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REDUCTION OF ACROLEIN DIALKYL ACETALS WITH $CrCl_2$. γ-ALKOXY SUBSTITUTED ALLYLIC CHROMIUM REAGENTS FOR SELECTIVE SYNTHESIS OF erythro-1,2-DIOLS.

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Abstract: Treatment of an aldehyde in THF at -30°C with a reagent derived by reduction of acrolein dialkyl acetal with $CrCl_2$ in the presence of Me_3SiI gave 1,2-erythro-3,4-butene-1,2-diol derivatives selectively.

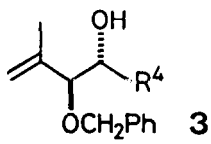
Formation of a new carbon-carbon bond under controlling vicinal stereochemistry is an important methodology for efficient synthesis of a complex molecule. Among the vicinal relationships, 1,2-diol moiety is one of the most common functional units in biologically significant natural products.[1] Reaction of α-alkoxy allylic anion equivalents with carbonyl compounds is an attractive method to construct the 1,2-diol units and has been intensively studied during the last decade.[2] While various methodologies have been developed as the consequence for the construction of threo-1,2-diols,[3] those for the synthesis of erythro compounds are relatively scarce.[4] We describe here a new and convenient method for preparation of erythro-1,2-diols using γ-alkoxy substituted allylic chromium reagents, derived by reduction of acrolein dialkyl acetals with chromium(II) chloride.

Allylic diethyl phosphates are reduced with chromium(II) salt to give allylic chromium reagents,[5] which add to aldehydes in a selective manner.[6] The transformation involves conversion of the electronic nature of allylic phosphates from electrophilic to nucleophilic by reduction with low-valent chromium. The **UMPOLUNG** ability of chromium(II) chloride allows us to employ acrolein dialkyl acetal as a precursor of a γ-alkoxy substituted allylic chromium reagent, which will add to an aldehyde at the same position of the alkoxy group (α-adduct of the alkoxy-substituted allyl anion synthon) to afford 3,4-butene-1,2-diol derivatives.

Treatment of a mixture of acrolein dibenzyl acetal (**1**) and benzaldehyde in tetrahydrofuran (THF) with a suspension of $CrCl_2$ in THF at 65°C for 10 h gave the desired α-adduct, 2-benzyloxy-1-phenyl-3-buten-1-ol (**2**), in 85% yield (erythro/threo=61/39). None of the γ-adduct was detected. To improve the reaction rate and the diastereomer ratio, several additives, especially Lewis acids, were examined. Among them,[6] Me_3SiI was found to accelerate the reaction rate substantially. Moreover, the diastereo-selectivity with Me_3SiI was proved to be highly dependent upon the reaction temperature. For example, while the erythro/threo selectivity of product **2** at 25°C was 71/29 (97% yield, Table 1, run 2), the ratio at -30°C was 88/12 (98% yield, run 3). Although better diastereomer ratio was observed at -42°C (erythro/threo=91/9), the reaction was sluggish for practical use (run 4).

A suspension of $CrCl_2$ (0.74 g, 6.0 mmol) in THF (14 mL) is cooled to -30°C. To the suspension at -30°C is added successively a solution of acrolein dibenzyl acetal (1, 0.51 g, 2.0 mmol) in THF (3 mL), a hexane solution of Me_3SiI (1.0 M, 2.0 mL, 2.0 mmol), and a solution of benzaldehyde (0.11 g, 1.0 mmol) in THF (3 mL). The color of the mixture turns gradually from gray to brownish red. After being stirred at -30°C for 3 h, the resulting mixture is poured into a solution of hydrochloric acid (1 M, 15 mL) and extracted with ether (3x15 mL). The combined organic layers are dried (Na_2SO_4) and concentrated. Purification of the crude product by column chromatography on silica gel (hexane-ethyl acetate, 10:1) affords 2-benzyloxy-1-phenyl-3-buten-1-ol in 98% yield (0.25 g, erythro-threo=88/12, run 3). Other examples are shown in Table 1. Commercially available acrolein dimethyl acetal reacted with benzaldehyde and the erythro-threo ratio of the methoxy products was almost the same as that of the benzyloxy ones (run 1). As with other organochromium reagents,[8] 1,2-adduct was produced selectively in the case of α,β-unsaturated aldehyde (run 9).

Effect of a substituent of acrolein dibenzyl acetal on the addition was examined. An acetal having a methyl group at β or α position of a benzyloxy group could also be employed under the same reaction condition and erythro isomers **3** (runs 10 and 11) and **4** (runs 12 and 13) were produced selectively. In contrast to these examples, reaction between crotonaldehyde dibenzyl acetal (**5**) and benzaldehyde resulted in decomposition of the acetal while the benzaldehyde remained.



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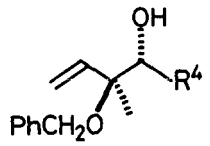

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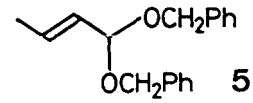

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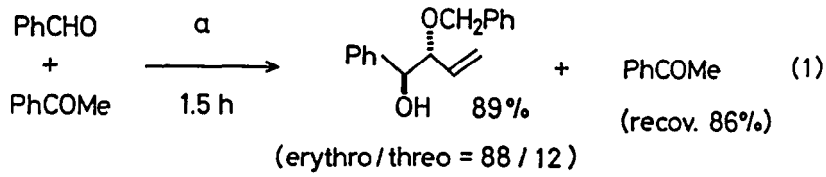
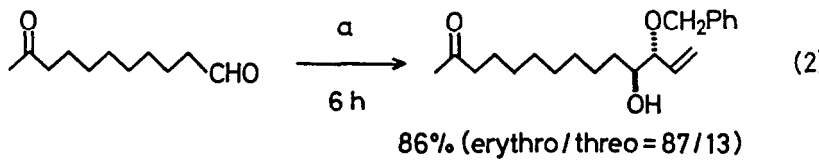
Mild nucleophilicity of organochromium reagents[8] enables selective addition of the γ-alkoxy allylchromium reagent to aldehydes without effect on the coexisting ketone groups (Eq 1 and 2).





a. CH_2=CHCH(OCH_2Ph)$_2$, $CrCl_2$, Me_3SiI, THF, -30°C

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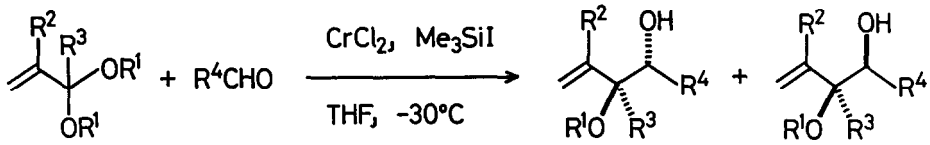
Table 1. Reaction between acrolein dialkyl acetals and aldehydes with $CrCl_2$ and Me_3SiI[a]



Run	R^1	R^2	R^3	R^4	Time / h	Yield[b] / %	erythro/threo[c]
1	Me	H	H	Ph	3	99	88/12
2	$PhCH_2$-	H	H	Ph	1.5	97[d]	71/29
3					3	98	88/12
4					9	33[e]	91/9
5				$^nC_8H_{17}$-	6	95	87/13
6				$PhCH_2CH_2$-	2.5	99	88/12
7				$^cC_6H_{11}$-	6	93	88/12
8				^{t}Bu	7	91	33/67
9				PhCH=CH-	2	97	76/24
10	$PhCH_2$-	Me	H	Ph	3	99	85/15
11				$^nC_8H_{17}$-	3	99	88/12
12		H	Me	Ph	8	88	92/8
13				$^nC_8H_{17}$-	5	83	93/7[f]

a) An aldehyde (1.0 mmol) was treated at -30°C with a reagent prepared from an acetal (2.0 mmol), Me_3SiI (2.0 mmol), and $CrCl_2$ (6.0 mmol) unless otherwise noted. b) Isolated yields. c) The diastereomer ratios were determined by isolation or NMR analysis. The adducts (runs 2-12) were subjected to hydrogenation in the presence of Pd-C to yield 1-substituted-1,2-butanediols. The stereochemistry of the diols was determined by comparison with samples derived from the corresponding E and/or Z-3-butenes unless otherwise noted. d) The reaction was conducted at 25°C. e) The reaction was performed at -42°C. Benzaldehyde (42%) was recovered unchanged. f) The adduct was compared with the authentic samples prepared from erythro- and threo-methyl 2-benzyloxy-3-hydroxy-2-methylundecanoate,[9] respectively.[10]

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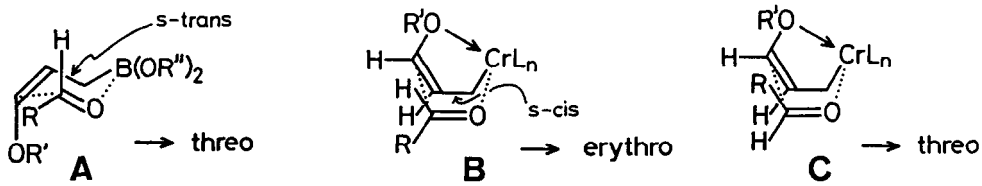
(10) Erythro adduct: bp 130°C (bath temp, 0.07 Torr); IR (neat): 3566, 2922, 1455, 1379, 1087, 925, 731, 694 cm^{-1}; NMR ($CDCl_3$): δ0.88 (t, J=6 Hz, 3H), 1.15-1.68 (m, 14H), 1.33 (s, 3H), 2.61 (d, J=3 Hz, 1H), 3.51-3.62 (m, 1H), 4.41 (s, 2H), 5.28 (dd, J=1, 18Hz, 1H), 5.39 (dd, J=1, 11 Hz, 1H), 5.99 (dd, J=11, 18 Hz, 1H), (threo adduct δ5.78 (dd, J=11, 17 Hz, 1H)) 7.26-7.45 (m, 5H); Found: C, 79.20; H, 10.60%. Calcd for $C_{20}H_{32}O_2$: C, 78.90; H, 10.59%.

(11) We are tempted to assume the following transition state for the unique erythro selectivity. The threo selectivity of γ-alkoxy substituted allylboron and -aluminum is explained by chair-like transition state **A**.[3] In contrast to these metals which have four coordination sites, chromium can possess six ligands. Thus, breaking of the intramolecular coordination of benzyloxy oxygen which fixes the γ-alkoxy substituted allylchromium as s-cis conformation, is not necessary when an aldehyde comes into the coordination sphere of chromium. As a consequence, reaction of the chromium reagent with an aldehyde takes place via boat-like transition state (**B** or **C**). As Lewis acids coordinate to a lone pair of aldehyde oxygen at the less hindered side, the same side of hydrogen,[12] **B** leading to an erythro adduct is more favorable than **C**.



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