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The Cross-Aldol Reaction of 3-Alkoxy-2-cyclohexen-1-ones with α,β-Enals. A Synthesis of 4-(*trans*-2-Butenylidene)-3,5,5-trimethyl-2-cyclohexen-1-ones

Sigeru Torii,* Tsutomu Inokuchi, and Hidenori Ogawa

Department of Industrial Chemistry, School of Engineering, Okayama University, Tsushima, Okayama 700

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Synopsis. The cross-aldol reaction of 3-alkoxy-2-cyclohexen-1-ones with α,β-enals afforded the corresponding 3-alkoxy-6-(1-hydroxy-2-alkenyl(or aryl)-2-cyclohexen-1-ones in 78—98 % yields. The condensation of a kinetic enolate anion of 3-ethoxy-5,5-dimethyl-2-cyclohexen-1-one with *trans*-2-butenal, and subsequent dehydration together with methylation, afforded 4-(*trans*-2-butenylidene)-3,5,5-trimethyl-2-cyclohexen-1-ones, one of the most important constituents of tobacco flavour, in a 74% yield.

Vinylogous aldols have recently become available by means of the cross-aldol reaction of α,β-enones[1a] and alkanals[1b] with a kinetic enolate anion of 1,3-diketone enol ether. In this paper, we will describe their reactions with alicyclic 1,3-diketone enol ethers and α,β-enals as well as the preparation of 4-(*trans*-2-butenylidene)-3,5,5-trimethyl-2-cyclohexen-1-ones (**4**),[2] characteristic flavouring components of Burley[2a,b] as well as Greek[2c] and Turkish[2d] tobaccos.

The cross-coupling[3] of a kinetic enolate anion of **1a** with *trans*-2-butenal at −78 °C for 5 min gave the corresponding aldol **2a** (R^1=Me, R^2=Et, R^3=–HC=CHMe) in a 98% yield. The yields and the *threo/erythro* ratios of the cross-aldol condensation of **1** with various α,β-enals are shown in Table 1.

Table 1. Yields of aldols and *threo/erythro* ratios

1,3-Diketone enol ether **1**	α,β-Enal	Product **2**	Yield, %	*threo/erythro* Ratio
1a	*trans*-2-butenal	**2a**	98	93/7[a]
1a	citral	**2b**	98	89/11[a]
1b	*trans*-2-butenal	**2c**	92	90/10[a]
1c	benzaldehyde	**2d**	96	67/33[b]
1c	2-furaldehyde	**2e**	78	67/33[c]

a) The gross ratios of *threo/erythro* were estimated by comparison with the heights of the ^{13}C NMR signals at the carbon of CH–OH of each compound measured in a NNE mode under the conditions of a 60 ° pulse and a 30 s pulse repetition. b) Estimated by the separation of each isomer through column chromatography on SiO_2 on the bases of ^1H NMR signals at δ 4.77 (d, J=9 Hz), and 5.51 (d, J=3Hz). c) Estimated by comparison with the ^1H NMR signals at 4.86 (d, J=9 Hz) and 5.38 (d, J=3 Hz).

The treatment of a *threo/erythro* mixture of **2a** (R^1=Me, R^2=Et, R^3=–HC=CHMe) with methanesulfonyl chloride in pyridine at 0 °C for 1 h, and subsequent heating at 45—50 °C for 2 h, afforded the dehydrated product **3** in an 89% yield. The reaction of the enone **3**, without isolating each geometrical isomer at the C-7 carbon, with methyllithium at 0 °C in ether, followed by stirring at room temperature for 1 h, gave a mixture of **4a** and **4b** in an 85% yield. The gross abundance of the isomers **4a** and **4b**[4] was estimated from the heights of the ^{13}C NMR signals at the C-10 methyl group, giving the ratio of 7 to 4.

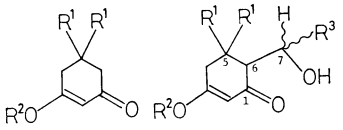
We have found that the reaction of the kinetic enolate anion of **1** with α,β-enals is completed within a few minutes at −78 °C without the use of a chelating reagent. It is reasonable to argue that the electron-donating nature of the alkoxyl group for the conjugated enone systems would contribute to the stabilization of lithium alcoholate, which is assumed to be the bidentate chelate **5**, and that this would prevent the progress of the counter-aldol reaction of the condensate **2**. In contrast to the alkoxyl-stabilized enone systems, aldols derived from the reaction of kinetic enolate anions of simple α,β-enones with carbonyl compounds are generally unobtainable without employing a chelating reagent.[5]

We have found that the aldols **2** consist 67—93% of *threo*-rich stereomers (Table 1), which are assumed to suggest a transition state which implies the specified orientation of the enolates of **1** and enals. Therefore, it is necessary to postulate that the favorable attack of the carbanion of **1** would occur on the less hindered side of the carbonyl group of enals.

Experimental

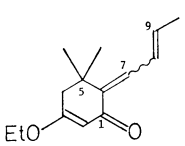
The melting and boiling points are uncorrected. The instruments used in analyses have been described elsewhere.[1b]

*3-Ethoxy-6-(*trans*-1-hydroxy-2-butenyl)-5,5-dimethyl-2-cyclohexen-1-one (**2a**, R^1=Me, R^2=Et, R^3=–HC=CHMe).* To a cold solution (−78 °C) of *i*-Pr_2NLi (578 mg, 5.4 mmol) in THF (6 ml) we added a solution of **1a** (505 mg, 3.0 mmol) in THF (3 ml). After the mixture had been stirred for 6 h, *trans*-2-butenal (316 mg, 4.5 mmol) was added and the solution was stirred for 5 min at −78 °C. The mixture was



1 **2**

1a: R^1=Me, R^2=Et
1b: R^1=H, R^2=Et
1c: R^1=H, R^2=Me



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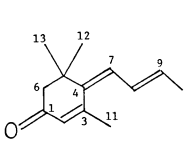
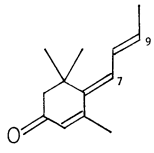
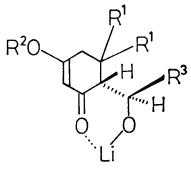


4a



4b



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quenched with cold aqueous tartaric acid and extracted with benzene. The extracts were worked up to give 700 mg (98 %) of a *threo/erythro* mixture of **2a** (R^1=Me, R^2=Et, R^3=–HC=CHMe): mp 44.0—45.5 °C; IR (Nujol) 3320 (OH), 1654, 1633 (C=O), 1610 cm^{-1} (C=C); ^1H NMR δ 1.08 (s, 3, CH_3), 1.12 (s, 3, CH_3), 1.37 (t, 3, J=7 Hz, CH_3), 1.68 (d, 3, J=6 Hz, CH_3), 2.27 (br, 2, CH_2), 2.48 (d, 1, J=4 Hz, COCH), 3.73 (br, 1, OH), 3.96 (q, 2, J=7 Hz, OCH_2), 4.32 (d, d, 1, J=8, 4 Hz, CHO), 5.42 (s, 1, HC=C), 5.58—5.82 (m, 2, HC=C); ^{13}C NMR δ 14.1 (q), 17.8 (q), 24.6 (q), 29.8 (q), 34.4 (s, C-5), 43.3 (t, C-4), 60.4 (d, C-6), 64.5 (t), 72.2 (d, C-7), 102.3 (d, C-2), 129.0 (d, C-9), 131.2 (d, C-8), 176.8 (s, C-3), 202.1 (s, C-1). Found: C, 70.53; H, 9.43 %. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30 %.

The reaction of 3-alkoxy-2-cyclohexen-1-ones (**1a—c**) with α,β-enals was carried out similarly; the results are listed in Table 1. The physical properties, spectral data, and elemental analyses of **2b—e** are given below.

Compound **2b** *(R^1=Me, R^2=Et, R^3=C_9H_{15},* threo-erythro *mixture)*; IR (neat) 3440 (OH), 1640 (C=O), 1610 cm^{-1} (C=C); ^1H NMR δ 1.03, 1.11 (s, 6, CH_3), 1.36 (t, 3, CH_3), 1.59, 1.66, 1.74 (s, 9, CH_3), 2.01—2.19 (m, 4, CH_2), 2.25 (s, 2, CH_2), 2.51 (d, 1, J=4 Hz, COCH), 3.26 (br, 1, OH), 3.92 (q, 2, OCH_2), 4.56 (d, d, 1, J=10, 4 Hz, CHO), 5.05 (m, 1, HC=C), 5.28 (m, 1, HC=C), 5.37 (s, 1, HC=C); ^{13}C NMR δ 14.1 (q), 16.4 (q), 17.6 (q), 24.6 (q), 25.7 (q), 26.1 (t, C-4), 29.8 (q), 34.5 (s, C-5), 39.9 (t), 43.3 (t), 60.5 (d, C-6), 64.5 (t), 67.0 (d, C-7), 102.4 (d, C-2), 124.0 (d), 124.5 (d), 131.6 (s), 139.0 (s), 176.9 (s, C-3), 202.4 (s, C-1). Found: C, 74.66; H, 10.04 %. Calcd for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87 %.

Compound **2c** *(R^1=H, R^2=Et, R^3=–HC=CHMe,* threo-erythro *mixture)*; IR (neat) 3400 (OH), 1648, 1639 (C=O), 1609 cm^{-1} (C=C); ^1H NMR δ 1.28—2.36 (m, 4, CH_2), 1.37 (t, 3, J=7 Hz, CH_3), 1.73 (d, 3, J=6 Hz, CH_3), 2.44 (m, 1, COCH), 3.95 (q, 2, J=7 Hz, OCH_2), 4.23 (d, d, 1, J=8 Hz, CHO), 4.40 (br, 1, OH), 5.33—5.95 (m, 2, HC=C), 5.39 (s, 1, HC=C); ^{13}C NMR δ 14.1 (q), 17.7 (q), 24.0 (t, C-5), 28.7 (t, C-4), 49.5 (d, C-6), 64.6 (t), 74.2 (d, C-7), 102.4 (d, C-2), 128.9 (d), 131.0 (d), 178.6 (s, C-3), 203.0 (s, C-1). Found: C, 68.67; H, 8.74%. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63 %.

Compound **2d** *(R^1=H, R^2=Me, R^3=Ph,* threo*)*; IR (neat) 3400 (OH), 1635 (C=O), 1605 cm^{-1} (C=C); ^1H NMR δ 1.23—1.63 (m, 2, CH_2), 2.00—2.38 (m, CH_2), 2.55 (m, 1, COCH), 3.70 (s, 3, OCH_3), 4.77 (d, 1, J=9 Hz, CHO), 5.33 (br, 1, OH), 5.41 (s, 1, HC=C), 7.32 (br s, 5, Ph); ^{13}C NMR δ 24.3 (t, C-5), 28.5 (t, C-4), 51.0 (d, C-6), 56.0 (q, OMe), 75.9 (d, C-7), 102.1 (d, C-2), 127.1 (d, 2C), 127.9 (d), 128.3 (d, 2C), 141.3 (s), 179.5 (s, C-3), 203.1 (s, C-1). Found: C, 72.51; H, 7.05 %. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94 %.

Compound **2d** *(R^1=H, R^2=Me, R^3=Ph,* erythro*)*; IR (neat) 3400 (OH), 1635 (C=O) cm^{-1}; ^1H NMR δ 1.48—1.95 (m, 2, CH_2), 2.04—2.40 (m, 2, CH_2), 2.63 (m, 1, COCH), 2.98 (br, 1, OH), 3.67 (s, 3, OCH_3), 5.41 (s, 1, HC=C), 5.51 (d, 1, J=3 Hz, CHO), 7.30 (br s, 5, Ph); ^{13}C NMR δ 20.5 (t, C-5), 28.6 (t, C-4), 52.0 (d, C-6), 55.8 (q, OMe), 71.7 (d, C-7), 102.7 (d, C-2), 125.9 (d, 2C), 127.0 (d), 128.2 (d, 2C), 141.9 (s), 179.1 (s, C-3), 200.5 (s, C-1). Found: C, 72.56; H, 7.09 %. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94 %.

Compound **2e** *(R^1=H, R^2=Me, R^3=2-furyl,* threo-erythro *mixture)*; IR (neat) 3380 (OH), 1635 (C=O), 1605 cm^{-1} (C=C); ^1H NMR δ 1.32—2.07 (m, 2, CH_2), 2.20—2.49 (m, 2, CH_2), 2.52—2.97 (m, 1, COCH), 3.73 (*erythro*) (s, OCH_3), 3.75 (*threo*) (s, OCH_3), 4.91 (*threo*) (d, J=9 Hz, CHO), 5.33 (*erythro*) (d, J=3 Hz, CHO), 5.41 (s, 1, HC=C), 6.30 (complex, 2, HC=C), 7.37 (complex, 1, HC=C); ^{13}C NMR (*threo*) δ 23.8 (t, C-5), 28.5 (t, C-4), 48.9 (d, C-6), 55.9 (q, OMe), 69.2 (d, C-7), 102.0 (d, C-2), 108.0 (d), 110.0 (d), 142.3 (d), 153.7 (s), 179.5 (s, C-3), 203.5 (s, C-1); (*erythro*) δ 22.0 (t, C-5), 28.5 (t, C-4), 49.2 (d, C-6), 56.0 (q, OMe), 67.8 (d, C-7), 102.5 (d, C-2), 106.8 (d), 110.2 (d), 141.4 (d), 155.2 (s), 179.1 (s, C-3), 200.3 (s, C-1). Found: C, 64.95; H, 6.42 %. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35 %.

*6-(*trans*-2-Butenylidene)-3-ethoxy-5,5-dimethyl-2-cyclohexen-1-one (3).* A solution of **2a** (R^1=Me, R^2=Et, R^3=–HC=CHMe, 171 mg, 0.72 mmol) and $MeSO_2Cl$ (330 mg, 2.9 mmol) in pyridine (2 ml) was stirred for 1 h at 0 °C and for 2 h at 45—50 °C. The cooled mixture was quenched with cold aqueous tartaric acid. A subsequent work-up gave 141 mg (89 %) of **3**: bp 75.5—76.5 °C/0.015 Torr (Kugelrohr); IR (neat) 1663, 1650 (C=O), 1630, 1615 (C=C) cm^{-1}; ^1H NMR δ 1.20 (s, 6, CH_3), 1.35 (t, 3, CH_3), 1.83 (d, d, J=7, 1 Hz, CH_3), 2.33 (br s, 2, CH_2), 3.92 (q, 2, OCH_2), 5.34 (br s, 1, HC=C), 5.55—7.35 (m, 3, HC=C). Found: C, 76.52; H, 8.88 %. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15 %.

*4-(*trans*-2-Butenylidene)-3,5,5-trimethyl-2-cyclohexen-1-one (4a, 4b).* To a solution of **3** (122 mg, 0.55 mmol) in ether (9 ml) at 0 °C we added an ether solution of 0.9 M MeLi (0.95 ml, 0.86 mmol). The mixture was stirred for 1 h at room temperature and worked up to give 89 mg (85 %) of a mixture of **4a** and **4b**: bp 85.0—86.0 °C/0.007 Torr (Kugelrohr); IR (neat) 1660 (C=O), 1632, 1584 cm^{-1} (C=C); ^1H NMR δ 1.19, 1.36 (s, 6, CH_3), 1.85 (d, 3, J=7 Hz, CH_3), 2.06—2.36 (m, 2, $COCH_2$), 2.29 (complex, 3, CH_3), 5.72—6.95 (m, 3, HC=C), 5.92 (br s, 1, HC=C); ^{13}C NMR δ 18.7, 18.9 (q, C-10), 22.3, 25.2 (q, C-11), 28.2 (q, C-12), 29.8 (q, C-13), 38.4, 40.5 (s, C-5), 52.5, 54.0 (t, C-6), 125.8, 128.4 (d), 128.6, 128.9 (d), 129.6, 132.6 (d), 134.7, 137.0 (d, C-7), 140.1, 140.7 (s, C-4), 155.2, 155.4 (s, C-3), 198.9, 199.1 (s, C-1).

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