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REGIO- AND DIASTEREOSELECTIVE ALDOL REACTION OF 1,2-CYCLOHEXANEDIONE DIANIONS WITH ALDEHYDES

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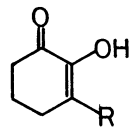
The aldol reaction of 1,2-cyclohexanedione dianions with various aldehydes afforded threo and erythro aldols in a ratio of 82:18—>99:1 in 60—85% yields. A diastereoselective synthesis of racemic corynomycolic acid was achieved by using the reaction.

The aldol reaction has received much study carried out by conventional methods[1,2] or new methods for the directed reaction.[3] However, little attention has been given to the use of 1,2-cyclohexanediones (1) for the aldol reaction.

Here we wish to introduce the directed aldol reaction of lithium enolate dianion of 1,2-cyclohexanediones with aldehydes,[4] which usually proceeds with a complete regioselectivity and a high threo:erythro ratio of 82:18—>99:1 in 60—85% yields. The aldol reaction endowed with the high diastereoselectivity looks promising, in contrast to the reaction of the lithium enolate derived from cyclohexanone.[5] The results are shown in Table 1.

A typical reaction procedure is as follows. A solution of diisopropylamine (0.42 g, 0.58 ml, 4.2 mmol) in dry THF (8 ml) was cooled to -10 °C and 1.55 M butyllithium in hexane (2.7 ml, 4.2 mmol) was added. After stirring for 30 min, 3-methyl-1,2-cyclohexanedione (1, R=CH_3)[6] (252 mg, 2.0 mmol) dissolved in THF (1 ml) was added dropwise to the solution and the mixture was stirred for 20 min. Then the bath was cooled to -78 °C and benzaldehyde (212 mg, 2.0 mmol) was added.



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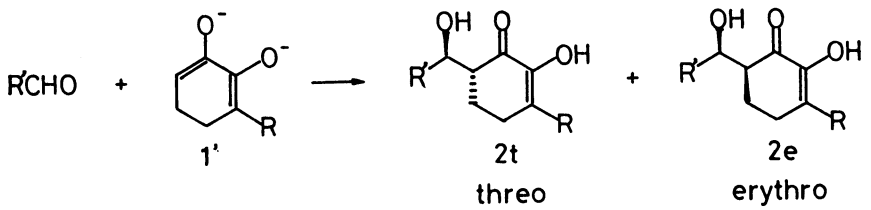


The homogeneous solution was stirred for 30 min and then quenched with dilute hydrochloric acid. The solution adjusted to pH 7–8 was extracted with ether. The ether extract was dried ($MgSO_4$) and evaporated under reduced pressure. The residual oil was column-chromatographed over silica gel (Wako gel C-200, hexane–AcOEt 5:1) to afford 371 mg (86%)[7] of aldols 2t and 2e (R=CH_3, R'=C_6H_5)[8] in a ratio of 88:12 and 16 mg (6%) of 1 (R=CH_3) recovered.

The threo selectivity can be understood in terms of the six-membered transition state[9] involving the E-enolate (Fig. 1). The ratio of 88:12 is much higher than that of 52:48 for the reaction of lithium enolate of cyclohexanone with benzaldehyde.[5] The results shown in Table 1 indicate that the threo:erythro ratio for substituted diketones (R=CH_3 or n-$C_{11}H_{23}$) is comparable to that for the unsubstituted diketone (R=H), showing that the presence of 3-alkyl group is not essential for the high ratio. Thus the high ratio can tentatively be attributed to the presence of the adjacent enolate which may control the approach of an aldehyde molecule. In this connection, it can be said that the stereochemistry of the present aldol reaction is controlled kinetically, not thermodynamically, because the intermediate metal chelate generated in the reaction solution is hardly in equilibrium with the dianion 1'. The dianion 1' is generated only in the presence of a strong base such as LDA. The fact that the threo:erythro ratio does not depend upon the reaction time is consistent with the reasoning.

We can also state that the keto-enol tautomerism does not occur under the conditions used for reaction and purification. Aldols 2t and 2e substituted with a methyl or undecyl group (R=CH_3 or n-$C_{11}H_{23}$) were stable and could be stored without isomerization. However, unsubstituted aldols 2t and 2e (R=H) tautomerized to 3 slowly in $CDCl_3$ for NMR measurement or completely during purification by LC on silica gel.

The aldol reaction of 1 (R=alkyl) is also characterized by the complete regioselectivity that the regioisomer 4 was not obtained at all. Fortunately, this result is in contrast with the fact that the dianion 1' yielded two regioisomers 5 and 6 in a ratio of 4–7:1 when alkylated with alkyl halides.[11]

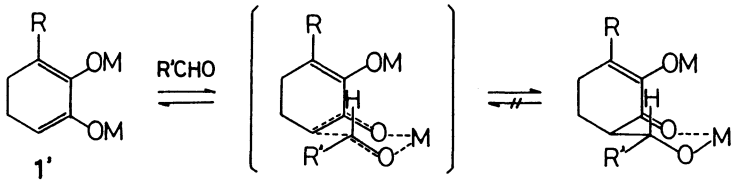


Fig. 1. The six-membered transition state involving the E-enolate with an adjacent enolate and the intermediate metal chelate.

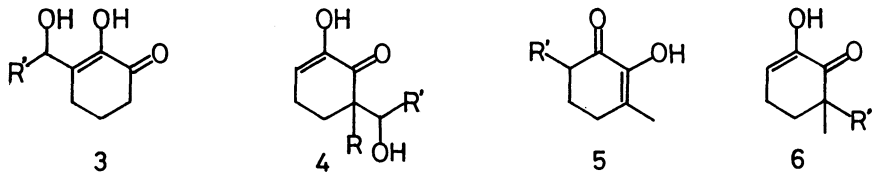


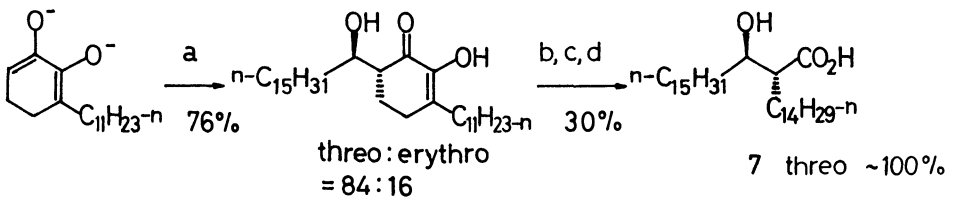
Table 1. Aldol Reaction of 1,2-Cyclohexanedione Dianions (1') with Aldehydes (R'CHO)

R	R'	Temp / °C	Time / min	Aldol 2 Yield/%[a]	Threo: Erythro[b]	Diketone 1 Recovered/%
CH_3	C_6H_5	-78	1	73	88:12	6
		-78	10	73	92:8	0
		-78	30	86	88:12	6
		0	360	78	86:14	0
CH_3	2-furyl	-78	30	64	89:11	5
CH_3	C_2H_5	-78	1	84	82:18	0
		-78	30	74	83:17	5
CH_3	i-C_3H_7	-78	1	59	>99:1	8
		-78	30	60	>99:1	0
CH_3	n-C_5H_{11}	-78	30	82	86:14	0
CH_3	n-$C_{15}H_{31}$	-78	10	60	84:16	7
		-78	30	75	84:16	0
		-30	10	67	86:14	16
		-30	240	73	88:12	0
n-$C_{11}H_{23}$	n-$C_{15}H_{31}$	-78	30	0	—	—
		-30	60	50	89:11	9
		-30	120	76	84:16	12
H	C_6H_5	-78	30	59	88:12	0

a) The aldols 2t,e were identified by using IR, ^1H and ^{13}C NMR spectra and elemental analyses. The yields are based on the diketone 1 consumed.
b) Determined by ^1H and /or ^{13}C NMR.

The application of the present aldol reaction is exemplified by a diastereoselective synthesis of racemic corynomycolic acid (7),[12] which gave a result better than that from the acyclic aldol reaction reported.[13,14]

The work will be reported in detail in due course.



a, $n\text{-}C_{15}H_{31}CHO$
b, O_2, $CuCl_2$, EtOH–H_2O[15]
c, Zn, HCl, ether
d, HPLC

References

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2) H. O. House, "Modern Synthetic Reactions," 2nd ed , Benjamin, New York(1972), Chap. 10.
3) T. Mukaiyama, Org. React., 28, 203 (1982).
4) The reaction of lithium enolate monoanions with aldehydes resulted in the recovery of starting diketone 1 (R=CH_3 or H).
5) C. H. Heathcock, C. T. Buse, W. A. Kleschick, M. C. Pirrung, J. E. Sohn, and J. Lampe. J. Org. Chem., 45, 1066 (1980). Use of the boron enolate of cyclohexanone was reported to improve the threo:erythro ratio up to 96:4. See: D. A. Evans, J. V. Nelson, E. Vogel, and T. R. Taber, J. Am. Chem. Soc., 103, 3099 (1981).
6) Conveniently prepared according to the method described in M. Utaka, S. Matsushita, and A. Takeda, Chem. Lett., 1980, 779.
7) Based on the diketone 1 consumed.
8) 2 (R=CH_3, R'=C_6H_5): ^{1}H NMR ($CDCl_3$) δ 1.2–1.8(m, 2H), 1.93(m, 3H), 2.0–2.4(m, 2H), 2.65(m, 1H), 4.87(d, J=8.8 Hz, 0.88H (threo)), 5.60(d, J=3.0 Hz, 0.12H (erythro)), 6.0(br s), 7.40(m, 5H); ^{13}C NMR ($CDCl_3$) δ (threo) 17.0(q), 24.5(t), 29.1(t), 51.2(d), 74.6(d), 127.0(d), 127.8(d), 128.2(d), 132.7(s), 140.9(s), 143.6(s), 196.8(s); (erythro) 17.0(q), 20.5(t), 29.6(t), 52.1(d), 70.6(d), 125.8(d), 126.8(d), 127.8(d), 131.7(s), 142.3(s), 144.2(s), 194.9(s).
9) H. E. Zimmernan and M. D. Traxler, J. Am. Chem. Soc., 79, 1920 (1957) and Ref. 5.
10) 3 (R=H, R'=C_6H_5): ^{1}H NMR ($CDCl_3$) δ 1.6–2.0(m, 2H), 2.1–2.6(m, 4H), 4.7(br s), 5.87(s, 1H), 7.1–7.5(m, 5H); ^{13}C NMR ($CDCl_3$) δ 22.3(t), 23.1(t), 36.0(t), 70.7 (d), 125.8(d), 127.7(d), 128.5(d), 133.8(s), 141.6(s), 142.6(s), 195.6(s).
11) M. Utaka, M. Hojo, and A. Takeda, Chem. Lett., 1984, 445.
12) E. Lederer, J. Med. Chem., 23, 819 (1980).
13) C. H. Heathcock, M. C. Pirrung, S. H. Montgomery, and J. Lampe, Tetrahedron, 37, 4087 (1981).
14) The crude product 7 contained no erythro isomer as checked by HPLC. Methyl ester of 7: mp 56–59 °C (lit.[13] mp 56–58 °C); ^{1}H NMR ($CDCl_3$) δ 0.86(t, 6H), 1.0–1.8(m, 54H), 2.40(m, 1H), 3.65(m, 1H), 3.72(s, 3H); ^{13}C NMR ($CDCl_3$) δ 14.1 (q, 2C), 22.7(t, 2C), 25.8(t), 27.5(t), 29.4–29.7(t, 20C), 32.0(t, 2C), 35.7 (t), 51.0(d), 51.5(q), 72.4(d), 176.2(s).
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