# Notes

## Novel Synthesis of α-Hydroxy Ketones and γ- or δ-Keto Esters from Cyclic Iodo Carbonates and Iodo Lactones

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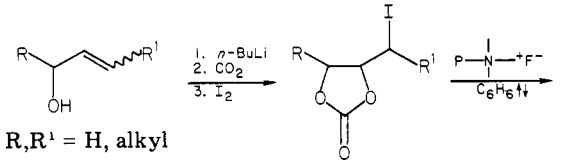
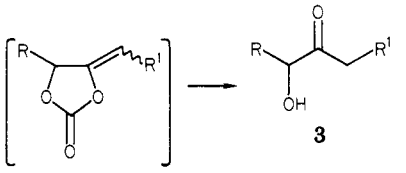
The introduction of neighboring functional groups in a sequence directed to the total synthesis of natural products, including macrolide antibiotics, is of great importance in modern synthetic strategy.[1] In previous papers we described new methods for regio- and stereocontrolled functionalization of the double bonds of allylic and homoallylic alcohols. Thus amino diols and hydroxyaziridines were obtained via iodoxazolines and iododihydrooxazines,[2] while 1,2- and 1,3-diols, triols, and expoxy alcohols were synthesized by starting from cyclic iodo carbonates,[3,4] versatile intermediates susceptible to several chemical transformations.

We report here a short, regioselective synthesis of α-hydroxy ketones starting from allylic alcohols via cyclic iodo carbonates. This goal is reached by treatment of iodo carbonates **1** with fluoride anion on polymeric support,[5] as outlined in eq 1.




R,R¹ = H, alkyl

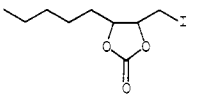
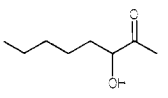
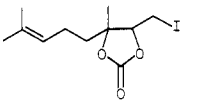
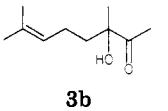
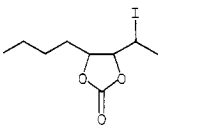
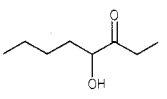
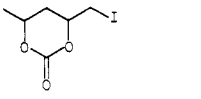
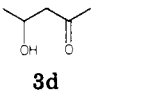
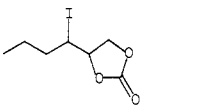
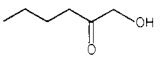
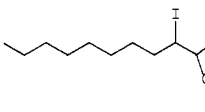
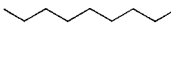
**1**



**2** **3** (1)

The reaction proceeds through the intermediate **2** (isolated for entry **3b**), which successively undergoes hydrolysis in the reaction medium to yield the α-hydroxy ketone **3**.

Table I. Synthesis of Hydroxy Ketones

| substrate | product | yield,[a,b] % |
|---|---|---|
|  **1a** |  **3a** | 82 |
|  **1b** |  **3b** | 74 |
|  **1c** |  **3c** | 68 |
|  **1d** |  **3d** | 54 |
|  **1e** |  **3e** | 71 |
|  **1f** |  **3f** | 70 |

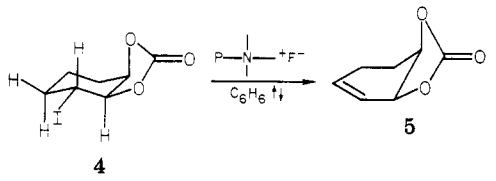
[a] Yields refer to pure compounds isolated by silica gel chromatography with cyclohexane/ethyl acetate (9:1) as the eluant. [b] Satisfactory analytical data (±0.4% for C and H) were obtained for all new compounds listed in the table.

The reaction seems to be general for five-membered cyclic iodo carbonates, while six-membered iodo carbonates, obtained from homoallylic alcohols, give only poor yields of β-hydroxy ketones (a retro-Aldol reaction due to the basicity of fluoride anion is involved). The good results observed are reported in Table I. This approach to α-hydroxy ketones is preferable in some respects to the hitherto reported methods,[6] because of the total regioselectivity, the mild reaction conditions, and the easy workup, due to the use of a polymeric reagent. To confirm the supposed trans elimination mechanism of this reaction, we treated cyclic iodo carbonate **4**, with assigned stereostructure,[3b] with fluoride anion on a polymeric support: the expected unsaturated cyclic carbonate **5** was obtained in 75% yield (eq 2).

Since the results above were reported, we have evolved a procedure for the conversion of γ- and δ-iodo lactones

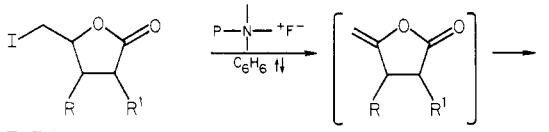
(1) (a) Nicolaou, K. C. *Tetrahedron* **1977**, *33*, 683. (b) ApSimon, J. W.; Seguin, R. P. *Ibid.* **1979**, *35*, 2797.
(2) (a) Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. *J. Chem. Soc., Chem. Commun.* **1982**, 1308. (b) Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. *Ibid.* **1982**, 1309.
(3) (a) Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. *J. Chem. Soc., Chem. Commun.* **1981**, 465. (b) Bongini, A.; Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. *J. Org. Chem.* **1982**, *47*, 4626.
(4) For further examples of cyclofunctionalization reactions see also: (a) Overman, L. E.; Campbell, C. B. *J. Org. Chem.* **1974**, *39*, 1474. (b) Haslanger, M. F.; Ahmed, S. *J. Org. Chem.* **1981**, *46*, 4808. (c) Bartlett, P. A.; Meadows, J. D.; Brown, E. G.; Morimoto, A.; Jernstedt, K. K. *J. Org. Chem.* **1982**, *47*, 4013. (d) Pauls, H. W.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1980**, *102*, 3956.
(5) (a) Cainelli, G.; Manescalchi, F.; Panunzio, M. *Synthesis* **1976**, 472. (b) Cainelli, G.; Cardillo, G.; Orena, M. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1597.
(6) (a) Kipnis, F.; Soloway, H.; Ornfelt, J. *J. Am. Chem. Soc.* **1948**, *70*, 142 (b) Gardner, J. N.; Carlon, F. E.; Gnoj, O. *J. Org. Chem.* **1968**, *33*, 3294. (c) Katzenellenbogen, J. A.; Bowlus, S. B. *J. Org. Chem.* **1973**, *38*, 627. (d) Rubottom, G. M.; Vasquez, M. A.; Pelegrina, D. R. *Tetrahedron Lett.* **1974**, 4319. (e) Lee, T. V.; Toczek, J. *Ibid.* **1982**, 2917.

0022-3263/84/1949-0701$01.50/0 © 1984 American Chemical Society

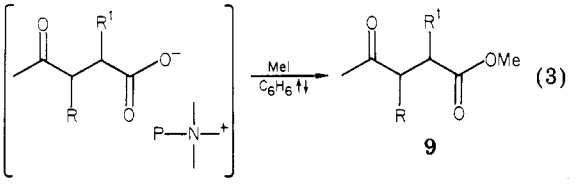


4 5 (2)

to γ- and δ-keto esters by treating iodo lactones **6** with supported fluoride anion in refluxing benzene (eq 3). The



**6**, R,R¹ = H, phenyl **7**



**8** **9** (3)

intermediates enol lactones **7** under the reaction conditions hydrolyze to keto acids which fix on the polymer as carboxylate anions **8**. By successive treatment with methyl iodide,[7] the methyl keto esters **9** are isolated in very good yield, as reported in Table II.

This procedure is a noteworthy improvement for the preparation of methyl γ- and δ-keto esters,[8] since it is rapid, operationally simple, and affords pure products in high yields under mild conditions. Furthermore, the elimination of hydrogen iodide by fluoride anion on polymeric support constitutes a convenient alternative to the use of DBU.[9]

## Experimental Section

**General Methods.** $^1H$ nuclear magnetic resonance ($^1H$ NMR) spectra were measured with a Perkin-Elmer R12B instrument (60 MHz) with tetramethylsilane ($Me_3Si$) as the internal standard and $CDCl_3$ as the solvent. Chemical shifts are reported as δ values. Infrared (IR) spectra were recorded on a Perkin-Elmer 710B spectrophotometer, and the absorptions are given in reciprocal centimeters. Mass spectra (MS) were taken on a double-focusing Varian MAT 112S instrument at an ionizing voltage of 70 eV. Column chromatography separations were performed on silica gel (Merck, 70–230 mesh). Melting points (mp) are uncorrected.

**General Procedure for Synthesis of Hydroxy Ketones.** To a solution of the iodo carbonate 1 (4 mmol) in benzene (20 mL) was added Amberlyst A 26 in the $F^-$ form[10] (8 g, ~30 mequiv), and the suspension was refluxed for 5 h. The resin was then filtered off, the solvent evaporated in vacuo, and the residue chromatographed on silica gel (cyclohexane/ethyl acetate 9:1) to give the hydroxy ketone **3** in good yield (see Table I).

**3-Hydroxyoctan-2-one (3a)**: IR 3450, 1720; $^1H$ NMR 0.9 (t, 3 H, $CH_3$), 1.15–1.9 (m, 8 H, $CH_2$), 2.11 (s, 3 H, $CH_3CO$), 3.6 (br s, 1 H, OH), 4.05 (t, 1 H, CHOH, $J$ = 10 Hz); MS, $m/e$ 144 ($M^+$), 87, 57.

**3-Hydroxy-3,7-dimethyloct-6-en-2-one (3b)**: IR 3490, 1710; $^1H$ NMR 1.3 (s, 3 H, $CH_3$), 1.6 and 1.67 (2 s, 6 H, $CH_3$), 1.5–2 (m, 4 H, $CH_2$), 2.15 (s, 3 H, $CH_3CO$), 3.7 (br s, 1 H, OH), 5.05 (br t, 1 H, CH=, $J$ = 6 Hz); MS, $m/e$ 170 ($M^+$), 127, 109, 88, 79.

**4-Hydroxyoctan-3-one (3c)**: IR 3450, 1710; $^1H$ NMR 0.95 (complex pattern, 6 H, $CH_3$), 1.4–2 (m, 6 H, $CH_2$), 2.5 (q, 2 H, $CH_2CO$), 3.6 (br s, 1 H, OH), 4.15 (m, 1 H, C*H*OH); MS, $m/e$ 144 ($M^+$), 87, 69, 57.

**4-Hydroxypentan-2-one (3d)**: IR 3410, 1710; $^1H$ NMR 1.2 (d, 3 H, $CH_3$, $J$ = 6 Hz), 2.18 (s, 3 H, $CH_3CO$), 2.58 (d, 2 H, $CH_2$, $J$ = 6 Hz), 3.35 (br s, 1 H, OH), 4.22 (sextet, 1 H, C*H*OH); MS, $m/e$ 102 ($M^+$), 84, 69, 58.

**1-Hydroxyhexan-2-one (3e)**: IR 3460, 1720; $^1H$ NMR 1 (t, 3 H, $CH_3$), 1.2–1.9 (m, 4 H, $CH_2$), 2.5 (br t, 2 H, $CH_2CO$), 3.2 (br s, 1 H, OH), 4.3 (s, 2 H, $CH_2OH$); MS, $m/e$ 116 ($M^+$), 85, 57.

**1-Hydroxyundecan-2-one (3f)**: mp 47 °C; IR 3460, 1715; $^1H$ NMR 0.9 (t, 3 H, $CH_3$), 1.1–1.5 (m, 14 H, $CH_2$), 2.4 (br t, 2 H, $CH_2CO$, $J$ = 6 Hz), 3.15 t, 1 H, OH, $J$ = 5 Hz), 4.22 (d, 2 H, $CH_2OH$, $J$ = 5 Hz); MS $m/e$ 186 ($M^+$), 155, 143, 85.

**4-(4-Methylpent-3-en-1-yl)-4-methyl-5-methylene-1,3-dioxacyclopentanone (2b)**: IR 1830, 855; $^1H$ NMR 1.4–1.7 (3 s, 9 H, $CH_3$), 1.75–2.3 (m, 4 H, $CH_2$), 4.3 (d, 1 H, $CH_2$=C, $J$ = 6 Hz), 4.75 (d, 1 H, $CH_2C$=, $J$ = 6 Hz), 5.1 (t, 1 H, CH=, $J$ = 6 Hz); MS, $m/e$ 196 ($M^+$), 152, 137, 110, 109, 95.

**1,3-Dioxatetrahydroind-5-en-2-one (5)**: IR 1800; $^1H$ NMR 1.85–2.5 (m, 4 H, $CH_2$), 4.9 (m, 2 H, CHO–), 5.5–6.4 (m, 2 H, CH=CH); MS, $m/e$ 140 ($M^+$), 96, 95, 68, 55.

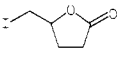
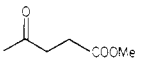
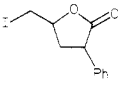
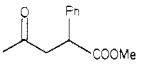
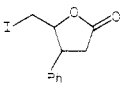
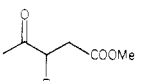
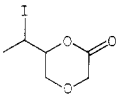
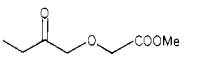
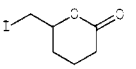
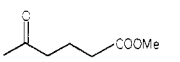
**General Procedure for Synthesis of Methyl Keto Esters.** To a solution of the iodo lactone **6** (4 mmol) in benzene (20 mL), was added Amberlyst A 26 in the $F^-$ form[10] (8 g, ~30 mequiv), and the suspension was refluxed for 3 h. The resin was then filtered off and added to a solution of methyl iodide (1 mL) in benzene (20 mL), and the suspension was refluxed for 1 h. After filtration of the resin and evaporation in vacuo of the solvent, the methyl ester **9** was obtained practically pure in good yield (see Table II).

**Methyl 4-oxopentanoate (9a)**: IR 1740, 1720; $^1H$ NMR 2.15 (s, 3 H, $CH_3CO$), 2.6 (m, 4 H, $CH_2$), 3.65 (s, 3 H, $OCH_3$); MS, $m/e$ 130 ($M^+$), 99, 85, 43.

**Methyl 2-phenyl-4-oxopentanoate (9b)**: mp 44 °C; IR 1740, 1720; $^1H$ NMR 2.1 (s, 3 H, $CH_3CO$), 2.7 (dd, 1 H, $CH_2CO$, $J_{gem}$ = 20 Hz, $J_{vic}$ = 4 Hz), 3,4 (dd, 1 H, $CH_2CO$, $J_{gem}$ = 20 Hz, $J_{vic}$ = 10 Hz), 3.6 (s, 3 H, $OCH_3$), 4.1 (dd, 1 H, CHCO, $J$ = 4 Hz, $J$ = 10 Hz), 7.35 (5 H arom); MS, $m/e$ 206 ($M^+$), 174, 131, 121, 102.

**Methyl 3-phenyl-4-oxopentanoate (9c)**: IR 1740, 1720; $^1H$ NMR 2.1 (s, 3 H, $CH_3CO$), 2.55 (dd, 1 H, $CH_2CO$, $J_{gem}$ = 18 Hz, $J_{vic}$ = 6 Hz), 3.3 (dd, 1 H, $CH_2CO$, $J_{gem}$ = 18 Hz, $J_{vic}$ = 9 Hz), 3.65 (s, 3 H, $OCH_3$), 4.25 (dd, 1 H, CHCO, $J$ = 9 Hz, $J$ = 6 Hz), 7.35 (5 H arom); MS, $m/e$ 206 ($M^+$), 176, 164, 131, 121, 104.

Table II. Synthesis of Keto Esters

| substrate | product | yield,[a,b] % |
|---|---|---|
|  **6a** |  **9a** | 73 |
|  **6b** |  **9b** | 79 |
|  **6c** |  **9c** | 83 |
|  **6d** |  **9d** | 74 |
|  **6e** |  **9e** | 72 |

[a] Yields refer to pure isolated compounds. [b] Satisfactory analytical data (±0.4% for C and H) were obtained for all new compounds listed in the table.

(7) Cainelli, G.; Manescalchi, F. *Synthesis* **1975**, 723.
(8) (a) Le Guillanton, G. *Bull. Soc. Chim. Fr.* **1969**, 2871. (b) Temple, R. D. *J. Org. Chem.* **1970**, *35*, 1275. (c) Hooz, J.; Layton, R. B. *Can. J. Chem.* **1972**, *50*, 1105. (d) Pelter, A.; Harrison, C. R.; Kirkpatrick, D. *Tetrahedron Lett.* **1973**, 4491.
(9) Jaeger, V.; Gunther, H. I. *Tetrahedron Lett.* **1977**, 2543.
(10) The resin was partially dried by azeotropic removal of the water from refluxing 1:1 dioxane/benzene.

**Methyl 3-oxa-5-oxoheptanoate (9d)**: IR 1750, 1730; $^1$H NMR 1.1 (t, 3 H, $CH_3$, $J$ = 8 Hz), 2.55 (q, 2 H, $CH_2CO$, $J$ = 8 Hz), 3.8 (s, 3 H, $OCH_3$), 4.25 (s, 4 H, $OCH_2CO$); MS, $m/e$ 160 ($M^+$), 103, 101, 75, 57.

**Methyl 5-oxohexanoate (9e)**: IR 1735, 1710; $^1$H NMR 1.6–2 (m, 2 H, $CH_2$), 2.13 (s, 3 H, $CH_3$), 2.2–2.7 (m, 4 H, $CH_2$), 3.65 (s, 3 H, $OCH_3$); MS, $m/e$ 144 ($M^+$), 112, 99, 74, 71.

**Registry No.** **1a**, 87761-86-2; **1b**, 87761-87-3; **1c**, 83134-77-4; **1d**, 78947-93-0; **1e**, 87761-88-4; **1f**, 87761-89-5; **2b**, 87761-95-3; **3a**, 37160-77-3; **3b**, 87761-93-1; **3c**, 87761-94-2; **3d**, 4161-60-8; **3e**, 73397-68-9; **3f**, 76917-16-3; **4**, 83134-80-9; **5**, 87761-96-4; **6a**, 1729-32-4; **6b**, 1729-26-6; **6c**, 87761-90-8; **6d**, 87761-91-9; **6e**, 87761-92-0; **9a**, 624-45-3; **9b**, 74457-44-6; **9c**, 25359-49-3; **9d**, 61363-67-5; **9e**, 13984-50-4.

## Direct Synthesis of Ferrocenyl Alcohols from Aldehydes and Ketones

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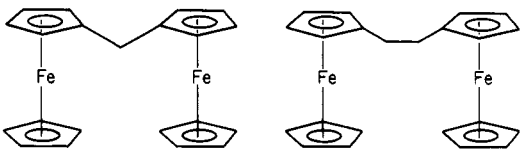
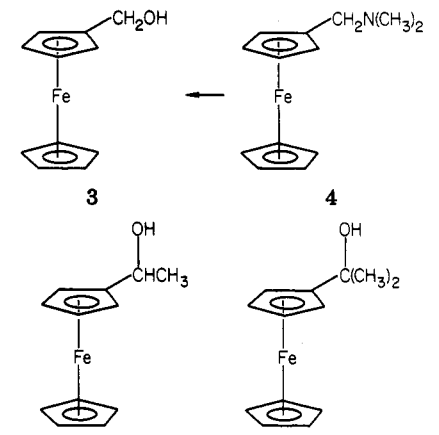
The number of reports dealing with the chemistry of ferrocene is staggering; if one limits the survey of the chemistry of ferrocene only to those reactions that are categorized under the name of the Friedel–Crafts reaction, the volume of literature seems little reduced. It is, therefore, surprising that the reaction of ferrocene with aldehydes and ketones in strongly acidic medium to produce ferrocenyl alcohols and olefins derived from these alcohols has not been previously described. To be sure, reaction conditions that might be expected to yield these products have been extensively employed, but none of the reports dealing with them, as far as we are able to determine, have described the isolation of these monomeric products. Instead, it appears that the alcohols and olefins have been assumed to be transient intermediates that give rise to dimeric and oligomeric products, depending on reaction conditions. Pauson and Watts, for example, have described the synthesis of diferrocenylmethane (1) from ferrocene and paraformaldehyde in concentrated sulfuric acid when ferrocene is present in relatively large excess,[1] while under similar conditions, others have reported that diferocenylethane (2) is the major product of the reaction.[2]




1 2

Similar results have been realized with other catalyst systems such as $ZnCl_2$/HCl at elevated temperatures[3] and $AlCl_3$.[4] Analogous conclusions, using $AlCl_3$ as the Friedel–Crafts catalyst, were realized by Shiga et al., with the important difference that in some cases, e.g., when propiophenone and cyclohexanone were the carbonyl compounds employed, monomeric olefins containing only one ferrocenyl moiety were isolated.[5]

The monomeric products to which we have referred are often prepared in sequences involving a number of steps. For example, ferrocenylmethanol (3) has been most successfully prepared from [(dimethylamino)methyl]ferrocene (4) in three steps;[6] obvious methods of synthesis of 1-ferrocenylethanol (5) and 2-ferrocenyl-2-propanol (6) from acetylferrocene require two steps from ferrocene.




3 4

5 6

By modifying the conditions that have been previously employed to provide oligomeric products, we have been able to produce a number of monomers containing a single ferrocene unit, and we believe our method is a general one for the synthesis of ferrocenylmethanols or the olefins derived from them. The conditions under which we have been able to isolate these monomeric products are, in contrast to those usually reported, extraordinarily mild, normally involving low temperatures and very short reaction times. In general, the carbonyl compound is dissolved in cold concentrated sulfuric acid, to which ferrocene is subsequently added, and after a short reaction time, the reaction mixture is worked up by addition of ice or cold water followed by ether extraction. We have found that most aldehydes provide the expected alcohol in good yield, while ketones, except for acetone, provide the olefin derived from the expected alcohol. (Acetone provides **6** in excellent yield.) In many cases, the reaction appears to be extraordinarily capricious; a first attempt, even in experienced hands, often leads to failure, and repeated attempts, even with no apparent modifications, may ultimately be rewarded. For this reason, we recommend that our directions for the synthesis of specific alcohols or olefins be followed exactly, and in only a general way when attempting the synthesis of one of these products not reported here, with the anticipation of repeated trials with small procedure modifications until success is realized.

We have studied the Friedel–Crafts syntheses of a number of ferrocenyl alcohols and their olefinic derivatives (in the usual cases, one or the other was isolated; often the alcohols appeared to be very unstable toward dehydration), using formaldehyde (as formalin), acetaldehyde, propionaldehyde, butyraldehyde, benzaldehyde, ferrocene carboxaldehyde, and the ketones acetone, 2-butanone, cyclopentanone, and cyclohexanone. With aldehydes, only alcoholic products were isolated and identified, in yields ranging from 39% in the case of propionaldehyde to 57%

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