Study on the Regioselective Alkylation of Methyl Vinyl Ketone Dimer for the Synthesis of C1 Substituted Bicyclic Ketal

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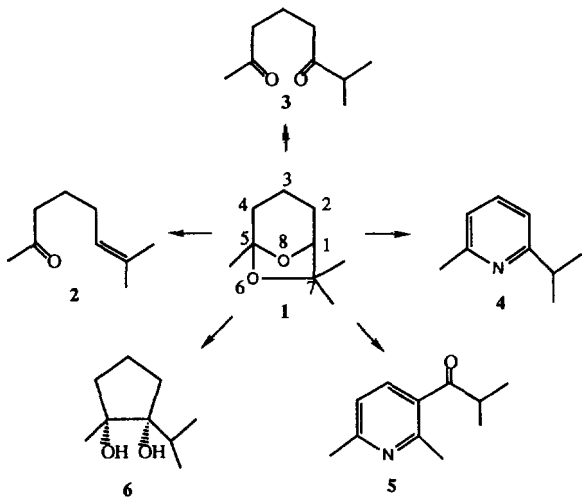
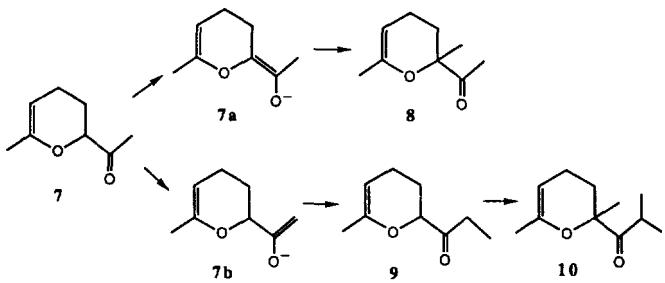
6,8-Dioxabicyclo[3.2.1]octane (**1**) has been showed the potential utility as a reactive intermediate for the natural product synthesis[1] and for the transforming ability to other structures, such as δ,ε-unsaturated ketone **2**,[2] 1,5-diketone **3**,[3] 2,6-disubstituted pyridine **4**,[4] 2,3,6-trisubstituted pyridine **5**,[5] and cis-1,2-cyclopentanediol **6**[6] (Scheme 1). It was required for the demonstration of the general use of bicyclic ketal **1** to introduce functional groups at different positions of the ketal **1** (C1-C5 and C7).

In order to introduce alkyl group at C1 of the bicyclic ketal **1**, the regioselective alkylation of the methyl vinyl ketone (MVK) dimer was essential. We report herein the convenient regioselective alkylation method of the MVK dimer for the introduction of the methyl group at C1 of the bicyclic ketal **1**. It is important to develop the relevant conditions controlling the type of enolates **7a** or **7b** as an intermediate for the regioselective alkylation of the MVK dimer **7** (Scheme 2).

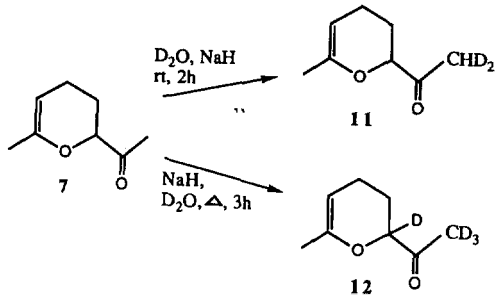
More substituted enolate (**7a**) could introduce the methyl group at ring position to give **8**, but less substituted enolate (**7b**) could introduce the methyl group at terminal position to give **9**. It has been known that the less substituted enolate is favored in kinetic condition because of lack of steric hindrance.[7] On the other hand, the more substituted enolate, which is more stable,[8] is favored in thermodynamic condition.[9] Enamine alkylation has been known as less substituted alkylation because of steric effect[10] and we used this methodology for the brevicomin synthesis.[11] The more substituted enolate should be required in our system for the alkylation at C1 of the bicyclic ketal **1**. But the regioselective methylation



Scheme 1.



Scheme 2.



Scheme 3.

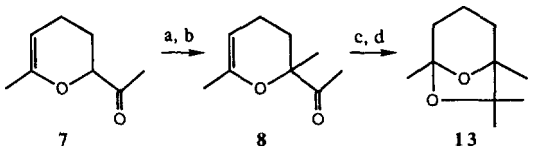
at more substituted position in this system has been known in very low yield (20%) by using trityl anion.[12] In the study of the mechanism for the formation of 1,5-diketone from the bicyclic ketal,[13] we also found the difficulty of regioselective deuteriation at more substituted position via thermodynamic enolate **7a**. The deuterium was exchanged rapidly at terminal position to give **11** in kinetic condition and exchanged slowly at ring position to give **12** which contains deuterium on both positions even in thermodynamic condition as shown in Scheme 3. This forced us to do the study of regioselective methylation of MVK dimer in several different conditions (Table).

Several bases were used for this enolate methylation and we found that NaH and sodium *t*-butoxide gave better yield of thermodynamic product **8** than KH, potassium *t*-butoxide, lithium hexamethyldisilazane (LHMDS), potassium hexamethyldisilane (KHMDS), sodium metoxide and LDA. The best condition for the desired regioselective alkylation was the use of NaH (4 eq.) with MeI (3 eq.) at rt (entry 4, 68%). But in most cases, the kinetic products **9** and **10** were also obtained and the isopropyl ketone **10** could be derived from ethyl ketone **9** by further methylation.[14] When 1 eq. of MeI was used, even though the reaction was not complete the product **10** was still obtained. From the variation of using MeI from 1 ed. to 5 eq., the use of 3 eq. of MeI was the best condition.

Solvent effects in enolate alkylation are studied by Zaugg[15] and known that the solvent of higher dielectric constant (ε) gave the faster reaction rate. For instance, the reaction rate of enolate alkylation with sodium diethyl n-buthylmalonate in DMSO (ε 47) was much faster than that in THF (ε 7.3). The slower reaction by using the solvent of lower dielectric constant should favor the thermodynamic product in our system. In result, the desired product **8** was obtained in better yield with THF (entries 4, 11, 18) compared with DMSO (entries 8, 16, 21) or DMF (entries 9, 17). Ether, methylene chloride, and mixed solvents such as THF-DMSO and THF-

Table 1. Regioselective Methylation of MVK Dimer 7

Entry	Solvent	Base (eq.)	Temp.	Rxn. Time (hr)	% yield 8	9	10
1	THF	NaH (1.5)	rt	16	10	2	8
2	THE	NaH (2)	rt	16	23	2	8
3	THF	NaH (3)	rt	16	55	5	13
4	THF	NaH (4)	rt	15	68	5	12
5	THF	NaH (5)	rt	15	63	7	15
6	THF	NaH (4)	reflux	3	46	9	10
7	THF	NaH (4)	0℃	16	31	10	12
8	DMSO	NaH (4)	rt	16	3	10	33
9	DMF	NaH (4)	rt	16	11	10	34
10	THF	*t*-BuONa (1.5)	rt	2.5	45	3	10
11	THF	*t*-BuONa (2)	rt	2.5	62	3	11
12	THF	*t*-BuONa (3)	rt	2	55	4	10
13	THF	*t*-BuONa (4)	rt	2	55	6	12
14	THF	*t*-BuONa (2)	reflux	0.5	47	5	12
15	THF	*t*-BuONa (2)	0℃	3	37	3	10
16	DMSO	*t*-BuONa (2)	rt	2	3	10	45
17	DMF	*t*-BuONa (2)	rt	2	10	13	35
18	THF	*t*-BuOK (1.5)	rt	4	26	10	19
19	THF	*t*-BuOK (2)	rt	3	11	10	23
20	THF	*t*-BuOK (1.5)	reflux	0.5	16	10	13
21	DMSO	*t*-BuOK (1.5)	rt	6	7	7	21
22	THF	KH (1.5)	rt	26	0	2	26
23	THF	KH (3)	rt	21	0	9	35
24	THF	KH (4)	rt	17	23	10	64
25	THF	LHMDS (1.5)	rt	20	30	5	10
26	THF	LHMDS (3)	rt	20	32	6	11
27	THF	KHMDS (1.5)	rt	20	21	6	18
28	THF	KHMDS (3)	rt	20	24	8	22
29	THF	MeONa (1.5)	rt	20	10	3	5
30	THF	MeONa (3)	rt	20	39	6	10



a) NaH, THF, rt b) MeI c) MeLi d) HCl, overall 68% yield

Scheme 4.

HMPA did not give any advantage.

Another consideration for this enolate alkylation, also, should be the metal counterion. The reaction rate of enolate alkylation has been known to increase by using the bigger metal ion; the smaller and the tighter metal ion should introduce the tighter enolate coordination with metal and should diminish the reactivity of enolate.[16] The tighter enolate should favor the thermodynamic product and this principle was well fit in our system; the use of NaH or *t*-BuONa as a base gave much better yield for the formation of thermodynamic product **8** than KH or *t*-BuOK.

In conclusion, we found the convenient method for the alkylation at more substituted position of MVK dimer by using NaH (4 eq.) with MeI (3 eq.) in THF at rt. This methylated ketone **8** reacted with MeLi and cyclized under acidic condition to desired C1 methylated bicyclic ketal **13**, 1,5,7,7-tetramethyl-6,8-dioxabicyclo[3.2.1]octane, in quantitative yield (Scheme 4).[17]

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14. Spectral data of **9**: IR (neat): 2917, 1713 (C=O), 1682 (C=C), 1448, 1381, 1237, 1104, 1066, 926 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 4.55 (br s, 1H, =CH), 4.30 (br, t, 1H, J=7 Hz, OCHCO), 2.65 (q, 2H, *J*=7 Hz, $COCH_2$), 2.10-1.45 (m, 4H, CH_2CH_2), 1.94 (br s, 3H, $=CCH_3$), 1.10 (t, 3H, *J*=7 Hz, $COCH_2CH_3$). Spectral data of **10**: IR (neat): 2919, 1710 (C=O), 1682 (C=C), 1465, 1380, 1216, 1106, 1068, 1031 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 4.50 (br s, 1H, =CH), 3.22 (septet, 1H, *J*=7 Hz, $COCHMe_2$), 2.22-1.46 (m, 4H, CH_2CH_2), 1.80 (s, 3H, $=CCH_3$), 1.34 (s, 3H, $OCCH_3$), 1.12 (d, 3H, *J*=7 Hz, isopropyl CH_3), 0.99 (d, 3H, *J*=7 Hz, isopropyl CH_3).
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17. Spectral data of **8**: IR (neat): 2918, 1716 (C=O), 1681 (C=C), 1448, 1097 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 4.50 (br s, 1H, =CH), 2.19 (s, 3H, $COCH_3$), 2.20-1.40 (m, 4H, CH_2CH_2), 1.79 (s, 3H, $=CCH_3$), 1.32 (s, 3H, OC(CO)CH_3). Spectral data of **13**: IR (neat): 2961, 1459,

1376, 1245, 1227, 1204, 1168, 1106, 986, 902 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.05-1.45 (m, 6H, methylene envelope), 1.40 (s, 3H, C5 methyl), 1.28 (s, 3H, endo methyl), 1.15 (s, 3H, exo methyl), 1.14 (s, 3H, C1 methyl); ^{13}C NMR ($CDCl_3$): 105.6 (C5), 82.5 (2×C, C1 and C7), 33.4, 31.7, 26.9, 25.9, 21.1, 20.6, 18.2.

Study on the Rearrangement Reaction of Bicyclic Ketal with Aluminum Iodide

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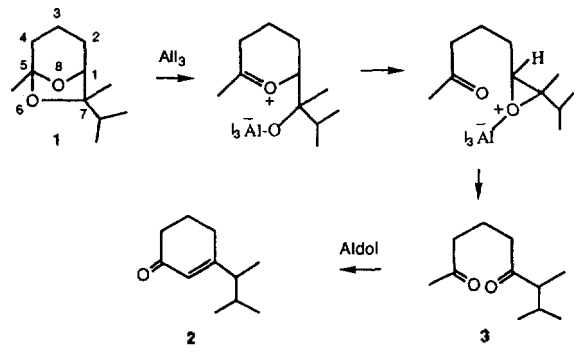
Aluminum iodide prepared from aluminum foil and iodine has been known as easily accessible and versatile ether-cleaving reagent by Bhatt *et al.*[1] In the course of our continuing research into the bicyclic ketals in the 6,8-dioxabicyclo[3.2.1] octane series, we applied this reagent in our system and found interesting results. We report herein the novel ketal rearrangement reaction with aluminum iodide in acetonitrile to give cyclohexenone and pyridine derivatives.

In the fragmentation reaction of bicyclic ketal **1** with aluminum iodide in acetonitrile, we found two products in a ratio of about 5 : 1. The major product had higher mobility on TLC (silica gel, hexane/ether, 7 : 3). The structure of the minor product **2** (9% isolated yield) was readily identified from analysis of spectral data.[2] HRMS required a formular of $C_{11}H_{18}O$ (Found: 166.1359. requires *M*, 166.1358). The IR (thin film) spectrum gave a strong signal at 1669 cm^{-1}, indicative of an enone. Relevant proton and carbon NMR spectral data are provided for the structure **2**. A mechanism to account for formation of the cyclohexenone product is relatively straightforward (Scheme 1). Initial attack of the Lewis acid on O-6 has been suggested in prior fragmentation reactions.[3,4]



Scheme 1.

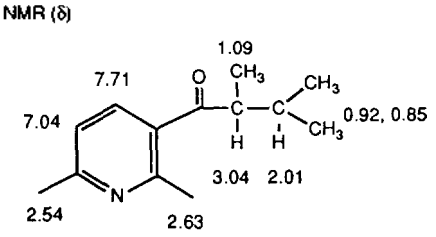


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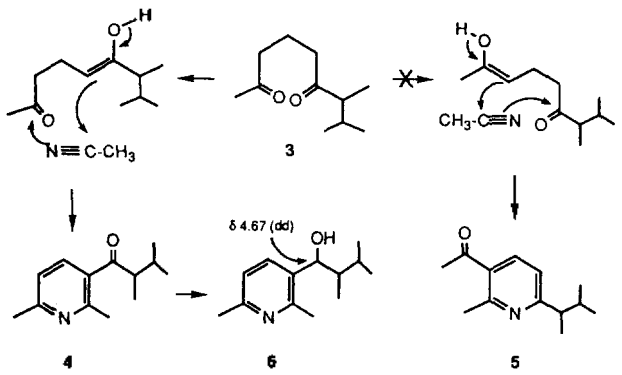
Figure 1.



4 **6** **5**

Scheme 2.

The 1,5-diketone intermediate **3** seems to be critical for formation of the cyclohexenone via the aldol condensation.

The structure of the major product (46%) was much difficult to assign. The proton NMR indicated five methyl peaks. Three doublets appeared at δ 1.09, δ 0.92 and δ 0.85, and two highly deshielded singlets were observed at δ 2.63 and δ 2.54. Two complex methine signals were found at δ 2.01 and δ 3.04. These two protons are coupled with one another. Irradiation of the δ 3.04 signal frequency collapsed the δ 1.09 doublet while irradiation of the δ 2.01 signal gave two singlets at δ 0.92 and δ 0.85. The proton NMR spectrum also exhibited two highly deshielded aromatic protons at δ 7.71 and δ 7.04. These two protons are coupled, with J=8 Hz. The carbon NMR spectrum revealed 13 signals for carbon. There were four highly deshielded singlets (δ 207.3, δ 159.9, δ 157.2 and δ 121.2), 4 doublets (δ 30.2, δ 50.0, δ 119.9 and δ 135.7), and 5 quartets (δ 12.5, δ 18.4, δ 21.4, δ 23.9 and δ 24.4). The UV spectrum (EtOH) contained maxima at 274 nm (ε 4140) and 239 nm (ε 6640). HRMS required a formula of $C_{13}H_{19}NO$ (Found: 205.1472. requires *M*, 205.1466). The two highly-deshielded adjacent protons (δ 7.71 and δ 7.04) are useful clue to the final assembly of the pieces. This suggested the structure **4** for the major product (Figure 1), which has been synthesized in different way.[5]

The origin of the two new carbon atoms and the nitrogen must be the acetonitrile. Based on our isolation of the diketone intermediate **3**,[6] we suggest that the formation of the pyridine compound arises from insertion of the acetonitrile by way of an enol intermediate. An alternative insertion mode can be imagined to give **5** (Scheme 2). This structure **5** was readily eliminated by reduction of the carbonyl group to an alcohol **6**. The carbinol proton at δ 4.67 was observed as a doublet of doublets confirming **4** as its precursor.

The role of the diketone **3** as an intermediate for both