Notes

A Novel Route to α-Substituted γ-Lactones via Lactone Enolates

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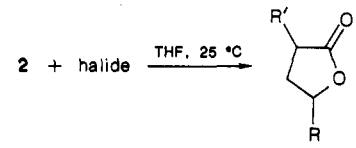
Much attention has been focused on alkali metal solutions in the last decade.[1] We recently examined the kinetics of alkali metal dissolution in THF containing cation-complexing agents (e.g., 18-crown-6) and the nature of the active species formed.[2] We found that the concentrations of metal anions and solvated electrons in such solutions depend strongly on the reaction conditions and kinetic parameters. According to this study, solvated electrons and not K^- anions are the initial products of dissolution of potassium in THF solutions of 18-crown-6 at room temperature. However, after several minutes the predominant species become K^- anions accompanied by K^+ cations complexed by the crown ether.[2]

We have previously reported that these alkali metal solutions are powerful reagents for opening β-lactone rings by C–C bond cleavage.[3] We here report on a novel, direct method for introducing α-substitution into γ-lactones by using this reagent.

α-Alkyl γ-lactones can be synthesized via their enolates in several ways;[4] for example, α-methyl-γ-butyrolactone was obtained from γ-butyrolactone by reaction with methyl iodide and a lithium dialkylamide in THF at −78 °C.[5] The procedure now reported can be employed in the synthesis of both α-alkyl and α-acyl γ-lactones in good yields; side reactions such as O-acylation do not occur.

When a THF solution of potassium, containing K^- anions and K^+ cations complexed by 8-crown-6, is introduced at room temperature into a THF solution of a γ-lactone, the lactone enolate is formed (Scheme I). Thus lactones **1a** and **1b** yielded almost quantitatively the corresponding 3-(2-oxolanonyl) anions **2a** and **2b**; the latter was isolated under argon and characterized by IR spectroscopy.[6] The enolates **2a** and **2b** can react, either in situ or after isolation, with a variety of alkyl and acyl halides to provide good yields of the corresponding α-substituted γ-lactones (Table I). The physical and spectral data for these lactones agreed well with those reported in the literature.[7–10]

Table I. Reaction of Alkyl and Acyl Halides with γ-Lactone Enolates



enolate	halide	R	R′	reacn time, h	yield, %
2a	CH_3I	H	CH_3	3	89
2a	C_2H_5I	H	C_2H_5	4	82
2a	n-C_4H_9I	H	n-C_4H_9	5	80
2a	n-$C_5H_{11}I$	H	n-C_5H_{11}	6	79
2a	$PhCH_2Cl$	H	$PhCH_2$	5	86
2a	PhCOCl	H	PhCO	3	93
2a	CH_3COCl	H	CH_3CO	5	85
2b	CH_3I	CH_3	CH_3	3	88
2b	C_2H_5I	CH_3	C_2H_5	4	81
2b	$PhCH_2Cl$	CH_3	$PhCH_2$	5	85
2b	PhCOCl	CH_3	PhCO	3	95

This procedure constitutes a novel route to α-alkyl or α-acyl-γ-lactones.[4] Deprotonation of the γ-lactone ring and formation of the lactone enolate take place by interaction with K^- anions. The highest yields and shortest reaction times were obtained in the formation of the α-acyl, α-methyl, and α-benzyl γ-lactones (Table I). Such side reactions as formation of α,α-disubstituted derivatives, self-condensation, or O-acylation (which occurs with some previously described methods)[11] did not take place as confirmed by GC analysis, MS, NMR, and IR spectroscopy. We did not observe any significant influence of the methyl substituent in the γ-position (e.g., lactone **2b**) on the reaction yield.

Studies of the extension of this reaction to other heterocycles containing carbonyl groups are under way.

Experimental Section

Chromatography. Gas chromatographic analyses were performed on a Varian 2800 gas chromatograph equipped with a preparative unit and an electronic integrator. GC analyses were carried out in a 2 mm i.d. glass column, 2 m long, packed with OV-17, 15% on Chromosorb W DMSC, with an injector temperature of 225 °C and a detector temperature of 295 °C. The column temperature was increased from 100 to 285 °C at the rate of 12 deg/min, and argon was the carrier gas (flow rate, 25 mL/min). A flame ionization detector (FID) was used. Preparative separations were run on a 10 mm i.d., 6 m long, aluminum column packed with OV-17, 20% on Chromosorb W, 45–60 mesh.

Spectroscopy. IR spectra were recorded on a UR-20 Carl Zeiss Jena spectrophotometer. ^1H NMR spectra were recorded on a Varian XL-100 spectrometer, using Me_4Si as an internal standard. GC–MS data were obtained on a Varian MAT 711 mass spec-

(1) (a) Dye, J. L. *Pure Appl. Chem.* **1977**, *49*, 3. (b) Lacoste, J.; Schue, F. *J. Organomet. Chem.* **1982**, 231, 279. (c) Grobelny, Z.; Stolarzewicz, A. *Pol. J. Chem.* **1981**, *55*, 1933.

(2) Jedliński, Z.; Stolarzewicz, A.; Grobelny, Z.; Szwarc, M. *J. Phys. Chem.* **1984**, *88*, 6094.

(3) (a) Jedliński, Z.; Kurcok, P.; Kowalczuk, M. *Macromolecules* **1985**, *18*, 2679. (b) Jedliński, Z.; Kurcok, P.; Kowalczuk, M. *Makromol. Chem. Macromol. Symp.* **1986**, *3*, 277–293.

(4) (a) Grieco, P. A. *Synthesis* **1975**, 67 and references therein. (b) Cohen, B. J.; Kraus, M. A.; Patchornik, A. *J. Am. Chem. Soc.* **1981**, *103*, 7620.

(5) Posner, G.; Loomis, G. *J. Chem. Soc., Chem. Commun.* **1972**, 892.

(6) The IR spectrum of **2a**, obtained in dry Nujol under an argon atmosphere, was as follows: 2970 (m), 1740 (w), 1680 (s), 1580 (s), 1510 (s), 1330 (m), 1300 (m), 1270 (m), 1240 (m), 1170 (m), 1130 (m), 1110 (m), 1050 (m), 990 (s), 720 (s) cm^{-1}. A strong absorption band at 1680 cm^{-1} (corresponding to the stretching vibrations of the carbon–carbon double bond) and a weak absorption band at 1740 cm^{-1} (corresponding to the stretching vibrations of the carbonyl group) in the IR spectrum of **2a** indicate that the corresponding lactone enolates are formed.

(7) Flechtner, T. W. *J. Org. Chem.* **1977**, *42*, 901.

(8) Cannone, P.; Regnault, A. *Can. J. Chem.* **1969**, *47*, 2837.

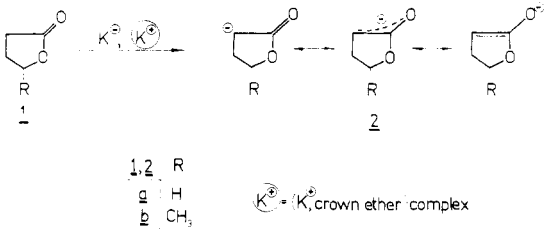
(9) Kametani, T.; Nemoto, H. *Chem. Pharm. Bull.* **1971**, *19*, 1325.

(10) Temnikova, T. J.; Merkina, G. W.; Borodawko, W. A.; Jaskina, N. J. *Zh. Org. Khim.* **1970**, *6*, 739.

(11) Reppe, W. *Justus Liebigs Ann Chem.* **1955**, *596*, 158.

0022-3263/87/1952-4601$01.50/0

Scheme I



trometer at 70 eV, with ion source temperature of 200 °C.

Reagents. γ-Butyrolactone (FLUKA) was distilled twice over CaH_2 in an atmosphere of dry argon. The fraction boiling at 80–81 °C (11 mmHg) was collected (99.8%, GC). γ-Valerolactone (FLUKA) was dried in a similar manner. The fraction boiling at 82–83 °C (10 mmHg) was collected (99.7%, GC). Methyl iodide (FLUKA) was dried over calcium chloride and distilled in an atmosphere of dry argon. The fraction boiling at 42 °C was collected (99.6%, GC). Ethyl iodide (FLUKA, bp 71 °C, 99.8%, GC), *n*-butyl iodide (FLUKA, bp 129 °C, 99.7%, GC), and *n*-pentyl iodide (FLUKA, bp 155 °C, 99.8%, GC) were dried in a similar manner. Benzoyl chloride (FLUKA) was distilled over magnesium sulfate in an atmosphere of dry argon. The fraction boiling at 73–74 °C (11 mmHg) was collected. Acetyl chloride (FLUKA, bp 51 °C, 98.9%, GC) and benzyl chloride (FLUKA, bp 65.5 °C (11 mmHg), 99.6% GC) were dried similarly.

Solvent. THF was purified according to a described method[12] and was finally distilled over a sodium–potassium alloy in an atmosphere of dry argon.

Preparation of Potassium Solutions and Enolates 2. Preparation of the potassium solution and alkylation or acylation of the lactone enolate were conducted in the apparatus depicted in Figure I. The apparatus was dried before use for several hours under high vacuum at 60 °C. A potassium mirror was obtained in part a of the apparatus by high-vacuum distillation of metallic potassium placed in tube b. The potassium solution was formed by the contact of the potassium mirror with a solution of 18-crown-6 in THF (0.2 mol/L). After exactly 15 min the required amount of the resulting blue solution was filtered through a coarse frit (c) to the calibrated tube (d). The lactone enolates **2** were obtained at room temperature after introduction of the potassium solution from tube d into the reactor (e) containing the THF solution of lactone **1**.

Dihydro-3-methyl-2(3*H*)-furanone (α-Methyl-γ-butyrolactone). General Procedure for Alkylation of γ-Lactones 1. Methyl iodide (0.54 mL, 8.7 mmol) was added slowly (syringe), under a dry argon atmosphere into the reactor containing the THF solution of **2a** obtained from 0.7 g (8 mmol) of **1a**. The reaction was conducted for 3 h at room temperature and then was quenched with saturated ammonium chloride solution (10 mL). Extraction with ether (three times, 15 mL), washing with water, drying with anhydrous $MgSO_4$, solvent evaporation, and distillation under reduced pressure afforded 710 mg (89%) of the product: IR (capillary cell) ν_{max} 1770 cm^{-1}; MS, *m/e* 100 (M^+); ^1H NMR ($CDCl_3$) δ 1.2 (d, 3 H, *J* = 6.0 Hz), 1.4–3.3 (m, 3 H), 4.1–4.3 (m, 2 H). Anal. Calcd for $C_5H_8O_2$: C, 59.99; H, 8.05. Found: C, 59.96; H, 8.06.

Similarly obtained were the following.

Dihydro-3-ethyl-2(3*H*)-furanone (α-ethyl-γ-butyrolactone): yield, 750 mg (82%); IR (capillary cell) ν_{max} 1776 cm^{-1}; MS, *m/e* 114 (M^+); ^1H NMR δ 1.0 (t, 3 H, *J* = 7.5 Hz), 1.5–2.7 (m, 5 H), 4.2–4.6 (m, 2 H). Anal. Calcd for $C_6H_{10}O_2$: C, 63.14; H, 8.83. Found: C, 63.20; H, 8.82.

Dihydro-3-butyl-2(3*H*)-furanone (α-butyl-γ-butyrolactone): yield, 910 mg (80%); IR (CCl_4) ν_{max} 1776 cm^{-1}; MS, *m/e* 142 (M^+); ^1H NMR ($CDCl_3$) δ 0.9 (t, 3 H), 1.2–2.6 (m, 9 H), 4.1–4.4 (m, 2 H). Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.60; H, 9.98.

(12) Wiesserberger, A. *Organic Solvents*; Wiley: New York, 1970; p 704.

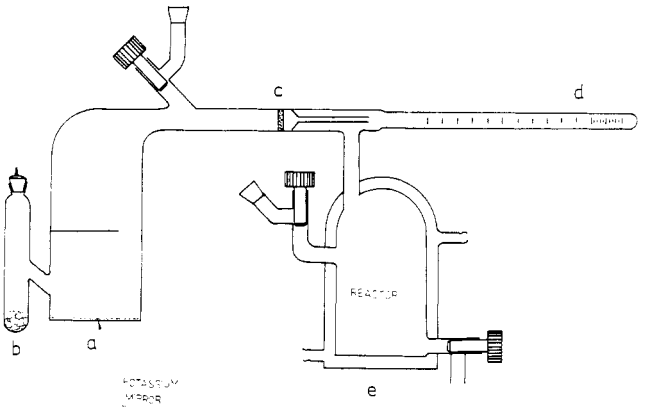


Figure 1. Apparatus used for the preparation of potassium solution and formation of γ-lactone enolates.

Dihydro-3-pentyl-2(3*H*)-furanone (α-pentyl-γ-butyrolactone): yield, 980 mg (79%); IR (CCl_4) ν_{max} 1776 cm^{-1}; MS, *m/e* 156 (M^+); ^1H NMR ($CDCl_3$) δ 0.9 (t, 3 H), 1.1–2.7 (m, 11 H), 4.1–4.4 (m, 2 H). Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.22; H, 10.36.

Dihydro-3-(phenylmethyl)-2(3*H*)-furanone (α-benzyl-γ-butyrolactone): yield, 1.2 g (86%); IR (capillary cell) ν_{max} 1775 cm^{-1}; MS, *m/e* 176 (M^+); ^1H NMR ($CDCl_3$) δ 1.3–3.3 (m, 6 H), 4.0–4.3 (m, 2 H), 7.4–7.6 (m, 5 H, Ar). Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.85; H, 6.79.

Dihydro-3,5-dimethyl-2(3*H*)-furanone (α-methyl-γ-valerolactone): yield, 800 mg (88%), mixture of two stereoisomers (mole ratio 3:2, GC); IR (CCl_4) ν_{max} 1760 cm^{-1}; MS, *m/e* 114 (M^+); ^1H NMR ($CDCl_3$) δ 1.2 (d, 3 H, *J* = 6.4 Hz) 1.4 (d, 3 H, *J* = 6.3 Hz), 1.5–2.9 (m, 3 H), 4.2–4.6 (m, 1 H). Anal. Calcd for $C_6H_{10}O_2$: C, 63.14; H, 8.83. Found: C, 63.12; H, 8.84.

Dihydro-3-ethyl-5-methyl-2(3*H*)-furanone (α-ethyl-γ-valerolactone): yield, 830 mg (81%), mixture of two stereoisomers (mole ratio 2:1, GC); IR (capillary cell) ν_{max} 1770 cm^{-1}; MS, *m/e* 128 (M^+); ^1H NMR δ 1.0 (t, 3 H, *J* = 7.0 Hz), 1.2–2.6 (m and d, 8 H, *J* = 6.2 Hz), 4.0–4.5 (m, 1 H). Anal. Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.62; H, 9.50.

Dihydro-5-methyl-3-(phenylmethyl)-2(3*H*)-furanone (α-benzyl-γ-valerolactone): yield, 1.29 g (85%), mixture of two stereoisomers (mole ratio 1:2, ^1H NMR); IR (capillary cell) ν_{max} 1770 cm^{-1}; MS, *m/e* 190 (M^+) (14); ^1H NMR δ 1.23, 1.29 (d, d, 3 H, *J* = 6.2 Hz), 1.4–3.3 (m, 5 H), 4.2–4.4 (m, 1 H), 7.16 (s, 5 H, Ar). Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.77; H, 7.42. Found: C, 75.91; H, 7.45.

3-Benzoyldihydro-2(3*H*)-furanone (α-Benzoyl-γ-butyrolactone). General Procedure for Acylation of Lactones 1. A solution of 1 mL (8.6 mmol) of dry benzoyl chloride in dry THF was introduced by syringe into a THF solution of **2a**, obtained from 0.7 g (8 mmol) of **1a**. After 3 h of being stirred at room temperature, the solution was filtered. Evaporation followed by distillation under reduced pressure gave the product: yield, 1.4 g (93%); IR (capillary cell) ν_{max} 1770 cm^{-1}; MS, *m/e* 190 (M^+) (4); ^1H NMR ($CDCl_3$) δ 2.3–3.1 (m, 2 H), 4.1–4.7 (m, 3 H), 7.3–8.2 (m, 5 H, Ar). Anal. Calcd for $C_{11}H_{10}O_3$: C, 69.47; H, 5.30. Found: C, 69.53; H, 5.32.

Similarly obtained were the following.

Dihydro-3-acetyl-2(3*H*)-furanone (α-acetyl-γ-butyrolactone): yield, 870 mg (85%); IR (capillary cell) ν_{max} 1776 cm^{-1}; MS, *m/e* 128 (M^+); ^1H NMR δ 1.8–3.8 (m, 3 H), 2.4 (s, 3 H), 4.1–4.5 (m, 2 H). Anal. Calcd for $C_6H_8O_3$: C, 56.25; H, 6.29. Found: C, 56.35; H, 6.31.

Dihydro-3-benzoyl-5-methyl-2(3*H*)-furanone (α-benzoyl-γ-valerolactone): yield, 1.55 g (95%); MS, *m/e* 204 (M^+)(5); IR (capillary cell) ν_{max} 1770 cm^{-1}; ^1H NMR δ 1.2–3.4 (m, and dd, 5 H, *J* = 6.1 Hz), 3.9–5.4 (m, 2 H), 7.2–8.3 (m, 5 H, Ar). Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.60; H, 5.92. Found: C, 70.45; H, 6.02.