracted with 15 ml of ethyl ether. Carboethoxyhydrazine (1.2 g, 0.013 moles) in three ml of warm toluene was pipetted with stirring into the ether solution containing the free pyruvic acid. An oil separated immediately but stirring was continued for 2.5 hours. Most of the solvent was decanted and the remainder was removed under vacuum. Two ml of thionyl chloride (large excess) were added to the α-N-carboethoxyhydrazonopropionic acid-2-^{13}C and the mixture was stirred for four hours. A precipitate formed, which was collected by suction filtration and washed with ethyl acetate. By this procedure one obtains 4-carboxy-4-^{13}C-1,2,3-thiadiazole (0.53 g, 44% of theoretical based on sodium pyruvate-2-^{13}C) ν_{max}: 3090, 1638, 1428 and 1209 cm^{-1}. 4-Carboxy-4-^{13}C-1,2,3-thiadiazole (**2**) was immersed in a Wood's metal bath preheated to 260°. A vigorous reaction ensued producing a liquid product. The tube was opened and the contents were extracted with 0.5 ml of deuteriochloroform. Purification by VPC on an SE-30 column at 90° (flow rate = 60 CC/min, retention time: 2.5 min) yielded ∿ 74 mg (58% of theoretical) of 4-^{13}C-1,2,3-thiadiazole (**3**) which was characterized from the following spectral features: ν_{max}: 3142 (w) cm^{-1}, 1300 (w) cm^{-1}, 1230 (m) cm^{-1}, 1225 (m) cm^{-1}, 1095 (w) cm^{-1}, 1035 (w) cm^{-1}, 869 (s) cm^{-1}, 755 (m) cm^{-1}, 745 (m) cm^{-1} and 532 (w) cm^{-1}. δ (CDCl$_3$): 9.05 (1H, $J_{^{13}C-H}$ = 201 Hz, J_{H-H} = 3.2 Hz), 8.91 (1H, $J_{^{13}C-H}$ = 8.3 Hz,

J_{H-H} = 3.2 Hz). λ_{max} (H_2O) 248 nm (ε = 2400), 219 nm (2270). m/e: 87 (26.3%), 86 (2.9%), 59 (100%).

4-Deuterio-4-^{13}C-1,2,3-Thiadiazole (4)

4-Carboxy-4-^{13}C-1,2,3-thiadiazole (2) (0.1 g, 7 x 10^{-4} moles) was dissolved in 100 g of deuterium oxide. The deuterated water was removed under vacuum with a minimum exposure of the solution to the air. The resulting 4-deuterio-carboxy-4-^{13}C-1,2,3-thiadiazole (5), ν_{max}: 3090 (s), 2220 (broad, m), 2050 (broad, m), 1638 (s) cm^{-1}, was transferred to a glass tube which was evacuated, filled with N_2 and then sealed. The end of the tube containing 5 was immersed in a Wood's metal bath preheated to 260°. A clear liquid was formed as the violent decarboxylation reaction ensued. The tube was allowed to cool, and then it was opened and its contents extracted with 0.25 ml of $CDCl_3$. The resulting 4-deuterio-4-^{13}C-1,2,3-thiadiazole (4) was purified by VPC on an SE-30 column at 90° producing ∿ 38 mg (4.3 x 10^{-4} mole, 62% of theoretical) of a substance displaying the following spectral characteristics: ν_{max}: 3143 cm^{-1} (w), 2430 cm^{-1} (w), 1247 cm^{-1} (m), 1225 cm^{-1} (s), 912 cm^{-1} (m), 800 cm^{-1} (s). δ ($CDCl_3$): 8.91 (1H, $J_{^{13}C-CH}$ = 8.3 Hz).

5-Deuterio-4-^{13}C-1,2,3-Thiadiazole (6)[3]

4-^{13}C-1,2,3-thiadiazole (3) (62 mg, 0.71 mmol) was dissolved in 1.0 ml of approximately 0.5 N sodium deuteroxide prepared by adding sodium (5 mg, 0.22 mmol) to 5 ml of deuterium oxide. The base catalyzed exchange of the 5-hydrogen was followed to completion by NMR. The organic product was extracted out of the base solution with ether (∿ 100 ml), and then was dried over magnesium sulfate and concentrated by distillation. Purification by VPC using an SE-30 column at 90° yielded 48 mg (0.54 mmol, 76% of theoretical) of the compound 6 which was characterized by the following spectroscopic data: ν_{max}: 3142 (w) cm^{-1}, 2380 (w) cm^{-1}, 1260 (m) cm^{-1}, 1236 (m) cm^{-1}, 1220 (s) cm^{-1}, 855 (s) cm^{-1}, 749 (w) cm^{-1}, 597 (m) cm^{-1}, 528 (m) cm^{-1}. δ ($CDCl_3$): 9.05 (1H, $J_{^{13}C-H}$ = 201 Hz).

5-^{13}C-1,2,3-Thiadiazole (7)

A 50 ml round bottom flask equipped with a side arm to accommodate a 7 mm septum was fitted with a dry ice condenser and assembled hot under a nitrogen atmosphere. Acetonitrile-2-^{13}C (0.5 g, 12 mmol) was added to the round bottom flask through a specially designed filtering apparatus containing a small amount of anhydrous calcium chloride. This special apparatus consisted of a regular sintered glass filter mated to a 6", 20 gauge needle which was inserted through a rubber septum into the round bottom flask. Five ml of dry toluene (distilled over sodium and benzophenone) were also added through the filter into the round bottom flask.

The reaction flask was cooled with an ice bath and 13 ml of one molar diisobutyl aluminum hydride in n-heptane were added over six minutes with stirring. The solution was stirred for an additional 30 minutes. Dry ice and acetone were added to the dry ice condenser and then 13 ml of water were added to the reaction mixture. A vigorous reaction with the formation of a precipitate and evolution of gas ensued. Immediately three ml of toluene containing carboethoxyhydrazine (1.27 g, 12 mmol) were added to the round bottom flask. After five minutes, ten ml of chloroform were added and the precipitate was subjected to suction filtration and washed with 200 ml of chloroform. The chloroform was removed on the rotary evaporator yielding 0.86 g (55% of theoretical) of crude acetaldehyde-2-^{13}C carboethoxyhydrazone (8).

To 8 (0.86 g, 6.6 mmol) in a ten ml round bottom flask were added four ml of thionyl chloride. The mixture was stirred for one hour, hydrolyzed, neutralized with sodium bicarbonate solution and extracted with 250 ml ether. The solution was dried over magnesium sulfate and concentrated down to two ml by distillation at atmospheric pressure. The product, 5-^{13}C-1,2,3-thiadiazole (7) (257 mg, 2.9 mmol, 45% of theoretical based on 8) was purified by VPC on a carbowax-20M column at 90° and characterized from the following spectroscopic data: ν_{max}: 3118 (w) cm^{-1}, 3091 (w) cm^{-1}, 1297 (m) cm^{-1}, 1230 (s) cm^{-1}, 1232 (s) cm^{-1}, 855 (s) cm^{-1}, 752 (m) cm^{-1}, 748 (m) cm^{-1}, 744 (m) cm^{-1}, 530 (m) cm^{-1}. δ ($CDCl_3$) 8.79 (doublet of doublets, $J_{^{13}C-C-H} = 15.1$ Hz, $J_{H-H} = 3$ Hz), 8.61 (doublet of doublets, $J_{^{13}C-H} = 192$ Hz, $J_{H-H} = 3$ Hz). m/e: 87 (20.7%), 86 (2.0%), 59 (100%).

5-Deuterio-5-^{13}C-1,2,3-Thiadiazole (9)[3]

5-^{13}C-1,2,3-Thiadiazole (7) (24 mg, 0.28 mmol) was dissolved with stirring in 25 ml of approximately 0.05 N sodium deuteroxide solution prepared by adding sodium (29 mg, 1.25 mmol) to 25 ml of deuterium oxide. A dry nitrogen atmosphere was maintained inside the 50 ml round bottom reaction flask. After 10 minutes, 25 ml of anhydrous ether were added to the reaction flask, the layers were separated, and the deuterium oxide solution was extracted with an additional 100 ml of anhydrous ether. The combined ether layers were dried over magnesium sulfate and concentrated on a rotary evaporator. The product, 5-deuterio-5-^{13}C-1,2,3-thiadiazole (9) (16 mg, 0.18 mmol, 66% of theoretical) which was purified by VPC on an SE-30 column at 80° exhibited the following spectral characteristics: ν_{max}: 3100 (vw) cm^{-1}, 2310 (w) cm^{-1}, 1259 (s) cm^{-1}, 1219 (s) cm^{-1}, 1100 (m) cm^{-1}, 1091 (m) cm^{-1}, 1035 (m) cm^{-1}, 1030 (m) cm^{-1}, 850 (s) cm^{-1}, 750 (w) cm^{-1}, 590 (m) cm^{-1}. δ ($CDCl_3$): 8.79 (d, $J_{H-C-^{13}C} = 15.1$ Hz). m/e: 88 (27.4%), 87 (4.8%), 86 (0.4%), 60 (100%).

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