

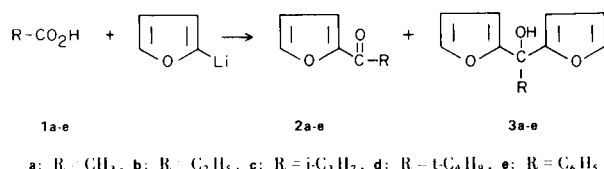
Reaction of Furyllithium with Carboxylic Acids

Clayton H. Heathcock, (1), L. Gray Gulick, (2) and Thomas Dehlinger

Department of Chemistry, University of California, Berkeley

In connection with a projected synthesis, we desired a method for the production of α -furyl ketones under non-acidic conditions. The traditional method for preparing α -furyl ketones, Lewis-acid catalyzed Friedel-Crafts acylation (3) was unsuitable for our purpose. In light of the ready availability of α -furyllithium (4), we investigated the reaction of this organometallic reagent with a series of carboxylic acids. The reaction of alkylolithium reagents with acids has previously been used for the synthesis of numerous ketones (5).

The transformation (1 \rightarrow 2) is extremely simple to accomplish. Addition of butyllithium to an ethereal solution of furan leads to an immediate production of α -furyllithium (4). Subsequent dropwise addition of an ethereal solution of the carboxylic acid (1), followed by aqueous workup, then yields the desired furyl ketone (2), admixed with the corresponding difurylcarbinol (3). The composition of the product mixture in each case was determined by integration of the nmr spectrum of the



crude product. The ratio of the areas of C-3 resonances (2.5 τ for 2, 3.8 τ for 3) was used for the analysis.

The results obtained are summarized in Table I. As will be seen from the table, all acids studied gave substantial amounts of carbinol, as well as the desired α -furyl ketone. Increasing branching at the α -carbon of the acid has a relatively minor effect on the ratio of 2:3. Inverse addition did not change the ketone-carbinol ratio. Addition of acetic acid to the furyllithium suspension at -70° in ether or tetrahydrofuran, followed by reaction at room temperature, gave a higher 2a:3a ratio, but the total yield was much lower. Working the reaction mixture up by adding it to a large excess of water, improved the 2:3

ratio slightly.

In summary, it appears that the reaction of α -furyllithium with carboxylic acids offers an alternative method for the preparation of α -furyl ketones under non-acidic conditions, but that isolated yields are low, due to competing formation of difuryl carbinol.

EXPERIMENTAL

General Procedure for the Reaction of Carboxylic acids with α -Furyllithium.

To 17 g. (0.25 mole) of freshly-distilled furan in 300 ml. of anhydrous ether was added 125 ml. of *n*-butyllithium (1.6 *M* in hexane, 0.20 mole). The resulting suspension was stirred at room temperature for 20 minutes. Thereupon, a solution of 0.10 mole of acid in 125 ml. of ether was added dropwise to the rapidly-stirring furyllithium slurry over a period of 1-2 hours. At this point, the reaction was quenched by: (A) addition of 100 ml. of water to the mixture or (B) addition of the reaction mixture in a thin stream to 1-2 l. of rapidly-stirring distilled water over a period of 2-3 minutes. In either case, the layers were separated, the aqueous phase was additionally extracted with ether, and the combined ether layers were dried over magnesium sulfate.

Evaporation of the ether gave a crude, slightly yellow oil, which was assayed by nmr, and fractionated at reduced pressure. The furyl ketone (2) was collected first, followed by a mixed cut, and then the difurylcarbinol (3). Isolated (distilled) yields from acids 1a-e follow (acid, ketone, yield (%), b.p.; carbinol, yields (%), b.p.): 1a, 2a, 14, 53-57 $^\circ$ - 8 mm; 3a, 28, 65-75 $^\circ$ - 8 mm. 1b, 2b, 35, 55 $^\circ$ - 3 mm; 3b, 16, 90-100 $^\circ$ - 3 mm; 1c, 2c, 32, 51 $^\circ$ - 8 mm; 3c, 8, 100-105 $^\circ$ - 8 mm; 1d, 2d, 28, 67 $^\circ$ - 10 mm; 3d, 18, 114 $^\circ$ - 10 mm; 1e, 2e, 54, 130-143 $^\circ$ - 3 mm.

Compounds 2a-e have all been described previously (3). Difurylcarbinols 3a-d are extremely sensitive and decompose, even under nitrogen at -20° , in a matter of hours. Consequently, these materials were characterized only spectrally. The nmr data are summarized in Table II.

Acknowledgment.

This research was generously supported by Public Health Service Research Grant No. GM-15302.

TABLE I

Reaction of α -Furyllithium with Carboxylic Acids (a)

Run	Acid	% Total Crude Yield	% 2 (b)	% 3 (b)	Workup Procedure (c)
8	1a	63	60	40	A
17	1a	52	80	20	B
21 (d)	1a	25	82	18	B
9	1b	68	58	42	A
18	1b	91	67	33	B
11	1c	86	66	34	A
15	1d	100	60	40	A
16	1d	—	71	29	A
6	1e	90	84	16(e)	A

(a) Unless otherwise stated, all reactions were carried out in ether at room temperature, adding 0.1 mole of the appropriate acid to 0.2 mole of preformed α -furyllithium. (b) Estimated by integration of the nmr spectrum of the crude product. For isolated yields, see experimental section. (c) Procedure A: addition of 100 ml. of water to the reaction mixture; procedure B: addition of the reaction mixture slowly to 1-2 l. of water, under conditions of vigorous stirring. (d) Carried out by addition of **1a** at -70° , followed by reaction at room temperature. (e) Difurylcarbinol **3e** was not isolated in the pure state.

TABLE II

Nuclear Magnetic Resonance Spectra of Carbinols **3a-e**

Compound	α -H	β -H	Other
3a	2.70 τ (t, J = 1.5 cps)	3.85 τ	8.17 τ (S, CH ₃)
3b	2.82 τ (t, J = 1.5 cps)	3.85 τ	7.83 τ (q, J = 7 cps, CH ₂); 9.18 τ (t, J = 7 cps, CH ₃)
3c	2.97 τ (t, J = 1.5 cps)	3.97 τ	7.50 τ (SP, J = 6.5 cps, CH); 9.17 τ (d, J = 6.5 cps, CH ₃)
3d	2.75 τ (t, J = 1.5 cps)	3.78 τ	9.00 τ (S, CH ₃)

REFERENCES

- (1) Fellow of the Alfred P. Sloan Foundation.
 (2) NDEA Fellow, 1966-1968.
 (3) A. P. Dunlop and F. N. Peters, "The Furans," Reinhold Publishing Co., New York, 1953.

(4) W. E. Truce and E. Wellisch, *J. Am. Chem. Soc.*, **74**, 5177 (1952).

(5) For a review, see M. J. Jorgenson, "Organic Reactions," Editor-in-Chief, W. G. Dauben, Vol. 18, in press.

Received November 21, 1968

Berkeley, California 94720