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Preparation of Orthoesters Having Functional Group

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During the course of studies on the selective protection of hydroxyl group of nucleosides reported in our previous communication,[1] it became necessary to prepare orthoesters in which alcohol residue is substituted by functional group. Among various orthoesters, methyl and ethyl orthoformate are most commonly used in organic synthesis but their applications as a protecting reagent is rather limited.

Most of the orthoesters already known are those in which the alcohol residue is alkyl, aryl, aralkyl, or alkylene[2] and only a few orthoesters are prepared hitherto in which alcohol residue has a functional group. Hence the author attempted the synthesis of orthoesters having functional group in alcohol residue.

One of the most convenient and practical method of preparation of orthoesters is the ester interchange between methyl or ethyl orthoformate and alcohol and in this note the ester interchange between ethyl orthoformate or orthoacetate with alcohols having functional group are described. As substituted alcohols, ethylene chlorohydrin, 3-chloro-1-propanol, 1,3-dichloro-2-propanol, 2,2,2-trichloroethanol, 2-aminoethanol, 2-dimethylaminoethanol, and ethylene cyanohydrin were used.

The ester interchange reactions were carried out in the usual manner by heating the mixture of alcohol and ethyl orthoformate in the presence or absence of catalyst, ethanol being continuously removed through fractionating column. After nearly the theoretical amount of ethanol was removed, the residual reaction mixture was fractionated.

The interchange reaction proceeds partially or completely depending on the structure of substituted alcohol and the reaction conditions such as the molar ratio of the reactants. The orthoesters which were obtained in this study are listed in Table 1.

The ester interchange between ethyl orthoacetate and ethylene chlorohydrin was also attempted and 2-chloroethyl orthoacetate was obtained.

In our detailed examination on the reaction conditions of the ester interchange between ethyl orthoformate and ethylene chlorohydrin, it was found that the presence of catalyst such as zinc chloride, *p*-toluenesulfonic acid, or sulfosalicyclic acid reduced the reaction time but not affected the yield and increasing amount of catalyst decreased the yield due to the decomposition of ethyl orthoformate to form ethyl formate.

The reaction of ethyl orthoformate with 2-aminoethanol was failed to give interchanged orthoester. Thus, when 1 mol of orthoformate was heated with 4 mol of 2-aminoethanol in the presence of *p*-toluenesulfonic acid, 3 mol of ethanol distilled over, but on distilling the reaction mixture, 2 mol of 2-aminoethanol

TABLE 1. REACTION OF ETHYL ORTHOFORMATE WITH SUBSTITUTED ALCOHOL (ROH)

R	$CH(OC_2H_5)_3$/ROH g/g	$CH(OC_2H_5)_3$/ROH mol/mol	Catalyst	$CH(OR)_3$ (g)	$CH(OR)_2OC_2H_5$ (g)	$CH(OR)(OC_2H_5)_2$ (g)
$ClCH_2CH_2$	30/48	1/3	—	11[a]	23[b]	—
$ClCH_2CH_2$	30/65	1/4	$ZnCl_2$	35	—	—
$ClCH_2CH_2CH_2$	30/75	1/4	$ZnCl_2$	31[c]	—	—
$(ClCH_2)_2CH$	15/52	1/4	$ZnCl_2$	10[d]	11[e]	—
Cl_3CCH_2	13/50	1/4	—	—	16[f]	6[g]
$(CH_3)_2NCH_2CH_2$	30/71	1/4	TsOH	9[h]	10[i]	—
$NCCH_2CH_2$	18/21	1/3	—	—	residue[j]	—

Bp (°C/mmHg) and elemental analysis [Found (Calcd), %] of the products.
a) 125—130/4. C, 33.52 (33.39); H, 5.44 (5.16); Cl, 42.76 (42.34).
b) 95—100/4. Cl, 32.24 (32.74). c) 155—156/3. C, 41.03 (40.88); H, 6.45 (6.47).
d) 184—185/3. Cl, 52.07 (53.65). e) 132—134/3. C, 34.65 (34.39); H, 5.11 (5.09); Cl, 46.02 (45.22).
f) 150—152/12. C, 23.99 (23.65); H, 3.00 (2.81). g) 105—110/12. C, 32.92 (33.39); H, 5.13 (5.13).
h) 125/2. C, 56.90 (56.31); H, 11.00 (10.87); N, 15.48 (15.70).
i) 133—135/17. N, 11.44 (11.11). j) C, 54.41 (54.53); H, 7.07 (7.12); N, 14.20 (14.13).

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2) A. W. Williamson and G. Kay, *Ann.*, **92**, 346 (1854); P. P. T. Sah and T. S. Ma, *J. Amer. Chem. Soc.*, **54**, 2965 (1932); F. Tieman, *Ber.* **15**, 2686 (1882); H, Baines and J. E. Driver, *J. Chem. Soc.*, **125**, 907 (1924); E. R. Alexander and H. M. Buch, *J. Amer. Chem. Soc.*, **74**, 554 (1952); F. F. Beilstein and E. Wiegand, *Ber.*, **18**, 482 (1885).

was recovered and on further distillation caused decomposition and the distillate was found to be 2-aminoethanol.

Experimental

In all cases the ethyl orthoformate and the alcohols employed were redistilled before use. Unless otherwise stated, the experiments summarized in Table 1 were carried out according to the following procedure using the same apparatus. It is illustrated here with the preparation of 2-chloroethyl orthoformate. All boiling points are uncorrected.

2-Chloroethyl Orthoformate. In a 100 m*l* flask was added 30 g (0.2 mol) of ethyl orthoformate, 65 g (0.8 mol) of ethylene chlorohydrin and 0.1 g of anhydrous zinc chloride. In order to remove the ethanol as it was formed, a 25 cm column packed with glass helices was used and adjusted so that a maximum temperature of the condensing vapor was 79°C by controlling the heating of the flask. After 2—3 hr, nearly theoretical amount of ethanol (27 g) was removed. The residual reaction mixture was distilled under vacuum and the fraction boiling at 125—130°C/4 mmHg was collected.

Reaction of Ethylene Chlorohydrin with Ethyl Orthoacetate. The reaction was carried out using 32 g (0.2 mol) of ethyl orthoacetate and 65 g (0.8 mol) of ethylene chlorohydrin. After 3.5 hr, 27 g of ethanol was removed. The residual mixture was distilled under vacuum and 19.5 g of unreacted ethylene chlorohydrin and 30 g (56%) of 2-chloroethyl orthoacetate (bp 135°C/4 mmHg) was obtained.

Found: C, 36.98; H, 5.98; Cl, 38.92%. Calcd for $C_8H_{15}O_3Cl_3$: C, 36.15; H, 5.90; Cl, 40.10%.

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