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An Efficient Method for α–Alkylation of γ–Butyrolactone

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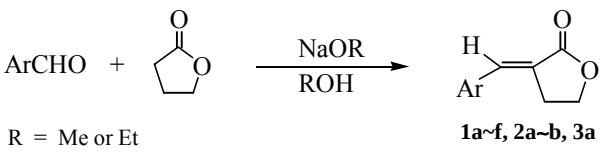
Abstract: This paper provides a simple, convenient and mild condition method for α-alkylation of γ-butyrolactone. Three types of (E)-α-alkenyl-γ-butyrolactone compounds were synthesized by condensation of corresponding aldehydes and γ-butyrolactone, using MeONa and EtONa as base. Then the α-alkyl-γ-butyrolactones were gained by reducing the former alkenyl compounds through catalytic transfer hydrogenation under Pd/C catalyst with sodium hypophosphite at room temperature.

Keywords: α-Alkylation of γ-butyrolactone, condensation, catalytic transfer hydrogenation, Pd / C-sodium hypophosphite.

Alkylated lactone is a common structure and segment in many natural products and medicines. The examples of alkylating lactone system at α-position, obtained by reaction with alkyl halide such as MeI, in the presence of strong base LDA or it's derivatives, are very few[1a, 1b]. When this method was applied to the aromatic compound, the self-condensation of γ-butyrolactone could not be avoided. In our previous work we have reported the hydrogenation of α, β-unsaturated carbonyl compounds by catalytic transfer hydrogenation with hypophosphorous acid[2], which was in common used to hydrogenating the nitro group of aromatics. So we design another new route of alkylation of γ-butyrolactone.

Here we wish to report a simple, convenient method of synthesizing α-alkenyl-γ-butyrolactone. The three types of α-alkenyl-γ-lactone derivatives **1a~f, 2a~b**, **3a** were synthesized by condensation of substituted phenyl aldehyde, biphenyl and naphthyl aldehyde, and heterocyclic aldehyde with γ-butyrolactone, under normal condition (0-10°C), in the presence of sodium alcoholate (**Scheme 1** and **Table 1**). The ^{1}HNMR spectral data of these compounds were listed in **Table 2**.

Scheme 1



R = Me or Et

1a~f, 2a~b, 3a

Table 1 The condensation of γ-butyrolactone with aromatic aldehydes[3]

Ar	Products	mp. (°C)	Yield (%) [a]
C_6H_5	**1a**	120	60
o-MeO-C_6H_4	**1b**	90-3	68
p-MeO-C_6H_4	**1c**	124-6	65
p-Cl-C_6H_4	**1d**	145.5-6.5	52
p-Br-C_6H_4	**1e**	158-9.5	55
p-Me_2N-C_6H_4	**1f**	198-9	40
p-Ph-C_6H_4	**2a**	202-4	99
α-$C_{10}H_7$ (α-Naphthyl)	**2b**	oil	10
α-C_4H_3O (α-Furanyl)	**3a**	91-2.5	40

a) Yields were based on the isolated products.

Table 2 The ^{1}HNMR (200MHz, $CDCl_3$) data of **1a~f, 2a~b, 3a**

Compd.	^{1}HNMR ($CDCl_3$, δ_{ppm}, J_{Hz})
1a	3.25 (td, 2H, 7.2, 3.0), 4.46 (t, 2H, 7.2), 7.41-7.49 (m, 5H), 7.57 (t, 1H, 3.0).
1b	3.20 (td, 2H, 7.2, 2.8), 3.88 (s, 3H), 4.44 (t, 2H, 7.2), 6.93-7.04 (m, 2H), 7.34-7.45 (m, 2H), 8.00 (t, 1H, 2.8).
1c	3.22 (td, 2H, 7.3, 2.9), 3.86 (s, 3H), 4.46 (t, 2H, 7.3), 6.96 (dd, 2H, 6.8, 2.0), 7.47 (dd, 2H, 6.8, 2.0), 7.53 (t, 1H, 2.9).
1d	3.23 (td, 2H, 7.4, 3.0), 4.49 (t, 2H, 7.4), 7.43 (s, 4H), 7.52 (t, 1H, 3.0).
1e	3.21 (td, 2H, 7.2, 2.8), 4.48 (t, 2H, 7.2), 7.36 (d, 2H, 8.6), 7.48 (t, 1H, 2.8), 7.57 (d, 2H, 8.6).
1f	3.04 (s, 6H), 3.21 (td, 2H, 7.4, 2.8), 4.44 (t, 2H, 7.4), 6.72 (d, 2H, 9.0), 7.41 (d, 2H, 9.0), 7.50 (t, 1H, 2.8).
2a	3.29 (td, 2H, 7.2, 3.0), 4.48 (t, 2H, 7.2), 7.38-7.50 (m, 3H), 7.52-7.70 (m, 7H).
2b	3.09 (td, 2H, 7.2, 2.9), 4.36 (t, 2H, 7.2), 7.46-7.55 (m, 4H), 7.85 (t, 1H, 2.5), 7.87 (s, 1H), 8.08-8.10 (m, 1H), 8.27 (t, 1H, 2.9).
3a	3.28 (td, 2H, 7.4, 2.8), 4.47 (t, 2H, 7.4), 6.54 (dd, 1H, 3.4, 1.8), 6.67 (d, 1H, 3.4), 7.33 (t, 1H, 2.8), 7.59 (d, 1H, 1.2).

Table 3 Results of the catalytic transfer hydrogenation[4]

Ar	Substrates	Products	Yield (%) [a]
C_6H_5	**1a**	**4a**	99.7
o-MeO-C_6H_4	**1b**	**4b**	95.7
p-MeO-C_6H_4	**1c**	**4c**	87.0
p-Cl-C_6H_4	**1d**	**4d**	-- [b]
p-Br-C_6H_4	**1e**	**4e**	-- [b]
p-Ph-C_6H_4	**2a**	**4f**	55.6
α-C_4H_3O (α-Furanyl)	**3a**	**4g**	61.5

a) Yields were based on the isolated products. b) Halogen elimination

Sodium hypophosphite plus Pd/C were applied for reducing the α-alkenyl-γ-lactone derivatives. This catalytic system was effective for reduction of **1a~c, 2a, 3a** to afford the target compounds **4a~c, 4f~g** in 55-99% yields, but for those compounds, which contain the halide **1d~e**, this system catalyzed halogen elimination to form **4d~e** instead of catalytic reduction. The results were summarized in **Table 3** (**Scheme 2**), and the spectral data of these compounds were listed in **Table 4.**

Scheme 2

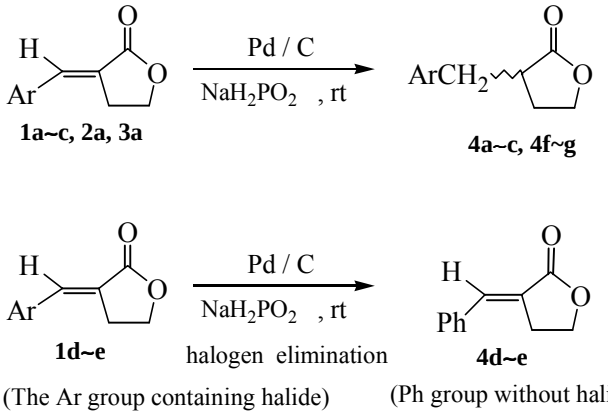


Table 4 The spectral data of compouds **4a~c, 4f~g**

Compd.	MS (EI) *m/z* (%)	^{1}HNMR (δ_{ppm}, J_{Hz}) *	^{13}C NMR (δ_{ppm},) **
4a	176 (M^+, 28.2), 148 (39.0), 147 (31.2), 43 (100).	1.95-2.10 (m, 1H), 2.19-2.32 (m, 1H), 2.61-2.92 (m, 2H), 3.25 (dd, 1H, 12.8, 3.4), 4.06-4.30 (m, 2H), 7.18-7.38 (m, 5H).	27.88, 35.97, 40.94, 66.44, 126.60, 128.55, 128.75, 138.30, 178.63.
4b	207 (M+1, 7.0), 206 (M^+, 44.0), 121 (100), 108 (10.2), 91 (81.0).	1.85-2.23 (m, 2H), 2.65 (dd, 1H, 13.4, 9.6), 2.84-3.02 (m, 1H), 3.31 (dd, 1H, 13.4, 4.4), 3.81 (s, 3H), 4.05-4.31 (m, 2H), 6.84-6.92 (m, 2H), 7.12-7.26 (m, 2H).	28.09, 30.68, 39.44, 55.00, 66.44, 110.16, 120.36, 126.75, 127.88, 130.38, 157.35, 179.08.
4c	206 (M^+, 16.2), 178 (8.3), 121 (100).	1.86-2.08 (m, 1H), 2.12-2.30 (m, 1H), 2.65-2.84 (m, 2H), 3.14 (dd, 1H, 12.8, 3.0), 3.77 (s, 3H), 4.06-4.24 (m, 2H), 6.84 (d, 2H, 8.8), 7.11 (d, 2H, 8.8).	27.64, 34.95, 40.98, 55.03, 66.37, 113.85, 129.71, 130.13, 158.23, 178.66.
4f	252 (M^+, 39.2), 224 (31.0), 205 (46.8), 167 (B).	1.90-2.35 (m, 2H), 2.72-2.96 (m, 2H), 3.26 (d, 1H, 10), 4.05-4.24 (m, 2H), 7.24-7.64 (m, 9H).	27.95, 35.62, 40.95, 66.47, 126.87, 126.90, 127.19, 127.27, 127.35, 128.70, 129.24, 137.38, 139.56, 140.57, 178.61.
4g	166 (M^+, 25.0), 138 (26.2), 81 (B).	1.83-2.13 (m, 1H), 2.30-2.45 (m, 1H), 2.77-2.98 (m, 2H), 3.22 (d, 1H, 11), 4.12-4.32 (m, 2H), 6.10 (d, 1H, 3.2), 6.30 (dd, 1H, 3.2, 2.0) 7.33 (d, 1H, 2.0).	28.13, 28.53, 38.87, 66.49, 106.86, 110.32, 141.69, 152.16, 178.34.

* ^{1}HNMR (200MHz, $CDCl_3$), ** ^{13}CNMR (50MHz, $CDCl_3$)

From **Table 1** one can see, that the electronic effect and the steric hindrance of the aromatic aldehydes affect the yields of the condensation reaction. More interestedly the products α-alkenyl-γ-lactones are all in (E)-configuration. Further studies are in progress.

Acknowledgment

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References and Notes

1. a) J. L. Herrmann and R. H. Schlessinger, *J.C.S. Chem. Comm.*, **1973**, 711.
   b) Gary H. Posner and Gary L. Loomis, *J.C.S. Chem. Comm.*, **1972**, 892.
2. Xue Wang, Yedi Guan, *Chin. Chem. Lett.*, **1993**, *4*, 407.
3. General procedure of preparation of **1a~f, 2a~b, 3a**: the solution of aromatic aldehyde (5 mmol), γ-butyrolactone (5 mmol) in anhydrous methyl alcohol was added dropwise to methyl alcohol solution of NaOEt (10 mmol) in ice-cooling. The mixture was stirred at 0-10˚C for 3 hours. Then, the product was precipitate.
4. General procedure of the catalytic transfer hydrogenation: the α-alkenyl-γ-butyrolactone (3~5 mmol) was dissolved in ethanol, heating to refluxing, then Pd/C (10%) was added (10%w/w starting compound). Then the solution of sodium hypophosphite in water was added dropwise. The mixture was stirred at room temperature for 3~5 h. Then the catalyst was filtered off and the mixture was extracted with ethyl acetate after removing ethanol. The product was gained from the organic phase after removing solvent or by conventional column chromatography if necessary.

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