

SYNTHESIS OF TRIDEUTEROMETHYL-3(5) PYRAZOLES

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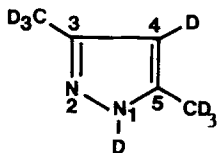
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SUMMARY

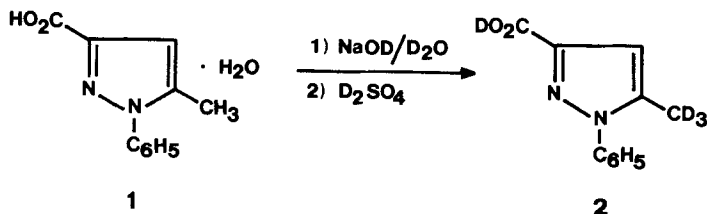
The synthesis of 3,5-bis(trideuteriomethyl)pyrazole was achieved by reaction of perdeuterated acetylacetone with perdeuterated hydrazine hydrate. Some unsuccessful attempts using alternative routes are also described.

Key Words: Proton-deuterium exchange; 3,5-Dimethylpyrazole-d₇.

For spectroscopic purposes, ²H n.m.r. and n.q.r., a sample of heptadeuterated 3,5-dimethylpyrazole was required. Our previous experience (1) suggested that deuteration at position 1 (N-D) and at position 4 (C-D) can be simply achieved by exchange with D₂O in different conditions, at room temperature, for N-D and at 200°C in a sealed tube for C₄-D. Concerning the direct transformation CH₃ → CD₃, almost nothing was known in the literature [a six step procedure, involving oxidation by KMnO₄, to the carboxylic acid, esterification, and several reductions with LiAlD₄, has been described (2)].

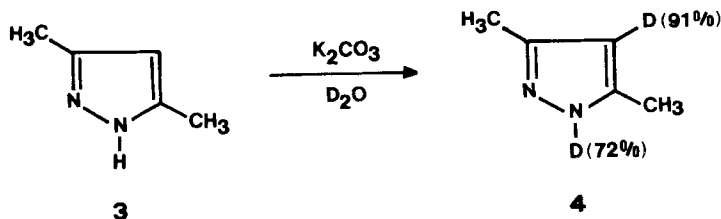


The only reference we found in the Chemical Abstracts was an old paper by Erlenmeyer, Weber and Wiessmer (3) who reported the following reaction:



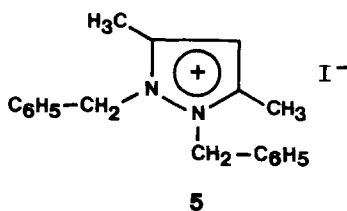
Although compound **2** was not well characterized (only densitometry), we repeated exactly the described procedure (using also a hydrate of **1**), but ^1H n.m.r. and mass spectrometry indicated that only the carboxylic proton was exchanged.

Then we tried to exchange directly the protons of 3,5-dimethylpyrazole **3** in basic medium, in the conditions in which all the protons of acetylacetone were exchanged:



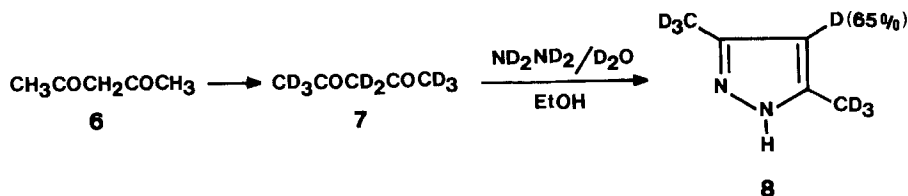
The isolated product, **4**, is labelled only on positions 1 and 4 (the lack of deuterium on N_1 is due to back-exchange with ambient humidity). The result is not unexpected since methyl groups on pyrazole are much less acidic than those α to a carbonyl group.

In order to increase their acidity, we thought of transforming the pyrazole into a pyrazolium cation. We selected $\underline{\text{N}}$ -benzyl substituents, compound **5**, in order to remove them after the exchange has been completed.



After 1 h reflux in D_2O containing a small amount of K_2CO_3 (6 mg/ml), the solution became very dark. A ^1H n.m.r. spectrum showed that deuteration had taken place on all the protons, including those of the $\underline{\text{N}}\text{-CH}_2$ (but not the phenyl protons). However, since much decomposition occurs, the purification becomes difficult and therefore the method was abandoned.

Finally, the desired compound was prepared in the following way:



After a first attempt to prepare perdeuterioacetylacetone **7** from acetylacetone **6** using the procedure described by Hayes, Sheldon and Bowie (4) ($\text{NaOD}/\text{D}_2\text{O}$ at 120°C in a sealed tube, formation of decomposition products only), we used the method of Doyle and Tobias (5) ($\text{K}_2\text{CO}_3/\text{D}_2\text{O}$ airreflux). Compound **7** was treated without purification with tetradeuterohydrazine in deuterium oxide (25%) and ethanol (75%) affording pyrazole **8** in a 98% yield.

A careful ^1H and ^{13}C n.m.r. and mass spectrometry study reveals that the methyl groups are enriched at $\geq 98\%$ but the the 4-position is only 5% labelled (probably due to the ethanol we use as solvent). For our purposes, the compound can be used as such, but a pure 3,5-dimethylpyrazole- d_7 was prepared by exchange with D_2O using the conditions already described (1).

EXPERIMENTAL

Material and methods.

Melting points were determined in open capillaries and are uncorrected. ^1H and ^{13}C n.m.r. spectra were recorded on a Bruker AM 200 spectrometer in CDCl_3 solutions with TMS as an internal standard. Mass spectra were determined with a modified Bruker CMS47 FT ICR mass spectrometer (6). Deuterated hydrazine hydrate was purchased from CEA (25% in D_2O). Deuterium oxide (Scharlau), acetylacetone (Carlo-Erba) and 3,5-dimethylpyrazole (Fluka) were used. Compound **1** was prepared according to reference (2) and compound **5** according to reference (7).

3,5-Bis(trideuteromethyl)pyrazole- d_6 and -d_7 . The compound was prepared by reaction of 2,4-pentanedione- d_8 (5) and hydrazine- d_4 deuterohydrate, as described for the synthesis of the unlabelled compound (7). M.p. $105\text{--}107^\circ\text{C}$ [Lit.: 107°C (7)].

^{13}C n.m.r. data: 11.39, CD_3 [$^1\text{J}(^2\text{H}\text{-}^{13}\text{C}) = 19.5 \text{ Hz}$]; 104.08, $\text{C}_4\text{-H}$ [$^1\text{J}(^1\text{H}\text{-}^{13}\text{C}) = 172.75 \text{ Hz}$], 103.87, $\text{C}_4\text{-D}$ [$^1\text{J}(^2\text{H}\text{-}^{13}\text{C}) = 26.4 \text{ Hz}$];

144.17, C₃ and C₅ of the C₄-D isotopomer, 144.30, C₃ and C₅ of the C₄-H isotopomer. Mass spectrometry data: m/z 100 (C₅H₂D₅N₂), 101 (C₅HD₆N₂), 102 (C₅H₂D₆N₂, M⁺) and 103 (C₅HD₇N₂, M⁺). After protonation (with acetone): m/z 103 (C₅H₃D₆N₂, MH⁺, 35%) and 104 (C₅H₂D₇N₂, MH⁺, 65%).

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REFERENCES

1. Elguero, J., Jacquier, R., Pellegrin, V. and Tabacik, V. Bull. Soc. Chim. Fr. 1974 (1970).
2. Luitjen, W.C.M.M. and van Thuijl, J. Org. Mass Spectrom. 17: 299 (1982).
3. Erlenmeyer, H., Weber, H.M. and Wiessmer, P. Helv. Chim. Acta 21: 1017 (1938).
4. Hayes, R.N., Sheldon, J.C. and Bowie, J.H. Int. J. Mass Spectrom. Ion Proc. 71: 233 (1986).
5. Doyle, G. and Tobias, R.S. Inorg. Chem. 7: 2479 (1968).
6. Tomás, F., Abboud, J.L.M., Laynez, J., Notario, R., Santos, L., Nilsson, S.O., Catalán, J., Claramunt, R.M. and Elguero, J. J. Am. Chem. Soc. 111: 7348 (1989).
7. Elguero, J., Jacquier, R. and Tizané, D. Bull. Soc. Chim. Fr. 1687 (1969).
8. Behr, L.C. Fusco, R. and Jarboe, C.H.- Pyrazoles, Pyrazolines, Pyrazolidines, Indazoles and Condensed Rings (Wiley, R.H. Ed.), John Wiley and Sons, New York (1967).