MICHAEL REACTION OF 1,2-CYCLOHEXANEDIONES AND 1,2-CYCLOPENTANEDIONES WITH METHYL VINYL KETONE

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The Michael reaction of 1,2-cyclohexanediones with methyl vinyl ketone is highly dependent upon the structure of dione or the catalyst, base or $ZnCl_2$, affording 3-(3-oxobutyl)-2-hydroxy-2-cyclohexen-1-one or 1-hydroxy-7-acetylbicyclo[3.2.1]octan-8-one as major products. 1,2-Cyclopentanediones react with methyl vinyl ketone somewhat differently.

The Michael reaction is widely used in organic synthesis as an effective method for forming C—C bonds.[1] Among various enolate anions used in the reaction, enolates of 1,3-cyclohexanediones or 1,3-cyclopentanediones have been used extensively. However, those of cyclic 1,2-diones have seldom been employed for the reaction.

In the course of our study on the chemistry of 1,2-cyclohexanediones,[2—4] we have investigated the Michael reaction of 1,2-cyclohexanediones and 1,2-cyclopentanediones with methyl vinyl ketone, methyl acrylate, and acrylonitrile. The reaction proceeded under mild conditions and afforded tri- or tetra-functionalized products in good yields which may be of practical use in organic synthesis, although only methyl vinyl ketone reacted with the diones in satisfactory manners. The results are shown in Scheme 1 and Table 1.[5] The following procedure illustrates the reaction of 1,2-cyclohexanedione (1) with methyl vinyl ketone (MVK) in methanol using KOH as catalyst.

A mixture of 1[6] (224 mg, 2.0 mmol), KOH (4.5 mg, 0.08 mmol), and MVK (210 mg, 3.0 mmol) in methanol (6 ml) was refluxed for 30 min under a nitrogen atmosphere. The methanol and the excess MVK were removed under reduced pressure and the residue was acidified to pH 2 with dilute hydrochloric acid. After drying ($MgSO_4$) and evaporation, the ethereal extract gave 358 mg of a yellow oil, which was passed through a silica gel column (Wako gel C200, hexane—acetone, 4:1) to afford 200 mg (60%) of 3-(3-oxobutyl)-2-hydroxy-2-cyclohexen-1-one (4) as a colorless oil.

It should be pointed out that the reaction described above provided only 4 as an isolated product. When $ZnCl_2$ in chloroform was used in place of KOH in methanol, the major product was 1-hydroxy-7-acetylbicyclo[3.2.1]octan-8-one (5a,b) in 27% yield, being accompanied by 4 in 18% yield. The role of zinc ion is considered to be the generation of enolate anion by forming a complex with 1[7] as well as the activation of MVK as a Lewis acid.

The formation of bicyclo[3.2.1]octane skeleton ($\underline{6a},\underline{b}$)[8] is the dominant fea-
ture of the reaction of 3-methyl-1,2-cyclohexanedione ($\underline{2}$)[6] with MVK using either
KOH or $ZnCl_2$ as catalyst. Adducts $\underline{10a},\underline{b}$ were not obtained at all. This fact is in
sharp contrast to the formation of adduct $\underline{4}$ from $\underline{1}$. Bicyclo[3.2.1]octane deriva-
tives $\underline{6a},\underline{b}$ may be formed by the intramolecular aldol reaction of the enolate anion
of the initially formed adduct as shown in Scheme 2. This may require a fast nucle-
ophilic attack of the enolate on the carbonyl carbon before it abstracts a proton
from solvent (methanol or water). In the reverse sense, a fast proton abstraction
by the enolate may occur intramolecularly in the reaction of $\underline{1}$ to $\underline{4}$. Then it was
expected that the dianion of $\underline{2}$ would prevent the intramolecular aldol reaction,
leading to $\underline{10}$ in preference to $\underline{6}$. This has proved to be the case, but the yield of
$\underline{10}$ was only 16%. The rest of starting $\underline{2}$ was lost as an intractable mixture of un-
identified materials.[9]

3-Methyl-1,2-cyclopentanedione (cyclotene) ($\underline{3}$) showed a somewhat different
reactivity that it reacted with two moles of MVK to form $\underline{8}$ as a major product when
KOH in methanol was used. Intramolecular trapping of the enolate anion by the
carbonyl carbon also occurs to afford $\underline{9a},\underline{b}$ in an aprotic solvent (acetonitrile)
with $ZnCl_2$ as catalyst. 1,2-Cyclopentanedione afforded a mixture of intractable
products under the reaction conditions used for $\underline{3}$.

Conversion of $\underline{4}$ to 5,8-dioxononanoic acid ($\underline{11}$), a precursor to cyclopentenone
derivatives,[10] was easily achieved by a dye-sensitized photooxygenation[2] in 83%
yield. Use of Michael adducts $\underline{6a},\underline{b}$ as synthetic intermediate is now in progress.
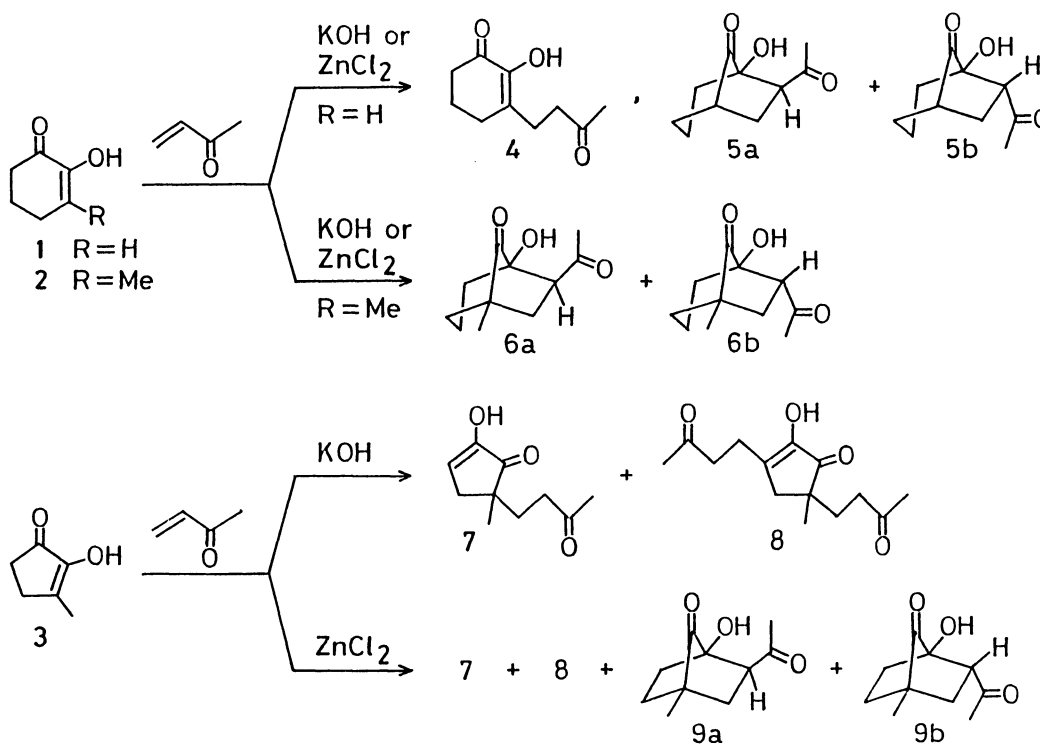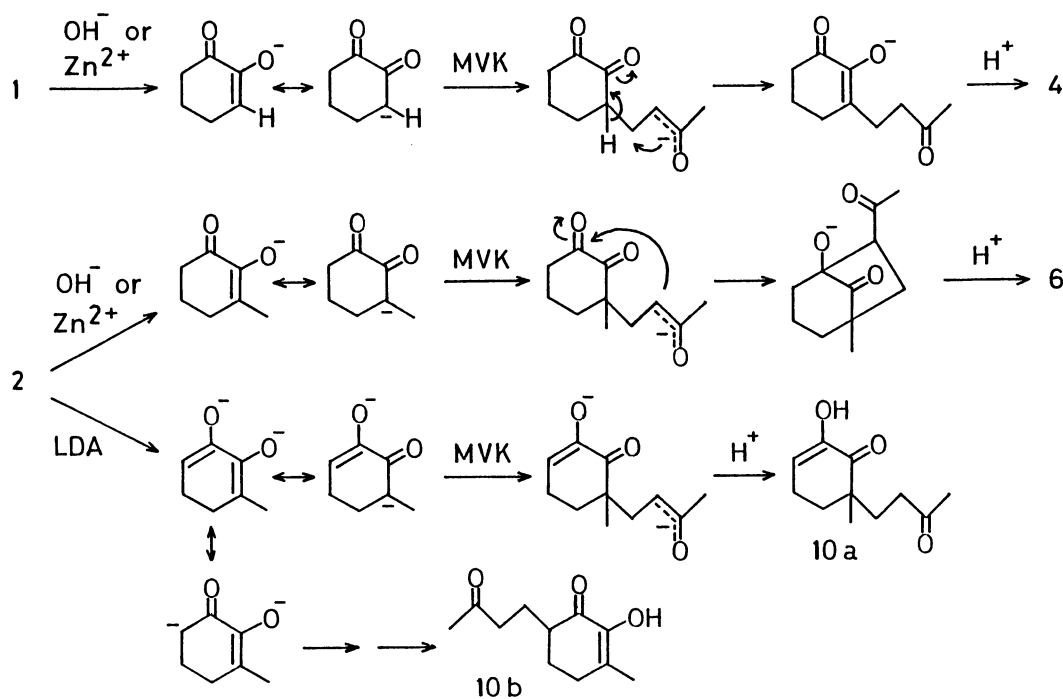

Scheme 1.

Table 1. Michael Reaction of 1,2-Cyclohexanediones (1,2) and 3-Methyl-1,2-cyclo-
pentanedione (3) with Methyl Vinyl Ketone

Diketone	MVK (equiv.)	Catalyst (equiv.)	Solvent	Temp °C	Time h	Product[a] (Yield/%)
1	1.5	KOH(0.04)	MeOH	reflux	0.5	4(60)
	1.5	ZnCl$_2$(1.0)	CHCl$_3$	reflux	3	4(18), 5a(22), 5b(5)[d]
	1.5	ZnCl$_2$(1.6)	CH$_2$Cl$_2$	reflux	4	4(16), 5a(24), 5b(5)[e]
	2.0	ZnCl$_2$(1.6)	CH$_2$Cl$_2$	reflux	4	4(8), 5a(28), 5b(8)
2	1.5	KOH(0.16)	MeOH	reflux	0.5	6a(30), 6b(26)
	1.5	KOH(0.16)	THF[b]	0	1	6a(42), 6b(31)
	1.5	KOH(0.16)	THF[b]	30	0.5	6a(35), 6b(29)
	3.0	ZnCl$_2$(1.6)	CHCl$_3$	reflux	4	6a(67), 6b(10)
	3.0	ZnBr$_2$(1.5)	CHCl$_3$	reflux	4	6a(65), 6b(13)
	3.0	ZnCl$_2$(1.5)	MeCN	reflux	4	6a(50), 6b(8)
	1.0	LDA(2.2)	THF[c]	-78	0.5	10a(8), 10b(8)
3	1.5	KOH(0.16)	MeOH	reflux	1	7(3), 8(43)[f]
	3.0	KOH(0.16)	MeOH	reflux	1	7(0), 8(60)
	4.0	KOH(0.16)	THF[b]	40	1	7(0), 8(48)
	3.0	ZnCl$_2$(1.1)	MeCN	reflux	5	7(8), 8(8), 9a(12), 9b(23)

a) Isolated yields by column or thin layer chromatography. b) A few drops of water were added to dissolve KOH. c) A similar result was obtained by using ether as solvent. d) The recovery of 1 was 14%. e) The recovery of 1 was 11%. f) The recovery of 3 was 36%.


Scheme 2.

4 $\xrightarrow[\text{MeOH}]{O_2, h\nu}$ HO$_2$C~~~~~ (1)

                                    83%   11
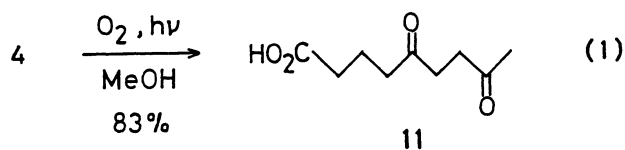
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3) M. Utaka, M. Hojo, and A. Takeda, Chem. Lett., 1984, 445.

4) M. Utaka, M. Hojo, Y. Fujii, and A. Takeda, Chem. Lett., 1984, 635.

5) All products listed in Table 1 were identified by ^{1}H and ^{13}C NMR, IR, MS, and elemental analyses.

6) Conveniently prepared according to the method described in M. Utaka, S. Matsushita, and A. Takeda, Chem. Lett., 1980, 779.

7) The formation of enolate anion is supported by an absorption maximum at 320 nm.

8) 6a: ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.125 (3H, s, CH$_3$), 1.965 (2H, d, J=7.1 Hz, C(6)—H$_2$(endo and exo)), 2.202 (3H, s, CH$_3$CO), 3.252 (1H, t, J=7.1 Hz, C(7)—H(endo)). Acetate of 6a: ^{1}H NMR (100 MHz, CDCl$_3$) δ 1.17 (3H, s, CH$_3$), 2.10 (3H, s, CH$_3$CO$_2$), 2.23 (3H, s, CH$_3$CO), 2.63 (1H, m, C(6)-H(endo)), 3.80 (1H, dd, J=4.9 and 10.0 Hz, C(7)—H(endo)).

6b: ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.111 (3H, s, CH$_3$), 1.540 (1H, J=1.5, 11.7, and 13.7 Hz, C(6)—H(exo)), 2.339 (3H, s, CH$_3$CO), 2.636 (1H, J=7.0 and 13.7 Hz, C(6)—H(endo)), 2.900 (1H, J=1.5, 7.0, and 11.7 Hz, C(7)—H(exo)).

The structures of 5a and 5b were established by using the NMR spectra which are similar to those for 6a and 6b except for the signals due to the presence of a methyl group.

9) When the dianion of 2 was alkylated with RX, the reaction proceeded via stabilized enolates as shown below, to afford the product in 60—80% yields.[3] In the present Michael reaction, a reactive enolate on the side chain (Scheme 2, 2→10) seems to be responsible for the low yield.
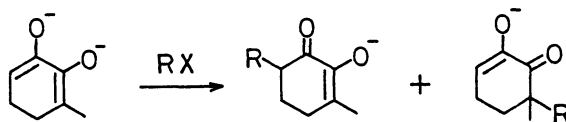
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