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Synthesis of δ-Lactones via Stable Anionic Dimer of Methyl α-Alkyl Acrylates

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Polyfunctional δ-Lactones were prepared conveniently by successive addition of α-alkyl acrylates and aldehydes to the Grignard reagent. The intermediate of the reaction is anionic dimer of α-alkyl acrylate which can react with various electrophiles.

It is well known that the polymer of acrylate and methacrylate is very important material. In addition, selective oligomerization of acrylic acid derivatives were recently studied extensively. Useful polyfunctional compounds were prepared by DABCO catalized aldol condensation[1)] and lithio enolate initiated cyclodimerization.[2)] From the view point of value addition of acrylate monomers, we also have reported the selective trimerization of methyl methacrylate[3)] and the dimerization of dimethyl 2-methylenesuccinate with organoaluminums.[4)] Organoaluminums, however, have some disadvantages, such as limitation of available alkyl group. So we try to use Grignard reagent, which are inexpensive and easy to handle and prepare, for selective oligomerization of acrylates instead of organoaluminums. Consequently, the selective formation of stable anionic dimer of methyl α-alkyl acrylates (3) were observed. We wish to report in this paper on the convenient synthesis of polyfunctional γ-, δ-lactones, and β-ketoesters by addition of various electrophiles to the anionic dimer.

Effect of mole ratio of ethylmagnesium bromide (1a) to methyl α-ethylacrylate (2a) (1a/2a) were shown in Fig.1 and yield of dimer, quenched with dil hydrochloric acid, were summarized in Table 1. At higher mole ratio of 1a/2a (> 1.0), acrylate (2a) was converted exclusively to a 1:2 adduct, dimethyl 2,4-diethyl-2-propyl-glutarate (8a),[5)] whereas predominantly to a cyclic 1:3 adduct, the 4-oxocyclohexanedicarboxylate (6), below this ratio. No formation of higher oligomers were observed by GPC. In general, complexed mixture was produced by the reaction of α,β-unsaturated ester with 1.[6)] The selective formation of dimer were reported only with bulky

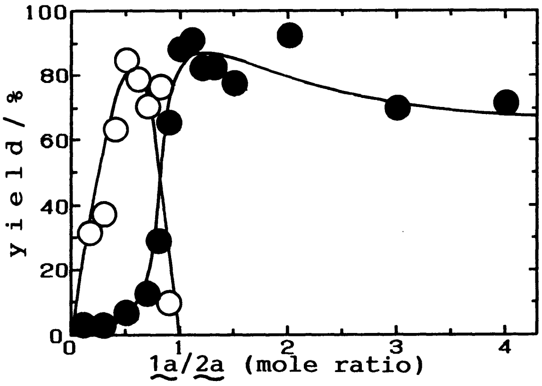


Fig. 1. Formation of 2:1 and 3:1 adducts by the reaction of ester 2a with Grignard reagent 1a in ether at 0 °C. (●) 2:1 adduct; (○) 3:1 adduct.

Table 1. Yield of dimer (8)[a]

R^1 in 1 / R^2 in 2	Et	n-Pr	i-Pr	n-Bu	i-Bu	t-Bu
Me	48[b]	47	58	35	21	51
Et	93	92	71	80	63	98
n-Pr	98	96	53	88	65	84
i-Pr	70	68	34	58	80	32
n-Bu	98	95	63	92	87	77
i-Bu	85	85	11	94	98	16

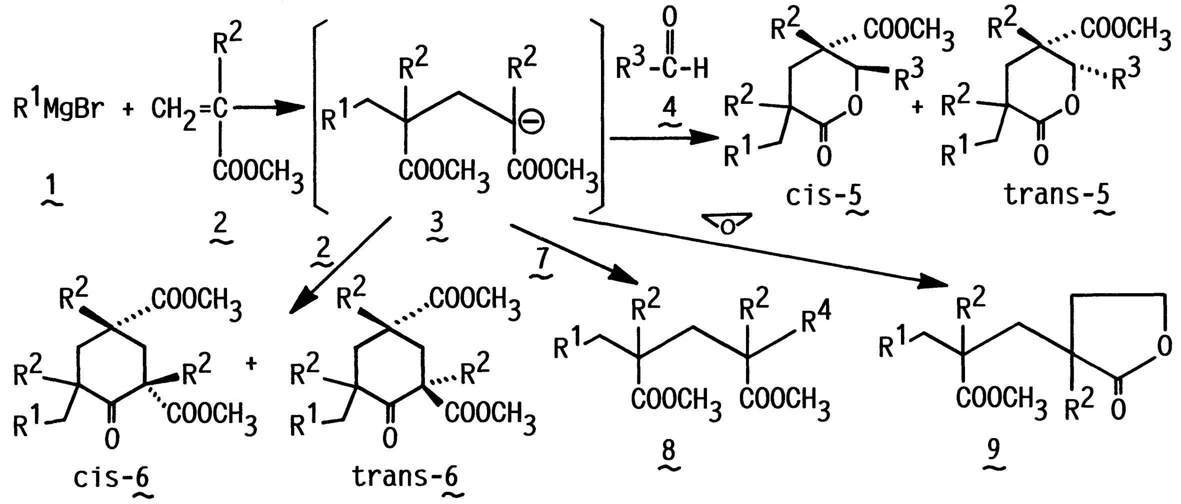
a) R^4= H. Reaction conditions ; solvent ether, time 1 h, temp 0 °C, 1:2=2:1 (mole ratio). b) Yield of 8 in % (determined by GLC based on 2 used).

Grignard (R^1=i-Pr)[7] or bulky α-substituent (R^2=Si(CH$_3$)$_3$) of acrylate.[8] Table 1 shows that dimer were produced quantitatively when R^2 is more bulky than Et. Small R^2, Methyl methacrylate (R^2=Me), afforded higher oligomer, bulky R^2, methyl α-i-butyl acrylate, afforded monomeric 1,4-adduct, and i-PrMgBr tend to cause side reaction (conversion of diester to ketoester).

Instead of hydrochloric acid, by use of some electrophiles as terminating agents, polyfunctional δ-lactones, β-ketoester, etc. could be prepared. Typical procedure is as follows. Ethylmagnesium bromide (1a) (4 mmol) was prepared in usual manner. The solution was cooled to 0°C and the ether solution of methyl α-ethylacrylate (2a) (2 mmol) was added dropwise under stirring. After 1 h, ether solution of propanal (4a) (2 mmol) was added at room temperature. Finally quenched with dil hydrochloric acid, purified by TLC, tetrahydro-3,5,6-triethyl-5-methoxycarbonyl-3-propyl-2H-pyran-2-one (5a)[9] was obtained in 77% yield .

Results of reactions for methyl α-ethyl acrylate (2a) with ethylmagnesium bromide (1a) are summarized in Table 2. Reactions with aldehydes (4) afforded δ-lactones (5) in moderate to good yield. Diastereoselectivity of product were increased with bulkiness of aldehyde employed (entries 1,3).[10] Yield was improved by addition of SnCl$_4$ (entry 5). Reaction with ketones were failed. Cyclopentanone derivatives (6) which was reported previously[3] and corresponding to backbiting product, was obtained by adding excess acrylate. Another electrophiles can react with 3 to give triester (8b), α-bromo-ester(8c), β-ketoester (8d), and γ-lactone (9a) in low to moderate yield.

Obviously, the reaction was initiated by 1,4-addition of Grignard



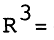
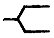
1a: R^1=Et
2a: R^2=Et
3a: R^1=R^2=Et
4a: R^3=Et
4b: R^3=octyl
4c: R^3= 
4d: R^3=t-Bu
4e: R^3= 
5a: R^1=R^2=R^3=Et
5b: R^1=R^2=Et, R^3=octyl
5c: R^1=R^2=Et, R^3= 
5d: R^1=R^2=Et, R^3=t-Bu
5e: R^1=R^2=Et, R^3= 
5f: R^1=t-Bu, R^2=R^3=Et

Table 2. Reactions of anionic dimer 3a with electrophiles[a)]

Entry	Electrophile	Product	Yield[b)] %	DS[c)]
1	4a	5a	77	2.3
2	4b	5b	55	2.3
3	4c	5c	52	>10
4	4d	5d	25	>10
5[d)]	4d	5d	56	>10
6	4e	5e	58	1.4
7[e)]	4a	5f	22	4.5
8	2a	6a	97[f)]	3.5
9[e)]	2a	6b	93[f)]	9.1
10	7a	8a	93[f)]	-
11	7b	8b	22[g)]	-
12	7c	8c	50	-
13	7d	8d	40	-
14	ethylene oxide	9a	12	-

a) Reaction conditions; 1a/2a mole ratio 2.0, Electrophile/3a mole ratio 1.0, solvent ether, temp r.t. b) Isolated yield based on 2a used.
c) Diastereoselectivity (ratio of cis/trans isomers) was characterized by ^1H NMR. d) Addition of 3 mol % of $SnCl_4$. e) t-BuMgBr was used as Grignard reagent. f) Yield was determined by GLC. g) Yield of triester after treated with CH_2N_2.

6 a: R^1=R^2=Et
b: R^1=t-Bu, R^2=Et

7 a: H_3O^+
b: CO_2
c: Br_2
d: acetyl chloride

8 a: R^1=R^2=Et
R^4=H
b: R^1=R^2=Et
R^4=$COOCH_3$
c: R^1=R^2=Et
R^4=Br
d: R^1=R^2=Et
R^4=acetyl

9 a: R^1=R^2=Et

reagent (1) to α,β-unsaturated ester (2) which is corresponding to initiation of anionic polymerization and then Michael addition afforded linear anionic dimer (3) as intermediate. It was stabilized as magnesium enolate. On the other hand, using organoaluminums, trimerization and Dieckmann-type cyclization was occurred. And n-BuLi converted part of MMA to butyl isopropenyl ketone.[11] By addition of various electrophiles, such as aldehydes (4), to the anionic dimer (3), enable to introduce new functional groups to the dimer. In the cases of 5 or 6 membered ring being constructed, terminal anion can attack to carbonyl carbon of ester unit. The reaction with aldehydes (4) corresponded to new variant of Stobbe condensation.

Three or 4 carbon-carbon bonds could be formed in one-pot by these reactions. Reaction condition is mild and procedure is convenient. Although two alkyl groups of product must be identical, this oligomerization may provide a convenient method for the preparation of regiospecific polysubstituted lactones, cyclopentanones, ketoesters, etc.

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5) 8a: IR (film) 1730; ^{1}H NMR ($CDCl_3$) δ 0.6-1.0 (12H, m, CH_3), 1.4-2.2 (9H, m), 2.45 (1H, m), 3.61, 3.63, 3.64, and 3.65 (6H, each s, OCH_3); m/z 259 (MH^+), 227 (M^+-OCH_3), and 199 (M^+-CH_2CH_3); Anal. Found C, 64.82 ; H, 10.14%. Calcd for $C_{14}H_{26}O_4$ C, 65.08; H, 10.14%.
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9) 5a: 2.3:1 mixture of 5,6-cis- and trans- dialkyl isomers, which was separated to each isomer by TLC.; IR (film) 1730; ^{1}H NMR ($CDCl_3$, 400 MHz) δ [5,6-cis diethyl isomer] 0.86-0.97 (9H, m, CH_3), 1.05 (3H, t, J=7.3 Hz, CH_3), 1.48 (1H, d, J=14.4 Hz), 1.55-2.05 (10H, m), 2.4 (1H, d, J=14.4 Hz), 3.69 and 3.73 (3H, each s, OCH_3), and 4.16 (1H, m); [5,6-trans diethyl isomer] 0.84-1.00 (12H, m, CH_3), 1.24-1.82 (10H, m), 1.86 (1H, d, J=14.7 Hz), 2.19 (1H, d, J=14.7 Hz), 3.74 and 3.75 (3H, each s, OCH_3), and 4.56 (1H, m); Anal. Found C, 67.67; H, 10.29%. Calcd for $C_{16}H_{28}O_4$ C, 67.57; H, 9.92%.
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