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One-Pot Synthesis of α-Mono- and α,α-Disubstituted Cyclic Ethers from Lactones

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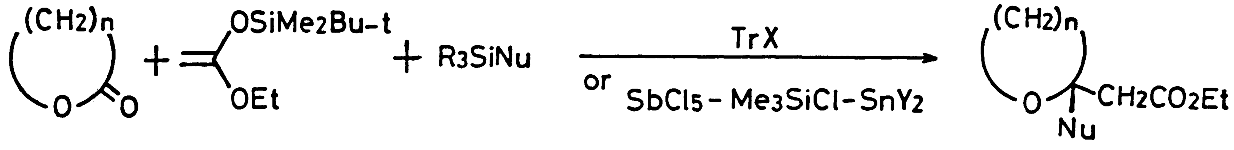
α-Mono- and α,α-disubstituted cyclic ethers are prepared in good yields by the successive treatment of lactones with t-butyldimethylsiloxy-1-ethoxyethene and silyl nucleophiles (triethylsilane, allyltrimethylsilane, trimethylsilyl cyanide, etc.) in the presence of a catalytic amount of trityl salts such as $TrSbCl_6$, $TrSbF_6$ and $TrClO_4$ or antimony pentachloride combined with chlorotrimethylsilane and tin(II) halide.

In recent years, much attention has been focused on α-substituted cyclic ethers, because cyclic ethers constitute a characteristic structural feature of many natural products including important C-glycosides.$^{1)}$ Concerning the preparation of α-substituted cyclic ether nucleus from lactones, Kishi and co-workers have described a stepwise method consisted of the treatment of lactones with aliphatic organometallics, followed by reduction of initially formed cyclic hemiketals with triethylsilane and boron trifluoride etherate.$^{2)}$ Kraus also reported a similar strategy for the synthesis of α-arylsubstituted cyclic ethers.$^{3)}$

In the previous papers,$^{4)}$ we have reported that the trialkylsiloxy group of silylated hemiacetals, generated in situ from aldehyde and alkoxytrialkylsilane, was replaced by hydrogen atom or allyl group to give the corresponding ethers. Now we wish to report a convenient one-pot synthesis of α-mono- and α,α-disubstituted cyclic ethers from lactones, t-butyldimethylsiloxy-1-ethoxyethene and silyl nucleophiles without isolation of the intermediate silylated cyclic hemiacetals.



n=3,4,5
Nu=H, allyl, CN, SCH_2Ph

X = $SbCl_6$, SbF_6, ClO_4
Y = Cl, Br, I

In the first place, we examined the effect of the catalysts such as trityl salts and the combination of tin(II) salts with Me_3SiCl and $SbCl_5$ on the yield of desired cyclic ether by taking the reaction of δ-valerolactone, t-butyldimethylsiloxy-1-ethoxyethene and allyltrimethylsilane as a model (Table 1).

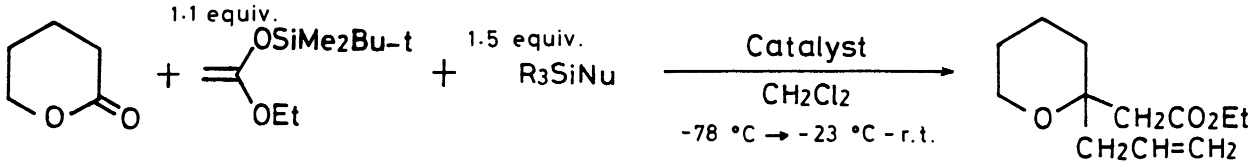


Table 1. The Effect of Catalyst

Entry	Catalyst (equiv.)	Yield /%
1	$SbCl_5(0.05)-Me_3SiCl(0.1)-SnF_2(0.1)$	2
2	$SbCl_5(0.05)-Me_3SiCl(0.1)-SnCl_2(0.1)$	64
3	$SbCl_5(0.05)-Me_3SiCl(0.1)-SnBr_2(0.1)$	77
4	$SbCl_5(0.05)-Me_3SiCl(0.1)-SnI_2(0.1)$	84
5	$TrClO_4(0.05)$	83
6	$TrSbF_6(0.05)$	82
7	$TrSbCl_6(0.05)$	87

The results show that the counter anions of these trityl salts made little difference on the yield and that a combined use of $SbCl_5$, Me_3SiCl and SnI_2 also catalyzed the reaction like trityl salts. Several examples of preparation of α-mono- and α,α-disubstituted cyclic ethers from lactones are demonstrated in Table 2 by using $TrSbCl_6$ or a combination of $SbCl_5$, Me_3SiCl, and SnI_2 as a catalyst.

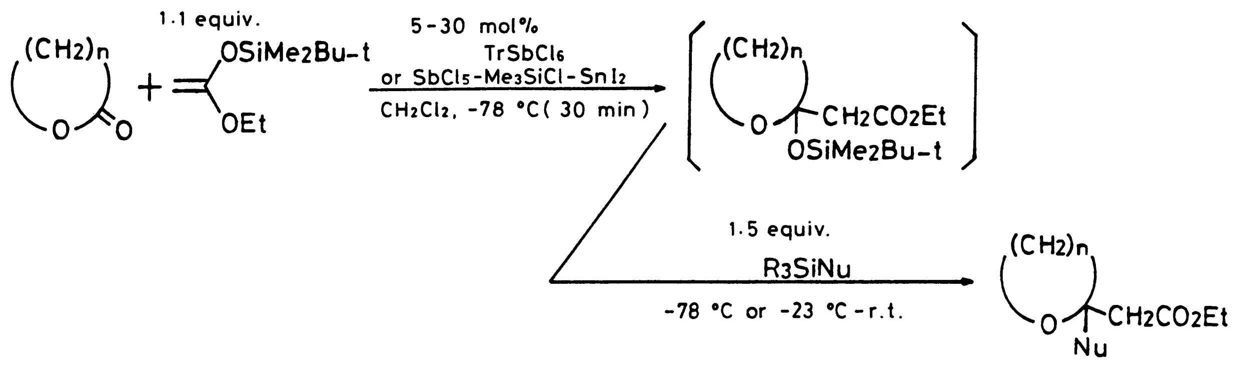
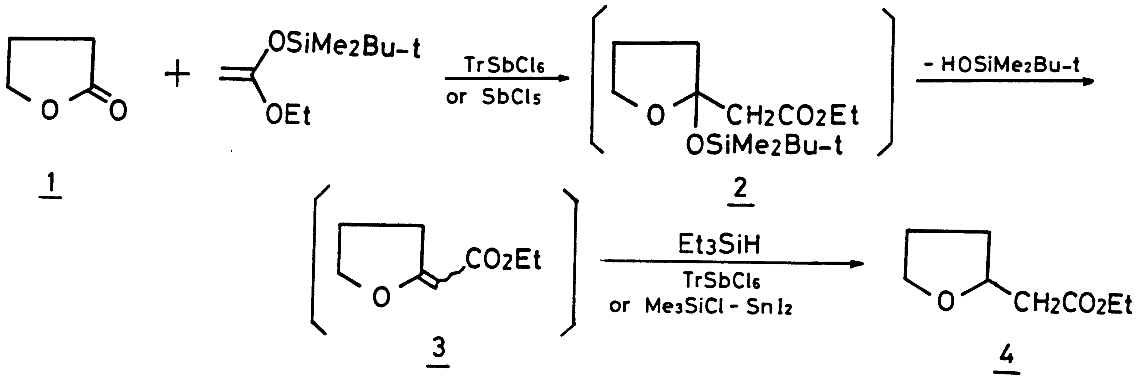


Table 2. The Reaction of Lactones with t-Butyldimethylsiloxy-1-ethoxyethene and Silyl Nucleophiles

Entry	n	R_3SiNu	Catalyst (equiv.)	Conditions[a]	Yield /%
1	5	Et_3SiH	$TrSbCl_6$(0.1)	B	87
2	5	Et_3SiH	$SbCl_5$(0.1)-Me_3SiCl(0.1)-SnI_2(0.1)	B	90
3	4	Et_3SiH	$TrSbCl_6$(0.1)	A	91
4	4	Et_3SiH	$SbCl_5$(0.05)-Me_3SiCl(0.1)-SnI_2(0.1)	B	95
5	3	Et_3SiH	$TrSbCl_6$(0.1)	B	75
6	3	Et_3SiH	$SbCl_5$(0.1)-Me_3SiCl(0.1)-SnI_2(0.1)	B	72
7	5	$Me_3SiCH_2CH=CH_2$	$TrSbCl_6$(0.3)	B	45
8	5	$Me_3SiCH_2CH=CH_2$	$SbCl_5$(0.3)-Me_3SiCl(0.1)-SnI_2(0.1)	B	67
9	4	$Me_3SiCH_2CH=CH_2$	$TrSbCl_6$(0.05)	B	87
10	4	$Me_3SiCH_2CH=CH_2$	$SbCl_5$(0.05)-Me_3SiCl(0.1)-SnI_2(0.1)	B	84
11	5	Me_3SiCN	$TrSbCl_6$(0.05)	A	70
12	5	Me_3SiCN	$SbCl_5$(0.3)-Me_3SiCl(0.1)-SnI_2(0.1)	B	62
13	4	Me_3SiCN	$TrSbCl_6$(0.05)	A	83
14	4	Me_3SiCN	$SbCl_5$(0.1)-Me_3SiCl(0.1)-SnI_2(0.1)	B	66
15	4	Me_3SiSCH_2Ph	$TrSbCl_5$(0.1)	B	51

a) Method A: At second step, the reaction was performed at -78 °C. Method B: At second step, the reaction was performed in the temperature range -23 °C-r.t.

As shown in Table 2, when trimethylsilyl cyanide was employed as the second silyl carbon nucleophile, $TrSbCl_6$ gave better results compared with the combined use of $SbCl_5$, Me_3SiCl, and SnI_2 (entries 11 and 12, 13 and 14). In the case of γ-butyrolactone (1), the elimination of t-butyldimethylsilanol from silylated cyclic hemiketal (2) took place readily to give 2-ethoxycarbonylmethylidenetetrahydrofuran (3). On the other hand, 2-ethoxycarbonylmethyltetrahydrofuran (4) was obtained in a good yield when triethylsilane was used as the second silyl nucleophile probably by the Michael addition of the hydride to unsaturated ester



(3) initially formed.

When a catalytic amount of $SbCl_5$, Me_3SiCl and SnI_2 is used, the lactone carbonyl would be activated by $SbCl_5$ and the elimination of t-butyldimethylsiloxy group to perform the substitution would be promoted by Me_3SiCl and SnI_2. Namely, the first step does not take place in the absence of $SbCl_5$ and second silyl nucleophiles do not react with intermediate silylated cyclic hemiketals without Me_3SiCl and SnI_2.

A typical procedure is described for the preparation of 2-allyl-2-ethoxycarbonylmethyltetrahydropyran from δ-valerolactone using $TrSbCl_6$ as a catalyst: Under an argon atmosphere, $TrSbCl_6$ (28 mg, 0.05 mmol) was added to a solution of δ-valerolactone (101 mg, 1.0 mmol), t-butyldimethylsiloxy-1-ethoxyethene (226 mg, 1.1 mmol) and allyltrimethylsilane (169 mg, 1.5 mmol) in CH_2Cl_2(4.5 ml) at -78 °C, and then the reaction mixture was stirred for 30 min. at the same temperature and for 4.5 h. at -23 °C. Gradually being warmed to room temperature, the reaction was quenched with aqueous saturated $NaHCO_3$. The organic materials were washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by preparative thin layer chromatography on silica gel (8:1 hexane-ethyl acetate as a developing solvent) to give 2-allyl-2-ethoxycarbonylmethyltetrahydropyran (186 mg, 87%).

References

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