Note

Alkylation of Diethyl
3-Oxoglutarate with
 α,ω -DibromoalkanesYoshinobu NAOSHIMA, Hirofumi YABUKI,
Hiroo UEDA,* and Mitsutoshi NAKAMURADepartment of Chemistry, Faculty of Science,
Okayama University of Science, Ridai-cho,
Okayama 700, Japan*Department of Agricultural Chemistry,
College of Agriculture,
University of Osaka Prefecture,
Mozu-Umemachi, Sakai-shi,
Osaka 591, Japan

Received September 25, 1986

We have reported a two-step method for the alkylation of diethyl 3-oxoglutarate (DEOG), in which the first alkylation took place regioselectively at one of the methylene carbons, with $\text{Mg}(\text{OEt})_2$ as the base. The second alkylation regioselectively occurred with NaH as the base.^{1,2)} This alkylation with alkyl monohalides has been used for synthesizing biologically active compounds such as insect pheromones³⁾ and prostaglandin analogs,⁴⁾ thus indicating the potential desirability of DEOG as a synthetic material.

In the expansion of the use of DEOG as a synthetic reagent, we now report the alkylation of DEOG with α,ω -dibromoalkanes and $\text{Mg}(\text{OEt})_2$.

Alkylation was done by treatment of DEOG with a dibromoalkane in the presence of $\text{Mg}(\text{OEt})_2$ in ethanol. A

1.5 molar ratio of $\text{Mg}(\text{OEt})_2$ to DEOG was used this time because of its significance in the regioselective alkylation of DEOG with alkyl monohalides.^{1,2)} When DEOG was alkylated with 1,3-dibromopropane⁵⁾ and 1,4-dibromo-

FIG. 1. Four Possible Alkylation Products Derived from DEOG.

TABLE I. YIELDS OF ALKYLATION PRODUCTS

α,ω -Dibromoalkanes $\text{Br}(\text{CH}_2)_n\text{Br}$	Yields (%) ^{a,b} of products			
	A	B	C	D
$n = 3$	—	—	28	—
4	—	—	—	58
5	35	12	—	3
6	40	15	—	—
8	42	14	—	—
10	42	14	—	—
12	44	13	—	—

^a Yields based on DEOG.^b Yields based on products purified by flash column chromatography.TABLE II. IR, ¹H NMR, AND EI AND CI MASS SPECTRAL DATA
OF MONO- AND BISALKYLATED PRODUCTS

Product	IR (neat) (cm ⁻¹)	¹ H NMR (δ)	EIMS (m/z)	CIMS (m/z)
A5	1730, 1710	3.35 (2H, t, $J=7$ Hz), 3.53 (2H, s)	352, 350, 307, 305, 156 ^c	353, 351, 307 ^c
A6	1730, 1710	3.37 (2H, t, $J=7$ Hz), 3.52 (2H, s)	366, 364, 321, 319, 156 ^c	367, 365, 321 ^c
A8	1740, 1720	3.40 (2H, t, $J=7$ Hz), 3.56 (2H, s)	394, 392, 349, 347, 156 ^c	395, 393, 349 ^c
A10	1735, 1710	3.37 (2H, t, $J=7$ Hz), 3.53 (2H, s)	422, 420, 377, 375, 156 ^c	423, 421, 377 ^c
A12	1740, 1720	3.36 (2H, t, $J=7$ Hz), 3.52 (2H, s)	450, 448, 405, 403, 156 ^c	451 ^c , 449
B5	1730, 1710	3.52 (4H, s), 3.56 (2H, t, $J=6$ Hz)	427, 156 ^c	473 ^c
B6	1730, 1710	3.50 (4H, s), 3.55 (2H, t, $J=6$ Hz)	441, 69 ^c	487 ^c
B8	1740, 1720	3.54 (4H, s), 3.59 (2H, t, $J=6$ Hz)	514, 469, 267 ^c	515 ^c
B10	1730, 1715	3.50 (4H, s), 3.54 (2H, t, $J=6$ Hz)	542, 497, 295 ^c	543, 471 ^c
B12	1740, 1715	3.52 (4H, s), 3.57 (2H, t, $J=6$ Hz)	570, 525, 369 ^c	571, 499 ^c

^c Base peaks.

butane, an endo-cycloalkylated product (**C**, $n=3$) and an exo-cycloalkylated product (**D**, $n=4$) were obtained with yields of 28% and 58%, respectively. In both cases, no mono- or bisalkylated products were formed. Next, the reaction of DEOG with 1,5-dibromopentane gave a mixture of mono- and bisalkylated compounds (**A** and **B**, $n=5$) as the main products. This was accompanied by a small amount of the exo-cycloalkylated product. For long chain dibromoalkanes, acyclic products were formed. Thus all of the reactions with $\text{Br}(\text{CH}_2)_n\text{Br}$ ($n=6, 8, 10, 12$) gave mainly a mixture of mono- and bisalkylated products with about a 3/1 ratio. (Table I) When similar reactions with $\text{Br}(\text{CH}_2)_n\text{Br}$ ($n=5\sim 12$) were done using a high dilution technique, compound **A** was formed exclusively but with a decreased yield of 18~23%, while the inter- or intramolecular alkylation products (**B,C,D**) were not obtained.

EXPERIMENTAL

IR spectra were observed on a Hitachi 260-10 spectrometer. ^1H - and ^{13}C NMR spectra were obtained on a Hitachi R-24B spectrometer and on a Hitachi R-90H NMR spectrometer, respectively, in CDCl_3 solutions using Me_4Si as an internal standard. EI and CI mass spectra were recorded on a JEOL JMS-D300 mass spectrometer at 70 eV and 200 eV (isobutane), respectively, using a direct insertion probe. IR, ^1H NMR, and EI and CI mass spectral data of **A5**~**A12** and **B5**~**B12** are shown in Table II.

A representative procedure. To a solution of the magnesium chelate prepared from DEOG (1.01 g, 5 mmol), magnesium turnings (0.81 g, 7.5 mmol) and a trace of iodine in absolute ethanol (12 ml) was added 1,6-dibromohexane (1.22 g, 5 mmol) and the solution was refluxed for 15 hr with constant stirring. The reaction mixture was worked up to give a brown oil which consisted mainly of mono- and bisalkylated products. The oil was chromatographed on a silica gel column (16 g) with a mixture of petroleum ether–benzene–ethyl acetate (30:3:1 and 10:3:1) to give 0.73 g of **A6** and 0.36 g of **B6**, respectively, as a pale yellow viscous liquid.

A high dilution procedure. Reactions were done by the same procedure as described above except for using 100 ml of EtOH and 72 hr of reaction time.

Ethyl 1-[2-(ethoxycarbonyl)-1-oxoethyl]-1-cyclopentane-carboxylate, D4. IR $\nu_{\text{max}}^{\text{neat}} \text{cm}^{-1}$ 1735, 1710; ^1H NMR δ 1.28 (6H, t, $J=7$ Hz), 3.48 (2H, s), 4.15 (4H, q, $J=7$ Hz);

^{13}C NMR δ 198.275 (s), 166.687 (s), 166.626 (s), 67.077 (s), 61.588 (t), 61.524 (t), 45.765 (t), 14.055 (q), 13.994 (q); EIMS m/z 256 (M^+ , 0.4), 211 ($\text{M}-\text{OEt}$, 12), 142 (100); CIMS m/z 257 ($[\text{M}+\text{H}]^+$, 100). *Anal.* Found: C, 60.68; H, 7.94. Calcd. for $\text{C}_{13}\text{H}_{20}\text{O}_5$: C, 60.92; H, 7.87%.

Ethyl 1-[2-(ethoxycarbonyl)-1-oxoethyl]-1-cyclohexane-carboxylate, D5. IR $\nu_{\text{max}}^{\text{neat}} \text{cm}^{-1}$ 1735, 1710; ^1H NMR δ 1.25 (6H, t, $J=7$ Hz), 3.46 (2H, s), 4.11 and 4.13 (4H, both q, $J=7$ Hz); EIMS m/z 225 ($\text{M}-\text{OEt}$, 2), 156 (100); CIMS m/z 271 ($[\text{M}+\text{H}]^+$, 100); *Anal.* Found: C, 62.34; H, 8.41. Calcd. for $\text{C}_{14}\text{H}_{22}\text{O}_5$: C, 62.20; H, 8.20%.

Ethyl 9-bromo-4-(ethoxycarbonyl)-3-oxononanoate, A5.

Ethyl 10-bromo-4-(ethoxycarbonyl)-3-oxodecanoate, A6.

Ethyl 12-bromo-4-(ethoxycarbonyl)-3-oxododecanoate, A8.

Ethyl 14-bromo-4-(ethoxycarbonyl)-3-oxotetradecanoate, A10.

Ethyl 16-bromo-4-(ethoxycarbonyl)-3-oxohexadecanoate, A12.

Tetraethyl 2,10-dioxo-1,3,9,11-undecanetetra-carboxylate, B5.

Tetraethyl 2,11-dioxo-1,3,10,12-dodecanetetra-carboxylate, B6

Tetraethyl 2,13-dioxo-1,3,12,14-tetradecanetetra-carboxylate, B8.

Tetraethyl 2,15-dioxo-1,3,14,16-hexadecanetetra-carboxylate, B10.

Tetraethyl 2,17-dioxo-1,3,16,18-octadecanetetra-carboxylate, B12.

REFERENCES

- 1) Y. Muramoto, K. Oishi, I. Ichimoto and H. Ueda, *Nippon Nōgeikagaku Kaishi*, **48**, 507 (1974).
- 2) Y. Naoshima, T. Yamamoto, S. Wakabayashi and S. Hayashi, *Agric. Biol. Chem.*, **44**, 2231 (1980).
- 3) Y. Naoshima, H. Mukaidani, S. Shibayama and T. Murata, *J. Chem. Ecol.*, **12**, 127 (1986) and references cited therein.
- 4) Y. Naoshima, T. Takehi, K. Doi, S. Wakabayashi and S. Hayashi, *Agric. Biol. Chem.*, **48**, 783 (1984) and references cited therein.
- 5) DEOG had been alkylated with short-chain dibromoalkanes, $\text{Br}(\text{CH}_2)_n\text{Br}$ ($n=1,2,3$), and the corresponding endo-cycloalkylated products produced.⁽⁶⁾
- 6) P. C. Guha and N. K. Seshadriengar, *Chem. Ber.*, **69**, 1207 (1936).