

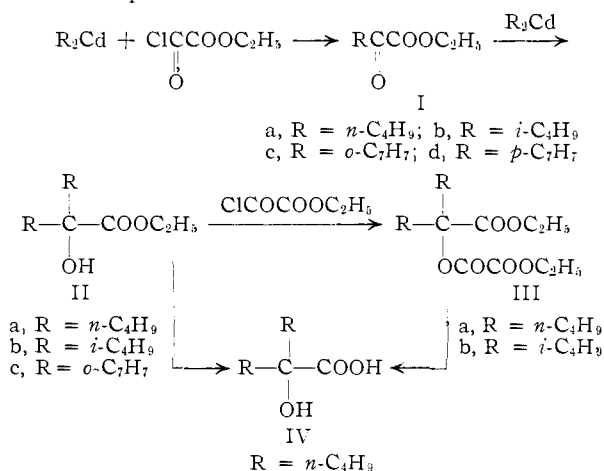
[CONTRIBUTION FROM THE FULMER CHEMICAL LABORATORY, THE STATE COLLEGE OF WASHINGTON]

Reaction of Organocadmium Reagents with Ethoxalyl Chloride¹BY GARDNER W. STACY AND RICHARD M. MCCURDY²

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Inverse addition of dibutylcadmium to ethoxalyl chloride under conditions designed to limit carbonyl addition, nevertheless, has resulted in the formation of only a very limited quantity of α -keto ester (less than 2%). The main products were those expected to result from carbonyl addition, namely, an α -hydroxy ester and its corresponding ethoxalyl derivative. These latter two compounds also could be synthesized by a stepwise procedure starting with authentic α -keto ester. The addition of an organocadmium reagent to a keto carbonyl in an α -keto ester was thus clearly demonstrated and is worthy of note because of the well recognized disinclination of organocadmium reagents toward addition to carbonyl groups in general. Increase in the relative amount of α -keto ester by possible steric inhibition of addition was investigated by employing selected organocadmium reagents. Diisobutylcadmium reacted to give a series of compounds isomeric with those resulting in the case of dibutylcadmium. The corresponding α -keto ester in this case was produced in a quantity several times larger than obtained with dibutylcadmium, although the yield was still small (7%). On the other hand, an even more marked effect was found if di-*o*-tolylcadmium were employed, for an α -keto ester was isolated as the exclusive product in a 50% yield. In the case of di-*p*-tolylcadmium, a lesser yield (22%) of the corresponding α -keto ester was obtained. Although suppression of additive tendencies in these two cases was realized, it was still possible to cause addition to occur if ethyl *o*-tolylglyoxylate were added to di-*o*-tolylcadmium, the corresponding α -hydroxy ester being formed in good yield.

The reaction of organocadmium reagents with ethoxalyl chloride appeared of interest as a possible method for synthesis of α -keto esters. In prior work Gilman and Nelson³ observed that addition of ethoxalyl chloride to a solution of diethylcadmium resulted in the formation of an α -hydroxy ester of the type II, while no α -keto ester similar to I was reported to have been isolated.



For purposes of further investigation, it seemed appropriate to experiment with conditions designed to limit consecutive addition to the carbonyl of the α -keto ester I, postulated as being initially formed in the reaction mixture. *Inverse* addition of the organocadmium reagent to ethoxalyl chloride accompanied by high-speed stirring at -30 to -40° was chosen as a set of conditions most likely to terminate the sequence at the α -keto ester stage. When such conditions were employed with dibutylcadmium as the reagent, it was found that the α -keto ester Ia could, indeed, be isolated from the reaction mixture, although the yield was restricted to less than 2%. Apparently, even under these conditions subsequent addition of the organo-

cadmium reagent could not be sufficiently retarded to afford a sizeable yield of the desired Ia, for the main products were the α -hydroxy ester IIa and its ethoxalyl derivative IIIa, obtained in yields of 8 and 42%, respectively. A product such as IIIa, which had not been obtained by Gilman and Nelson,³ was to be expected in the present case, if subsequent addition did occur, because of the relatively large excess of ethoxalyl chloride in the reaction mixture. The conditions of *inverse* addition, carried out at 80° instead of at low temperature, gave essentially the same results. The products, IIa and IIIa, were appropriately characterized and their structures confirmed by saponification to the same acid IV. Also, IIIa reacted readily with hydrazine to give the dihydrazide of oxalic acid.

Of further interest was the fact that IIa and IIIa could be synthesized by the discrete, intermediate steps, as outlined. That is, authentic ethyl α -ketocaproate (Ia), prepared by way of ethyl β -carbethoxy- α -ketocaproate,⁴ readily reacted with dibutylcadmium to form the α -hydroxy ester IIa, which in turn was found to react smoothly with ethoxalyl chloride to give IIIa. As it is well known that organocadmium reagents in general have little tendency to add to ketone or even aldehyde carbonyls,⁵ the presently observed addition to the carbonyl group of an α -keto ester would seem of considerable interest.⁶

It appeared desirable to investigate possible steric inhibition of such addition by employing selected organocadmium reagents of appropriate structure. The practical consequences of such situations might, of course, involve larger yields of α -keto esters. Toward this objective the reaction of diisobutylcadmium with ethoxalyl chloride was studied with exactly the same conditions being employed. A series of compounds, isomeric with

(4) (a) F. Adickes and G. Andresen, *Ann.*, **555**, 41 (1943); (b) E. Vogel and H. Schinz, *Helv. Chim. Acta*, **33**, 116 (1950).

(5) J. Cason, *Chem. Revs.*, **40**, 15 (1946).

(6) Another example of addition of an organocadmium reagent to a carbonyl group (or pseudocarbonyl group) has recently been reported, D. V. Nightingale, W. S. Wagner and R. H. Wise, *THIS JOURNAL*, **75**, 4701 (1953).

(7) Selection was limited to organocadmium reagents derived from aryl halides and primary alkyl halides, as these are the only types that may be prepared in good yield (ref. 5).

(1) Presented before the Division of Organic Chemistry at the 124th Meeting of the American Chemical Society, Chicago, Ill., Sept. 7, 1953.

(2) Abstracted from a thesis submitted by Richard M. McCurdy in partial fulfillment of the requirements for the Degree of Doctor of Philosophy, the State College of Washington, June, 1953.

(3) H. Gilman and J. P. Nelson, *Rec. trav. chim.*, **55**, 518 (1927).

those obtained in the reaction with dibutylcadmium was obtained. The α -keto ester Ib was, indeed, obtained in a quantity several times larger than in the initial case involving dibutylcadmium, although the yield was still small (7%).

On the other hand, when attention was turned to di-*o*-tolylcadmium, it was found that the α -keto ester Ic was obtained as the exclusive product in a yield of 50%, demonstrating a large degree of steric inhibition of consecutive addition.⁸ This result suggests that the approach might prove of value in the synthesis of certain glyoxylic esters. For comparison the di-*p*-tolylcadmium was also run, and here a lower yield (22%) of the α -keto ester Id was obtained. Although some *p*-ditolyl was also to be found in this case, Id again was the only product of significance that was isolated from the reaction mixture. In spite of the fact that the tendency toward addition was retarded in these two cases where the organocadmium reagent was present in the reaction mixture in relatively low concentration, it was to be noted that addition was still possible under the proper circumstances. When the ethyl *o*-tolylglyoxylate was added to di-*o*-tolylcadmium (organocadmium reagent in relatively high concentration), the α -hydroxy ester IIc was formed in good yield.

Experimental⁹

Inverse Addition of Dibutylcadmium to Ethoxalyl Chloride.—Into a conical flask, which was equipped with a stirrer, condenser, dropping funnel and a stopcock outlet in the bottom, were placed 10.0 g. (0.40 gram atom) of clean magnesium turnings and 25 ml. of absolute ether. A solution of butylmagnesium bromide was then prepared by addition of 54.6 g. (0.40 mole) of butyl bromide in 200 ml. of absolute ether. The flask was then used as a dropping funnel to introduce the Grignard reagent into another conical flask containing 36.7 g. (0.20 mole) of anhydrous cadmium chloride suspended in 300 ml. of absolute ether. The Grignard reagent was added to the stirred suspension of cadmium chloride at such a rate that the reaction mixture boiled gently. When the addition was complete, the resultant slurry was stirred until a negative Gilman test¹⁰ was obtained (20 minutes). To remove magnesium salts, the solution of organocadmium reagent was then filtered by suction through a sintered glass filter arranged so as to protect the solution from atmospheric moisture. The resulting clear solution of dibutylcadmium, in 400 ml. of ether, was placed in a 500-ml. dropping funnel (pressure-equalized).

In a 1-l. three-necked flask, which was equipped with a cold-temperature thermometer, a high-speed stirrer,¹¹ and the aforementioned dropping funnel, were placed 82.0 g. (0.60 mole) of ethoxalyl chloride¹² and 100 ml. of absolute ether. The flask was immersed in a Dry Ice-acetone mixture. With high-speed stirring, the solution of the organocadmium reagent was then added at such a rate that the temperature was maintained at -30 to -40° . Upon completion of the addition, which required one hour, the temperature of the reaction mixture was allowed to rise to room

temperature, and it was then poured onto a mixture of 100 g. of ice and 100 ml. of water. The mixture was shaken vigorously until no odor of ethoxalyl chloride could be detected. The ether layer was separated and washed with two 100-ml. portions of 10% sodium bicarbonate and once with 50 ml. of water. The ether solution was dried over anhydrous sodium sulfate and, after removal of the solvent, the residue was fractionally distilled through a 15-cm. column packed with glass helices. The products obtained were as follows.

Ethyl α -ketocaproate (Ia): yield of crude material, 2.70 g. (4%),¹³ b.p. $74-96^\circ$ (10 mm.), n_D^{20} 1.4178, d_4^{20} 1.0140. When 1.0 g. of this material was treated with 2,4-dinitrophenylhydrazine, 0.54 g. (25%) of the 2,4-dinitrophenylhydrazone of ethyl α -ketocaproate was obtained; m.p. $119-120^\circ$ after two recrystallizations from ethanol. When admixed with an authentic sample (m.p. $120.5-121^\circ$), no depression was observed, m.p. $119.5-120^\circ$.

Anal. Calcd. for $C_{14}H_{18}N_4O_6$: C, 49.70; H, 5.36; N, 16.56. Found: C, 49.57; H, 5.25; N, 16.61.

Ethyl α -butyl- α -hydroxycaproate (IIa): 3.60 g. (8%), b.p. $55-64^\circ$ (0.25 mm.), n_D^{20} 1.4309, d_4^{20} 0.9325. The physical properties of a redistilled sample were nearly identical with those of the authentic material subsequently described; b.p. $66-68^\circ$ (0.5 mm.), n_D^{20} 1.4293, d_4^{20} 0.9240.

When 1.0 g. of this substance was heated for three hours with 10 ml. of 5% sodium hydroxide, an alkali-insoluble salt precipitated. Upon acidification of the mixture with concentrated hydrochloric acid, an oil separated which solidified on standing. After this material had been recrystallized twice from ligroin (b.p. $60-90^\circ$), it melted at 87.5° and was identified as α -butyl- α -hydroxycaproic acid (IV).¹⁴

Anal. Calcd. for $C_{10}H_{20}O_3$: C, 63.79; H, 10.71; neut. equiv., 188. Found: C, 63.64; H, 10.56; neut. equiv., 188.

Ethyl α -butyl- α -ethoxaloxycaproate (IIIa): 26.5 g. (42%), b.p. $109-116^\circ$ (0.25 mm.), n_D^{20} 1.4389, d_4^{20} 1.0215. A redistilled sample had physical properties identical with those from the stepwise, synthetic approach, subsequently described; b.p. $107-111^\circ$ (0.25 mm.), n_D^{20} 1.4390, d_4^{20} 1.0240.

Anal. Calcd. for $C_{16}H_{28}O_6$: C, 60.74; H, 8.92; M_D , 81.04; sapon. equiv., 316. Found: C, 60.67; H, 8.69; M_D , 81.40; sapon. equiv., 318.

This ester also gave the acid IV when saponified in a manner similar to IIa. In addition, when 0.60 g. was treated with 2.0 ml. of 85% hydrazine hydrate, reaction occurred yielding a colorless, crystalline precipitate, which was identified as oxalic acid dihydrazide, m.p. 244° dec.¹⁵

Anal. Calcd. for $C_2H_6N_4O_2$: C, 20.36; H, 5.12. Found: C, 20.73; H, 4.98.

Ethyl α -Ketocaproate (Ia) by way of Ethyl β -Carbethoxy- α -ketocaproate.—Authentic ethyl α -ketocaproate, which had not been previously reported, was prepared by an adaptation of a method described by Vogel and Schinz.¹⁶ In a 300-ml. flask, containing 12.0 g. (0.50 mole) of sodium hydride and 200 ml. of anhydrous ether were placed 44.0 g. (0.30 mole) of diethyl oxalate and 34.0 g. (0.25 mole) of ethyl valerate. To initiate the reaction, 0.5 ml. of ethanol was added to the mixture. A reflux condenser was attached and, after the initial reaction had subsided, the mixture was heated on a steam-bath for 20 hours. At the end of this heating period, 5 ml. of ethanol was added to the solution to destroy any unreacted sodium hydride, and upon cessation of the hydrogen evolution (this and the above operations should be carried out in a hood), the mixture was poured onto 150 g. of ice and 20 ml. of concentrated sulfuric acid. The ether layer was separated, and the aqueous was extracted with ether, which was added to the original ether portion which had been separated. Ethyl β -carbethoxy- α -ketocaproate was then extracted from the ether extracts by shaking with three 150-ml. portions of 20% sodium carbonate solution. The alkaline solution was neutralized with sulfuric acid and then extracted once with 200 ml. of ether. After drying the solution and removing the ether under reduced pressure, the crude intermediate, ethyl β -carbethoxy- α -ketocaproate, amounted to 37.5 g. (65%).

(13) Percentage yields are based on the starting halide.

(14) Previously reported by R. W. Stoughton, *THIS JOURNAL*, **63**, 2376 (1941), but no elementary analysis given, m.p. $87-88^\circ$.

(15) T. Curtius, G. Schofer and N. Schwan, *J. prakt. Chem.*, **51**, 194 (1895), reported m.p. 235° dec.

(8) Compare the results of I. I. Lapkin and A. V. Lyubimova, *J. Gen. Chem. (U.S.S.R.)*, **19**, 707 (1949); *C. A.*, **44**, 1058 (1950).

(9) All melting points are corrected and boiling points are uncorrected. The microanalytical work was performed by the Galbraith Laboratories, Knoxville, Tennessee.

(10) H. Gilman and F. Schultz, *THIS JOURNAL*, **47**, 2002 (1925).

(11) A Morton type high-speed stirrer and flask were employed, Secor Scientific Corp., 73 Pond St., Waltham 54, Massachusetts.

(12) Prepared by way of ethyl ethoxydichloroacetate according to the procedure of R. Anschütz, *Ann.*, **254**, 1 (1889). One desirable modification should be noted; before distillation the reaction mixture containing ethyl ethoxydichloroacetate was cooled to 0° to effect the precipitation and subsequent removal of unreacted phosphorus pentachloride, which otherwise caused clogging of the condenser in the distillation to follow.

This was placed in a 300-ml. flask, fitted with condenser and stirrer, and was heated under reflux for four hours with 75 ml. of concentrated hydrochloric acid and 150 ml. of water. This mixture was then cooled and extracted continuously with ether for four hours. The ether was removed, after drying over anhydrous sodium sulfate, and the residue, consisting mainly of α -ketocaproic acid and its ethyl ester, was distilled through a 25-cm. Vigreux column; b.p. 90–95° (13 mm.), yield 14.0 g.

This mixture with converted to the pure ethyl ester by heating the material under reflux for 2.5 hours with 50 ml. of anhydrous ethanol, 30 ml. of benzene and two drops of concentrated sulfuric acid. The benzene and ethanol were removed by distillation, and the residue was distilled through a 15-cm. column packed with glass helices; yield 14.0 g. (31% over-all), b.p. 83.5–84° (10 mm.), n_D^{20} 1.4220, d_4^{20} 0.9777.

Anal. Calcd. for $C_{15}H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.62; H, 8.92.

Ethyl α -Butyl- α -hydroxycaproate (IIa) by Reaction of Dibutylcadmium with Ethyl α -Ketocaproate.—Butylmagnesium bromide was prepared from 12.5 g. (0.090 mole) of butyl bromide and 2.5 g. (0.1 gram atom) of magnesium turnings. The Grignard reagent in 100 ml. of anhydrous ether was decanted from unreacted magnesium and added slowly with stirring to a mixture of 16.8 g. (0.045 mole) of anhydrous cadmium chloride in 25 ml. of ether. The resulting solution of dibutylcadmium was cooled in an ice-bath, and 11.0 g. (0.070 mole) of ethyl α -ketocaproate (Ia) was added dropwise with stirring, a vigorous reaction occurring with the addition of each drop.

The mixture was then poured onto 50 g. of ice and 20 ml. of concentrated sulfuric acid. The ether layer was separated, washed once with water and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was distilled through a 15-cm. column packed with glass helices; yield 7.5 g. (80% on the basis of 4.0 g. of ethyl α -ketocaproate recovered), b.p. 62° (0.25 mm.), n_D^{20} 1.4300, d_4^{20} 0.9247.

Anal. Calcd. for $C_{19}H_{24}O_3$: C, 66.63; H, 11.18; M_D , 60.79. Found: C, 66.45; H, 10.99; M_D , 60.43.

Ethyl α -Butyl- α -ethoxaloxycaproate (IIIa) by Reaction of Ethoxalyl Chloride with IIa.—To a glass-stoppered bottle containing 5.0 g. (0.023 mole) of IIa were added 3.5 g. (0.023 mole) of ethoxalyl chloride, 10 ml. of anhydrous ether and 2.0 g. of pyridine. The pyridine hydrochloride which precipitated was removed by filtration, the ether was removed by distillation, and the residue was distilled to yield 5.0 g. (68%) of ethyl α -butyl- α -ethoxaloxycaproate; b.p. 111–112° (0.25 mm.), n_D^{20} 1.4390, d_4^{20} 1.0244.

Inverse Addition of Diisobutylcadmium.—Almost identically the same quantities and conditions were employed as in the dibutylcadmium experiment. Some differences were to be observed, however. In its conversion to the organocadmium reagent isobutylmagnesium bromide reacted more slowly than the corresponding *n*-butyl reagent and formed a sludge which settled to the bottom of the flask. Filtration, therefore, was unnecessary, and the supernatant liquid was simply siphoned off and added dropwise to 72.0 g. (0.53 mole) of ethoxalyl chloride in 100 ml. of absolute ether in the high-speed stirring apparatus at –30 to –40°. The reaction mixture was worked up as previously described and distilled through a 120-cm. Podbielniak column. A series of products similar to those of the previous case was obtained in various fractions.

Ethyl α -ketoisocaproate (Ib): 4.40 g. (7%), b.p. 76–77° (10 mm.), n_D^{20} 1.4175, d_4^{20} 0.9715.

Anal. Calcd. for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.32; H, 9.09.

A 2,4-dinitrophenylhydrazone prepared from this fraction melted at 79.5–80° after two recrystallizations from ethanol.

Anal. Calcd. for $C_{14}H_{18}N_4O_6$: C, 49.70; H, 5.36; N, 16.56. Found: C, 49.67; H, 5.38; N, 16.38.

Ethyl α -isobutyl- α -hydroxyisocaproate (IIb): 6.49 g. (15%), b.p. 101–102° (10 mm.), n_D^{20} 1.4284, d_4^{20} 0.9160.

Anal. Calcd. for $C_{12}H_{24}O_3$: C, 66.63; H, 11.18; sapon. equiv., 216. Found: C, 66.70; H, 11.18; sapon. equiv., 218.

Ethyl α -isobutyl- α -ethoxaloxycaproate (IIIb): 16.0 g. (25%), b.p. 154–156° (10 mm.), n_D^{20} 1.4375, d_4^{20} 1.0198.

Anal. Calcd. for $C_{16}H_{28}O_3$: C, 60.74; H, 8.92; sapon. equiv., 318. Found: C, 60.83; H, 8.82; sapon. equiv., 318.

Inverse Addition of Di-*o*-tolylcadmium. Ethyl *o*-Tolylglyoxylate (Ic).—A Grignard reagent was prepared from 45.0 g. (0.26 mole) of *o*-bromotoluene and 5.75 g. (0.24 gram atom) of magnesium powder. This was converted to the corresponding organocadmium reagent, using a proportionally comparable amount of anhydrous cadmium chloride relative to the procedures previously described. This was then added to a solution of 54.4 g. (0.40 mole) of ethoxalyl chloride in ether, and the reaction was carried out and product worked up as previously described; however, upon distillation the only product isolated was ethyl *o*-tolylglyoxylate (Ic); 23.4 g. (50%), b.p. 136–137° (8 mm.), n_D^{20} 1.5178, d_4^{20} 1.1016.

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.73; H, 6.30. Found: C, 68.72; H, 6.37.

A 2,4-dinitrophenylhydrazone was prepared in the usual manner; it melted at 147–148° after two recrystallizations from benzene.

Anal. Calcd. for $C_{17}H_{18}N_4O_6$: C, 54.83; H, 4.33; N, 15.05. Found: C, 54.80; H, 4.36; N, 15.17.

Ethyl Di-*o*-tolylglycolate (IIc).—In a 250-ml. three-necked flask containing 2.40 g. (0.10 gram atom) of powdered magnesium and 25 ml. of anhydrous ether was placed 17.0 g. (0.10 mole) of *o*-bromotoluene. When the reaction had started, an additional 100 ml. of anhydrous ether was added. The mixture was heated until all of the magnesium had reacted, whereupon 9.16 g. (0.05 mole) of anhydrous cadmium chloride was added. To the mixture was then added 7.0 g. (0.04 mole) of ethyl *o*-tolylglyoxylate at a rate slow enough to prevent boiling. The material reacted immediately and soon formed a sludge that stopped the stirrer. The reaction flask was warmed on a steam-bath briefly, and hydrochloric acid in an amount just sufficient to dissolve the precipitated salts was added. The ether layer was separated and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was crystallized by the addition of two volumes of ligroin (b.p. 60–90°) and cooling in a Dry Ice-bath. After two more crystallizations from ligroin, the material crystallized in colorless, rhombic crystals; m.p. 63–64°, 7.0 g. (75%).

Anal. Calcd. for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 76.03; H, 7.08.

Inverse Addition of Di-*p*-tolylcadmium. Ethyl *p*-Tolylglyoxylate (Id).—The organocadmium reagent was prepared in precisely the same manner and with the same amounts as previously described in the case of di-*o*-tolylcadmium. After removal of unreacted ethoxalyl chloride, the material was distilled, b.p. 147–149° (10 mm.).

A portion of the distillate (8.0 g.) was shaken with 15 ml. of saturated sodium bisulfite solution. A crystalline bisulfite addition product formed immediately, and it was removed by filtration. The salt was air-dried and washed repeatedly with ether. This was then treated with potassium carbonate solution to yield ethyl *p*-tolylglyoxylate (Id); 6.0 g.; total yield 10.5 g. (22%), b.p. 148–149° (10 mm.), n_D^{20} 1.5205, d_4^{20} 1.0901.

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.73; H, 6.30. Found: C, 68.80; H, 6.32.

A 2,4-dinitrophenylhydrazone prepared from this substance melted at 162° after three recrystallizations from benzene.

Anal. Calcd. for $C_{17}H_{18}N_4O_6$: C, 54.83; H, 4.33; N, 15.05. Found: C, 55.04; H, 4.23; N, 15.05.

Di-*p*-tolyl was obtained in 14% yield (3.40 g.) upon evaporation of the combined ether washings from the bisulfite addition compound. After crystallization from ligroin (b.p. 60–90°), the product melted at 118.5–119°.¹⁶

Anal. Calcd. for $C_{14}H_{14}$: C, 92.26; H, 7.74. Found: C, 92.12; H, 7.89.

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(16) T. Zincke, *Ber.*, **4**, 396 (1871), reported m.p. 121°.