A Direct Synthesis of α-Keto Five- and Six-Membered Cyclic Ethers

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A simple synthesis of tetrahydro-2*H*-pyran-2-yl and tetrahydrofuran-2-yl ketones from their corresponding carboxylic acids was studied. A comparison was made of organolithium and Grignard alkylating reagents as a means of reducing the formation of byproducts and improving the yields.

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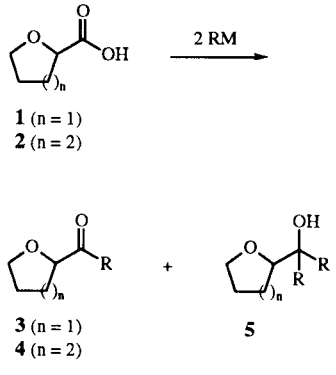
Common sized cyclic ethers bearing an α-ketone function are found in many biologically active natural products, such as carbohydrates, polyethers, and ionophoric antibiotics [1,2], and they are useful as intermediates in their construction [3]. Surprisingly, almost no general methods for the synthesis of these compounds have been published and one route we examined required 4-5 steps and had complex mixtures of diastereomeric intermediates [4]. Several other synthetic methods to prepare substituted THP and THF rings are available; unfortunately, nearly all require *de novo* construction of the cyclic ether portion [5], or a highly strained ring system [6], or do not afford any direct access to a valuable 2-ketone function. We now wish to report a general synthetic approach to this class of heterocycles from inexpensive commercial compounds which already contain five- or six-membered cyclic ethers intact. The focus of this work was to convert tetrahydrofuran-2-carboxylic acid (**1**) or tetrahydo-2*H*-pyran-2-carboxylic acid (**2**) to their corresponding ketones, **3** and **4**, by treatment with an organometallic species, RM.

Scheme 1



The procedure used to make these compounds uses mild conditions and inexpensive materials. In general, the lithium reagents functioned better than the Grignard reagents, as shown in Table 1; however, phenylmagnesium bromide still produced reasonable yields of the ketone. If the availability of the alkylating reagent RM is limited, the amount of alkylating agent can be reduced by preforming the lithium carboxylate salt.

Table 1

Five- and Six-Membered Cyclic Ethers with α-Ketones

Entry	R =	M =	Product	Yield %
1		Li	**3a**	77
2		MgBr	**3a**	60
3	*n*-Bu	Li	**4a**	48 [a]
4		Li	**4b**	67
5		MgBr	**4b**	51
6		Li	**4c**	65
7		MgBr	**4c**	0 [b]
8		Li	**4d**	45

[a] Yield (gc), isolated yield, 40%. [b] Carbinol was the only product.

An important feature in this synthesis was to determine reaction conditions which reduce the formation of the carbinol **5**. This adduct forms because ketones **3** and **4** are much more reactive to attack by the organometallic species than the carboxylate anions of **1** and **2**. It also can form by the *in situ* collapse of the dialkoxide intermediate to the ketone followed by an additional attack by RM. Higher yields indicate the lithium dialkoxide is more stable and did not readily liberate the ketone until hydrolysis [7].

Another way carbinol **5** forms is during hydrolysis, in which unreacted organolithium reagent rapidly reacts with the ketone as it becomes available. A variety of literature methods have been developed to reduce this side reaction, however, these were met with mixed success in this work. We examined several reactions which trap the intermediate dialkoxides as silyl ethers [8-9], and special quenching methods using several small portions of the reaction into ice and hydrochloric acid [10]. The best conditions had an extended reaction time with a careful balance of dilution

and equivalents of organometallic reagent. This afforded the ketones in the highest yields and clearly reduced the amount of byproduct carbinol observed.

In conclusion, a method for the preparation of α-keto five- and six-membered cyclic ethers has been developed. The approach uses carboxylic acids in a reaction with organometallic reagents and in most cases it avoids many pitfalls associated with this mode of alkylation.

EXPERIMENTAL

All spectra were recorded on a Perkin-Elmer 1600 FT IR spectrophotometer and are reported in wave numbers (cm^{-1}). Proton and carbon nuclear magnetic resonance spectra were recorded on a Varian VXR-300 (300 MHz) or on a General Electric QE-300 (300 MHz) spectrometer. Chemical shifts are reported in ppm (δ) downfield relative to tetramethylsilane as an internal standard. Column chromatography was performed using Kieselgel silica gel 60 (230-400 mesh). Tetrahydrofuran-2-carboxylic acid (**1**), tetrahydro-2*H*-pyran-2-methanol, *n*-BuLi (2.5 *M* in hexanes) and PhLi (2.0 *M* in cyclohexane-diethyl ether) were obtained from Aldrich Chemical Co. Benzyllithium was prepared from toluene [11]. All other lithium reagents were prepared by slow addition of an organohalide to excess lithium metal in ethyl ether at -40°.

Tetrahydro-2*H*-pyran-2-carboxylic Acid (**2**).

To tetrahydro-2*H*-pyran-2-methanol (10 g, 0.086 mole) dissolved in acetone (170 ml) at 0° was added Jones reagent (made from 27 g of chromium (VI) oxide, 23 ml of sulfuric acid and 75 ml of water) in small portions over 1 hour until the solution remained red in color. The reaction was quenched with 2-propanol, and the solvents were removed under reduced pressure. The remaining slush was extracted with ethyl acetate and filtered. The filtrate was washed with water and brine and dried over sodium sulfate. This solution was again filtered and the solvents were removed under vacuum, to produce 7.8 g (68%) of a colorless oil after column chromatography [12]; Rf 0.04 (35% THF/hexane); ^1H nmr (deuteriochloroform): δ 9.6 (broad s, 1 H), 4.1 (m, 2 H), 3.5 (m, 1 H), 2.1 (m, 1 H), 1.9 (m, 1 H), 1.6 (m, 4 H); ^{13}C nmr (deuteriochloroform): δ 174.8, 74.4, 67.1, 27.5, 24.0, 21.7; ir (neat): 3141, 2943, 1742, 1442, 1209, 1097, 1052, 906 cm^{-1}.

Anal. Calcd. for $C_6H_{10}O_3$: C, 55.37; H, 7.74. Found: C, 55.29; H, 8.14.

General Procedure for Alkylations Using Grignard Reagents.

To a solution of organomagnesium bromide (70 mmoles) in THF (50 ml) at 0°, was added the carboxylic acid (20 mmoles) in THF (25 ml) rapidly with stirring. After 30 minutes at 0°, the reaction was warmed to room temperature and quenched by pouring the reaction solution into an ice/hydrochloric acid mixture. The resulting solution was extracted with ethyl ether. The organic layer was separated and washed with saturated aqueous sodium bicarbonate solution and brine. Then the solution was dried over anhydrous sodium sulfate and reduced under vacuum to an oil which was chromatographed over silica gel.

General Procedure for Alkylations Using Organolithium Reagents.

To a rapidly stirred solution of the carboxylic acid (4 mmoles) in THF (10 ml) at 0°, the organolithium reagent (10 mmoles, 2 *M* in THF) was added dropwise over 0.5 hour. This solution will become very thick as the carboxylate salt is formed, but will become clear as the reaction proceeds. After complete addition the reaction was allowed to warm to room temperature, and was stirred for 24 hours. The reaction was quenched by pouring it slowly into a vigorously stirred solution of ice and dilute hydrochloric acid. The resulting solution was extracted with ethyl ether and washed with saturated aqueous sodium bicarbonate solution, brine, then dried over sodium sulfate. The solution was filtered and reduced under partial vacuum. The resulting oil was purified by column chromatography.

Phenyl Tetrahydrofuran-2-yl Ketone (**3a**).

This compound was obtained as a colorless oil; Rf = 0.17 (20% from diethyl ether-hexane); ^1H nmr (deuteriochloroform): δ 8.0 (m, 2 H), 7.6-7.4 (m, 3 H), 5.25 (dd, J = 6.8 Hz, 1 H), 4.1-3.9 (m, 2 H), 2.35-2.25 (m, 1 H), 2.2-2.05 (m, 1 H), 2.02-1.9 (m, 2 H); ^{13}C nmr (deuteriochloroform): δ 198.8, 134.9, 133.2, 128.6, 128.5, 79.9, 69.3, 29.2, 25.6.

Anal. Calcd. for $C_{11}H_{12}O_2$: C, 74.94; H, 6.87. Found: C, 74.69; H, 6.92.

1-(Tetrahydro-2'*H*-pyran-2'-yl)-1-pentanone (**4a**).

This compound was obtained as a colorless oil; Rf = 0.44 (35% from THF-hexane); ^1H nmr (deuteriochloroform): δ 4.05 (m, 1 H), 3.78 (dd, J = 2.3, 11.1 Hz, 1 H), 3.46 (m, 1 H), 2.54 (t, J = 7.5 Hz, 2 H) 1.88 (m, 2 H), 1.62-1.23 (m, 8 H), 0.91 (t, J = 8 Hz, 3 H); ^{13}C nmr (deuteriochloroform): δ 211.1, 82.8, 68.2, 37.5, 28.2, 25.5, 25.1, 23.1, 22.3, 13.8.

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.55; H, 10.65. Found: C, 70.22; H, 10.84.

Phenyl Tetrahydro-2*H*-pyran-2-yl Ketone (**4b**).

This compound was obtained as a colorless oil; Rf = 0.52 (35% from THF-hexane); ^1H nmr (deuteriochloroform): δ 7.97 (dd, J = 2.8 Hz, 2 H), 7.53 (m, 1 H), 7.44 (m, 2 H), 4.71 (dd, J = 2.8 Hz, 1 H), 4.14 (split d, 1 H), 3.62 (complex t, 1 H), 1.93 (m, 2 H), 1.75-1.54 (m, 4 H); ^{13}C nmr (deuteriochloroform): δ 198.3, 135.2, 133.1, 128.8, 128.4, 79.8, 68.6, 28.8, 25.5, 23.1; ir (neat): 2940, 2850, 1692, 1597, 1448, 1227, 1091, 971, 695 cm^{-1}.

Anal. Calcd. for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 76.12; H, 7.55.

2-Cyclohexyl-1-(tetrahydro-2'*H*-pyran-2'-yl)ethan-1-one (**4c**).

This compound was obtained as a colorless oil; Rf = 0.44 (5% from methanol-chloroform); ^1H nmr (deuteriochloroform): δ 4.0 (m, 1 H), 3.7 (dd, J = 2, 11 Hz, 1 H), 3.4 (m, 1 H), 2.3 (d, J = 7 Hz, 2 H), 1.9-1.7 (m, 3 H), 1.65-1.0 (m, 12 H), 0.95-0.75 (m, 2 H); ^{13}C nmr (deuteriochloroform): δ 210.4, 83.0, 68.2, 45.3, 33.2, 32.9, 28.0, 26.2, 26.0, 25.4, 23.1.

Anal. Calcd. for $C_{13}H_{22}O_2$: C, 74.24; H, 10.55. Found: C, 74.28; H, 10.51.

2-Phenyl-1-(tetrahydro-2'*H*-pyran-2'-yl)-1-ethanone (**4d**).

This compound was obtained as a colorless oil; Rf = 0.37 (20% from diethyl ether-hexane); ^1H nmr (deuteriochloroform): δ 7.4-7.2 (m, 5 H), 4.08 (m, 1 H), 3.87 (d, J = 5 Hz, 2 H), 3.8 (m, 1 H), 3.48 (m, 1 H), 1.9-1.8 (m, 2 H), 1.7-1.3 (m, 4 H); ^{13}C nmr (deuteriochloroform): δ 208.1, 134.1, 129.8, 128.4, 126.8, 82.2, 68.3, 44.8, 28.2, 25.6, 23.0; ir (neat): 2939, 2852, 1718, 1090 cm^{-1}.

Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.21; H, 7.90.

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