CHEMISTRY LETTERS, pp. 535-538, 1992.

Reaction of Chalcone Derivatives with Aromatic Aldehydes Promoted by Ytterbium Metal

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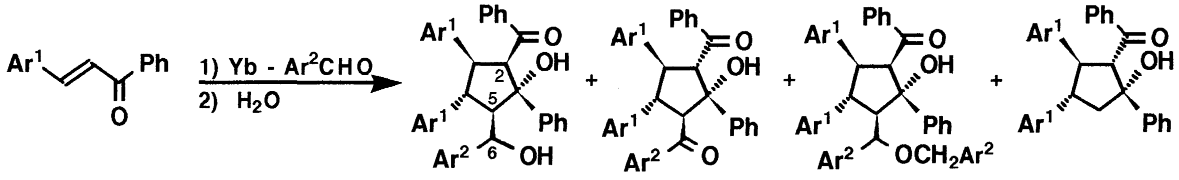
Ytterbium metal promoted reaction of chalcone with equimolar amount of benzaldehyde gave 2-benzoyl-5-phenylhydroxymethyl-1,3,4-triphenylcyclopentanol, whereas 2,5-bis(benzoyl)cyclopentanol was obtained by the reaction with excess amount of the aldehyde. In addition, similar reaction of 3-anisyl-1-phenyl-2-propen-1-one with anisaldehyde afforded 2:2 adduct, 5-[anisyl(anisylmethoxy)methyl]cyclopentanol, irrespective of amount of the aldehyde.

In the previous paper, we have reported the cyclodimerization of α,β-unsaturated carbonyl compounds promoted by Yb metal or $YbCl_3$-Zn, leading to cyclopentanols or cyclopentanones.1) This reaction was initiated by one electron transfer from low-valent Yb to the substrates to yield a radical enolate, which underwent radical addition and aldol cyclization to give the products. If the enolate moiety would react first, the intermediate could be utilized in a different manner. Thus we investigated the reaction with aromatic aldehydes to trap the enolate moiety. Although this trial was unsuccessful since the cyclodimerization took place first even in the presence of excess aldehyde, the aldehyde was incorporated at C-5 position of the cyclopentanols. We report herein this unusual reaction of chalcone derivatives with aromatic aldehydes promoted by Yb metal.

When a solution of chalcone (2.5 mmol) and benzalehyde (1 mmol) in THF-HMPA was treated with Yb metal (1 mmol) at room temperature for 3 h, 5-(phenylhydroxymethyl)cyclopentanol **2a** and cis dimer **5** were formed in 56 and 39 % yields, respectively. An addition of the aldehyde after treatment of chalcone with Yb for 3 h gave the similar result.2) The product **2a** was obtained as a single isomer whose stereochemistry was determined as shown in figure by spectral data, but configuration at C-6 was not clear.3) On the other hand, the reaction using five equivalents of the aldehyde gave 5-benzoylcyclopentanol **3a** 4) in 44% yield along with the

Table 1. Reaction of Chalcone Derivatives **1** with Aromatic Aldehydes Promoted by Yb Metala)



1 **2** **3** **4** **5**

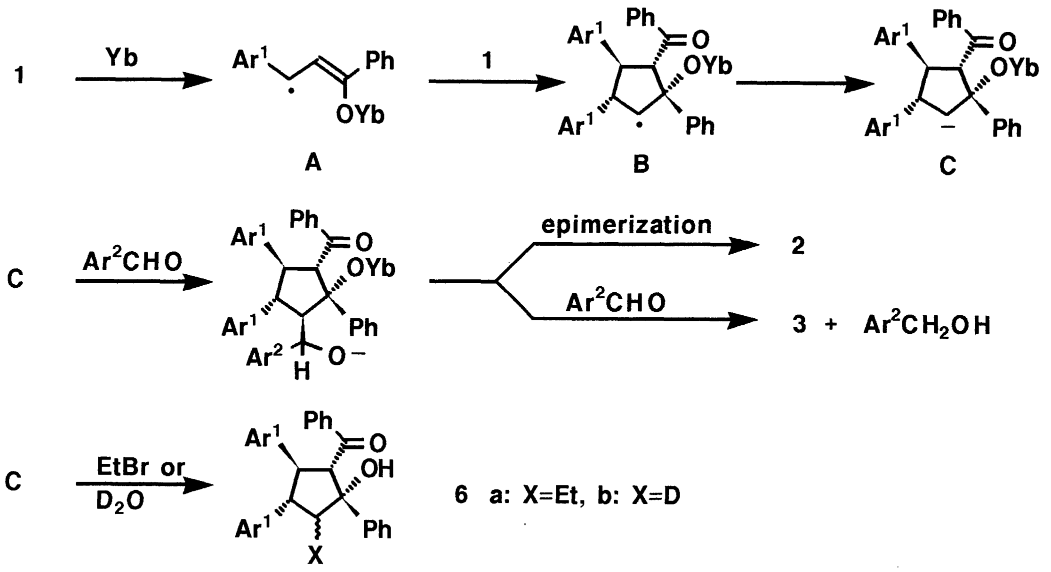
Run	Ar1	Ar2	Molar ratio (Ar2CHO / Yb)	Product and yield / %b) 2		3		4		5
1	Ph	Ph	1	**2a**	56	–		–		39
2	Ph	Ph	5	–		**3a**	44	–		24c)
3	Ph	p-anisyl	1	**2b**	22	–		–		66c)
4	Ph	p-anisyl	5	**2b**	43	–		–		44
5	p-anisyl	Ph	1	**2c**	58	–		–		41
6	p-anisyl	Ph	5	–		**3c**	58	**4c**	28	–
7	p-anisyl	p-anisyl	1	–		–		**4d**	30	52
8	p-anisyl	p-anisyl	5	–		–		**4d**	36	40

a) Conditions: **1** 2.5 mmol, Yb 1 mmol, rt, 3 h; then aldehyde addition,0 °C, 0.5 h. b) Isolated yield based on Yb. c) A mixture of cis dimer **5** and trans isomer (β-OH) (80 : 20).

dimer **5** (24%), and **2a** was not detected. The results in the reaction of chalcone derivatives **1** with aromatic aldehydes are summarized in Table 1.

The diol **2b** was exclusively obtained irrespective of the molar ratio in the reaction of chalcone with anisaldehyde (runs 3 and 4). 3-Anisyl-1-phenyl-2-propen-1-one reacted with excess benzaldehyde to afford 5-benzoylcyclopentanol **3c** and 2:2 adduct, 5-[benzyloxy(phenyl)methyl]cyclopentanol, **4c** 5) in 58% and 28% yields, respectively (run 6). The 2:2 adduct **4d** was formed from the propenone and anisaldehyde selectively (runs 7 and 8). With respect to stereochemistry, all substituents at C-5, derived from the aldehydes, were introduced from β-side of the cyclopentanol ring. The benzoyl group at the C-2 position of the product **3** was same stereochemistry as the original dimer **5**, but those of **2** and **4** were opposite.

The formation of **2** would be explained as follows (Scheme 1). Cyclodimerization of **1** took place first to give intermediate **B**, which was reduced further to dianion C and reacted with the aldehyde, giving rise to **2** after



Scheme 1.

epimerization at C-2.[6] One possibility for the product **3** is that benzaldehyde is converted to benzyl benzoate by Tischenco reaction,[7] followed by reaction with the dianion C. However trapping reaction with the ester was failed only to give the dimer. Another plausible mechanism is Meerwein-Ponndorf reaction catalyzed by trivalent ytterbium,[8] wherein excess benzaldehyde serves as a hydride acceptor. In fact, benzyl alcohol was detected by GC in the reaction mixture (Table 1, run 2).[9] Therefore the reaction using excess benzaldehyde afforded the benzoylated product **3**, whereas that of p-anisaldehyde, which was a poor hydride acceptor, gave the diol **2** even in the presence of excess amount of the aldehyde. The formation of 2:2 adduct **4** may be accounted for by acetalyzation and deoxygenation formally, but its mechanism is not clear at present.

The reaction described above is unusual since the second carbanion must be fixed on C-5, neither on C-2 nor benzylic positions. Thus trapping experiment with other electrophiles was carried out to get further information. After treatment of chalcone with Yb at room temperature for 3 h, the reaction was quenched with excess ethyl bromide to give 5-ethylcyclopentanol **6a** and cis dimer **5** in 51 and 45% yields, respectively. The ethyl group was selectively trapped from β-side of the ring. Similar reaction with D_2O afforded deuteriated (>98% D) cis dimer **6b** and trans isomer in 76 and 20% yields, respectively.[10] Ratio of α- : β-D was 63 : 37 in the both isomers, opposite to the above two electrophiles.

Although further work is necessary to investigate the mechanistic point and stereochemistry, it is clear that cyclodimerization of chalcone derivatives promoted by Yb metal includes dianion species, in which the negative charge is distributed on O and C-5 of the cyclopentanol rings unexpectedly.

This work was partially supported by Grant-in-Aids for Scientific Research from the Ministry of Education, Science and Culture of Japan (No. 02231220).

References

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2) This method is recommended since the reaction is somewhat difficult to start in the presence of aldehydes.

3) **2a**: White needles; mp 195-197 °C; IR (Nujol) 3475 (OH), 3236 (OH), 1644 (CO) cm^{-1}; MS (70 eV) m/e 524 (M$^+$), 417 (M$^+$-PhCHOH), 105 (PhCO$^+$); ^{1}H-NMR (CDCl$_3$) δ 1.56 (1H, br s, C-1 OH), 3.14 (1H, ddd, J=1.8, 3.3, 12.2 Hz, C-5 H), 3.91 (1H, dd, J=8.6, 12.2 Hz, C-3 H), 4.40 (1H, dd, J=8.6, 12.2 Hz, C-4 H), 4.59 (1H, d, J=12.2 Hz, C-2 H), 4.62 (1H, br d, J=8.6 Hz, C-6 OH), 4.84 (1H, dd, J=3.3, 8.6 Hz, C-6 H), 6.76-7.42 (25H, m); ^{13}C-NMR (CDCl$_3$) δ 56.6, 56.9, 60.8, 61.5, 72.8 (C-6), 87.2 (C-1), 125.0, 125.7, 125.9, 126.4, 126.6, 126.7, 127.1, 127.2, 127.9, 128.3, 128.7, 129.4, 133.4 (aromatic CH), 137.2, 140.2, 142.3, 142.8, 143.5, 204.0 (CO). Anal. Found: C, 84.70; H, 6.05%. Calcd for $C_{37}H_{32}O_3$: C, 84.70; H, 6.15%.

4) **3a**: White prisms; mp 225-228 °C; IR (Nujol) 3482 (OH), 1660 (CO) cm^{-1}; MS (70 eV) m/e 522 (M$^+$), 505 (M$^+$-OH), 312 (M$^+$-2xPhCO), 105 (PhCO$^+$); ^{1}H-NMR (CDCl$_3$) δ 4.21 (1H, dd, J=9.9, 12.0 Hz, C-3 H), 4.43 (1H, dd, J=5.5, 9.9 Hz, C-4 H), 4.60 (1H, d, J=5.5Hz, C-5 H), 5.21 (1H, d, J=12.0 Hz, C-2 H), 5.91 (1H, s, OH), 6.84-7.59 (25H, m); ^{13}C-NMR (CDCl$_3$) δ 55.2, 58.3, 59.4, 67.1, 87.2 (C-1), 126.4, 126.8, 127.2, 127.3, 128.7, 128.0, 128.3, 128.5, 128.6, 132.7, 133.5 (aromatic CH), 137.5, 137.9, 139.9, 141.6, 143.1, 202.5 (CO), 205.5 (CO). Anal. Found: C, 85.20; H, 5.69%. Calcd for $C_{37}H_{30}O_3$: C, 85.03; H, 5.69%.

5) **4c**: Colorless oil; IR (neat) 3387 (OH), 1657 (CO) cm^{-1}; MS (70 eV) m/e 462 (M$^+$-PhCO and C_6H_4OMe), 355 (462-$PhCH_2O^+$), 105 (PhCO$^+$); ^{1}H-NMR (CDCl$_3$) δ 3.04 (1H, br d, J=11.6 Hz, C-5 H), 3.64 (3H, s, OMe), 3.75 (3H, s, OMe), 3.83 (1H, dd, J=8.9, 12.0 Hz, C-3 H), 4.31 (1H, dd, J=8.9, 11.6 Hz, C-4 H), 4.53 (1H, d, J=12.0 Hz, C-2 H), 4.64 (2H, s, CH$_2$), 4.80 (2H, br s, C-6 H and OH); ^{13}C-NMR (CDCl$_3$) δ 55.0 (OMe), 55.2 (OMe), 55.9, 56.3, 60.6, 61.4, 65.2 (CH$_2$), 72.8 (C-6), 87.2 (C-1), 113.3, 114.1, 124.9, 125.6, 125.9, 126.3, 127.0, 127.2, 127.6, 127.8, 127.9, 128.3, 128.5, 128.8, 130.5, 133.4 (aromatic CH), 132.4, 134.3, 137.2, 142.9, 143.5, 158.0, 158.3, 204.3 (CO).

6) Alternatively, retro-aldol reaction of **B** and subsequent reaction of the resulting enolate with the aldehyde followed by cyclization may afford **2**. This mechanism is, however, less likely, since the deuterium was not scrambled on C-2 and C-5 in the reaction with D_2O, vide infra.

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8) J.Collin, L.Namy, and K.B.Kagan, *New J.Chem.*, **10**, 229 (1986).

9) Reduction of benzaldehyde to benzyl alcohol with Yb metal is difficult under these conditions.

10) Cis dimer means that both the hydroxy (C-1) and benzoyl (C-2) groups are α as shown in **5** and **6b**, and trans dimer has an opposite configuration at C-1, that is, β-hydroxy group.

(Received January 8, 1992)