Reductive Cyclization of Ketoesters Utilizing Sodium Cyanoborohydride: Synthesis of γ- and δ-Lactones

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A new one pot procedure to synthesize γ- and δ-lactones, in a 76-84% yield, is accomplished by the reductive cyclization of 1,4- and 1,5-ketoesters, utilizing sodium cyanoborohydride. The procedure is generally applicable to a wide variety of ketoesters with the exception of the ethyl ester of alkyl 1,5-ketoesters and α,β-unsaturated 1,4- and 1,5-ketoesters.

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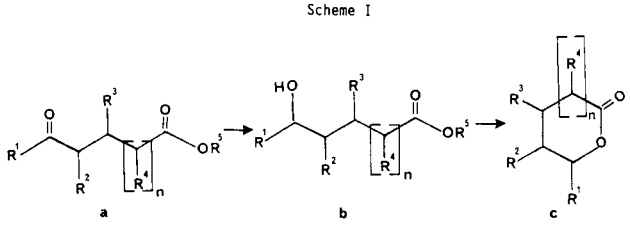
Methods to synthesize lactones are abundant in the literature. However, new methods which require fewer manipulations and result in good yields of the desired lactones are worth describing. This paper describes a new one pot procedure in which 1,4- and 1,5-ketoesters are converted to the corresponding lactone utilizing sodium cyanoborohydride. Several previous studies on the reduction of 1,4- and 1,5-ketoesters have examined the utility of sodium borohydride [1] or lithium in liquid ammonia [2]. In these cases side reactions occurred to generate, in addition to the desired hydroxyester, diol, cyclic ether, and hydroxy ketone derivatives resulting from reduction of the ester and lactone moieties. In contrast to these results, sodium cyanoborohydride is known to reduce ketones to alcohols under acidic conditions while not affecting the ester or lactone moiety [3]. In addition these acidic conditions, required for the reduction of the ketone carbonyl group of the ketoester, are utilized advantagously in the cyclization of the resulting hydroxyester yielding the desired lactone directly (Scheme I).

Scheme I



a b c

1 n= 0; R^1 R^2= $CH_2CH_2CH_2CH_2$; R^3= H; R^5= CH_2CH_3

2 n= 0; R^1= CH_3; R^2, R^3= H; R^5= CH_2CH_3

3 n= 1; R^1 R^2= $CH_2CH_2CH[C(CH_3)_3]CH_2$; R^3, R^4= H; R^5= CH_2CH_3

4 n= 1; R^1= CH_3; R^2, R^3, R^4= H; R^5= CH_2CH_3

5 n= 1; R^1= CH_3; R^2, R^3= H; R^4= $CH(CH_3)_2$; R^5= 2-(OCH_3)-4-$(CH_3)C_6H_4$

6 n= 0; R^1= Ph; R^2, R^3= unsaturated; R^5= CH_2CH_3

7 n= 0; R^1 R^2= $CH{=}CHCH_2CH_2$; R^3= H; R^5= CH_2CH_3

A variety of 1,4- and 1,5-ketoesters have been examined to determine the scope of this new procedure. The typical procedure involved mixing the ketoester with tetrahydrofuran (THF) followed by addition of one equivalent of sodium cyanoborohydride. The mixture was acidified to a *p*H of 2 (*p*H paper) with a solution of hydrochloric acid in tetrahydrofuran (1:4 concentrated hydrochloric acid in THF) and was stirred at room temperature or refluxed for the period indicated in Table I. The mixture was neutralized with aqueous saturated sodium bicarbonate, extracted with ether and purified chromatographically. The results from this investigation are summarized in Table I.

Table I

Reductive Cyclization of Ketoesters **1a-7a**

Substrate	Conditions	Yield % [a]
1a	room temp, 31 hours	39
	reflux, 4 hours	58 [b]
	reflux, 44 hours	76 [b]
2a	reflux, 18 hours	81
3a	room temp, 14 hours	84
4a	room temp, 25 hours	0
	reflux, 19 hours	0
5a	reflux, 19 hours	83 [c]
6a	reflux, 42 hours	0
7a	reflux, 18 hours	0

[a] Isolated yield of the corresponding lactone unless otherwise indicated. [b] Yield based on hplc integration with an external standard of the corresponding lactone. [c] Yield based on gc integration with an external standard of the corresponding lactone.

The reductive cyclization of ethyl 2-cyclohexanoneacetate (**1a**), at room temperature, resulted in a 39% yield of the corresponding lactone, hexahydro-2(3*H*)-benzofuranone (**1c**). This yield was increased to 58% by refluxing for 4 hours and to 76% when the reflux time was extended to 44 hours. In all cases the *trans/cis* ratio was approximately 4/1. By comparison, a previously reported reduction of ethyl 2-cyclohexanoneacetate (**1a**) with sodium

borohydride, followed by cyclization of the resulting hydroxyester, yielded **1c** in a *trans/cis* ratio of 1/1 [4].

The analysis of the reductive cyclization of ethyl 2-cyclohexanoneacetate (**1a**) revealed that when 1,4-ketoesters were utilized reflux conditions were required for a good yield of the lactone product to be obtained. Therefore, in the acyclic case, refluxing ethyl 4-oxopentanoate (**2a**) with sodium cyanoborohydride in tetrahydrofuran resulted in an 81% yield of γ-valerolactone (**2c**).

The synthesis of δ-lactones were examined with carbocyclic and acyclic 1,5-ketoesters. In the carbocyclic case, reductive cyclization of ethyl 3-(5-(1,1-dimethylethyl)-2-oxocyclohexyl)propanoate (**3a**), at room temperature, yielded 84% of the desired 6-(1,1-dimethylethyl)octahydro-2*H*-1-benzopyran-2-one (**3c**) with a *trans/cis* ratio of 1.6/1. An earlier report [4] employing sodium borohydride did not indicate the *trans/cis* ratio of the product. However, it has been reported that the reduction of ethyl 2-cyclohexanoneacetate (**1a**) or its corresponding acid with sodium borohydride yielded similar stereochemical carbocyclic products [4]. By analogy, this relationship should be valid for the 1,5-ketoester derivatives. The reduction of 3-(2-oxocyclohexyl)propionic acid with sodium borohydride was reported to yield octahydro-2*H*-1-benzopyran-2-one in a *trans/cis* ratio of 2/1 [4].

Investigation of the reaction utilizing ethyl 5-oxohexanoate (**4a**) resulted in no δ-valerolactone (**4c**) being formed under room temperature or reflux conditions. These results are attributed to the flexibility of the acyclic derivative as well as to the poor leaving group ability of the ethoxide group. This combination results in an ineffective system for cyclization in the acyclic system, derivative **4**, whereas in the carbocyclic case, derivative **3**, a poor leaving group is compensated for when the system is rigid. To investigate this in more detail, a 1,5-ketoester bearing an effective aryl leaving group was examined. Reductive cyclization of 2-methoxy-4-methylphenyl 2-isopropyl-5-oxohexanoate (**5a**) yielded the corresponding lactone **5c**, in an 83% yield, under reflux conditions. This confirms that cyclization of flexible acyclic 1,5-hydroxyesters requires a good leaving group.

In this procedure, reduction of the ketoester to the hydroxyester occurred, at room temperature, on addition of the acidic THF solution. This was evident by examination of the reaction products produced from the room temperature reduction of ketoester derivatives **1a** and **4a**. The only product observed, other than the lactone, was the hydroxyester **1b** and **4b** respectively. Therefore, the reflux conditions are required for ring closure of the *in situ* formed hydroxyester to occur in a reasonable period of time.

It is interesting to compare the ring closure ability of the 1,4- and 1,5-hydroxyester intermediates formed in the reaction. In the case of the 1,4-hydroxyesters, ring closure occurs in the acyclic as well as the carbocyclic case, regardless of the leaving group. This illustrates the ease at which 1,4-hydroxyesters form lactones, however, it should be noted that ring closure occurred to a greater extent when reflux conditions were utilized as compared to room temperature conditions, as illustrated in the carbocyclic case. In the 1,5-hydroxyester system, there is a major difference in the ease of ring closure to form lactones with respect to the acyclic and carbocyclic cases. In the acyclic case, a good leaving group is required for lactone formation, while in the carbocyclic system, lactone formation occurs with a poor leaving group, even at room temperature. The temperature difference required for the ring closure of the carbocyclic 1,4- and 1,5-hydroxyester derivatives **1b** and **3b** can be attributed to the strain associated with ring formation in a rigid system [5]. In the 1,4-hydroxyester system the transition state would exhibit more strain than the 1,5-hydroxyester derivatives and as a result require more vigorous conditions for ring closure to occur.

Finally, several α,β-unsaturated ketoesters were examined. Previous literature data on the use of sodium cyanoborohydride indicates that reduction of the carbonyl moiety of acyclic enone derivatives occurs in preference to the unsaturated portion to generate allylic alcohol derivatives [6]. In the case of cyclic enone derivatives, a mixture of allylic and saturated alcohols are obtained resulting from competing 1,2 and 1,4 addition [6]. Reductive cyclization of ethyl 3-benzoylacrylate (**6a**), under reflux conditions, resulted in no lactone product **6c**. The products isolated were the starting unsaturated ketoester, the saturated ketoester, and the unsaturated hydroxyester. The saturated ketoester and unsaturated hydroxyester were in a ratio of 1/2 demonstrating the preference for reduction of the carbonyl moiety over the unsaturated portion of the molecule. However, the generated unsaturated hydroxyester intermediate did not cyclize to form the lactone due to the double bond being in an *E* configuration. In the case of cyclic enones, reductive cyclization of ethyl-2-(2-oxocyclohex-3-enyl) acetate (**7a**) resulted in no desired unsaturated lactone product **7c**. The products isolated were the starting unsaturated ketoester, the saturated lactone, and the saturated hydroxy ester. Thus, 1,4 addition to the α,β-unsaturated ketoester **7a** is the preferred mode of the reaction.

EXPERIMENTAL

Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee. Infrared spectra were recorded on a Perkin-Elmer 1320 Spectrophotometer. The chemical shifts and coupling constants (J) are reported in δ and Hertz respectively, using a Varian XL-300 spectrometer, with TMS as the internal standard. Isocratic, normal phase high pressure liquid chromatography (hplc) was conducted with a Waters Associates Liquid Chromatograph (pump, 6000A; injector, UK6; RI detector, 401) equipped with a Partisil M20 10/15 or Partisil 10/25 column, solvent composition was 20% ethyl acetate in hexane. A Varian Model 3700

gas chromatograph (gc) was utilized with a 6 ft, OV-101 column. Ethyl 2-cyclohexanoneacetate (**1a**), ethyl 4-oxopentanoate (**2a**), ethyl 5-oxohexanoate (**4a**) were obtained from Aldrich Chemical Company and were used without purification. Ethyl 3-benzoylacrylate (**6a**) obtained from Aldrich Chemical Company was purified by chromatography (10% ethyl acetate in hexane on silica gel) before use. Ethyl 3-(5-(1,1-dimethylethyl)-2-oxocyclohexyl)propanoate (**3a**) [7] and ethyl-2-(2-oxocyclohex-3-enyl) acetate (**7a**) [8] were synthesized according to literature procedures.

2-Methoxy-4-methylphenyl 2-Isopropyl-5-oxohexanoate (**5a**).

A solution of 2-isopropyl-5-oxohexanoic acid (4.0 g, 23.4 mmoles) [9] in 4 ml of benzene was added to a chilled solution (0°) of oxalyl chloride (6.0 g, 46.8 mmoles) in 4 ml of benzene, under a nitrogen atmosphere. The solution was warmed to room temperature and stirred for 24 hours. The benzene was removed under reduced pressure and the residue was subjected to high vacuum pressure (0.1 mm Hg) for approximately 10 minutes. The residue was dissolved in 3 ml of fresh benzene and a solution of 2-methoxy-4-methylphenol (3.1 g, 22.2 mmoles) in 5 ml of benzene was added quickly at room temperature and stirred for 24 hours. Ether was added and the solution was washed with water, saturated sodium chloride, 5% potassium hydroxide and dried over calcium chloride. Evaporation of the solvent under reduced pressure yielded a dark residue, which was purified by Kugelrohr distillation, bp 120-125°/0.04 mm Hg, 1.02 (15%); ir (film): 1710, 1750 cm^{-1}; ^1H nmr (deuteriochloroform): δ 6.95-6.62 (m, 3H), 3.80 (s, 3H), 2.75-1.50 (m, 12H), 1.05 (dd, J = 6.0, 2.0 Hz, 6H).

Anal. Calcd. for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 69.82; H, 8.31.

Reductive Cyclization of 1,4- and 1,5-Ketoesters. General Procedure.

To a solution of the ketoester (5 mmoles) in tetrahydrofuran (10 ml) was added 5 mmoles of sodium cyanoborohydride at room temperature. The mixture was acidified to a *p*H of approximately 2 (*p*H paper) with a solution of hydrochloric acid in tetrahydrofuran (1:4 concentrated hydrochloric acid in THF). The mixture was stirred, under a nitrogen atmosphere, at room temperature for the period indicated in Table I or was stirred for 4 hours at room temperature followed by refluxing for the time indicated in Table I. The mixture was neutralized with aqueous saturated sodium bicarbonate, extracted with ether, dried over anhydrous magnesium sulfate, evaporated under reduced pressure and purified chromatographically.

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