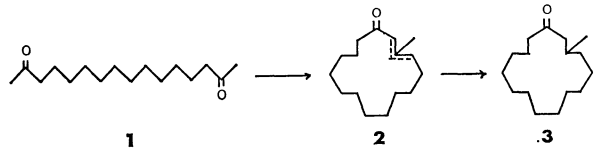
  Bull. Chem. Soc. Jpn., 53, 1417—1420 (1980)

Efficient Regioselective Aldol Condensation of Methyl Ketones Promoted by Organoaluminium Compounds, and Its Application to Muscone Synthesis

Jiro Tsuji,* Toshiro Yamada, Mitsumasa Kaito, and Tadakatsu Mandai
Department of Chemical Engineering, Tokyo Institute of Technology, Meguro, Tokyo 152
(Received November 16, 1979)

Dialkylaluminium aryloxide in combination with a tertiary amine was found to be a good reagent for regioselective aldol condensation of methyl ketones at the methyl side. Regioselective aldol condensation of 2-octanone was carried out using diisobutylaluminium phenoxide–pyridine. The intramolecular aldol condensation of 2,15-hexadecanedione promoted by the same reagent gave a mixture of dehydromuscones in 65% yield. Its hydrogenation produced muscone.

In our continuous effort to synthesize natural products from butadiene telomers, we attempted to synthesize muscone (3-methylcyclopentadecanone) (**3**). Muscone is a naturally occurring fragrant compound with musk odor. Many synthetic attempts for this unique 15-membered cyclic ketone have been made. One method carried out by Stoll is based on the intramolecular aldol condensation of 2,15-hexadecanedione (**1**) to form the 15-membered cyclic ketone (**2**).[1]

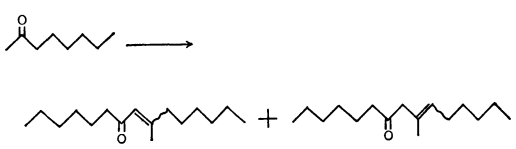


Scheme 1.

Since the methyl group at 3-position of muscone need not be introduced separately, this synthetic scheme would be an elegant method if two inherent problems are solved. The first problem is a good synthetic method for the diketone **1** and the second one is a good method of aldol condensation. Concerning the first problem, the known methods are somewhat tedious.[2,3] We have reported new synthetic methods for this diketone using butadiene telomers.[4,5] Especially the synthesis starting from ethyl 3,8-nonadienoate is the convenient one.[6] The second problem of the intramolecular aldol condensation is an extremely difficult one. Aldol condensation is one of the most important means of carbon–carbon bond formation, but its utility in organic synthesis has been rather limited because of lack of selectivity.[7] The reaction is reversible and other competing reactions take place. Recently several ingenious methods have been reported on the controlled aldol condensation. In these methods, regioselective formation of enolate is essential. Regioselective formation of silyl enolates is a typical example. They are treated with titanium tetrachloride or ammonium fluoride to undergo regioselective cross aldol condensation.[8,9] However, these methods can not be applied to the present purpose of the intramolecular aldol condensation of diketone, because it is impossible to generate silyl enolate from the methyl side of one carbonyl group of the diketone, leaving the other carbonyl group intact. Also common bases such as alkyllithiums, and alkali alkoxides, are not suitable. In order to carry out the intramolecular aldol condensation of a diketone to form a macrocyclic ketone efficiently, the reaction must be rapid, irreversible, and regioselective. For this aldol condensation of the diketone, Stoll used magnesium amide derived from *N*-methylaniline and ethylmagnesium bromide.[1] This base presumably generates a magnesium enolate regioselectively which undergoes the aldol condensation. However, the desired aldol product having the 15-membered ring was obtained only in 17% yield, which is far from satisfaction. Thus it is imperative for us to devise a new method for the aldol condensation of this specific diketone. Our mechanistic consideration of the Stoll's method that the magnesium reagent generates magnesium enolate by coordinating to carbonyl group, while *N*-methylaniline assists the deprotonation leads us to a conclusion that magnesium is not a strong Lewis acid and some other metal compounds which have stronger Lewis acidity should be better. For this purpose, we selected organoaluminium compounds, because stronger Lewis acidity and high affinity to oxygen are expected with aluminium. We found our own organoaluminium compounds, which are very effective for regioselective aldol condensation, and successful aldol condensation of the diketone was achieved. Few studies have been reported on the aldol condensation using aluminium enolate.[10] Recently, successful cross aldol condensation *via* aluminium enolate generated by the treatment of carbonyl compounds with diethylaluminium 2,2,6,6-tetramethylpiperidide at low temperature has been reported.[11] By using our own organoaluminium compounds, successful aldol condensation of the diketone was achieved. A preliminary account of the work has already been given[12] and the details of the studies on the aluminium-promoted aldol condensation are presented in this paper.

Results and Discussion

Aldol Condensation of 2-Octanone. The first requisite in our studies is the regioselective aldol condensation at the methyl side of methyl ketones. For this purpose, we selected 2-octanone as a model compound and studied its aldol condensation using organoaluminium reagents. After considerable screening exper-



Scheme 2.

iments, we found that the aluminium compounds represented by a general formula R_2AlOAr afforded the desired enone as the aldol product selectively, but the yield was not high. The addition of tertiary amines as a proton capture produced the enone in high yields by suppressing undesired proton transfer. Then screening of the reaction conditions using R_2AlOAr–tertiary amine system was carried out by the addition of 2-octanone (1.0 mmol) in THF (3 ml) to a refluxing THF (6 ml) solution of R_2AlOAr–tertiary amine (3.0 mmol–3.0 mmol). The progress of the reaction was monitored by GLC. In this experiment, the aluminium reagent was used in an excess.

Concerning R in the reagent, ethyl and isobutyl were used, but no appreciable difference was observed (Fig. 1). Therefore, the most easily available isobutyl was used throughout this study. Then several phenols were tested as shown in Fig. 2. Phenol and *p*-cresol gave the highest yields, and *p*-*t*-butyl-, 2,6-dimethyl-, and *p*-methoxyphenol were less effective and *p*-nitrophenol was not satisfactory. From these results, phenol was our choice. As for the tertiary amines, no difference was observed among pyridine, 2,6-lutidine, and triethylamine as shown in Fig. 3. From the results of these screening experiments, we decided to adopt *i*-Bu_2AlOPh–pyridine system as the reagent throughout this study.

Then the effect of solvents was studied. The reaction proceeded at room temperature at moderate rate, but very rapidly by heating. The experiments were carried out at boiling temperatures of solvents. As shown in Figs. 4 and 5, nonpolar solvents such as benzene, toluene, and hexane seem to be the best solvents. In ethers, which coordinate to aluminium, the reaction was slower. In dioxane or 1,2-dimethoxyethane at their boiling temperatures, decomposition of the aldol product by secondary reactions took place at the same time. THF gave the better result at its boiling temperature. The reaction was slower in diethyl ether and dichloromethane. Consideration of the solubility of the aluminium reagent leads us to use a mixture of THF and hexane as a suitable solvent. In these experiments, an excess of the aluminium reagent was used, because in the desired intramolecular

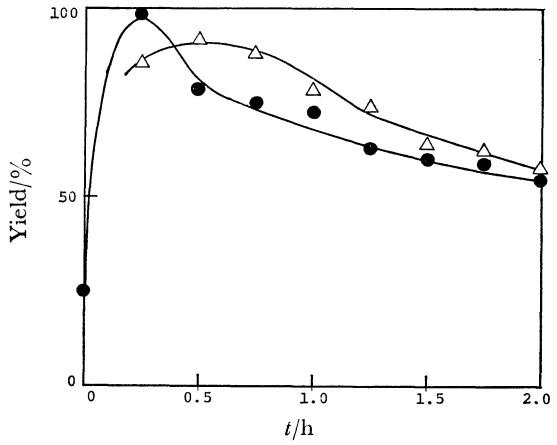


Fig. 1. Effect of alkyl groups in R_2AlOPh for aldol condensation of 2-octanone.
Conditions: R_2AlOPh/pyridine, THF reflux, △: R=^{i}Bu, ●: R=Et.

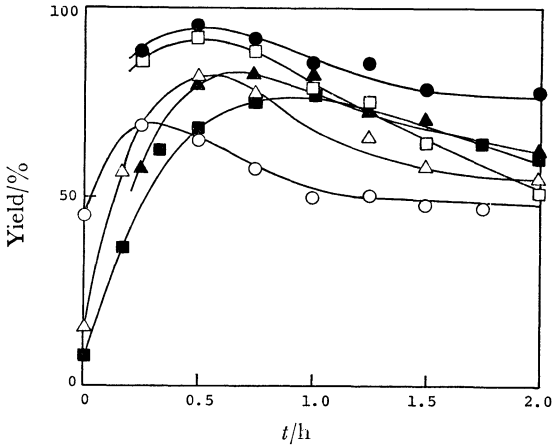


Fig. 2. Effect of aryloxy groups in $^i Bu_2AlOAr$.
Conditions: $^i Bu_2AlOAr$/pyridine, THF reflux, □: phenol, ▲: *p*-*t*-butylphenol, ■: 2,6-dimethylphenol, △: *p*-methoxyphenol, ○: *p*-nitrophenol, ●: *p*-cresol.

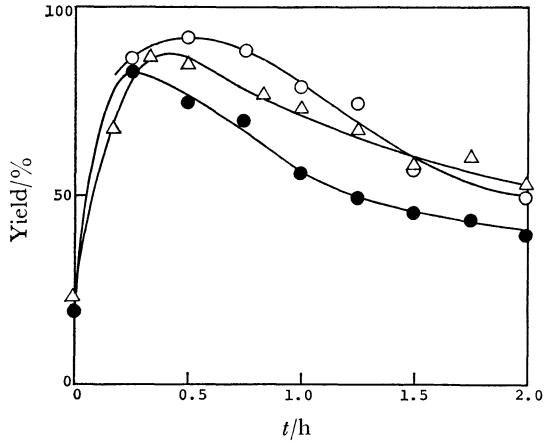


Fig. 3. Effect of amines.
Conditions: $^i Bu_2AlOPh$/*t*-amine, THF reflux, △: triethylamine, ○: pyridine, ●: 2,6-lutidine.

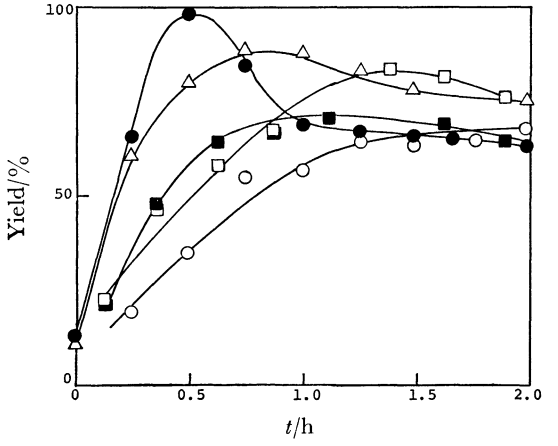


Fig. 4. Effect of solvents (1).
Conditions: $^i Bu_2AlOPh$/pyridine, temp 52—57 °C, □: THF, △: benzene, ○: DME, ■: dioxane, ●: toluene.

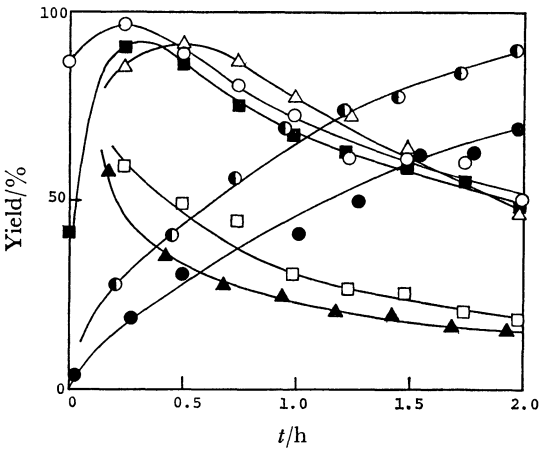


Fig. 5. Effect of solvents (2).
Conditions: $^{t}Bu_2AlOPh$/pyridine, reflux, ◐: Et_2O, ●: CH_2Cl_2, ○: hexane, ■: benzene, △: THF, □: DME, ▲: dioxane.

aldol condensation of the diketone, the aluminium reagent is present in an excess when the reaction is carried out under high dilution conditions by adding the diketone to the solution of the aluminium reagent, and the reaction conditions for the inter- and intramolecular reactions must be same. The yield of the desired aldol product reached at the maximum within one hour, and then other side reactions began to occur which decrease the yields of the aldol product. Therefore, the reaction must be stopped after short period of time.

Taking the above shown results into consideration, we have carried out the regioselective aldol condensation of 2-octanone in the following way. At first heptane solution of i-Bu_2AlH (7.6 mmol) was added at 0 °C to a solution of phenol (8.3 mmol) in THF. Then pyridine (9.0 mmol) was added at room temperature. The solution was brought to reflux and 2-octanone (10 mmol) was added in five minutes. After two hours, the reaction was quenched and the aldol product was isolated in 85% yield. The product was a mixture of 9-methyl-8-pentadecen-7-one and 9-methyl-9-pentadecen-7-one. Catalytic hydrogenation of the mixture afforded 9-methyl-7-pentadecanone as a single product. No product formed by the reaction at the methylene side was detected. 2-Butanone behaved similarly giving the expected aldol product.

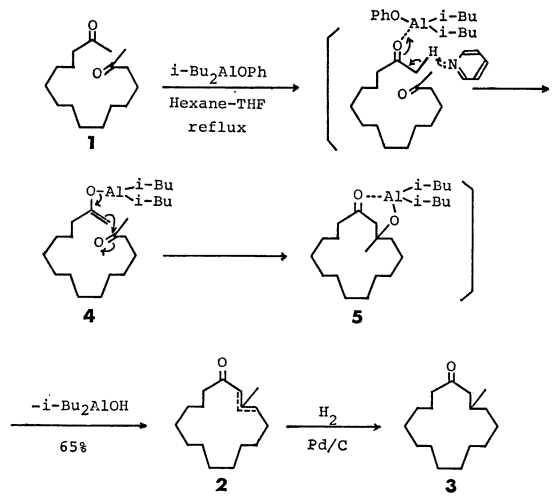
Regioselective Aldol Condensation of 2,15-Hexadecanedione. We have confirmed that i-Bu_2AlOPh–pyridine is a good reagent for rapid, regioselective aldol condensation of 2-octanone and then we applied this reagent to the intramolecular aldol condensation of 2,15-hexadecanedione (**1**). Results of the experiments carried out under various conditions are summarized in table 1. In order to obtain a high yield of the aldol product, the use of 3—5 equivalents of the aluminium reagent was found to be essential, and the reaction was carried out under high dilution conditions by adding a diketone solution slowly. As the best yield, the desired aldol product was obtained in 65% after column chromatographic separation. In this case, some diketone was recovered, and the yield based on conversion was 78%, which seems to be satisfactory for this type of intramolecular aldol condensation to form the macrocyclic ketone. The reaction was carried out by adding the diketone solution (0.025 M, 40 ml) to i-Bu_2AlOPh/pyridine (0.04 M, 100 ml) by using a mechanically driven syringe over a period of 11 h under reflux. The product obtained was a mixture of double bond isomers **2**. Detailed analysis of the NMR spectrum showed that the mixture consists of *trans*-3-methyl-2-cyclopentadecenone (50%), *cis*-3-methyl-2-cyclopentadecenone (30%), and *trans*- and *cis*-3-methyl-3-cyclopentadecenone (20%). The mixture was hydrogenated using palladium on carbon to give muscone as a single product, which was identified by comparing its NMR and IR spectra with those of an authentic sample.

This efficient regioselective aldol condensation can be explained by the following mechanism. Coordination of aluminium to carbonyl oxygen and abstraction of proton from the less hindered methyl side with pyridine proceed concertedly to form the aluminium enolate **4**, which has a considerable life even at refluxing conditions. Then the attack of another carbonyl group forms the aldol product **5** which strongly coordinates to aluminium. Then liberation of diisobutylaluminium

Table 1. Intramolecular aldol condensation of 2,15-hexadecanedione

Entry	R_2AlOAr/R_3N (equiv./diketone[a])		Solvent/ml (b, c)		Yield/% d (e)
1	i-Bu_2AlOPh/Pyridine	(5)	THF	(50, 40)	42 (49)
2	i-Bu_2AlOPh/Pyridine	(5)	THF	(100, 40)	51 (75)
3	i-Bu_2AlOPh/Pyridine	(5)	Benzene	(100, 20)	32 (43)
4	i-Bu_2AlOPh/Pyridine	(5)	Benzene	(100, 40)	50 (61)
5	i-Bu_2AlOPh/Pyridine	(3)	THF Hexane	(20, 20) (80, 20)	47 (58)
6	i-Bu_2AlOPh/Pyridine	(4)	Hexane		65 (78)
7	i-Bu_2AlOPh/Pyridine	(5)	Hexane		59 (69)
8	Et_2AlOPh/2,6-Lutidine	(3)	Hexane		38 (41)
9	i-Bu_2AlOPh/2,6-Lutidine	(3)	Hexane		36 (43)
10	i-Bu_2AlOPh/2,6-Lutidine	(5)	Hexane		40 (50)

a) The diketone (1.0 mmol) was used. b) Solvent for the aluminium reagent. c) Solvent for the diketone. d) Isolated by column chromatography. e) Based on the consumed diketone.



hydroxide forms the enone **2**.

Experimental

IR spectra were recorded as neat films on a JASCO-2 spectrometer. NMR spectra were recorded in CCl_4 on Hitachi R-24 (60 MHz) and Nippon Denshi PS-100 (100 MHz) with Me_4Si as an internal standard. Melting points were measured by Shibata (No. 297) melting point apparatus.

Materials: Diisobutylaluminium hydride was prepared by the thermal decomposition of triisobutylaluminium, followed by distillation, and used as a heptane solution (2.00 M). 2-Octanone, pyridine, and phenol were purified by distillation.

Aldol Condensation of 2-Octanone. A solution of phenol (880 mg, 8.3 mmol) in THF (10 ml) was placed in a 50 ml two-necked flask fitted with a reflux condenser and cooled to 0 °C. The heptane solution of *i*-Bu_2AlH (7.6 mmol, 3.8 ml) was added dropwise to the mixture at 0 °C with stirring. Then pyridine (9.0 mmol, 0.73 ml) was added at room temperature. The solution was gently refluxed and 2-octanone (1.28 g, 10 mmol) in THF (5 ml) was added dropwise in 5 min. After two hours, the mixture was cooled to 0 °C and 3 M-HCl was added. THF was removed *in vacuo*, and the residue was extracted with ether. The extract was washed with 5% NaOH, brine, and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography (silica gel, hexane–ether 30/1) to give a mixture of 9-methyl-8-pentadecen-7-one and 9-methyl-9-pentadecen-7-one (1.01 g, 8.5 mmol, 85%). IR (neat) 2920, 1715, 1690, and 1620 cm^{-1}. NMR (CCl_4) δ 0.60—1.10 (m, 6H), 1.10—1.80 (m, 15.2H), 1.80—2.70 (m, 7H), 2.85—3.05 (m, 0.8H), and 5.90 (broad s, 1H).

Aldol Condensation of 2,15-Hexadecanedione. A solution of phenol (414 mg, 4.40 mmol) in THF (20.0 ml) was placed in a three-necked flask fitted with a reflux condenser and cooled to 0 °C. The heptane solution of *i*-Bu_2AlH (2.00 ml, 4.00 mmol) was added dropwise to the mixture at 0 °C with stirring. Then pyridine (0.40 ml, 379 mg, 4.80 mmol) and hexane (80.0 ml) were added at room temperature. A solution of 2,15-hexadecanedione (254 mg, 1.00 mmol) in THF–hexane (20 ml+20 ml) was added dropwise using a mechanically driven syringe over a period of 11 h at refluxing temperature with vigorous stirring. The reaction mixture was stirred for an additional hour. The mixture was cooled to 0 °C, and 3 M-HCl was added. The organic layer was separated, and the aqueous layer was extracted with ether (50 ml×3). The combined extracts were washed with 5% NaOH, brine, and dried over $MgSO_4$. Concentration of the extract gave a yellow oil, which was purified by column chromatography (silica gel, hexane–ether 20/1) to give a mixture of dehydromuscones **2** (156 mg, 65%). IR (neat) 2920, 1710, 1680, and 1605 cm^{-1}. NMR (CCl_4) δ 1.00—1.80 (m, 19.6H), 1.80 and 2.10 (s, 3H), 1.85—3.10 (m, 4.4H), 5.10—5.45 (m, 0.2H), and 6.00 and 6.05 (s, 0.8H); mass spectrum *m/e* 236 (M^+).

Preparation of Muscone. Catalytic hydrogenation of the dehydromuscones by Pd on carbon gave (±)-muscone in a quantitative yield. Its NMR and IR data, and GLC analysis were completely identical with those of an authentic sample. IR (neat) 2920 and 1710 cm^{-1}. NMR (CCl_4) δ 0.75—1.05 (m, 3H), 1.05—1.90 (broad s, 23H), and 1.90—2.45 (m, 4H). Semicarbazone mp 131.5—132.5 °C (Lit,[13] 131—132 °C).

References

1) M. Stoll and A. Rouve, *Helv. Chim. Acta*, **30**, 2019 (1947).
2) M. Stoll, *Helv. Chim. Acta*, **34**, 1817 (1951).
3) Y. Tsuzuki and S. Motoki, Japan Patent, 6626 (1957), *Chem. Abstr.*, **52**, 9821e (1958).
4) J. Tsuji, M. Mizutani, I. Shimizu, and K. Yamamoto, *Chem. Lett.*, **1976**, 773.
5) J. Tsuji, M. Kaito, and T. Takahashi, *Bull. Chem. Soc. Jpn.*, **51**, 547 (1978).
6) J. Tsuji, M. Kaito, T. Yamada, and T. Mandai, *Bull. Chem. Soc. Jpn.*, **51**, 1915 (1978).
7) A. T. Nealsen and W. J. Houlihan, *Org. React.*, **16**, 1 (1968).
8) T. Mukaiyama, K. Narasaka, and K. Banno, *Chem. Lett.*, **1973**, 1011; T. Mukaiyama, K. Banno, and K. Narasaka, *J. Am. Chem. Soc.*, **96**, 7503 (1974).
9) I. Kuwajima, E. Nakamura, and M. Shimizu, *J. Am. Chem. Soc.*, **99**, 1265 (1977).
10) E. A. Jeffery, A. Meisters, and T. Mole, *J. Organomet. Chem.*, **74**, 373 (1974) and literatures cited therin.
11) H. Nozaki, K. Oshima, K. Takai, and S. Ozawa, *Chem. Lett.*, **1979**, 379.
12) J. Tsuji, T. Yamada, M. Kaito, and T. Mandai, *Tetrahedron Lett.*, **1979**, 2257.
13) V. R. Mamdapur, P. P. Pai, K. K. Chakravarti, U. G. Nayak, and S. C. Bhattacharyya, *Tetrahedron*, **20**, 2601 (1964).