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A NEW APPROACH FOR THE SYNTHESIS OF α-METHYLENE-γ-BUTYROLACTONES FROM α-BROMOMETHYLACRYLIC ACIDS (OR ESTERS)

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Abstract: This paper reports that a new approach for the synthesis of α-methylene-γ-butyrolactones from the reaction of α-bromomethyl acrylic acid (or ester), powdered tin and carbonyl compounds in one pot with excellent to good yields.

The α-methylene-γ-butyrolactone is a major class of skeleton in natural occurring sesquiterpene lactones which exhibit remarkable physiological activities[1]. It is also one of the most important building blocks in the synthetic organic chemistry of natural products. Its biological activities and synthetic approach are reviewed in a series of articles [2]. Recently Stampf reported a direct method for the preparation of α-

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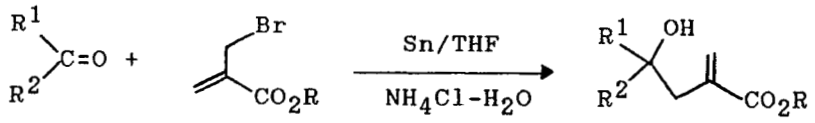

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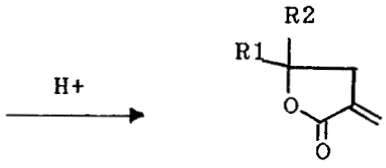


3

R=H, C_2H_5. R^1=H, R^2: a=n-C_4H_9; b=n-C_6H_{13}; c=CH_3CH=CH; d=C_6H_5; e=C_6H_5CH=CH; f=4-$NO_2C_6H_4$; g=2-ClC_6H_4.

R^1+R^2: h= $(CH_2)_5$.

methylene-γ-lactone based on 2-carboethoxyallylation of aldehydes by means of tin(II) chloride and Amberlyst 15[3].

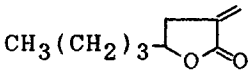
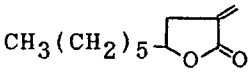
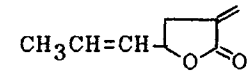
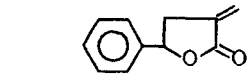
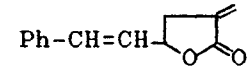
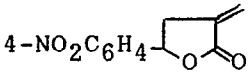
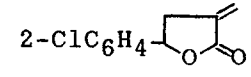
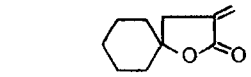
Here we report an approach for the synthesis of α-methylene-γ-butyrolactones based on 2-carboethoxyallylation of carbonyl compounds by means of organotin reagent. The α-methylene-γ-butyrolactones can be synthesized in one pot from α-bromomethylacrylic acid (or ester) in the medium of tetrahydrofuran and

saturated aqueous solution of ammonium chloride. The results of reactions are summarized in following table.

In above scheme, the reactions proceed smoothly under normal condition without demand on absolute anhydrous and deoxygenation. The intermediate organotin reagents need not to be isolated. The products α-methylene-γ-butyrolactones(3) can be obtained in one pot with excellent to good yields. Moreover, the reactions carry out without difficulty when the substrates containing reactive groups such as halogen, hydroxyl, methoxyl, or nitro group.

General procedure for the synthesis of α-methylene-γ-butyrolactions

A suspension of 8 mmol ethyl α-bromomethylacrylate(or α-bromomethylacrylic acid), 8 mmol of aldehyde (or ketone), 8 mmol of actived tin, THF(20 mL), and saturated aqueous solution of ammonium chloride (10 mL) is stirred for 14 h at 60 °C. After evaporating of THF, 10 mL of brine is added. The reaction mixture is extracted with ether (2x25 mL), the combined extracts are dried over anhydrous sodium sulfate. The ether is removed and the mixture is treated with catalytic amount of p-toluenesulforic acid in 40 mL of dimethoxy-

product*	structure of product	yield (%) R=C_2H_5	R=H
3a[4]		81.2	68.2
3b[4]		76.9	70.1
3c[5]		76.1	65.2
3d[4]		93.4	84.8
3e[6]		85.0	79.4
3f[7]		84.5	75.9
3g		80.9	73.1
3h[6]		70.8	52.0

* For 3f the reaction is carried out in two steps that 4-nitrobenzaldehyde is introduced after metallic tin has disappeared. The solvent THF is replaced by dimethoxyethane and the reaction mixture is stirred for 14 h at 80 °C.

ethane at room temperature for 2 h to converted 2 to 3. The products are purified by column chromatography on silica gel using petroleum ether/diethyl ether (1:1) as eluent.

All products are characterized by IR and ^1H NMR spectra, and the new compound 3g is also identified by mass spectra and elemental analysis.

3a: νmax(neat):1760(s,C=O),1660(w,C=C),930(m,CH_2=C)cm^{-1}. δ H(CCl_4,TMS):0.89-1.33(m,9H,C_4H_9),2.49-3.34(m,2H,CH_2), 4.20-4.50 (m,1H,O-CH), 5.33-5.40 (m,1H,C=CH),5.92-6.00 (m,1H,C=CH) ppm.

3b: νmax(neat):1775(s,C=O),1660(w,C=C),930(m,CH_2=C)cm^{-1}. δH(CCl_4,TMS):0.84-1.17(m,13H,C_6H_{13}),2.15-2.85(m,2H,CH_2), 3.95-4.33 (m,1H,O-CH), 5.33-5.50 (m,1H,C=CH), 5.83-6.11 (m,1H,C=CH) ppm.

3c: νmax(neat):1760(s,C=O),1670(w,C=C),920(m,CH_2=C)cm^{-1}. δ H(CCl_4,TMS): 1.67-1.77(d,3H,CH_3),2.33-3.33(m,2H,CH_2), 4.50-4.85 (m,1H,O-CH), 5.16-5.93 (m,3H,C=CH), 6.00-6.17 (m,1H,C=CH) ppm.

3d: νmax(neat):1755(s,C=O),1660(w,C=C),930(m,CH_2=C)cm^{-1}. δH(CCl_4,TMS): 2.46-3.45(m,2H,CH_2), 5.30-5.40(m,2H,O-CH, C=CH),6.00-6.13(t,1H,C=CH),7.08(s,5H,Ar-H) ppm.

3e: νmax(neat):1755(s,C=O),1660(w,C=C),940(m,CH_2=C)cm^{-1}. δH(CCl_4,TMS): 2.67-3.33(m,2H,CH_2),4.66-5.11(m,1H,O-CH), 5.33-6.67(m,4H,C=CH),7.00-7.31(m,5H,Ar-H) ppm.

3f: νmax(neat): 1765(s,C=O), 1660(w,C=C), 1520(m,NO_2), 1340 (m,NO_2), 930(m,CH_2=C)cm^{-1}. δH(CCl_4,TMS): 2.33-3.50 (m,2H,CH_2), 5.50-5.67 (m,2H,O-CH,C=CH), 6.17-6.33(m,1H, C=CH), 7.17-7.42(m,2H,Ar-H), 8.00-8.21 (m,2H,Ar-H) ppm.

3g: m.p. 77-79 °C(uncorrected). νmax(KBr): 1770(s,C=O), 1660(w,C=C), 930(m,CH_2=C) cm^{-1}. δH(CCl_4,TMS): 2.60-2.92 (m,1H,CH),3.40-3.76(m,1H,CH),5.60-5.92 (m,2H,OCH,C=CH), 6.28 (t,1H,C=CH), 7.20-7.51(m,4H,Ar-H) ppm. m/z(%): 208 (M^+), 68 (base, C_4H_4O). Anal. Calcd. for $C_{11}H_9ClO_2$: C, 63.32; H, 4.35. Found: C, 63.21; H, 4.03.

3h:νmax(neat):1760(s,C=O),1670(w,C=C),930(m,CH_2=C)cm^{-1}. δH(CCl_4,TMS): 1.33-1.85(m,10H,CH_2),2.50-2.66(m,2H,CH_2), 5.35-5.45(m,1H,C=CH),5.92-6.13(m,1H,C=CH) ppm.

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