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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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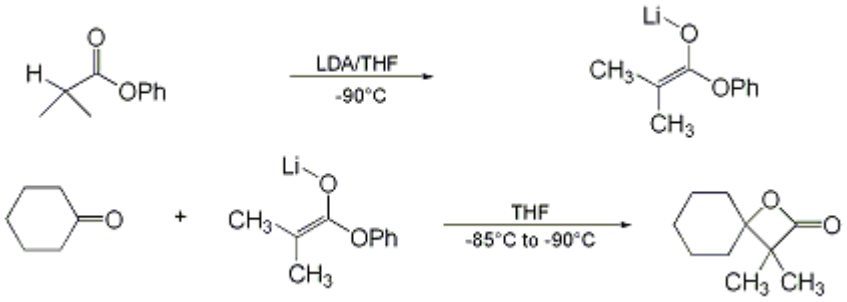
SYNTHESIS OF β-LACTONES BY ALDOLIZATION OF KETONES WITH PHENYL ESTER ENOLATES: 3,3-DIMETHYL-1-OXASPIRO [3.5]NONAN-2-ONE

[1-Oxaspiro[3.5]nonan-2-one, 3,3-dimethyl-]



Submitted by Christine Wedler and Hans Schick[1] .
Checked by Rajib Pal, Peter Belica, and Steven Wolff.

1. Procedure

A 1-L, three-necked, round-bottomed flask is equipped with a Teflon-coated magnetic stirrer bar, a thermometer, an argon inlet/outlet adapter, and a 100-mL, pressure-equalizing dropping funnel with a cooling jacket (Note 1). The flask is charged with dry tetrahydrofuran (THF, 350 mL) (Note 2) and diisopropylamine (18.2 g, 25.3 mL, 0.180 mol) (Note 3). The mixture is cooled to −20°C in a bath filled with acetone and dry ice. At this temperature a 1.56 M solution of butyllithium in hexane (105.8 mL, 0.165 mol) is added dropwise over 5 min (Note 4). The mixture is allowed to warm up to room temperature within 15 min and is then cooled to −90°C in a bath charged with ethanol and liquid nitrogen (Note 5). A precooled solution of phenyl 2-methylpropanoate (27.09 g, 0.165 mol) in THF (50 mL) is added dropwise within 90 min from the dropping funnel (Note 6) and (Note 7), which is rinsed with THF (3 mL) (Note 8). During the addition the temperature in the reaction flask is maintained at −85°C to −90°C. The reaction mixture is stirred at this temperature for 20 min. Thereafter a precooled solution of cyclohexanone (14.72 g, 0.150 mol) (Note 9) in THF (50 mL) is added over a period of 60 min. After stirring for another 30 min at −90°C the mixture is allowed to warm up to ambient temperature. After standing overnight the reaction mixture is poured into a mixture of aqueous 1 N sodium hydroxide (200 mL) and diethyl ether (200 mL) and stirred for 10 min. The organic phase is separated and the aqueous phase is extracted with diethyl ether (2 × 100 mL). The combined organic phases are washed with 0.5 N aqueous sodium hydroxide (2 × 100 mL) and an aqueous saturated solution of sodium chloride (3 × 100 mL). Drying over anhydrous sodium sulfate , filtration, and removal of the solvent under reduced pressure in a rotary evaporator afford the crude β-lactone. After recrystallization from diethyl ether/hexane (Note 10) 3,3-dimethyl-1-oxaspiro[3.5]nonan-2-one is obtained in a yield of 91%. Other β-lactones have also been prepared by the submitters; these were not checked (Note 11), (Note 12).

2. Notes

1. The evacuated apparatus is dried with a flameless heat gun at 150°C and then flushed with dry argon. An atmosphere of dry argon is maintained during the course of the reaction. The jacket of the dropping funnel is charged with acetone and dry ice or with ethanol and liquid nitrogen.
2. Tetrahydrofuran dried over 4 Å molecular sieves was purchased from Fluka Chemical AG and purged with dry argon.
3. Diisopropylamine was purchased from Fluka Chemical AG . The product was distilled and stored over calcium hydride .
4. Butyllithium in hexane was purchased from E. Merck and titrated according to the method of

Gilman.[2] The checkers used recently purchased material from Aldrich Chemical Company, Inc., without titration.

5. The checkers found that comparable yields could be obtained at −78°C. The submitters confirm this finding, but recommend the lower temperature especially when the β-lactone product is a liquid. Purification to remove small amounts of a β-keto ester by-product that forms at the higher temperature is more difficult with liquid products.

6. Phenyl 2-methylpropanoate was prepared by the following procedure:[3] A 1-L, three-necked, round-bottomed flask equipped with a magnetic stirrer bar, thermometer, an argon inlet adapter, a reflux condenser, and a 100-mL pressure-equalizing dropping funnel is charged with toluene (350 mL), phenol (37.64 g, 0.400 mol), and concentrated sulfuric acid (0.5 mL). A solution of 2-methylpropanoyl chloride (42.62 g, 0.400 mol) in toluene (50 mL) is added dropwise at ambient temperature over a period of 45 min. The mixture is refluxed for 5 hr and then washed with an aqueous saturated sodium hydrogen carbonate solution (100 mL), an ice-cold 1 M aqueous sodium hydroxide solution (2 × 100 mL), and an aqueous saturated sodium chloride solution (75 mL). The organic phase is dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure using a rotary evaporator to afford the crude ester as an oil. Fractionated distillation under reduced pressure affords phenyl 2-methylpropanoate (bp 89-91°C/13 mbar = 9.73 mm) in a yield of 90-95% with a purity of 98-99% (GLC).

7. The solution of phenyl 2-methylpropanoate in THF should be cooled in the dropping funnel to −70° C.

8. This portion of THF should be cooled to −70°C before adding it from the dropping funnel into the reaction flask.

9. Cyclohexanone was purchased from E. Merck and distilled prior to use.

10. Crude 3,3-dimethyl-1-oxaspiro[3.5]nonan-2-one was recrystallized from a mixture of diethyl ether (35 mL) and hexane (200 mL) to afford 20.60 g (82%) of colorless crystals, mp 110-112°C (the checkers obtained mp 100.5-103°C). The mother liquor is concentrated under reduced pressure and the residue is dissolved again in diethyl ether (4 mL) and hexane (20 mL) to afford another 2.27 g (9%) of colorless crystals, mp 100.5-103°C. If desired the procedure can be repeated again to provide another 0.45 g (1.8%) of colorless crystals. The compound exhibits the following analytical data: IR (CCl_4) cm^{-1}: 1820 ; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.31 (s, 6 H), 1.58-1.70 (m, 8 H), 1.94-1.97 (m, 2 H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 17.8, 22.4, 24.5, 32.0, 54.1, 84.9, 176.1 . Anal. Calcd for $C_{10}H_{16}O_2$: Calcd. C, 71.39; H, 9.59. Found C, 71.53; H, 9.80.

11. Crude (±)-3-ethyl-1-oxaspiro[3.5]nonan-2-one , prepared from phenyl butanoate (27.09 g, 0.165 mol) and cyclohexanone (14.72 g, 0.150 mol), was purified by flash chromatography on silica gel (300 g, 230-400 mesh, E. Merck) using hexane/ethyl acetate (12:1, 2.6 L, 60 mL/min) as eluant. Fractions of 75 mL were taken. Fractions 10-21 afforded 23.97 g (95%) and fractions 22-25 afforded another 0.96 g (3.8%) of a colorless oil. The purity of these fractions determined by HPLC was 98 and 95%, respectively. The compound exhibits the following anlaytical data: IR (film) cm^{-1}: 1815 ; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.07 (t, 3 H, J = 7), 1.62-1.97 (m, 12 H), 2.97-3.03 (m, 1 H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 12.3, 17.5, 22.3, 23.0, 25.0, 31.2, 37.5, 59.9, 82.3, 172.4 . Anal. Calcd for $C_{10}H_{16}O_2$: Calcd. C, 71.39; H, 9.59. Found C, 71.41; H, 9.81.

12. The crude 6:1 mixture of (3R*,4R*)- and (3R*,4S*)-4-isopropyl-4-methyl-3-octyl-2-oxetanone , prepared from phenyl decanoate (40.92 g, 0.165 mol) and 3-methylbutan-2-one (12.92 g, 0.150 mol), was purified by flash chromatography on silica gel (300 g, 230-400 mesh, E. Merck) using hexane/ethyl acetate (20:1, 2.6 L, 60 mL/min) as eluant. Fractions of 75 mL were taken. Fractions 8-22 afford 34.62 g (96%) of a colorless oil. The purity of this fraction determined by HPLC was 97%. The compound exhibits the following analytical data: IR (film) cm^{-1}: 1815 ; ^1H NMR (300 MHz, $CDCl_3$), main diastereoisomer with (3R*,4R*)-configuration δ: 0.88 (t, 3 H, J = 7), 0.93 (d, 3 H, J = 7), 1.01 (d, 3 H, J = 7), 1.27-1.44 (m, 12 H), 1.36 (s, 3 H), 1.52-1.85 (m, 2 H), 1.99 (sept, 1 H, J = 7), 3.14 (t, 1 H, J = 8); minor diastereoisomer with (3R*,4S*)-configuration δ: 1.44 (s, 3 H), 2.16 (sept, 1 H, J = 7), additional signals are superimposed by signals of the main diastereoisomer; ^{13}C NMR (75 MHz, $CDCl_3$), main diastereoisomer with (3R*,4R*)-configuration δ: 14.1, 14.9, 16.6, 17.0, 22.7, 25.2, 27.6, 29.2, 29.3, 29.5, 31.9, 37.6, 56.3, 85.1, 171.9; minor diastereoisomer with (3R*,4S*)-configuration δ: 59.0, 84.8, 172.0 (additional signals are superimposed by signals of the main diastereoisomer). The configuration of the diastereoisomer was established by a NOESY experiment at 500 MHz. According to the integration of the septets at 1.99 and 2.16 ppm the ratio of the diastereoisomers was 6:1. Anal. Calcd for $C_{15}H_{28}O_2$: Calcd. C, 74.95; H, 11.74. Found C, 75.35; H, 11.94.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Decarboxylation of β-lactones to olefins,[4,5,6] stereoselective reactions of β-lactones with a variety of electrophiles,[6,7,8,9] and the regioselective fission of β-lactones by many different nucleophiles[10,11,12] make these highly reactive compounds versatile intermediates for organic syntheses.[13] [14] Although several methods exist for the preparation of β-lactones, most β-lactones are now synthesized by [2+2] cycloaddition of carbonyl compounds to ketenes,[15] or by intramolecular cyclization of β-hydroxyalkanoic acids by means of benzenesulfonyl chloride in pyridine .[4]

The method described here belongs to a group of recently developed procedures comprising the spontaneous intramolecular acylation of active derivatives of metalated β-hydroxy alkanoates. These compounds are available by reactions of carbonyl compounds with ester enolates prepared from S-phenyl alkanethioates[6] or phenyl alkanoates,[16] as well as by Reformatsky[17] or Darzens[18] reactions of carbonyl compounds with phenyl α-halo alkanoates.

The method outlined here competes well with the method developed earlier by Danheiser, et al.[6,19] Its superiority is based on the fact that phenyl ester enolates give almost the same results as the S-phenyl thiolester enolates. However, handling the malodorous benzenethiol for the preparation of the active acid derivative and during workup of the β-lactone can be avoided. In addition, phenol is much cheaper than benzenethiol. The method is well suited for the preparation of β-lactones from symmetrical and unsymmetrical ketones. In addition to 3,3-dimethyl-1-oxaspiro[3.5]nonan-2-one, (±)-3-ethyl-1-oxaspiro [3.5]nonan-2-one and (3R*,4R*)- and (3R*,4S*)-4-isopropyl-4-methyl-3-octyl-2-oxetanone were prepared by this procedure in high yields (Note 11) and (Note 12). In the case of unsymmetrical ketones the less sterically crowded diasteroisomer is formed preferentially. With aldehydes as the carbonyl component the yields are unsatisfactory, because of the competitive formation of 1,3-dioxan-4-ones.[6]

References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

3,3-Dimethyl-1-oxaspiro[3.5]nonan-2-one:
1-Oxaspiro[3.5]nonan-2-one, 3,3-dimethyl- (9); (22741-15-7)

Diisopropylamine (8);
2-Propanamine, N-(1-methylethyl)- (9); (108-18-9)

Butyllithium:
Lithium, butyl- (8,9); (109-72-8)

Phenyl 2-methylpropanoate:
Propanoic acid, 2-methyl-, phenyl ester (9); (20279-29-2)

Cyclohexanone (8,9); (108-94-1)

Phenol: HIGHLY TOXIC (8,9); (108-95-2)

2-Methylpropanoyl chloride:
Isobutyryl chloride (8);
Propanyl chloride, 2-methyl- (9); (79-30-1)