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A Facile Synthesis of 5-Substituted 2-Furylacetates *via* 6-Hydroxy-3-oxo-4-hexenoates

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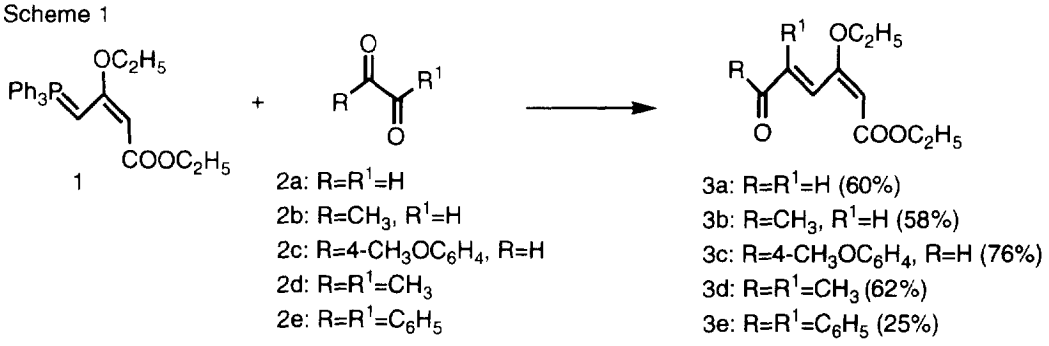
Abstract: 6-Substituted 3-ethoxy-6-hydroxy-2,4-hexadienoates (**4**) which were prepared by reaction of ethyl (4*E*)-3-ethoxy-5-formyl-2,4-pentadienoate (**3a**) with nucleophiles or sodium borohydride reduction of 6-substituted 3-ethoxy-6-oxo-2,4-hexadienoates (**3b-e**) have been converted in very good yields into 5-substituted 2-furylacetates (**5**) by treating with 47%HBr in THF.

The furan ring can be found in many natural products[1] and furan derivatives are of increasing interest in organic synthesis because of the facility of their transformation into a wide range of highly functionalized open chain and cyclic structures.[2] Therefore, numerous furans have been synthesized by ring-forming processes or electrophilic substitution on the aromatic ring.[3] Also, many methods for the construction of furan from acyclic precursors have been published.[4] Among these methods for the preparation of furan derivatives, the acid-catalyzed cyclization of γ-hydroxy-α,β-unsaturated ketone derivatives is one of the useful methods; the limitation to this method, however, has been scarce availability of suitably starting γ-hydroxy-α,β-unsaturated ketones.[5] Recently, we have reported that α-halocarbonyl compounds regioselectively react at the γ-position of (2*E*)-[2-ethoxy-3-(ethoxycarbonyl)-2-propenylidene]triphenylphosphorane (**1**) having two nucleophilic centers to give 1,3-cyclopentadienes.[6] On the other hand, reaction of **1** with glyoxals instead of α-halocarbonyl compounds has been shown to give normal Wittig products, which are easily converted to 3-ethoxy-6-hydroxy-2,4-hexadienoates bearing a masked "γ-hydroxy-α,β-unsaturated ketone" moiety, indicating that the reaction occurs selectively at the α-position.[7] In this paper, we would like to report synthesis of ethyl 6-substituted 3-ethoxy-6-hydroxy-2,4-hexadienoates (**4**) and their conversion into 5-substituted 2-furylacetates (**5**).

Scheme 1

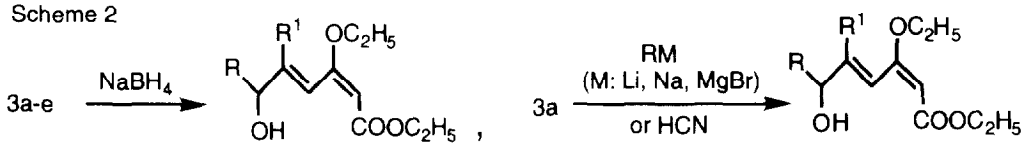


As shown in Scheme 1, reaction of **1**[6] with glyoxals (**2a-2c**) or α-diketones (**2d, 2e**) gave ethyl 6-substituted

3-ethoxy-6-oxo-2,4-hexadienoates (**3**)[8] which are precursors for the preparation of 6-substituted 3-ethoxy-6-hydroxy-2,4-hexadienoates (**4**)[8] in considerably good yields except for **3e**. When **2a** (1.1 mmol) was allowed to react with **1** (1.0 mmol) in THF at room temperature for 3 h , a (10 : 1) mixture of ethyl (4*E*)-3-ethoxy-5-formyl-2,4-pentadienoate (**3a**) and its (4*Z*)-isomer was obtained in 60% yield. Both isomers were separated easily by chromatography on a silica gel column, and conversion of the (4*Z*) derivative to the (4*E*) derivative was achieved in 89% yield by treating the mixture with saturated hydrochloric acid in ether. Thus, similar treatment of the mixture obtained by reaction of **1** with **2b-e** gave **3b-e** as (4*E*)-isomers.

Compounds **4** were prepared by two methods; one involved sodium borohydride reduction of **3a-e**, and the other involved reaction of **3a** with nucleophiles. When **3a-e** were allowed to react with sodium borohydride in methanol at 0 ℃, **4a-e** were obtained in high yields. Reaction of **3a** with nucleophiles such as ethyl- and phenylethynylmagnesium bromides, sodium nitronate, and 2-lithio-1,3-dithiane in THF gave the corresponding **4f-i** in good yields. Interestingly, reaction of **3a** with potassium cyanide in the presence of a catalytic amount of sulfuric acid gave **4j** in 75% yield.

Scheme 2

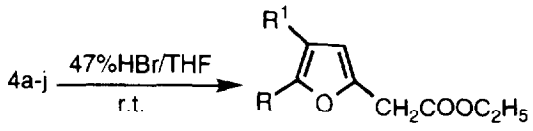


4a: R=R^1=H (100%)
4b: R=CH_3, R^1=H (100%)
4c: R=4-$CH_3OC_6H_4$, R^1=H (96%)
4d: R=R^1=CH_3 (97%)
4e: R=R^1=C_6H_5 (95%)

4f: R=C_2H_5, R^1=H (83%)
4g: R=O_2NCH_2, R^1=H (83%)
4h: R=$C_6H_5C{\equiv}C$, R^1=H (93%)
4i: R=  , R^1=H (62%)
4j: R=CN, R^1=H (75%)

Attempts to cyclize **4** to the furan ring were carried out under acidic conditions. The optimum conditions for the preparation of **5** involved the reaction of **4** in a (1 : 5; v/v) mixture of 47% hydrogen bromide and tetrahydrofuran at room temperature; the reaction presumably proceeds *via* 6-hydroxy-3-oxo-4-hexenoates (**6**). Yields of corresponding 2-furylacetates (**5**)[8] were 90% to quantitative yields (Scheme 3).

Scheme 3

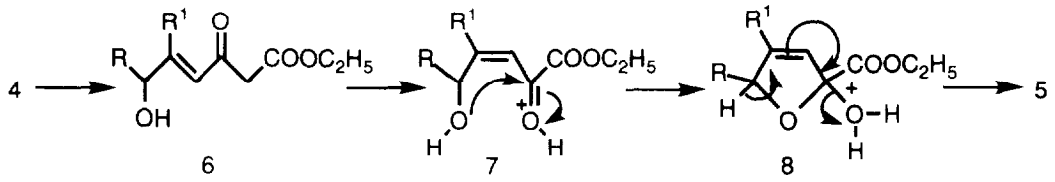


5a: R=R^1=H (100%)
5b: R=CH_3, R^1=H (100%)
5c: R=4-$CH_3OC_6H_4$, R^1=H (93%)
5d: R=R^1=CH_3 (90%)
5e: R=R^1=C_6H_5 (92%)

5f: R=C_2H_5, R^1=H (100%)
5g: R=O_2NCH_2, R^1=H (94%)
5h: R=$C_6H_5C{\equiv}C$, R^1=H (94%)
5i: R=  , R^1=H (92%)
5j: R=CN, R^1=H (96%)

On the formation of the furan ring, the ethoxy group at the 3-position of **4** was first hydrolyzed to give oxo derivative **6** which might have *trans*-butene configuration. The *trans*-butene (**6**) was transformed to *cis*-butene (**7**), which cyclized to **5** *via* dihydrofuran (**8**).

Scheme 4



In conclusion, a facile procedure for the preparation of ethyl 6-substituted 3-ethoxy-6-hydroxy-2,4-hexadienoates and their conversion to 5-substituted 2-furylacetates has been established. The method described here will enable the introduction of various nucleophilic groups at the 5-position of electron-rich heteroaromatic compounds such as furan, thiophene, and pyrrole.

Acknowledgements

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8) All new compounds in this paper gave satisfactory IR, NMR, Mass, and elementary analyses. Selected physical data are as follows. **3a**: Colorless needles, mp 37.0-39.0 ℃ (from hexane). ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.30 (3H, t, *J*=7.3 Hz), 3.94 (2H, q, *J*=7.0 Hz), 4.20 (2H, q, *J*=7.3 Hz), 5.33 (1H, s), 6.70 (1H, dd, *J*=16 and 8.1 Hz), 8.39 (1H, d, *J*=16 Hz), 9.75 (1H, d, *J*=7.9 Hz) ppm. IR (KBr) ν 2830, 1700, 1680, 1580, 1390 cm^{-1}. *Anal.* Calcd for $C_{10}H_{14}O_4$ 1/4H_2O: C, 59.24; H, 7.21%. Found: C, 59.29; H, 6.97%. **4a**: Oil. ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.28 (3H, t, *J*=7.3 Hz), 1.38 (3H, t, *J*=7.0 Hz), 1.40 (1H, br), 3.89 (2H, q, *J*=7.0 Hz), 4.15 (2H, q, *J*=7.3 Hz), 4.35 (1H, dd, *J*=5.0 and 1.5 Hz), 5.06 (1H, s), 6.61 (1H, dt, *J*=16 and 5.1 Hz), 7.54 (1H, dt, *J*=16 and 1.5

Hz) ppm. IR (neat) ν 3550, 1680, 1580 cm^{-1}. *HRMS*. Calcd for $C_{10}H_{16}O_4$: 200.1048. Found: 200.1034. **4g**: Colorless crystals, mp 69.0-70.0 ℃ (from IPE). ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.28 (3H, t, *J*=6.9 Hz), 1.38 (3H, t, *J*=6.9 Hz), 2.80 (1H, d, *J*=4.6 Hz), 3.88 (2H, q, *J*=6.9 Hz), 4.15 (2H, q, *J*=6.9 Hz), 4.50 (2H, m), 5.06 (1H, m), 5.12 (1H, s), 6.39 (1H, dd, *J*= 16 and 5.9 Hz), 7.70 (1H, d, *J*=16 Hz) ppm. IR (KBr) ν 3550, 1690, 1580, 1550 cm^{-1}. *Anal.* Calcd for $C_{11}H_{17}NO_6$: C, 50.79; H, 6.59; N, 5.38%. Found: C, 50.70; H, 6.43; N, 5.15%. **4j**: Oil. ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.29 (3H, t, *J*=7. 3 Hz), 1.40 (3H, t, *J*=6.9 Hz), 2.05 (1H, br), 3.91 (2H, q, *J*=6.9 Hz), 4.16 (2H, q, *J*=7.3 Hz), 5.16 (2H, br), 6.49 (1H, dd, *J*=16 and 5.6 Hz), 7.76 (1H, dd, *J*= 16 and 1.3 Hz) ppm. IR (neat) ν 3500, 2240, 1690, 1580 cm^{-1}. *Anal.* Calcd for $C_{11}H_{15}NO_4$: C, 58.66; H, 6.71; N, 6.22%. Found: C, 58.51; H, 6.72; N, 6.35%. **5d**: Oil. ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.27 (3H, t, *J*=7.3 Hz), 1.90 (3H, s), 2.17 (3H, s), 3.57 (2H, s), 4.18 (2H, q, *J*=7.3Hz), 5.97 (1H, s). IR (neat) ν 3000, 1740, 1030 cm^{-1}. *Anal.* Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74%. Found: C, 65.65; H:7.56%. **5g**: Oil. ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.36 (3H, t, *J*=7.2 Hz), 3.88 (2H, s), 4.31 (2H, q, *J*=7.2 Hz), 5.49 (2H, s), 6.39 (1H, d, *J*=3.0 Hz), 6.60 (1H, d, *J*=3.0 Hz) ppm. IR (neat) ν 2950, 1740, 1560, 1020 cm^{-1}. **5h** Oil.^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.30 (3H, t, *J*=7.3 Hz), 3.68 (2H, s), 4.19 (2H, q, *J*=7.3 Hz), 6.26 (1H, d, *J*= 3.0 Hz), 6.60 (1H, d, *J*=3.0 Hz), 7.43 (5H, m) ppm. IR (neat) ν 2970, 2230, 1740, 1030 cm^{-1}. *Anal.* Calcd for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55%. Found: C, 75.36; H, 5.28%. **5i**: Oil. ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.27 (3H, t, *J*=7.3 Hz), 1.90-2.20 (2H, m), 2.97 (4H, m), 3.67 (2H, s), 4.18 (2H, q, *J*=7.3 Hz), 5.19 (1H, s), 6.20 (1H, d, *J*=3.0 Hz) 6.34 (1H, d, *J*=3.0 Hz) ppm. IR (neat) ν 2950, 1740 cm^{-1}. *Anal.* Calcd for $C_{12}H_{16}O_3S_2$: C, 52.91; H, 5.92; S, 23.54%. Found: C, 52.65; H, 5.75; S, 23.16%. **5j**: Oil. ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.28 (3H, t, *J*=7.3 Hz), 3.73 (2H, s), 4.21 (2H, q, *J*=7.3 Hz), 6.40 (1H, d, *J*=3.5 Hz), 7.05 (1H, d, *J*=3.5 Hz) ppm. IR (neat) ν 3000, 2240, 1740 cm^{-1}. *Anal.* Calcd for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82%. Found: C, 60.30; H, 5.08; N, 7.71%.

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