A NEW METHOD FOR THE GENERATION OF A BORON ENOLATE OF AN ESTER ----- A NEW SYNTHESIS OF 2-DEOXY-D-RIBOSE -----

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A boron enolate of an ester was generated in situ by the treatment of ethoxyacetylene with mercury(II) acetate and diphenylborinic acid, and the boron enolate thus formed further reacted with aldehydes to give β -hydroxyesters and β -acetoxyesters in good yields. The reaction was successfully applied to the stereoselective synthesis of 2-deoxy-D-ribose.

An enolate anion is one of the most important sources of carbanionic species in carbon-carbon bond-forming reactions. In particular, boron enolates have proved to be a useful means for the stereoselective cross-aldol reaction.¹⁾ Concerning the generation of boron enolates, several useful methods are already known.²⁾ However, it still seems quite valuable to develop new methods for the preparation of boron enolates, potent intermediates for the aldol reaction.

In this communication, we wish to report a novel and useful procedure for the generation of a boron enolate of an ester by the treatment of ethoxyacetylene (1) with diphenylborinic acid (2) in the presence of mercury(II) acetate (3). The enolate reacted smoothly with aldehydes (4) to afford β -hydroxyesters (5) and their acetates (6), and the reaction was successfully applied to the stereoselective synthesis of 2-deoxy-D-ribose $(\underline{13})$.

Previously, we reported³⁾ that a zinc enolate of an ester was generated by the successive treatment of ethoxyacetylene with mercury(II) chloride, pyridine-1-oxide and zinc dust. In the present investigation, the formation of a boron enolate by the addition of a borinic acid to an acetylenic compound in the presence of mercury(II) salts was studied. At first, ethoxyacetylene (1) was allowed to react with borinic acids and benzaldehyde in the presence of several mercury(II) salts under various reaction conditions, and it was found that the treatment of ethoxyacetylene (1) with diphenylborinic acid (2), mercury(II) acetate (3) and benzaldehyde at room temperature for 1 d in tetrahydrofuran (THF) gave ethyl 3-hydroxy-3-phenylpropionate (5a) and its acetate (ethyl 3-acetoxy-3-phenylpropionate, 6a) in a 32% yield and a 57% yield, respectively, after quenching. Under similar conditions, a variety of aldehydes were transformed to the corresponding β -hydroxyesters (5) and their acetates (6) in good yields as shown in Table.

A typical procedure is described for the preparation of ethyl 4-benzyloxy-3hydroxybutyrate (5f) and its acetate (ethyl 3-acetoxy-4-benzyloxybutyrate, 6f):



Table	The synthesis of β -	hydroxyesters	and β -a	acetoxyesters
Entry	RCHO	Yield (%)		
		<u>5</u> *)	<u>6</u> *)	Total
а	PhCHO	32	57**)	89
b	p-C1C ₆ H ₄ CHO	42	42 ^{**)}	84
с	p-CH ₃ C ₆ H ₄ CHO	30	48**)	78
d	PhCH ₂ CH ₂ CHO	44	38 **)	82
е	$n - C_7 H_{15} CHO$	29	38**)	67
f	PhCH20CH2CHO	42	42	84

*) All products gave satisfactory NMR and IR spectra. Yields are based on aldehydes.

**) These products were purified by Kugel-Rohr distillation to remove phenol formed by oxidation of diphenylborinic acid.

To a suspension of mercury(II) acetate (165 mg, 0.52 mmol) in THF (0.5 ml) under an argon atmosphere was added a THF solution (1.8 ml) of diphenylborinic acid (182 mg, 1.0 mmol), prepared from 2-aminoethyl diphenylborinate by the procedure in literature.⁴⁾ The solid disappeared and to the resulting slightly yellow solution a THF solution (2.0 ml) of benzyloxyacetaldehyde (76 ml, 0.51 mmol) was added. Then a THF solution (2.1 ml) of ethoxyacetylene (74 mg, 1.1 mmol) was added at room temperature with slight liberation of heat. After stirring for 1 d, the reaction was quenched by the addition of methanol (5 ml), phosphate buffer solution (pH 7, 5 ml) and 28% aqueous H_2O_2 (3 ml). Then the mixture was concentrated under reduced pressure in order to remove most of the methanol. The organic materials were extracted with ether and the ethereal layer was sequentially washed with water and a saturated aqueous solution of NaCl, and dried over MgSO4. Ethy1-4benzyloxy-3-hydroxybutyrate (5f, 51 mg, 42%) and its acetate (6f, 59 mg, 42%) were isolated by TLC (silica gel). 5f: Bp 145°C/0.1mmHg(by Kugel-Rohr distillation); Found: C,65.47; H,7.41%. Calcd for $C_{13}H_{18}O_4$: C,65.53; H,7.61%; NMR(CC1₄) & 1.19 (3H,t,J=7Hz),2.39(2H,d,J=6Hz),2.8-3.1(1H,m),3.34(2H,d,J=6Hz),3.8-4.3(1H,m),4.01 (2H,q,J=7Hz),4.41(2H,s),7.16(5H,s); IR(neat) 3450,1730cm⁻¹. <u>6f</u>: Bp 155°C/0.1mmHg (by Kugel-Rohr distillation); Found: C,64.07; H,7.26%. Calcd for $C_{15}H_{20}O_5$: C,64.27; H,7.19%; NMR(CC1₄) δ 1.18(3H,t,J=7Hz),1.94(3H,s),2.54(2H,d,J=6Hz),3.47(2H,d,J=5Hz), 4.01(2H,q,J=7Hz),4.41(2H,s),4.9-5.4(1H,m),7.15(5H,s); IR(neat) 1740cm⁻¹.

Arens et al. reported that ethoxyacetylene reacted with aldehydes in the presence of water to give β -hydroxyesters via a cyclic mechanism.^{5a)} But aldehydes were restricted to those with short alkyl chains such as formaldehyde and acetaldehyde, and water was essential. When ethoxyacetylene was treated with carbonyl compounds in the presence of an equimolar amount of $BF_3 \cdot OEt_2$ instead of water, α, β -

unsaturated esters were produced.^{5b)} In the present reaction, not only aldehydes with long alkyl chains but also aromatic aldehydes gave the corresponding β -hydroxyesters (5) and β -acetoxyesters (6) in good yields. Further as 5 and 6 were not obtained in the absence of diphenylborinic acid (2), the present reaction seems to proceed by a mechanism different from those reported by Arens et al. It is known⁰ that 1-alkoxyvinyl esters are formed by the addition of carboxylic acids to alkoxyacetylenes. So, we assume that a boron enolate of an ester (7) is generated as a key intermediate by the addition of diphenylborinic acid (2) to ethoxyacetylene (1) (Scheme II). It was reported^{1b)} that dialkylboryl carboxylates were enolized using tertiary amine and dialkylboryl triflate, but alkyl esters could not be converted to the corresponding boron enolates by the similar procedure. Therefore, the present reaction provides a novel and useful method for the generation of a boron enolate of an alkyl ester.

EtOC=CH + Ph₂BOH
$$\xrightarrow{Hg(OAc)_2}$$
 EtO C=C X Scheme II
1 2 Ph₂BO \xrightarrow{T} X = H_{or} HgOAc

Next, we examined the stereoselectivity of the reaction with an aldehyde possessing a chiral center at α -carbon. Ethoxyacetylene (1) was added over 10 min at 0°C to the mixture of diphenylborinic acid (2), mercury(II) acetate (3) and 2,3-0-isopropylidene-D-glyceraldehyde (8) and the mixture was stirred for 16 h at that temperature. The reaction proceeded in a stereoselective manner to give the corresponding β -hydroxyester (9, 31%)⁷) and its acetate (10, 24%)⁸) with erythro: threo ratios⁹⁾ (9a:9b and 10a:10b) of 93:7 and >90:10 respectively. The observed diastereoselection can be explained by assuming the Felkin's model¹⁰⁾ in the transition state. As $\underline{9}$ and $\underline{10}$ are useful synthetic intermediates, we next transformed them to 2-deoxy-D-ribose (13). When 9 and 10 were treated with trifluoroacetic acid containing a small amount of water, 2-deoxy-D-ribono-1,4-lactone (11, 87%) and its acetate (12, 68%)¹¹⁾ were obtained. The lactones (11 and 12) were reduced with bis(3-methyl-2-butyl)borane according to the procedure of Nakagawa et al.¹¹⁾ to give 2-deoxy-D-ribose $(13, 79\%)^{13}$ and its acetate $(14, 70\%)^{14}$ respectively. The acetate (14) was hydrolyzed with MeONa to form 13 (73%).¹³⁾ The structure was confirmed by converting 13 to 2-deoxy-D-ribose anilide (15).¹⁵⁾ (Scheme III)

Recently, we have reported several examples ¹⁶⁾ of the syntheses of sugar derivatives using carbon-carbon bond-forming reactions. The present synthesis of 2-deoxy-D-ribose is achieved by a stereoselective cross-aldol reaction employing a boron enolate generated by the new method, that is, the addition of diphenylborinic acid to ethoxyacetylene.

References

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- 8)
- The configurational assignment was based on the transformation into 13. 9)
- 9) The configurational assignment was based on the transformation into 13.
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 13) The synthetic 13 thus obtained gave identical TLC with that of authentic sample. 1H-NMR and ¹³C-NMR spectra were in agreement with those in literature.16b)
 14) 14: [α]^{21=52°}(after 3 b, c 0.97 MeOH).

- <u>14</u>: $[\alpha]_{D}^{21} = -52^{\circ}$ (after 3 h, c 0.97, MeOH). 14)
- 15) $\overline{15}$: $[\alpha]_{D}^{20} = +56^{\circ}$ (after 30 h, c 0.99, pyridine); mp 167-169°C (decomp., EtOH). cf. reference 12.
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