A NEW SYNTHESIS OF (±)METHYL-(HYDROBENZO[*B*]FURAN-5-YL)-3-METHYLBUTANOATE

N.Vijayakumari, K.Shireesha and Lingaiah Nagarapu*
Organic Chemistry-II Division, Indian Institute of Chemical Technology, Hyderabad

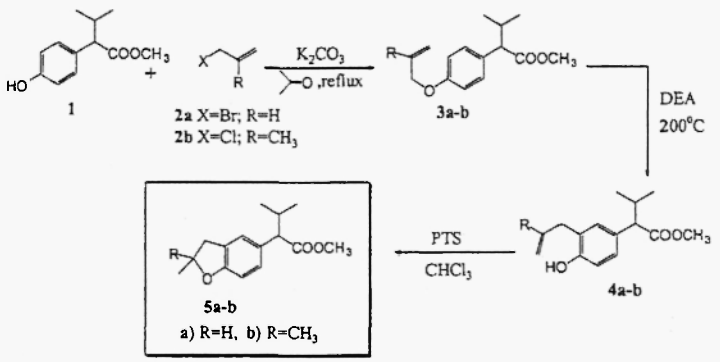
Abstract: (±)Methyl-2-(2-methyl-2,3-dihydrobenzo[*b*]furan-5-yl)-3-methylbutanoate (**5a**) and (±)methyl-2-(2,2-dimethyl-3-hydrobenzo[*b*]furan-5-yl)-3-methylbutanoate (**5b**) have been synthesized from methyl-2-(4-hydroxyphenyl)-3-methylbutanoate (**1**) via Claisen rearrangement and PTS, in good yield.

Introduction

In view of the general interest in the pharmacological and biological activities of furanobenzo systems and naturally occurring oxygen heterocycles.[1-6] Natural dihydrobenzofurans are homochiral.[7-10] We are reporting here for the first time hitherto unreported (±)methyl-2-(2-methyl-2,3-dihydrobenzo[*b*]furan-5-yl)-3-methylbutanoate (**5a**) and (±)methyl-2-(2,2-dimethyl-3-hydrobenzo[*b*]furan-5-yl)-3-methylbutanoate (**5b**) have been synthesized from methyl-2-(4-hydroxyphenyl)-3-methylbutanoate (**1**).

Chemistry

Methyl-2-(4-hydroxyphenyl)-3-methylbutanoate (**1**) was alkylated with equimolar proposition of allyl bromide (**2a**) /methallyl chloride (**2b**) in dry acetone, potassium carbonate medium to give methyl-2-(4-allyloxy phenyl)-3-methylbutanoate (**3a**) and methyl-2-(4-methallyl phenyl)-3-methylbutanoate (**3b**). This on heating in *N,N'*-diethyl aniline at 200°C gave the methyl-2-(3-allyl-4-hydroxy phenyl)-3-methylbutanoate (**4a**) and methyl-2-(3-methallyl-4-hydroxy phenyl)-3-methylbutanoate (**4b**) by Claisen rearrangement which were cyclized with PTS in chloroform at reflux temperature for 4h. to give (±)methyl-2-(2-methyl-2,3-dihydrobenzo[*b*]furan-5-yl)-3-methylbutanoate (**5a**) and (±)methyl-2-(2,2-dimethyl-3-hydrobenzo[*b*]furan-5-yl)-3-methylbutanoate (**5b**). (**Scheme-1**).. Their structures were established by ^{1}H NMR, IR and Mass.



Scheme-1

Experimental Section

Melting points were determined in open glass capillaries on a polmon melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Gemini (200 MHz) spectrometers (chemical shifts are recorded in δ, ppm); internal standard was TMS and IR spectra were recorded in KBr on a Perkin-Elmer bio-spectrometer.

Methyl 2-(4-allyloxy phenyl)-3-methyl butanoate (3a)

Phenol (1.16 g, 0.02 mole) was condensed with allyl bromide (2.6 mL) in dry acetone (100 mL), potassium iodide (0.16 g) anhydrous potassium carbonate (4.08 g) to give 1-allyloxy benzene and refluxed for 12 hrs. After cooling to room temperature the reaction mixture was filtered to remove potassium carbonate ethyl acetate (100 mL) was added to the filtrate and then washed with 0.8% NaOH with brine to neutrality, dried and concentrated. The residue on chromatography over silica gel by eluting with benzene: pet ether (2:8) gave methyl 2-(4-alkyloxy phenyl) 3-methyl butanoate as a liquid (86%).^{1}H NMR ($CDCl_3$) :δ 0.65 (d, -CH_3-, 3H), 1.00 (d, -CH_3-3H), 2.25 (m, -CH-, 1H), 3.00 (d, -CH, H), 3.80 (s, -OCH_3-, 3H), 4.50 (d, -CH_2-, 2H), 5.30 (m, -CH_2-, 2H), 6.00 (m, -CH-, 1H), 6.75 (d, ArH, 2H, J = 10 Hz), 7.10 (d, ArH, 2H, J = 10 Hz). ^{13}C NMR ($CDCl_3$, 150.2 MHz) : δ 20.0 (CH_3), 20.1 (CH_3), 30.1 (CH), 50.1 (CH-COO), 50.9 (OCH_3), 60.9 (C-1'), 113 (ArC-2,6), 118 (C-3'), 129 (ArC-3,5), 130 (C-2'), 133 (ArC-4), 158 (ArC-1), 175 (C=O). MS : m/z 248 ($M^{+\cdot}$, 40), 205 (100), 189 (60), 165 (15), 145 (20), 117 (15), 77 (20), 41 (91).

Methyl 2-(4-alkyloxy phenyl) 3-methyl butanoate (3b)

Liquid (88%). ^{1}H NMR ($CDCl_3$) : δ 0.65 (d, -CH_3-, 3H), 1.00 (d, -CH_3-3H), 1.80 (s, -CH_3, 3H), 2.25 (m, -CH-, 1H), 3.00 (d, -CH, H), 4.25 (s, -OCH_3-, 3H), 4.20 (s, -OCH_2-, 2H), 4.65-5.05 (dd, -CH_2-, 2H), 6.75 (d, ArH, 2H, J = 10 Hz), 7.10 (d, ArH, 2H, J = 10 Hz).

Methyl 2-(3-allyl 4-hydroxyphenyl)-3-methyl butanoate (4a)

Methyl 2-(4-allyloxy phenyl) 3-methyl butanoate on heating in *N,N'*-diethyl aniline at 200°C for 12 h gave 2-allyl phenol by Claisen rearrangement. The reaction mixture was evaporated to dryness in vacuo and the residual oil was chromatographed over silica gel by eluting with pet. ether : ethyl acetate (6:4) give methyl 2-(3-allyl-4-hydroxy phenyl) 3-methyl butanoate as a liquid. IR (KBr) : λ_{max} 3500 (OH), 2900 (C=C), 1700 (C=O) cm^{-1} ; ^{1}H NMR ($CDCl_3$) :δ 0.80 (d, -CH_3-, 3H), 1.00 (d, -CH_3-, 3H), 2.25 (m, -CH-, 1H), 3.00 (d, -CH-, 1H), 3.30 (d, -

CH_2-, 2H), 3.75 (s, -OCH_3-, 3H), 4.60 (s, -OH-, 1H, D_2O), 5.10 (m, -CH_2-, 2H), 5.98 (m, -CH-, 1H), 6.60 (m, Ar-H, 2H), 7.00 (d, Ar-H, 1H).

Methyl 2-(3-methallyl-4-hydroxy phenyl) 3-methyl butanoate (4b)

Liquid in 98% yield. ^{1}H NMR ($CDCl_3$) : δ 0.80 (d, -CH_3-, 3H), 1.00 (d, -CH_3-, 3H), 2.25 (m, -CH-, 1H), 3.00 (d, -CH-, 1H), 3.30 (d, -CH_2-, 2H), 3.25 (s, -CH_2-, 2H), 3.65 (s, -OCH_3-, 3H), 4.60 (s, -OH-, 1H,), 4.85-5.10 (dd, -CH_2-, 2H), 6.60 (m, Ar-H, 2H), 7.00 (d, Ar-, 1H).

(±) Methyl-2-(2-methyl-2,3-dihydro benzo [*b*]furan-5-yl)-3-methyl butanoate (5a)

The mixture of methyl 2-(3-allyl 4-hydroxy phenyl) 3-methyl butanoate (3.0g) and PTS (2.06g) were dissolved in chloroform (20mL) and refluxed for 4 h. After cooling to room temperature poured on crushed ice and extracted with chloroform. The chloroform layer was washed with water (50mL), dried and concentrated. The residue on column chromatography over silica gel, eluting with benzene : EtOAc (8:2) gave the final product (**5a**) in 76% yield, m.p.86.3^{0}C. IR (KBr) : λ_{max} 2900 (C=C), 1600 (C=O) cm^{-1} ^{1}H NMR ($CDCl_3$) : δ 0.90 (d, -CH_3-, 3H), 1.00 (d, -CH_3, 3H), 2.24 (m, -CH-, 1H), 3.00 (d, -CH, 1H), 3.89 (s, -OCH_3-, 3H), 7.60 (d, furan- H, 1H), 6.40 (d, fuan-H, 1H), 6.80 (d, Ar-H, 1H, J = 9.3 Hz), 6.89 (d, Ar-H, 1H, J = 9.3 Hz) and 7.00 (s, Ar-H, 1H). MS : m/z 232 (M^+, 10), 201, 173, 117 (100), 89, 65, 51, 39, 28.

(±) Methyl 2-(2,2-dimethyl -3 hydro benzo[*b*]furan-5-yl) 3-methyl butanoate (5b)

Semi-solid, Yield 72%. ^{1}H NMR ($CDCl_3$) : δ 0.69 (d, -CH_3-, 3H), 1.00 (d, -CH_3, 3H), 1.42 (s, 2CH_3, 6H), 2.25 (m, -CH-, 1H), 3.00 (s, -CH_2-, 2H), 3.08 (d, -CH-, 1H), 3.62 (s, -OCH_3-, 3H), 6.85-7.25 (m, Ar-H, 3H).

References

1. I.R. Nascimento and L.M.X. Lopes, *Phytochemistry* **52**, 345 (1999).
2. P.J.C. Benevides, P. Sartorelli and M.J. Kato, *Phytochemistry* **52**, 339 (1999).
3. H. Ishii and T. Ishikawa, *Tetrahedron Lett.* **23**, 4245 (1982).
4. F. Bohlmann, C. Scheidges, C. Zdero, R.M. King and H. Robinson, *Phytochemistry* **23**, 1109 (1984).
5. M.R. Hellberg, A. Namil, P. Delgado, K.C. David, T.L. Kesler, G. Graff, K.S. Heggard and J.C. Nixon, *J. Med. Chem.* **42**, 267 (1999).
6. L. Pieters, T.D. Bryne, M. Claeys and A. Vlietinck, *J. Nat. Prod.* **56**, 899 (1993).

7. G.S. Cokerill, P.C. Levett and D.A. Whiting, *J.Chem. Soc. Perkin* **1**, 1103 (1995).

8. B.B. Jarvis, N.B. Pena, S.N. Comezoglu and M. Madhusudhan Rao, *Phytochemistry* **25**, 533 (1986).

9. H. Achenbach, W. Utz, A, Usubillaga and A.H. Rodriguez, *Phytochemistry* **30**, 3753 (1991).

10. N. Lingaiah and V. Peesapati, *Org. Prep. Proced. Int.* **24**, 27 (1992).

Received on September 9, 2005.