Hydroxyalkylation and Lactone Formation from Dialkyl Malonate by Means of a Eu^{III}/Eu^{II} Photoredox System

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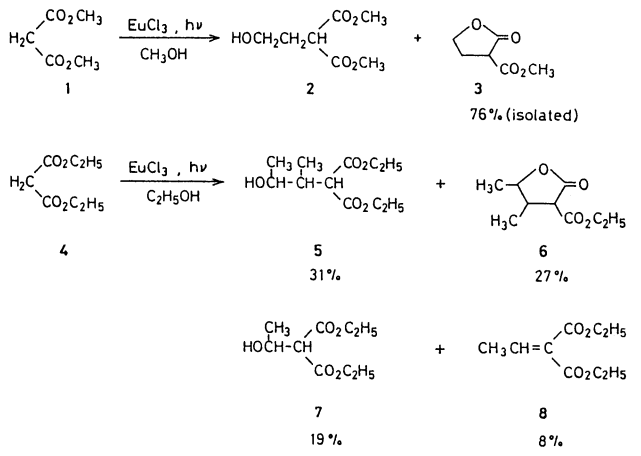
Synopsis. A Eu^{III}/Eu^{II} photoredox system in alcohol induced an effective hydroxyalkylation at an α-position of a dialkyl malonate. The alcohol adduct was then converted to the lactone. A step-by-step hydroxyalkylation mechanism was suggested in which the Eu ion is used as a photocatalyst and also as a condensation catalyst for the reaction of dialkyl malonates and aldehydes.

We have investigated a series of photo-hydroxyalkylations of various unsaturated compounds induced by a Eu^{III}/Eu^{II} photoredox system in alcohols. The reaction of aromatic and aliphatic alkenes provided dihydrodimers and alcohol adducts as main products via a radical mechanism.[1,2] On the other hand, 1,3-dimethyluracil and its derivatives provided a hydroxyalkylation product at the C-6 position in a very high yield; a one-electron reduction mechanism has been suggested.[3,4] In this paper, we present an effective hydroxyalkylation and lactone formation of dialkyl malonates by the use of a Eu^{III}/Eu^{II} photoredox system in which the Eu ion is used as a photocatalyst and also catalyzes the condensation of dialkyl malonates and aldehydes.

Results and Discussion

A 180 mL methanol solution of dimethyl malonate (**1**: 85 mmol dm^{-3}) and $EuCl_3$ (2.2 mmol dm^{-3}) was saturated with Ar and irradiated in a Pyrex cell with a 350-W high-pressure mercury lamp at the temperature of running water. During the irradiation, the evolution of hydrogen gas was observed much as in substrate-free solution.[1,2] After a 22-h irradiation, all the substrate has been consumed; the reaction mixture was then worked up. The crude product was a mixture of a hydroxyethylated product **2** and its lactone **3**, which were confirmed by the NMR spectra. By distillation, **3** was isolated as a sole product in a yield of 76%. Without $EuCl_3$, no reaction was observed, and **1** was recovered. The absorption spectra suggested that $EuCl_3$ was the main light-absorbing agent. The reaction of diethyl malonate (**4**) in ethanol was carried out under similar reaction conditions, but the reaction rate was rather lower than that of **1** and the conversion was 77% at an 84-h irradiation.[5] In addition to a 1 : 2 alcohol adduct **5** (31%, based on conversion) and its lactone **6** (27%), a 1 : 1 adduct **7** (19%) and its dehydrated product **8** (8%) were obtained. They were presumed to be the primary products. The NMR spectra of **6** suggested the presence of two diastereomers **6a** and **6b**.[6].

The time course observation of the reaction of **4** was carried out to get an insight into the initial step of the reaction. The conversion of **4** and the product-formation were monitored by means of GLC(FID), so that **5** and **7** were determined to be **6** and **8** respectively. The reaction of dialkyl malonates needed a very long risetime compared with that of other olefinic substrates reported previously.[1,2] In the initial 20 h, hydrogen gas and acetaldehyde were obtained as the photolytic products of ethanol by means of a Eu^{III}/Eu^{II} photoredox stem.[1,2] After the 20-h irradiation, the products derived from **4** were barely observed. After a 75-h irradiation, **6** (and/or **5**) was determined in a yield of 24% (absolute yield). Furthermore, **8** (and/or **7**) which had been slightly observed during the irradiation, increased and became the main product (26%) upon standing for 45 h in the dark after a 75-h irradiation. These facts suggest that **8** might be a product of the dark reaction of **4** with acetaldehyde, which is a photolytic product of ethanol.[7] Indeed, the intentional addition of acetaldehyde (0.5 mol dm^{-3}) to this system obviously shortened the risetime of the photoproducts (**6** and/or **5**). In order to confirm this process, the reac-

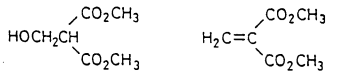


1 2 3 (76% isolated)
4 5 (31%) 6 (27%)
7 (19%) 8 (8%)

Table 1. Reaction of Dialkyl Malonate and Aldehydes in the Dark in the presence of $EuCl_3$[a]

Ester	Aldehyde	Solvent	Reaction time/h	Conv. %	Product yield/%[b]
1	HCHO	MeOH	24	100	**9**+**10**[c] 0[d]
4	CH_3CHO	EtOH	72	70	**7**+ **8**[c] 100

a) [ester]=100 mmol dm^{-3}, [$EuCl_3$]=10 mmol dm^{-3}, [aldehyde]=1.2 mmol dm^{-3}; at room temp., in the dark. b) Yields are based on the amounts of esters consumed. c) **9** and **7** were determined by GLC(FID) as **10** and **8** respectively. d) Oligomerization products were observed.



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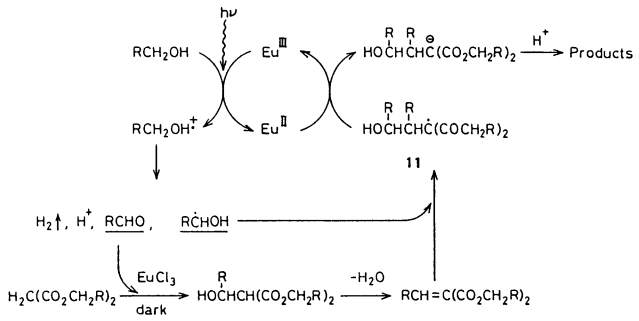
tion of dialkyl malonates with aldehydes were carried out in the dark.

The monitoring of reactions was carried out by means of GLC(FID). Thus, the alcohol adducts were determined to be the dehydrated esters. In the presence of $EuCl_3$, an ethanol solution of **4** and acetaldehyde provided an ethanol adduct **7** and/or **8** quantitatively, while no product was observed when there was no $EuCl_3$ (Table 1). In the reaction of **1** with formaldehyde, **1** disappeared. However, only oligomeric products were obtained instead of **9** (and/or **10**). This is consistent with the fact that **9** is easily dehydrated to provide **10**, which is very unstable and polymerizable under these conditions.[7] These observations suggest that the present reaction proceeds by the two steps shown in Scheme 1:

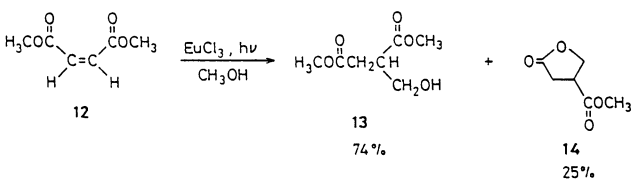


Scheme 1.

The first step is a reaction in the dark of dialkyl malonate with aldehyde, which is a primary photoproduct. This type of reaction, known as Knoevenagel reaction, was catalyzed by a Lewis acid, and the product was easily dehydrated to provide an unsaturated ester.[8] In this stem, $EuCl_3$ may act as a Lewis acid for the condensation. In the photoreaction of **1**, **9** may be supplied in a very low concentration; thus, the further reaction of **9** to produce **3** is preferred to the oligomerization.

The second step of the reaction, the photo-addition of alcohol to unsaturated esters **8** and **10**, is presumed to be induced by a hydroxyalkyl radical. The radical **11** produced by the addition of the hydroxyalkyl radical has two methoxycarbonyl group and is supposed to be easily reduced by Eu^{II}, thus generating the carbanion, which then, gives the product by protonation (Scheme 1).

Dimethyl maleate (**12**), another α,β-unsaturated ester, was irradiated in the presence of $EuCl_3$ in methanol. An alcohol adduct **13** and its lactone **14** were thus obtained in high yields. There, the Eu^{III}/Eu^{II} photoredox reaction is an efficient system for the hydroxyalkylation and successive lactone formation of unsaturated esters. The photo-reaction of dimethyl maleate in CH_3OD resulted in the incorporation of the D atom at the α-carbon of the product **13**,[9] which was consistent with the mechanism via a carbanion.



Experimental

The ^1H and ^{13}C NMR spectra were recorded on a Bruker WM-360 instrument using tetramethylsilane as the internal standard. The gas chromatography was carried out on a Shimadzu GC-7A apparatus with FID using OV-17 or Porapak Type QS. The mass spectra were recorded on a JEOL DX-300 apparatus with a JEOL JMA-3100 data processor.

Reaction of 1. A 180 mL methanol solution of **1** (2.0 g, 15.2 mmol) and $EuCl_3$ (150 mg, 0.4 mmol) was irradiated in a Pyrex cell with a high-pressure mercury lamp for 22 h under an Ar atmosphere. After the irradiation, the methanol was removed in vacuo. The residue was extracted with $CHCl_3$, after which, the solution was washed with water two times and dried with $MgSO_4$, and the $CHCl_3$ was removed in vacuo. The crude product, a colorless oil (1.96 g), was distilled (bath temp 80—100 °C/4 mmHg††) with a "One-Pot Still" after the NMR analyses. As the sole product, **3** was obtained (1.66 g).

2: Not isolated, but identified as a mixture with **3** by ^1H NMR and ^{13}C NMR; ^1H NMR ($CDCl_3$ δ=2.15 [d (J=6.1 Hz) and t (J=6.6 Hz), 2H], 3.17 (bs, 1H), 3.68 (t, J=6.1 Hz, 1H), and 3.75 (s, 6H). The 2H of $-CH_2OH$ was not identified, because it was in the multiplet of 4.52—4.32 ; ^{13}C NMR ($CDCl_3$) δ=29.5, 48.1, 52.8, 63.4, and 174.3.

3: Colorless oil; ^1H NMR ($CDCl_3$) δ=2.54 (dddd, J=5.3, 7.5, 9.3, and 13.1 Hz, 1H), 2.68 (dddd, J=7.4, 7.9, 8.2, and 13.1 Hz, 1H), 3.59 (dd, J=7.9 and 8.9 Hz, 1H), 3.81 (s, 3H), 4.35 (ddd, J=7.4, 7.5, and 8.9 Hz, 1H), and 4.48 (ddd, J=5.3, 8.2, and 8.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ=26.5 (t), 45.8 (d), 53.0 (q), 67.4 (t), 168.3 (s), and 172.3 (s); EIMS, m/z (relative intensity) 145 (M^++1, 2), 144 (4, M^+), 113 (29), 100 (32), 69 (100), 59 (22), 55 (39), and 41 (51); Found C, 49.74; H, 5.62%. Calcd for $C_6H_8O_4$: C, 50.00; H, 5.60%.

Reaction of 4. The crude product, which had been obtained much as in the photoreaction of **1**, was a colorless oil (22.29 g); and when it was separated by column chromatography on silica gel (eluent; a mixture of Et_2O and hexane, 2 : 1 v/v), and the three fractions were obtained: a mixture of **4** and **7**: 0.57 g; a mixture of **7** and **8**: 0.29 g; and a mixture of **5** and **6**: 0.91 g. The product yields were calculated by the use of the product ratio obtained by means of the ^1H NMR data.

5: Not isolated but identified by NMR analyses as a mixture with **6**; ^1H NMR ($CDCl_3$) δ=0.98 (d, J=7.0 Hz, 3H), 1.28 (t, J=7.1 Hz, 6H), 1.29 (d, J=6.4 Hz, 3H), 2.31 [d (J=2.5 Hz), t (J=7.0 Hz), and t (J=8.5 Hz), 1H], 2.47 (bs, 1H), 3.49 (d, J=8.5 Hz, 1H), 3.93 [d (J=2.5 Hz) and q (J=6.4 Hz), 1H], and 4.21 (q, J=7.1 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ=10.7 (q), 14.1 (q), 20.7 (q), 39.5 (d), 55.7 (d), 61.5 (t), 68.3 (d), 169.1 (s), and 169.5 (s); m/z 204.

6a: Colorless oil. ^1H NMR ($CDCl_3$) δ=1.18 (d, J=6.6 Hz, 3H), 1.32 (t, J=7.1 Hz, 3H), 1.46 (d, J=6.2 Hz, 3H), 2.56 (m, 1H), 3.25 (d, J=11.6 Hz, 1H), 4.13 [d (J=9.4 Hz) and q (J=6.1 Hz), 1H], and 4.27 (q, J=7.1 Hz 2H); ^{13}C NMR ($CDCl_3$) δ=14.1 (q), 15.1 (q), 18.4 (q), 42.8 (d), 55.1 (d), 61.9 (t), 81.6 (d), 167.6 (s), and 171.1 (s).

6b: Colorless oil; ^1H NMR ($CDCl_3$) δ=1.11 (d, J=7.1 Hz, 3H), 1.29 (d, J=6.7 Hz, 3H), 1.32 (t, J=7.1 Hz, 3H), 3.00 (m, 1H), 3.26 (d, J=8.3 Hz, 1H), 4.26 (q, J=7.1 Hz, 2H), and 4.82 (quintet, J=6.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ=13.3 (q), 14.1 (q), 15.5 (q), 38.0 (d), 53.6 (d), 61.9 (t), 78.7 (d), 167. 1 (s), and 171.5 (s); Found: m/z (mixture of **6a** and **6b**) 186.08935. Calcd

†† 1 mmHg=133.322 Pa.

for $C_9H_{14}O_4$: M, 186.08912.

7: Not isolated but identified by NMR analyses as a mixture with **8**; ^{1}H NMR ($CDCl_3$) δ=1.25 (d, J=7.0 Hz, 3H), 1.27 (t, J=7.0 Hz, 3H), 1.28 (t, J=7.0 Hz, 3H), 3.46 (d, J=9.2 Hz, 1H), 3.62 [d (J=9.1 Hz) and q (J=7.0 Hz), 1H], 4.19 (q, J=7.1 Hz, 2H), and 4.21 (q, J=7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ=14.1 (q), 18.0 (d), 59.0 (d), 61.4 (t), 73.9 (d), 167.3 (s), and 167.7 (s).

8: Colorless oil; ^{1}H NMR ($CDCl_3$) δ=1.29 (t, J=7.1 Hz, 3H), 1.34 (t, J=7.1 Hz, 3H), 1.96 (d, J=7.2 Hz, 3H), 4.25 (q, J=7.1 Hz, 2H), 4.31 (q, J=7.1 Hz 2H), and 7.09 (q, J=7.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ=14.2 (q), 15.4 (q), 61.2 (t), 130.1 (s), 144.6 (d), 163.4 (s), 165.4 (s).

Reaction of 4 for the Quantitative Analysis. A 5-mL ethanol solution of **4** (100 mmol dm^{-3}) and $EuCl_3$ (5 mmol dm^{-3}) was saturated with Ar and irradiated in a Pyrex cell this with a 350-W high-pressure mercury lamp for 75 h. After this irradiation, the reaction mixture was left in the dark for 45 h. The reaction was followed by GLC every 5 h.

Reaction of 4 in the Dark. A 5-mL ethanol solution of **4** (800 mg, 5.0 mmol), $EuCl_3$ (180 mg, 0.5 mmol), and acetaldehyde (7 mL, 60 mmol) was stirred for the 72 h at room temperature in the dark, and then the EtOH was removed in vacuo. The mixture was extracted with $CHCl_3$, washed with water two times, and dried with $MgSO_4$; and $CHCl_3$ was then removed in vacuo. The products were distilled under reduced pressure (110 °C/4 mmHg). The NMR data were identical with those of photogenerated **10**.

Reaction of 12. A 180-mL methanol solution of **12** (123 mmol dm^{-3}) and $EuCl_3$ (2.2 mmol dm^{-3}) was saturated with Ar and irradiated in a Pyrex cell with a 350-W high-pressure mercury lamp for 24 h (conv. 100%). After the irradiation, the methanol was removed in vacuo, and the residue was extracted with a large amount of ether. The ether solution was filtered through Hyflosuper-cel to remove the $EuCl_3$; and a colorless oil was then obtained by removing the ether. The crude product was separated by column chromatography on silica gel (eluent: $CHCl_3$).

13: Colorless oil; ^{1}H NMR ($CDCl_3$) δ=2.63 (dd, J=6.2 Hz and 16.8 Hz, 1H), 2.78 (dd, J=7.5 Hz and 16.8 Hz, 1H), 2.87 (bs, 1H), 3.04 (dist. quintet, 1H), 3.70 (s, 3H), 3.73 (s, 3H), and 3.82 (d, J=5.4 Hz, 2H); ^{13}C NMR δ=32.7 (t), 44.1 (q), 50.3 (q), 52.0 (q), 62.6 (t), 172.7 (s), and 173.9 (s); Found: C, 47.77, H, 6.86%. Calcd for $C_7H_{12}O_5$: C, 47.72; H, 6.87%.

14: Colorless oil; ^{1}H NMR ($CDCl_3$) δ=2.76 (dd, J=9.6 Hz and 17.9 Hz, 1H), 2.88 (dd, J=7.3 Hz and 18.0 Hz, 1H), 3.48 (dist. quintet, 1H), 3.78 (s, 3H), 4.46 (dd, J=6.6 Hz and 9.4 Hz, 1H), and 4.52 (dd, J=8.4 Hz and 9.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ=39.9 (d), 52.7 (q), 69.2 (t), 171.9 (s), and 175.3 (s); Found: C, 49.74; H, 5.46%. Calcd for $C_6H_8O_4$: C, 50.00; H, 5.60%.

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9) The product **14** incorporated a deuterium (ca. 100% d_1) which was confirmed by NMR.