Convenient Preparations of Mono- and Dideuterated 2-Furoic and 2-Thiophenecarboxylic Acids

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Received January 4, 1971

2-Furoic (1) (1a) and 2-thiophenecarboxylic (2) (1a) acids and their derivatives are useful starting materials for the preparation of furans and thiophenes containing various side-chains, including compounds of biological interest.

We wish to report convenient and very simple preparations of mono- and dideuterated forms of these two acids. Deuterium labelling was achieved by hydrogen exchange reactions either at position 5 (2) or at positions 3,5 (3) of each acid.

The following conditions were found to be optimum for monodeuteration (method Λ). The appropriate carboxylic acid was heated at 165° in a deuterium oxidecarbonate buffer (pD ~ 10). The monodeuterated product (2) was obtained on cooling and acidifying the reaction mixture. NMR analyses revealed that in each case the H-5 signal of the acid had almost completely disappeared (> 95%D); the remainder of the spectrum was that of a

simple AB system. Note that the chemical shift order (decreasing τ values) for **1a** is H-4>H-3>H-5 (3) but for **1b** it is H-4> H-5> H-3 (2,4). Mass spectral analysis indicated the formation of less than 6% dideuterated acid. While it was not possible to determine clearly the position of the second deuterium atom, the results given below suggest that it is position 3.

Deuteration at the 3,5 positions was conveniently effected by heating the dry acid containing the COOD group at 250° (method B). Deuterium was introduced into the carboxyl group by recrystallizing 1 from deuterium oxide. The amount of deuterium in the carboxyl group was determined by nmr analysis of a methylene chloride solution. In the case of 3b the amount of deuterium introduced into the 3,5 positions was that expected for a statistical distribution of deuterium among these two positions and the carboxyl group. Deuteration was not statistical in the case of 3a, the 5-position underwent more exchange than the 3-position. Statistical distribution of deuterium was not observed since a shorter reaction period was necessary due to the extensive decarboxylation of 1a at the temperature employed.

Although higher degrees of deuteration could be achieved in method B, no attempt was made in this direction. By relabelling the carboxyl material, additional hydrogen-deuterium exchange would result.

TABLE 1

Deuterated 2-Furoic and 2-Thiophenecarboxylic Acids
Prepared by Hydrogen-Deuterium Exchange (a)

Deuterated Acid	Method	T, °C	Time	% 3-1)	% 5-D	% Yield Acid
2a	Α	165	6 hr.		95	52
3a	B (b)	250	45 min.	19	28	26
2b	Α	165	5 hr.		~100	63
3b	B (b)	250	2 hr.	32	32	63

⁽a) NMR analyses of percent deuteration have about a 3% uncertainty, II-4 being used as an internal standard. (b) >90%D in the COOD group initially.

EXPERIMENTAL

Materials.

2-Furoic acid (1a), m.p. 133-134°, Matheson, Coleman and Bell and thiophene-2-carboxylic acid (1b) m.p. 127-128°, (Aldrich Chemical Co.) were used as received. Deuterium oxide (>99%) was supplied by Columbia Organic Chemicals Company. A Parr Instrument Company Monel Bomb was employed.

Hydrogen-Deuterium Exchange.

Method A. Exchange at H-5.

Deuterium oxide (16 ml.) was added to an equimolar mixture of 0.008 M of 1a or 1b and sodium carbonate. The solution having p1 > 10 was heated in a bomb at 165° . After cooling, the reaction mixture was acidified with dilute hydrochloric acid and the precipitate was collected. Recrystallization from proteo water gave the corresponding carboxylic acid-5-d. NMR analyses were obtained on methylene chloride solutions. Results are summarized in Table 1. Mass spectral analysis of 2a showed $d_0 = 8.0\%$, $d_1 = 86.2\%$, and $d_2 = 5.8\%$; 2b showed $d_0 = 3.6\%$, $d_1 = 95.0\%$, and $d_2 = 1.4\%$.

Method B. Exchange at H-3,5.

2-Furoic acid-0-d or 2-thiophenecarboxylic acid-0-d (2.0 g.) was heated in a bomb at 250° . The product obtained from the cooled bomb was dissolved in methylene chloride for nmr analysis. Prior to nmr analysis of **2a**, the solid was gently warmed to remove furan formed by decarboxylation. Results are given in Table I. The dideuterated products were recrystallized from proteo water before mass spectral analysis: **3a** showed d₀ = 59.9%, d₁ = 34.6%, d₂ = 5.5%; **3b** showed d₀ = 46.2%, d₁ = 43.6%, d₂ = 10.2%.

Acknowledgment.

Notes

Partial support by the National Science Foundation (grant GP 9488) is gratefully acknowledged.

REFERENCES

- (1) A. P. Dunlop and F. N. Peters, "The Furans," Reinhold Publishing Corp., New York, N. Y., 1953.
 - (2) S. Gronowitz, Advan. Heterocycl. Chem., 1, 2 (1963).
- (3) Sadtler Standard Spectra, NMR No. 633M, Sadtler Research Laboratories, Inc., Philadelphia, Pennsylvania.
 - (4) Ibid., NMR No. 523M.