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The Reaction of β-Hydroxy Acids with Aldehydes

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Abstract

β-Hydroxy acids react with various aldehydes in the presence of acidic materials to give spiro lactones in good yields. For example, 2-isopropyl-5-methyl-1,3-dioxaspiro[5,5]undecan-4-one was obtained in 90% yield from the reaction of 2-(1′-hydroxycyclohexyl)propionic acid and isobutyraldehyde.

Introduction

Recently, we reported[1] that β-hydroxy acids react with paraformaldehyde (1,3,5-trioxan) in the presence of 97% sulfuric acid to give 2,3-unsaturated δ-lactones at 118° and spiro lactones at 25°. This article describes a convenient method for the preparation of spiro lactones from the reaction of β-hydroxy acids with aldehydes other than formaldehyde in the presence of acidic materials in acetic acid.

Experimental

Reaction of 2-(1′-Hydroxycyclohexyl)propionic Acid with Isobutyraldehyde

A mixture of 2-(1′-hydroxycyclohexyl)propionic acid (4·3 g, 25 mmol), isobutyraldehyde (3·6 g, 50 mmol) and aluminium chloride (2·7 g, 20 mmol) in acetic acid (50 ml) was stirred for 8 h at 25°. Water (200 ml) was slowly added to the reaction mixture which was then extracted with diisopropyl ether. The ether solution was washed with water, and the acidic materials were completely removed from it with 10% sodium carbonate solution. Then the ether solution was washed with water and dried over anhydrous sodium sulfate; the solvent was removed, and the residue was distilled in a vacuum to give the following fractions: (i) b.p. 50–75°/4 Torr, yield 0·2 g; (ii) b.p. 123–124°/4 Torr, yield 5·3 g. Fraction (i) contained self-condensation products of isobutyraldehyde. Fraction (ii) consisted of *2-isopropyl-5-methyl-1,3-dioxaspiro[5,5]undecan-4-one* (yield 93%) (Found: M^+, 226·1751. $C_{13}H_{22}O_3$ requires M^+, 226·1569). The characterization of this compound was as follows. I.r. (film) 1745, 1220 cm^{-1}. N.m.r. δ 1·0, d, *J* 6 Hz, 6H, $(CH_3)_2CH$; 1·15, d, *J* 7 Hz, 3H, CH_3CH; 1·3–1·75, m, 10H, $(CH_2)_5$; 1·9, m, 1H, $(CH_3)_2CH$; 2·6, q, *J* 7 Hz, 1H, CH_3CH; 5·15, d, *J* 5 Hz, 1H, OCHO.

The aqueous sodium carbonate solution was made acidic with concentrated hydrochloric acid. The acid was completely removed from the aqueous layer by extraction with diisopropyl ether. The ether solution was washed with water, dried over anhydrous sodium sulfate and then evaporated at reduced pressure to give 2-(1′-hydroxycyclohexyl)propionic acid (0·2 g).

Other Reactions

The same technique was used to synthesize a series of substituted spiro lactones. The results are listed in Table 1.

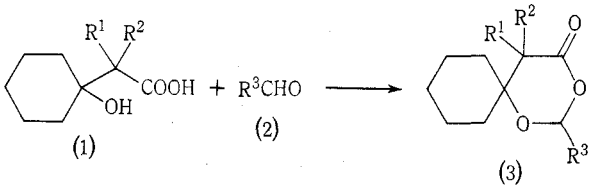
[1] Fujita, T., Watanabe, S., Suga, K., Yanagi, R., and Tsukagoshi, F., *J. Org. Chem.*, 1978, **43**, 1248.

Results and Discussion

Synthetic methods for saturated,[2–6] unsaturated[7] and α-methylene[8] lactones are well known. However, the synthesis of lactones from β-hydroxy acids is not well known. We previously reported the reaction of β-hydroxy acids with paraformaldehyde to afford 2,3-unsaturated δ-lactones and spiro lactones[1] (see Introduction), and the reaction of β-hydroxy acids with ethyl vinyl ether at 25° to give spiro lactones.[9]

Table 1. Reaction of β-hydroxy acids with aldehydes: (1)+(2) → (3)

The β-hydroxy acid (25 mmol), aldehyde (50 mmol) and acidic materials (20 mmol), in acetic acid (50 ml), were used. ppa, polyphosphoric acid. The yields of the products are based on the β-hydroxy acids. The physical and spectral data of the products are available on application to the Editor-in-Chief, Editorial and Publications Service, CSIRO, 314 Albert Street, East Melbourne, Vic. 3002



Hydroxy acid R^1	R^2	Aldehyde R^3	Acidic material	Yield (%)	Hydroxy acid R^1	R^2	Aldehyde R^3	Acidic material	Yield[A] (%)
Me	H	Pr^i	$ZnCl_2$	88	Me	H	hexyl	ppa	67
Me	H	Pr^i	$FeCl_3$	78	Me	H	Ph	ppa	—
Me	H	Pr^i	$AlCl_3$	93	Me	H	*p*-MeC_6H_4	ppa	—
Me	H	Pr^i	$TiCl_4$	17	Me	H	*p*-$MeOC_6H_4$	ppa	—
Me	H	Pr^i	$SnCl_4$	62	Me	H	*p*-HOC_6H_4	ppa	—
Me	H	Pr^i	BF_3–ether	60	Me	H	*o*-HOC_6H_4	ppa	—
Me	H	Pr^i	H_2SO_4	—	Me	H	MeCH=CH	ppa	—
Me	H	Pr^i	H_3PO_4	59	H	H	Pr^i	$AlCl_3$	45 (62)
Me	H	Pr^i	ppa	96	Et	H	Pr^i	$AlCl_3$	95 (95)
Me	H	Me	ppa	61	Me	Me	Pr^i	$AlCl_3$	47 (87)
Me	H	Et	ppa	48	Pr	H	Pr^i	$AlCl_3$	47 (71)
Me	H	Pr	ppa	79	Pr^i	H	Pr^i	$AlCl_3$	42 (63)
Me	H	Bu	ppa	98	Bu	H	Pr^i	$AlCl_3$	61 (68)
Me	H	Bu^i	ppa	83	hexyl	H	Pr^i	$AlCl_3$	42 (69)
Me	H	pentyl	ppa	69					

[A] Values in parentheses are for those cases where polyphosphoric acid was used.

We have now extended these reactions to aldehydes other than formaldehyde. Thus, the reaction of β-hydroxy acids (1) with isobutyraldehyde in the presence of acidic materials in acetic acid at 25° yields spiro lactones (3). For example, 2-isopropyl-5-methyl-1,3-dioxaspiro[5,5]undecan-4-one (3; $R^1 = Me$, $R^2 = H$, $R^3 = Pr^i$) was obtained from 2-(1′-hydroxycyclohexyl)propionic acid (1; $R^1 = Me$, $R^2 = H$)

[2] Ijima, A., Mizuno, H., and Takahashi, K., *Chem. Pharm. Bull.*, 1972, **20**, 197.
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[4] Ali, S. M., and Roberts, S. M., *J. Chem. Soc., Perkin Trans. 1*, 1976, 1934.
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[6] Fujita, T., Watanabe, S., and Suga, K., *Aust. J. Chem.*, 1974, **27**, 2205.
[7] Rao, Y. S., *Chem. Rev.*, 1976, **76**, 625.
[8] Grieco, P. A., *Synthesis*, 1975, 67.
[9] Fujita, T., Watanabe, S., Suga, K., Isobe, T., and Miura, T., *Synthesis*, 1979, 910.

and isobutyraldehyde (2; $R^3 = Pr^i$). However, under reflux conditions, 2,3-unsaturated δ-lactones were not obtained.

The effect of acidic materials on this reaction has been examined, and typical results are presented in Table 1. Use of aluminium chloride or polyphosphoric acid as a catalyst gave good yields of the spiro lactones. The reactions of other β-hydroxy acids with isobutyraldehyde and with other aldehydes in the presence of aluminium chloride or polyphosphoric acid were examined; the results are also listed in Table 1. Interestingly, our observations indicate that saturated aliphatic aldehydes readily react with the hydroxy acids (1), and that unsaturated aliphatic aldehydes and aromatic aldehydes are lesss reactive. The reactions of the β-hydroxy acids with ketones, epoxides, acetals and vinyl esters were unsuccessful under these conditions.

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