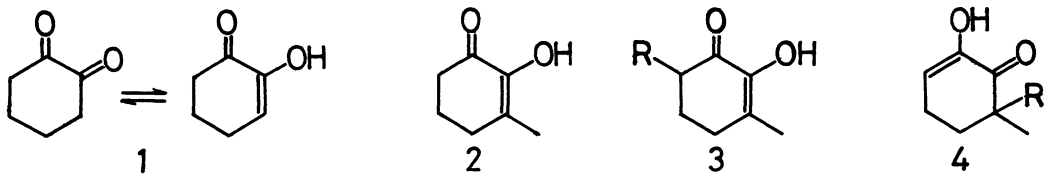
CHEMISTRY LETTERS, pp. 445 - 448, 1984.

REGIOSELECTIVE MONOALKYLATION OF 3-METHYL-1,2-CYCLOHEXANEDIONE

Masanori UTAKA, Makoto HOJO, and Akira TAKEDA*
Department of Synthetic Chemistry, School of Engineering,
Okayama University, Tsushima, Okayama 700

Monoalkylation of 3-methyl-1,2-cyclohexanedione was achieved regioselectively to give 6-alkyl-3-methyl-1,2-cyclohexanedione as a major product without the formation of O-alkylated or polyalkylated products.

The α-alkylation of ketones constitutes a very important and synthetically useful class of organic reactions.[1] However, very little attention has been given to that of α-diketones, although a direct α-alkylation of 1,2-cyclohexanedione (1) via its dianion was reported by Kende in 1973.[2] Recently we have succeeded in the facile synthesis of jasmine lactone and the related δ-lactones by using 3-substituted 1,2-cyclohexanediones as key intermediates which were obtained by the direct α-alkylation of the dione.[3] Further attempts to synthesize di- and trisubstituted δ-lactones required 3,6-disubstituted 1,2-cyclohexanedione (3) which was expected to be obtained by the direct α-alkylation of 3-substituted 1,2-cyclohexanedione (2). It is also very interesting to examine the regioselectivity of the direct introduction of a second alkyl group to 2, since polyalkylation or nonregioselective alkylation generally occurs in the case of monoketones, unless appropriate procedures were adopted to avoid these undesirable alkylations.[1]

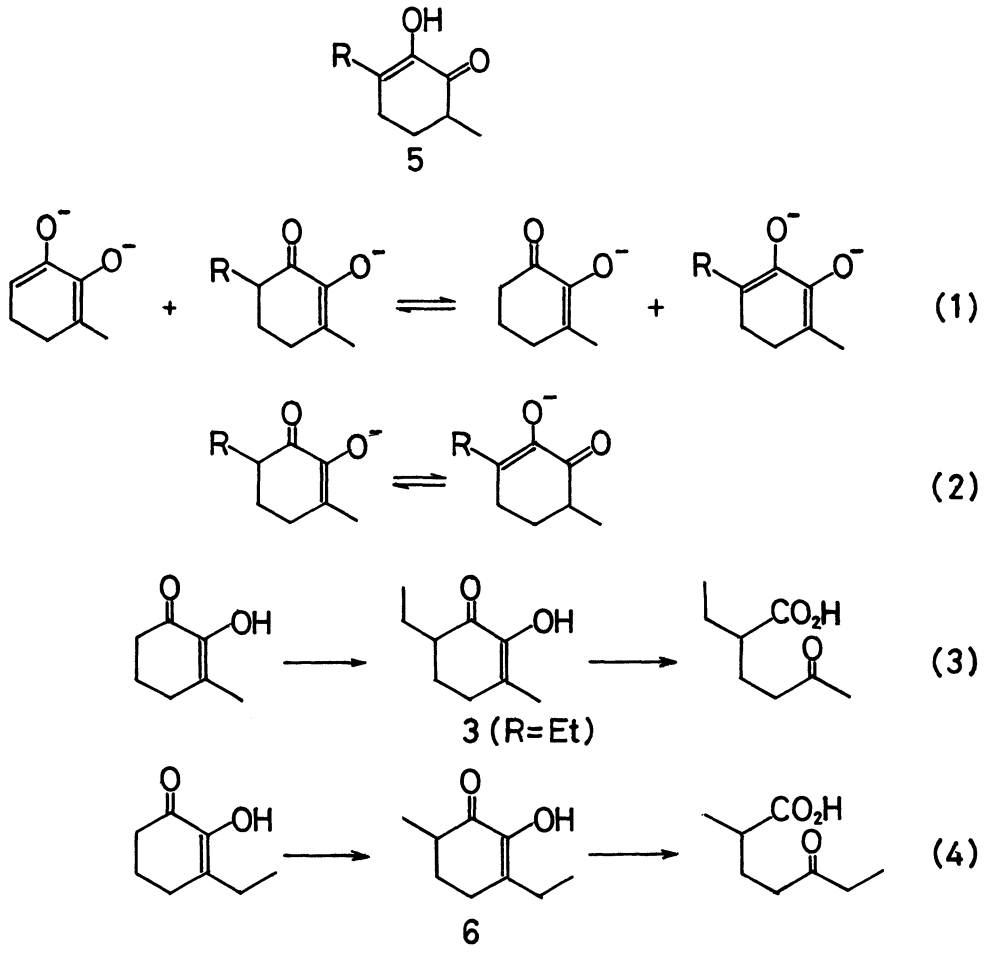


Herein we report a novel result of the α-alkylation of 3-methyl-1,2-cyclohexanedione (2). The reaction always afforded 6-alkyl-3-methyl-1,2-cyclohexanedione (3) as a major product and 6-alkyl-6-methyl-1,2-cyclohexanedione (4) as a minor one, in a ratio which depended on the solvent, temperature, and the alkyl group used. Byproducts such as O-alkylated or polyalkylated ones were not obtained. The results are shown in Table 1.[4]

The following procedure is representative. In a reaction flask flushed with nitrogen were placed 0.42 g (0.58 ml, 4.2 mmol) of diisopropylamine and 8.0 ml of THF. The flask was cooled to -10 °C and 2.5 ml (4.2 mmol) of 1.65 M butyllithium

in hexane was added with magnetic stirring. After stirring for 30 min, 252 mg (2.0 mmol) of 2[5] dissolved in 1 ml of THF was added dropwise and the solution was stirred further for 20 min at -10 °C. Then the flask was warmed to 24 °C and 0.5 ml (1.1 g, 8 mmol) of methyl iodide was added. After stirring for 2 h at 24 °C,[6] the reaction mixture was neutralized with dilute hydrochloric acid and extracted with ether. Drying ($MgSO_4$) and evaporation of the ethereal extract gave 288 mg of a brown oil. The crude product was purified by bulb-to-bulb distillation to give 221 mg of a pale yellow oil (bath temp 100–180 °C (2 mmHg)). The oil was analyzed by GLC (SE-30, 100 °C) to give 54% and 17% yields of 3 (R=Me) and 4 (R=Me), respectively. Analytical samples[7] were obtained by preparative GLC (Apiezone grease L, 120 °C).

The present alkylation involves several characteristics worthy of note. (1) It is concluded that the less highly substituted enolate is more reactive contrary to the usual order of reactivity,[1a] as observed in the proportion of 3 and 4 which reflects the relative reactivity of the two enolate anions in the dianion. (2) The finding that O-alkylated products were not obtained is contrary to the result reported for 1.[2] (3) The absence of polyalkylated products is explained by the very



slow equilibration rate among enolates (Eq. 1). (4) Similarly the absence of enol tautomer 5 indicates that the equilibration of Eq. 2 is also very slow under the reaction conditions used.[8] This leads to the generation of specific enols which, in turn, can be transformed specifically into synthetic intermediates as exemplified by Eqs. 3 and 4.[9,10]

The outcome of the present alkylation obtained so far suggests the versatility of the dianion as nucleophile. Full details of the work, the scope, and the limitation will be reported in due course.

Table 1. Regioselective Monoalkylation of 3-Methyl-1,2-cyclohexanedione (2)

RX	Solvent	Temperature	Time	Product 3	Product 4	2
		°C	h	yield[a]/%	yield[a]/%	recovered[a]/%
MeI	Ether	-50	6.5	13	3	43
		-20	7	46	8	5
		0	4.5	56	8	3
		23	3	57	8	4
		reflux	2	50	9	6
	THF	-78	6.5	63	28	0
		-50	3	52	20	0
		-30	3	56	16	1
		0	2.5	53	17	1
		24	2	54	14	1
EtI	Ether	25	10	18	4	24
	THF	0	5	41	20	9
		25	4	41	19	2
n-PrI	Ether	25	10	12	1	36
		reflux	15	4	1	49
	THF	0	8	36	10	9
		24	8	54	12	2
i-PrI	THF	24	19	17	5	27
	Ether	25	10	21	7	21
	THF	0	3	50	15	1
		25	2	50	14	1

a) Determined by GLC.

References

1) a) For a general review on alkylation of enolates, see: H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, California (1972), Chap. 9; b) For a recent paper, see: I. Kuwajima, E. Nakamura, and M. Shimizu, J. Am. Chem. Soc.,

104, 1025 (1982).
2) A. S. Kende and R. G. Eilerman, Tetrahedron Lett., 1973, 693.
3) M. Utaka, H. Kuriki, T. Sakai, and A. Takeda, Chem. Lett., 1983, 911.
4) Trials not listed in Table 1 such as the use of DME or ether–HMPA as solvent and the use of NaH–LDA as base in ether proved unsatisfactory for improving the regioselectivity. In practice, however, 4 and its reaction products in the reaction shown by Eq. 3 or 4 are easily eliminated in the workup process.
5) Conveniently prepared by the method described in M. Utaka, S. Matsushita, and A. Takeda, Chem. Lett., 1980, 779.
6) The progress of reaction was checked by TLC (silica gel, ethyl acetate–hexane (1:5)).
7) 3 (R=Me): ^{1}H NMR ($CDCl_3$) δ 1.19 (d, 3H), 1.91 (br s, 3H), 1.5–2.2 (m, 2H), 2.2–2.7 (m, 3H), 6.0 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 15.3 (q), 17.0 (q), 29.3 (t), 30.4 (t), 39.7 (d), 129.9 (s), 143.2 (s), 197.0 (s). Found: C, 68.42; H, 8.50%. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63%.
4 (R=Me): ^{1}H NMR ($CDCl_3$) δ 1.15 (s, 6H), 1.81 (t, 2H), 2.35 (q, 2H), 6.06 (t, 1H), 5.1 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 20.5 (t), 24.1 (q, 2C), 36.7 (t), 40.9 (s), 116.5 (s), 145.3 (s), 200.9 (s).
For other products 3 and 4 (R=Et, n-Pr, i-Pr, and allyl), IR and NMR spectra and elemental analyses were satisfactory also.
8) We also found that monoalkylation of 1 afforded 6-alkyl-2-hydroxy-2-cyclohexen-1-one, accompanied by a small amount of 3-alkyl-2-hydroxy-2-cyclohexen-1-one which was formed from the former by tautomerization during the workup process. See ref. 3.
9) 3 (R=Et): ^{1}H NMR ($CDCl_3$) δ 0.93 (t, 3H), 1.15–2.1 (m, 4H), 1.91 (m, 3H), 2.1–2.7 (m, 3H), 6.1 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 11.3 (q), 16.9 (q), 22.5 (t), 26.9 (t), 29.1 (t), 46.0 (d), 129.4 (s), 143.4 (s), 196.5 (s). Found: C, 70.24; H, 9.22%. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15%.
6: ^{1}H NMR ($CDCl_3$) δ 1.08 (t, 3H), 1.18 (d, 3H), 1.6–2.0 (m, 2H), 2.0–2.6 (m, 5H), 6.1 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 11.4 (q), 15.3 (q), 23.9 (t), 26.7 (t), 30.7 (t), 39.8 (d), 135.0 (s), 142.6 (s), 197.3 (s).
The tautomer 6 was prepared from 3-ethyl-1,2-cyclohexanedione in a similar way in 56% yield, accompanied by 6-methyl-6-ethyl-2-hydroxy-2-cyclohexen-1-one in 15% yield.
10) Ref. 3; M. Utaka, M. Nakatani, and A. Takeda, Tetrahedron Lett., 24, 803 (1983).

(Received December 22, 1983)