Tetrahedron Letters No. 21, pp 1817 - 1820, 1976. Pergamon Press. Printed in Great Britain.

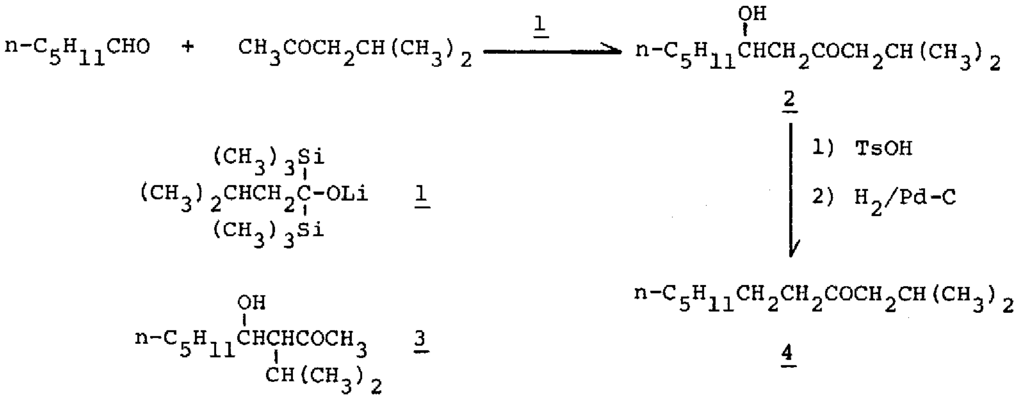
REGIOSPECIFIC DIRECTED ALDOL REACTIONS OF METHYL KETONES WITH ALDEHYDES

Isao Kuwajima, Toshio Sato, Masahiko Arai, and Naoki Minami
Department of Chemistry, Tokyo Institute of Technology
Ookayama, Meguro-ku, Tokyo

(Received in Japan 15 March 1976; received in UK for publication 12 April 1976)

The aldol condensation[1] is one of the most versatile methods for carbon-carbon bond formation and the intramolecular reaction has been widely used for construction of five- and six-membered enone systems.[2] However, the intermolecular one has not been feasible for synthetic purposes, except in the case that one of the carbonyl components has no α-hydrogen, because of equilibrium of the enolate anions which results in complex mixtures. Various methods[3-7] have hitherto been devised for the circumvention of these problems. In most of the cases, the masked carbonyl compounds have been employed for generation of the specific enolate or its equivalent. Recently, Stork et al[8] reported kinetic generation of the enolates from the corresponding methyl ketones, followed by treatment with aldehydes, which afforded the directed aldols. We wish to report here that specific enolate of the methyl ketone can be generated effectively even in the co-existence of aldehydes, which leads to the efficient way to the aldol synthesis.

In the course of our studies on the sterically hindered base, we have found that methyl ketones react with aldehydes in the regiospecific and directed manner to give the corresponding aldols in good yields in the presence of a hindered base such as lithium 1,1-bis(trimethylsilyl)-3-methylbutoxide 1. The following example is illustrative; lithium 1,1-bis(trimethylsilyl)-3-methylbutoxide was prepared by treating the corresponding alcohol[9] (0.278 g, 1.2 mmol) with an equimolar amount of n-butyllithium in 2 ml of dry tetrahydrofuran (THF). A mixture of n-hexanal (0.100 g, 1.0 mmol) and 4-methyl-2-pentanone (0.120 g, 1.2 mmol) in 2 ml of THF was added to the solution at -40° under argon atmosphere. After the mixture was stirred for 3 hr at that temperature, it was worked up with aq NH_4Cl. Removal of the solvent from the ether extracts followed by separation on silica gel chromatography (n-hexane-ether = 3:1) afforded 6-hydroxy-2-methyl-4-undecanone (0.168 g, 84%); bp 80°/0.1 mmHg; ir (neat); 3420, 1705 cm^{-1}; nmr (CCl_4); δ 0.8-1.8 (m, 18H), 2.3 (d, J=2 Hz, 2H, $(CH_3)_2C\underline{H}CH_2C{=}O$), 2.5 (d, J=6 Hz, 2H, $CH(OH)C\underline{H}_2C{=}O$), 3.2 (br, 1H, OH), 3.9 (m, 1H, $C\underline{H}OH$). Anal. Calcd for $C_{12}H_{24}O_2$: C, 71.95; H, 12.08. Found: C, 72.20; H, 12.31.



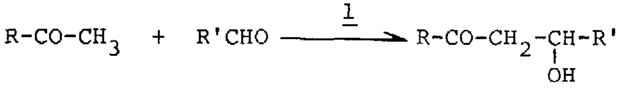
In the nmr of the product, the absorption at ca. δ 2.1 characteristic of acetyl group, is little detected, showing the reaction took place exclusively on the methyl site of the ketones. Absence of the regioisomer 3 in the product was confirmed further (a) by comparison with an authentic mixture of 2 and 3[10] (seperable on 10% QF_1 at 130°) and (b) by showing identity of the product 4 obtained by dehydration (p-toluenesulfonic acid, benzene, 12 hr room temp. 83%) followed by hydrogenation (Pd-C in methanol) with an authentic sample of 2-methyl-4-undecanone.

Similarly, various methyl ketones reacted with aldehydes regiospecifically in the presence of 1 to afford the directed aldols in good yields as shown in Table 1.

The results are explicable by assuming that a hindered compound of appropriate basicity such as 1 possesses a specific character which differentiates[12] the proton of the methyl group from that of the methylene(or methyne) group of the ketone or the aldehyde. This ability of the base enables to abstract the proton of the methyl group preferencially to generate the specific enolate of the ketone, which is trapped simultaneously by the co-existent aldehyde to afford the directed aldol. Although the equlibrium between less and more highly substituted enolates may exist in the presence of ketone, the reaction rate of the enolate generated kinetically with aldehyde is considered to be much faster[12] than that of the equlibrium under the reaction condition.

Efficacies of several other bases are also examined in the reactions of 3-methyl-2-butanone with 3-phenylpropanal and of 4-methyl-2-pentanone with

Table I. Regiospecific Directed Aldol Reaction[a]



$$R\text{-}CO\text{-}CH_3 + R'CHO \xrightarrow{1} R\text{-}CO\text{-}CH_2\text{-}\underset{OH}{CH}\text{-}R'$$

Ketone	Aldehyde	Yield of Aldol,[c] %
$CH_3CH_2CH_2COCH_3$	$n\text{-}C_5H_{11}CHO$	71[d]
$C_6H_5CH_2CH_2COCH_3$	$(CH_3)_2CHCHO$	71[b]
$(CH_3)_2CHCOCH_3$	$C_6H_5CH_2CH_2CHO$	83
	$n\text{-}C_5H_{11}CHO$	81
$C_2H_5(CH_3)CHCOCH_3$	$C_6H_5CH_2CH_2CHO$	80
	$n\text{-}C_5H_{11}CHO$	78
$(CH_3)_2CHCH_2COCH_3$	$C_6H_5CH_2CH_2CHO$	86[e]
	$n\text{-}C_5H_{11}CHO$	84[d]

[a] All of the reactions were performed under similar reaction conditions described in the text. [b] Reactant ratio; base:ketone:aldehyde=1.0:1.0:1.2. [c] All of the products gave satisfactory nmr, ir, and elemental analysis data for the assigned structures. [d] Absence of the regioisomer was confirmed by the procedures (a) and (b) described in the text. [e] Absence of the regioisomer was confirmed by the procedure (b) described in the text.

Table II. Effect of Bases[a]

$$C_6H_5CH_2CH_2CHO + CH_3COCH(CH_3)_2 \xrightarrow{\text{Base}} C_6H_5CH_2CH_2CH(OH)CH_2COCH(CH_3)_2 \quad \underline{5}$$

Base	Aldol,%		Base	Aldol,%	
	5	2		5	2
EtOLi	50		(2-Norbornyl)$_3$COLi[b]	65[c]	
t-BuOLi	76	65	Me(Me$_3$Si)$_2$COLi	80	
(iso-Pr)$_2$NLi	67	75	1	83	84
(Me$_3$Si)$_2$NLi	68				

[a] All of the reactions were performed under similar reaction conditions described in the text. [b] See reference 11. [c] This lithium alkoxide is insoluble under the reaction condition.

n-hexanal. The results are shown in Table II. Among the bases examined, 1 proved to be the most efficient one in both of the reactions.Comparison of lithium diisopropylamide with lithium t-butoxide did not afford any conclusive results. Thus, the former appears to be more efficient in the reaction of 4-methyl-2-pentanone with n-hexanal, while the latter does so in the reaction of 3-methyl-2-butanone with 3-phenylpropanal.

Further studies on the specific generation of the enolates are currently investigated in more details.

References and Notes

1. Reviews; (a) A. T. Nielsen and W. J. Houlihan, *Org. React.*, **16**, 1 (1968); (b) H. O. House, "Modern Synthetic Reactions," 2nd ed, Benjamin, Reading, Mass., 1972, pp 629-682.
2. See reference 1 (b), pp 492-509.
3. Silyl enol ethers to lithium, magnesium, or zinc enolates; H. O. House, D. S. Crumine, A. Y. Teranishi, and H. D. Olmstead, *J. Am. Chem. Soc.*, **95**, 3310 (1973).
4. Silyl enol ethers to titanium enolates; T. Mukaiyama, K. Banno, and K. Narasaka, *ibid.*, **96**, 7503 (1974).
5. Aluminium enolates; E. F. Jeffery and A. Meisters, *J. Organometal. Chem.*, **74**, 373 (1974); idem, *ibid.*, **82**, 307 (1974).
6. Enol borate; T. Mukaiyama, K. Inomata, and M. Muraki, *J. Am. Chem. Soc.*, **95**, 967 (1973).
7. Imines to lithio derivatives; G. Wittig and H. Reiff, *Angew. Chem., Int. Ed. Engl.*, **7**, 7 (1968); G. Wittig and A. Hesse, *Org. Syn.*, **50**, 66 (1970).
8. G. Stork, G. A. Kraus, and G. A. Garcia, *J. Org. Chem.*, **39**, 3459 (1974). In this report, regiospecific lithium enolates of methyl ketones were generated kinetically by using lithium diisopropylamide at low temperature.
9. J.-P. Picard, R. Calas, J. Dunogues, and N. Duffaut, *J. Organometal. Chem.*, **26**, 183 (1971). By the modified method, this type of alcohols can be prepared in much higher yields; I. Kuwajima, T. Sato, N. Minami, and T. Abe, manuscript in preparation.
10. Authentic mixture of *2* and *3* was prepared, according to the method of Mukaiyama (see ref. 4) by treating n-hexanal with a mixture of 2-trimethylsiloxy-4-methyl-1-pentene and -2-pentene[13] in the presence of $TiCl_4$.
11. Potassium tri-2-norbornylmethoxide was used as a ramified tertiary alkoxide in a dehydrohalogenation reaction; K. A. Bartsch and D. D. Ingram, *J. Org. Chem.*, **40**, 3138 (1975).
12. These assumptions are also supported by the results reported by Stork (see ref. 8).
13. A mixture of these silyl enol ethers was prepared by the method established in our laboratory; E. Nakamura, T. Murofushi, M. Shimizu, and I. Kuwajima, *J. Am. Chem. Soc.*, in press.