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EFFICIENT REGIOSELECTIVE ALDOL CONDENSATION OF METHYL KETONES PROMOTED BY ORGANOALUMINUM COMPOUNDS, AND ITS APPLICATION TO MUSCONE SYNTHESIS

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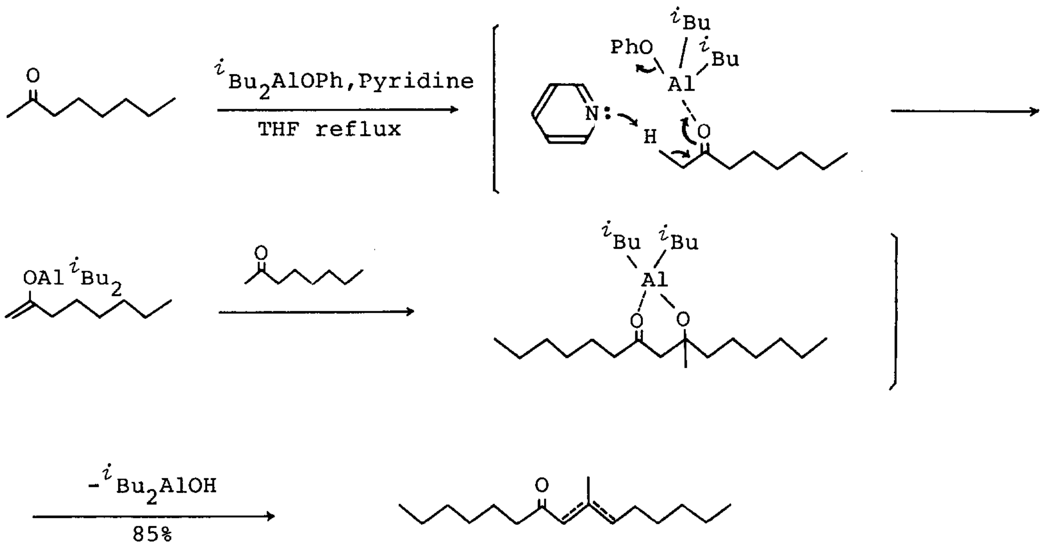
Summary: Regioselective aldol condensation of 2-octanone and 2-butanone at the methyl side proceeded in high yields using a system of dialkylaluminum phenoxide/tertiary amine. The intramolecular aldol condensation of 2,15-hexadecanedione was carried out by the same system, especially di-*i*-butylaluminum phenoxide/pyridine, to give dehydromuscone in 65% yield. Its hydrogenation afforded muscone (3-methylcyclopentadecanone).

3-Methylcyclopentadecanone (3) is called muscone and a famous naturally occurring fragrant compound. Among numerous synthetic methods for muscone so far reported,1) the classical one is intramolecular aldol condensation of 2,15-hexadecanedione (1) carried out by Stoll.2) Since the methyl group at 3-position of muscone is introduced by the aldol condensation, 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 an efficient aldol condensation. However, the intramolecular aldol condensation of the diketone 1 is extremely difficult, and Stoll obtained the desired cyclized product 2 by the aldol condensation using magnesium *N*-methylanilide only in 17%, which is far from satisfactory.

Concerning the first problem of the diketone synthesis, we have reported facile syntheses of this diketone 1 using butadiene telomers as starting materials,3) and the diketone 1 is now easily available to us. Then we have concentrated our effort on the efficient aldol condensation. For this purpose, a better condensing reagent is necessary. To carry out the efficient intramolecular aldol condensation, the reaction must proceed regioselectively at the methyl side of the diketone 1. In addition, the reaction must be rapid and irreversible, so that the competing intermolecular reaction can be minimized. A commonly used method of aldol condensation *via* silyl enol ether4) can not be applied to this symmetrical diketone.

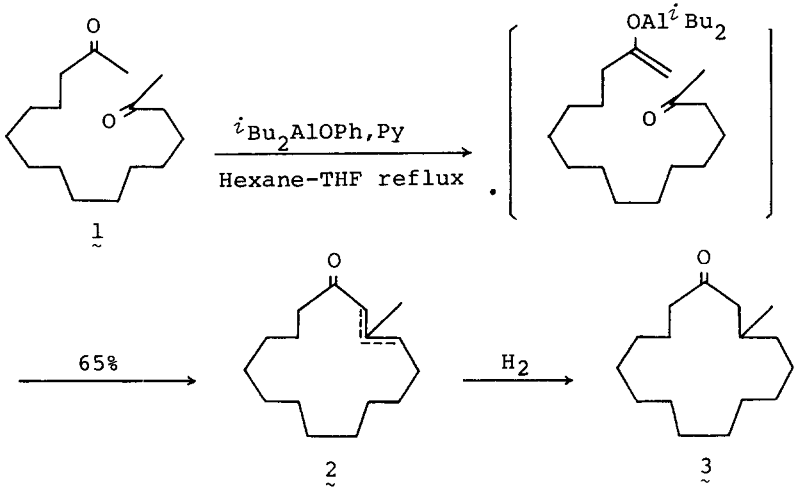
At first we carried out regioselective aldol condensation of 2-octanone as a model reaction. After considerable screening experiments, we selected aluminum enolate. Recently a successful cross aldol condensation *via* organoaluminum enolate generated by the treatment of carbonyl compounds with diethylaluminum 2,2,6,6-tetramethylpiperidide at a low temperature has been carried out by Nozaki and coworkers.5) We found that dialkylaluminum phenoxide in the presence of a tertiary amine is a very good condensing reagent for the regioselective and rapid aldol condensation of 2-octanone to give a mixture of 9-methyl-8-pentadecen-7-one and 9-methyl-9-pentadecen-7-one in 85% isolated yield. Absence of the tertiary amine decreased the yield, (at most 40% yield). Also the regioselective reaction of 2-butanone proceeded in a high yield. The reaction can be explained by the following mechanism.



In this aldol condensation, selection of solvents seems to be more important than that of amines or phenols. We obtained best results in aprotic nonpolar solvents such as hexane, benzene, and toluene due to absence of their coordination to aluminum atom as Lewis acid, although ethers such as ethyl ether, THF, DME, and dioxane gave satisfactory results.

In a typical example, di-*i*-butylaluminum hydride (7.6 mmol, 3.8 ml of 2.0 M heptane solution) was added to a solution of phenol (780 mg, 8.3 mmol) in THF (10 ml) at 0° and then pyridine (0.75 ml, 9.0 mmol) was added. The solution was gently refluxed and 2-octanone (1.28 g, 10 mmol) in THF (5 ml) was added dropwise in 5 min. After 2 h, the reaction mixture was quenched and the enone was isolated in 85% yield (silica gel column, hexane-ether 30/1): 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).

After confirming the usefulness of the dialkylaluminum phenoxide/tertiary amine system for the aldol condensation of methyl ketones, we attempted an intramolecular aldol condensation of 2,15-hexadecanedione (**1**), which leads to a convenient synthesis of *dl*-muscone (**3**)



1 **2** **3**

Reaction conditions were examined and the results are summarized in the Table. A combination of di-*i*-butylaluminum phenoxide and pyridine seemed to be most effective. A mixed solvent of hexane-THF is suitable for this cyclization (entries 6,7). THF was used in order to increase the solubility of the diketone **1** in hexane. Also, 3 ~ 5 equivalents of the reagent are essential for this cyclization. Optimum concentration of the aluminum reagent was found to be in a range of 0.03 ~ 0.05 M. Other combinations of reagents shown in entries 8-10 did not give good results. These reagents caused further aldol condensation and polymerization of the product.

A typical procedure is as follows: In a 500 ml three-necked flask, a solution of the aluminum reagent in THF-hexane (20 ml + 80 ml) (4 equivalents of the diketone **1**) was prepared at 0°. Then a solution of the diketone **1** (254 mg, 1.0 mmol) (THF-hexane 20 ml + 20 ml) was added slowly to the gently refluxed solution of the aluminum reagent using a mechanically driven syringe over 12 h. The product was purified by column chromatography (silica gel, hexane-ether 20/1) to give dehydromuscone (**2**) as a mixture of 2- and 3-olefins in 65% yield (78% yield based on the consumed diketone **1**): IR (neat) 2920, 1710, 1690, 1605 cm^{-1}; NMR (CCl_4) δ 1.10-1.80 (m, 18.5H), 1.80-2.55 (m, 7H), 2.55-3.10 (m, 1.5H), and 6.05 (broad s, 1H); mass spectrum m/e 236 (M^+). No product resulting from a carbanion of the methylene side could be detected by analyses of GLC and NMR spectral data. Dehydromuscone (**2**) thus obtained was converted to *dl*-muscone by a catalytic hydrogenation (5% palladium carbon, ethanol) in a quantitative yield. GLC analysis of the product showed a single peak, and its retention time, IR and NMR spectral data were fully 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). 1.90-2.45 (m, 4H); semicarbazone mp 131.5-132.5° (Lit.$^{6)}$ 131-132°).

Table Intramolecular Aldol Condensation of 2,15-Hexadecanedione^a

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

a) The diketone **1** (1.0 mmol) was used.
b) Solvent for the aluminum reagent.
c) Solvent for the diketone.
d) Isolated by column chromatography.
e) Based on the consumed diketone.

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