A SIMPLE AND GENERAL APPROACH FOR THE SYNTHESIS OF 2-SUBSTITUTED 4-ETHOXYCARBONYLFURAN

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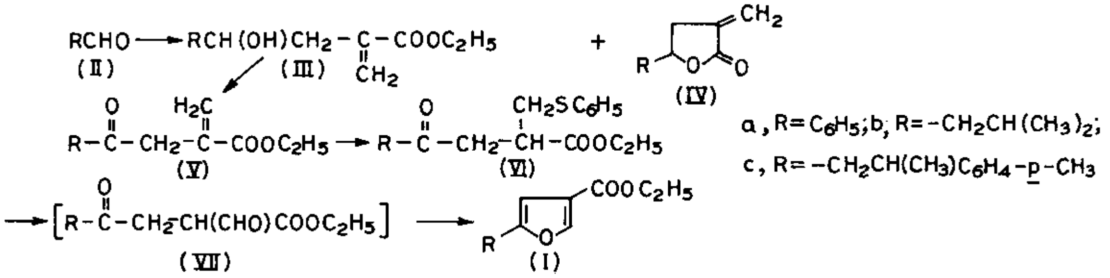
Abstract - A four step strategy has been devised to synthesize 2-substitututed 4-ethoxycarbonylfuran starting from an aldehyde.

2-Alkyl/aryl-4-functionalized furan is present in many naturally occurring furanoterpenoids.[1] However, literature does not record[2] any general and convenient pathway for the synthesis of such substituted furan derivatives. We wish to report in the present paper a simple approach for the synthesis of 2-substituted 4-ethoxycarbonylfuran (I). In view of convenient elaboration of the ester functionality into variety of substituents, the present route may be useful in the synthesis of several naturally occurring 2,4-disubstituted furanoterpenoids.



The starting compound could be any aldehyde (II) depending upon the requirement of the substituent at 2-position. Reformatsky reaction of ethyl 2-bromomethyl-2-propenoate on the aldehyde (II) in the presence of Zn dust either in anhydrous THF[3] or aq. NH_4Cl-THF mixture[4] invariably gives a mixture of hydroxy ester (III) and lactone (IV) in different proportions. However, it was observed that if the reaction is carried out in saturated NH_4Cl-THF mixture at $60^{o}C$, and the progress of the reaction is monitored on tlc, it was possible to isolate the hydroxy ester (III) exclusively when the reaction is worked up before the formation of lactone (IV) starts. By using this technique, the hydroxy ester (III) was afforded in 76-90% yield during 3 to 5 h of stirring (depends upon nature of aldehyde). PCC oxidation of the alcohol (III) was smoothly carried out to furnish the keto ester (V) in 85-90% yield. Conjugate addition of thiophenol in V gave phenylsulfide (IV) in 83-89% yield after chromatography on silica gel. The sulfide (VI) was treated with N-chlorosuccinimide and the crude chlorinated product thus obtained, was hydrolysed in aq. acetone[5] containing $CuCl_2$-CuO mixture to generate keto aldehyde (VII) which on stirring with H_2SO_4 formed 2-substituted 4-ethoxycarbonylfuran (I) in 60-72% yield.

EXPERIMENTAL (General Procedure):

Ethyl 4-alkyl/aryl-4-oxo-2-methylenobutanoate (V)

A mixture of aldehyde (II, 0.05 mol), ethyl bromoacrylate (9.65 g, 0.05 mol), Zn dust (3.60 g, 0.055 mol) was stirred in sat. NH_4Cl solution (100 ml) containing THF (20 ml) at 60°C. The reaction was monitored by tlc and was worked up when the starting aldehyde had completly reacted, by extraction with ether. The ether layer was washed with brine, dried over anhyd. Na_2SO_4 and the solvent was removed. The crude hydroxy ester (III) was dissovled in CH_2Cl_2 (25 ml) and added to PCC (0.057 mol) in CH_2Cl_2 (120 ml). It was stirred for 5 h and diluted with ether (100 ml). The organic layer was passed through silica gel column using ether as the eluent. The solvent was removed and the residue was distilled *in vacuo* (Va): bp 120-124°C/7mm ; yield 88%. νmax (neat): 1720, 1680, 1665 cm^{-1}. Nmr ($CDCl_3$): δ 1.31 (3H, t, J=7 Hz), 3.88 (2H, s), 4.20 (2H, q, J=7 Hz), 5.81 (1H, m), 6.41 (1H, m), 7.50 (3H, m), 7.98 (2H, m). Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.26; H, 6.79. (Vb): bp 110-112°C/8-9mm; yield 90%. νmax (neat) 3037, 1725-1710, 1622, 1385, 1368 cm^{-1}. Nmr ($CDCl_3$) : δ 0.92 (6H, d, J=6 Hz), 1.25 (3H, t, J=7 Hz), 2.05 (1H, m), 2.25 (2H, d, J=6 Hz), 3.28 (2H, s), 4.08 (2H, q, J=7 Hz), 5.63(1H, m), 6.26(1H, m). Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64, H, 9.15.

Found : C, 66.54, H, 9.18 (Vc) : bp 150-154°C/1mm; yield 88%. νmax (neat) 1723, 1712cm^{-1}. Nmr ($CDCl_3$) : δ 1.31 (6H, m), 2.38 (3H, s), 2.68(2H, d, J=8 Hz), 3.05-3.68 (3H, m), 4.32(2H, q, J=7 Hz), 5.52 (1H, m), 6.38 (1H, m), 7.21 (4H, s). Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.42, H, 8.08. Found : C, 74.58, H, 8.25.

Ethyl 4-alkyl/aryl-4-oxo-2-phenythiomethylbutanoate (VI)

To a solution of $NaOC_2H_5$(2.31 g, 0.034 mol) in C_2H_5OH (85 ml) was added C_6H_5SH (13.94 ml,0.136 mol). After 0.5 h, keto ester (V,0.034 mol) in C_2H_5OH(20 ml) was added and then stirred for 4 h. It was poured in ice water and extracted with CH_2Cl_2 and dried over anhyd. Na_2SO_4. The solvent was removed and the residue was chromatographed on silica gel using n-hexane as eluent. (VIa): yield 83%. νmax (neat) 1745, 1680 cm^{-1}. Nmr ($CDCl_3$): δ 1.18(3H, t, J=7 Hz), 2.48-2.88 (5H, m), 4.18 (2H, q, J=7 Hz), 7.51 (8H, m), 7.98 (2H, m). Anal. Calcd for $C_{19}H_{20}O_3S$: C, 69.49; H, 6.14. Found : C, 69.38; H, 6.09. (VIb): yield 88%. νmax (neat) 3050, 1740, 1715, 1580, 1400, 1380, 742cm^{-1}. Nmr ($CDCl_3$) : δ 0.90 (6H, d, J=6 Hz), 1.21(3H, t, J=7 Hz), 2.05 (1H, m), 2.32(4H, d, J=6 Hz), 2.68 (3H, m), 4.12 (2H, q, J=7 Hz), 7.32(5H, m). Anal. Calcd for $C_{17}H_{24}O_3S$: C, 66.20; H, 7.84. Found : C, 66.18; H, 8.16. (VIc): yield 89%. νmax (neat) 1744, 1712 cm^{-1}. Nmr ($CDCl_3$) : δ 1.33(6H, m), 2.36(3H, s), 2.68-3.20(8H, m), 4.12(2H, q, J=7 Hz), 7.08-7.30 (9H, m). Anal. Calcd for $C_{23}H_{28}O_3S$: C, 71.84; H, 7.34. Found : C, 72.11; H, 7.62.

2-Alkyl/aryl-4-ethoxycarbonylfuran (I)

To a solution of thioether (VI, 0.039 mol) in CCl_4 (300 ml) was added NCS (7.48 g, 0.056 mol) at 0-5°C and the mixture stirred at 30°C for 3.5 h under N_2 atmosphere. It was filtered and the residue after removal of solvent from filtrate was dissolved in acetone (225 ml), H_2O (4.5 ml) followed by addition of $CuCl_2.2H_2O$ (12.0 g, 0.07 mol) and CuO(12.0g, 0.15 mol). It was refluxed under N_2 atmosphere for 1.5 h and then filtered, the solvent from the filterate was removed. The residue was taken in ether , washed with H_2O, dried over anhyd. Na_2SO_4 and the solvent was removed. The residue was chromatographed on silica gel using n-hexane as eluent. To this keto aldelyde (VII) at 0-5°C was added conc. H_2SO_4 (5 ml) dropwise and then the mixture was stirred for 5 min at 50°C. It was extracted with ether and the ether layer was washed with H_2O and dried over anhyd. Na_2SO_4. The solvent was evaporated and the residue was chromatographed on silica gel using n-hexane as the eluent. (Ia) : bp 100-110°C/6-7mm; yield 72%. νmax (neat) 1714 cm^{-1}. Nmr ($CDCl_3$) : δ 1.32 (3H, t,J=7 Hz), 4.32 (2H, q, J=7 Hz), 6.91 (1H, s), 7.38 (3H, m), 7.61 (2H, m), 7.98 (1H, s). Anal. Calcd for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59. Found : C, 77.09; H, 5.52. (Ib) : bp 85-90°C/7-8 mm; yield 65%. νmax (neat) 1730, 1390, 1382 cm^{-1}. Nmr ($CDCl_3$) : δ 0.92 (6H, d, J=6 Hz), 1.28 (3H, t, J=7 Hz), 1.98 (1H, m), 2.44 (2H, d, J=7 Hz), 4.32(2H, q, J=7 Hz), 6.31 (1H, s), 7.84(1H, s). Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found : C, 67.65; H, 8.55. (Ic): yield 58%. νmax (neat) 1725 cm^{-1}. Nmr ($CDCl_3$) : δ 1.28 (6H, m), 2.28 (3H, s), 2.82 (2H, m), 3.12 (1H, m), 4.26(2H, q, J=7 Hz), 6.20 (1H, s), 7.19 (4H, s), 7.83(1H, s). Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found : C, 75.23; H, 7.64.

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