Scientific paper

Synthesis of Alkyl 2-(3-acetyl-2-oxotetrahydro-3-furanyl)acrylates and alkyl 3-[2-oxodihydro-3(*2H*)furanyliden]propanoates

Sakineh Asghari* and Samaneh Ramezani

Chemistry Department, Mazandaran University, P. O. Box 453, Babolsar, Iran
** Corresponding author: Fax: 0098 11 252 420 02, E-mail: s.asghari@umz.ac.ir*

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Abstract

Reaction of triphenylphosphine with unsymmetrical electrophiles such as alkyl propiolates in the presence of 2-acetylbutyrolactone gives alkyl 2-(3-acetyl-2-oxotetrahydro-3-furanyl)acrylate and α-methylene-γ-butyrolactone derivatives.

Keywords: Alkyl propiolate, 2-acetylbutyrolactone, triphenylphosphine, α-methylene-γ-butyrolactone.

1. Introduction

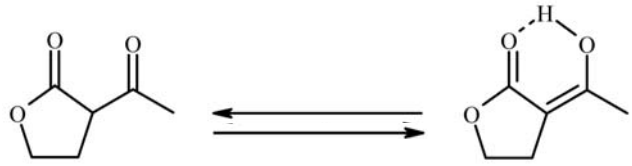
There are many studies on the reaction between trivalent phosphorus nucleophiles and alkyl propiolates in the presence of OH, NH, or CH acids.[1–3] In the some cases stable ylides are produced that can be isolated, but in other cases they can not be isolated and appear to occur as an intermediate on the pathway to an observed product. We have already described the synthesis of the stable phosphorus ylides **1** from the reaction of triphenylphosphine, 2-acetylbutyrolactone and dialkyl acetylenedicarboxylate as a symmetrical electrophile.[4] We performed the reaction of triphenylphosphine with an unsymmetrical electrophile alkyl propiolates and 2-acetylbutyrolactone. The products were not phosphorus ylide **2** but yielded alkyl 2-(3-acetyl-2-oxotetrahydro-3-furanyl)acrylates **5** and the α-methylene-γ-butyrolactone derivatives **7** (Scheme 1).

The α-methylene-γ-butyrolactone moiety is known to be responsible for various biological activities such as antitumour,[5] phytotoxic[6] and antibacterial.[7] Moreover, they are useful as synthetic intermediates.[8]

2. Results and Discussion

The ^{1}H NMR spectrum of 2-acetylbutyrolactone exhibited an equilibrium between keto and enol forms. The enol form showed a broad band at 15.2 ppm for OH group.

On the basis of the well established chemistry of trivalent phosphorus nucleophiles,[9–13] it is reasonable to assume that the compounds **5** and **7** result from the initial



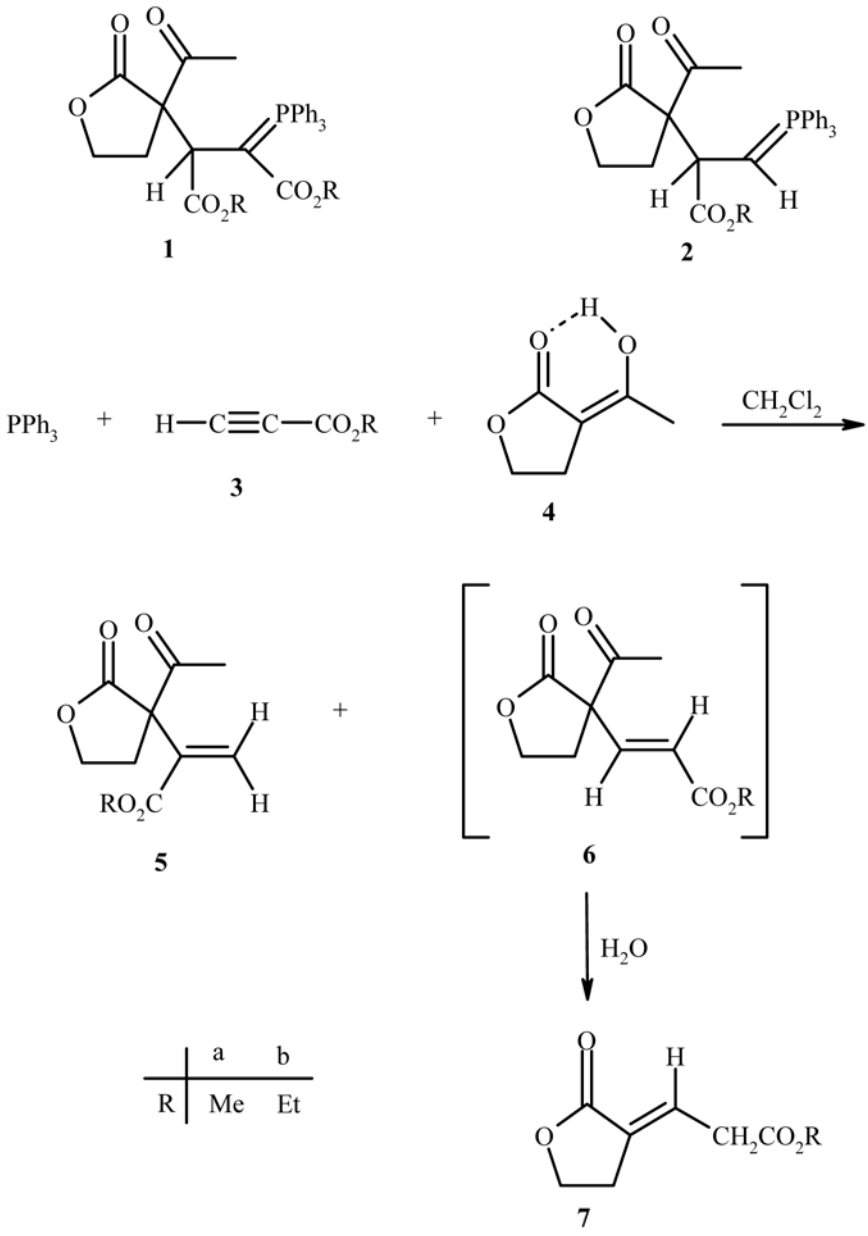
addition of triphenylphosphine to alkyl propiolates and subsequent protonation of the 1:1 adduct forms the vinylphosphonium cation **8**. Then, the positively charged ion **8** can be attacked at two positions by negative carbon atom of the enolate anion of 2-acetylbutyrolactone *via* two routes (Scheme 2).

If the enolate anion attacks to vinylphosphonium cation *via* ***a*** route, the phosphorus ylide **9** will form. Then, it was followed by 1,2-proton transfer and elimination of triphenyl phosphine (as a catalyst) to be recycled which lead to alkyl 2-(3-acetyl-2-oxotetrahydro-3-furanyl)acrylates **5**.

If the enolate anion attacks *via* ***b*** route, the intermediate **10** will form that elimination of triphenylphosphine would lead to the intermediate **6**. This compound was attacked by H_2O that with losing acetyl group as acetic acid, gives the α-methylene-γ- butyrolactone **7**.

The two products **5** and **7** were isolated with high purity and then were assigned by spectral data (i.e. ^{1}H, ^{13}C NMR, IR, Mass and elemental analysis).

The ^{1}H NMR spectrum of **5a** exhibited a singlet at δ 2.22 ppm for acetyl group, two multiplets at about 3.19–3.21 ppm and 4.3–4.41 ppm for the CH_2 and OCH_2 groups of the butyrolactone moiety, respectively and two singlets at about 5.99 and 6.54 ppm for two geminal



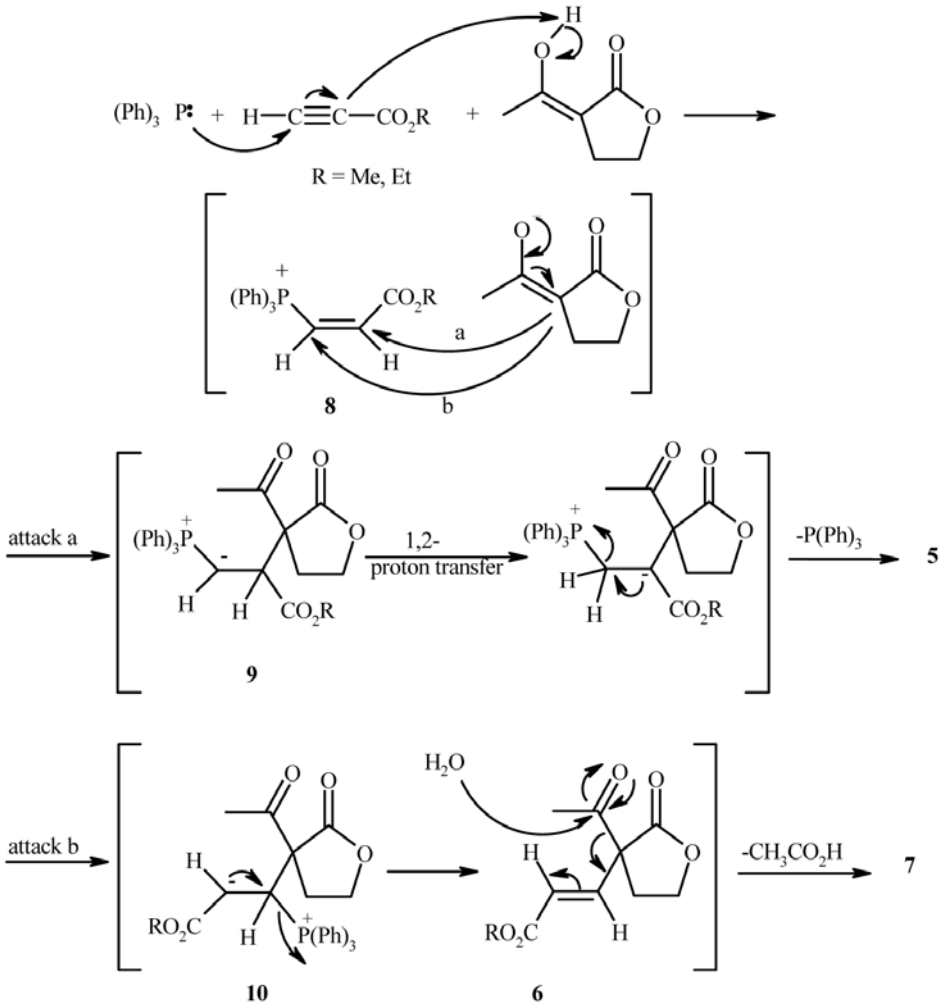
Scheme 1

olefinic protons. The ^{13}C NMR spectra **5a** showed signals for CH_2 (26.14 ppm), CH_3 (31.43 ppm), OCH_3 (52.61 ppm) and olefinic (128.89 and 137.25 ppm) carbons in agreement with the proposed structure, respectively. The structure of **5a**, in agreement with the mass spectrum, displayed the protonated molecular ion peak at *m/z* 213.

Initial fragmentations involve loss or complete loss of the side chains of the heterocyclic ring system. The structural assignment of **5a** on the basis of its NMR and mass spectra was supported by its IR spectra which showed the strong absorption bands at about 1755 and 1730 cm^{-1} for the esteric groups and 1665 cm^{-1} for C=C group, respectively.

The ^{1}H , ^{13}C NMR and IR spectra of **5b** were similar to that of **5a**, except for the ester moieties.

The ^{1}H NMR spectrum of **7a** exhibited a doublet at 3.2 ppm (^3JHH = 7.4 Hz) for two allylic protons and a triplet of triplet at 6.82 ppm (^3JHH = 7.4 Hz and ^4JHH = 2.9 Hz) for an olefinic proton. Also, it exhibited a triplet at 4.36 ppm (^3JHH=7.4 Hz) for OCH_2 group which was splitted with adjacent CH_2 group. Therefore, the stereogenic center should be lost in the reaction condition. The ^{13}C NMR spectrum of **7a** exhibited signals for two methylenes (25.14 and 35.29 ppm), methoxy (51.99 ppm), OCH_2 (65.33 ppm), olefinic (128.67 and 131.10 ppm) carbons in agreement with the proposed structure. The Mass spectrum of **7a** displayed the protonated molecular ion peak at *m/z* 171 and the IR spectrum showed strong absorption bands at 1727, 1675 cm^{-1} and 1663 cm^{-1} for C=O and C=C groups, respectively.



Scheme 2

To confirm the suggested mechanism, we tried to isolate the intermediate **6** as a pure compound. Unfortunately the isolation of intermediate **6** was unsuccessful, because of the hydrolysis of compound **6** during work-up on silicagel column, on which compound **7** was obtained exclusively. The ^{1}H NMR spectrum of this mixture showed two doublets at 6.07 and 6.73 ppm (^{3}JHH=11.8 Hz), assigned to the olefinic protons, and singlet at about 2.21 ppm associated to the protons of the acetyl group of the intermediate **6**. The ^{13}C NMR spectum of this mixture showed two signals at 123.62 and 144.01 ppm, assigned to the olefinic carbons, and signals located at 32.1 and 198.44 ppm denoted to the methyl and ketonic carbonyl carbons of the acetyl group of **6**, respectively. From these results, it can be deduced that compound **6** is an intermediate in the formation of the product **7**.

3. Conclusion

We have found that the reaction between triphenylphosphine and alkyl propiolate in the presence of 2-acetylbutyrolactone conveniently leads to α-methylene-γ-butyrolactone derivatives. Therefore, this is an alternative procedure for the synthesis of biologically active compound which bearing the α-methylene-γ-butyrolactone moiety. The one-pot method makes it as an unique procedure relative to the multi-step approaches. In addition, the present method carries some advantages including mild and neutral reaction conditions without any activation or modification.

4. Experimental

Methyl and ethyl propiolates, triphenylphosphine and 2-acetylbutyrolactone were obtained from Fluka (Buches, Switzerland) and were used without further purification. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. ^{1}H and ^{13}C NMR spectra were measured with a BRUCKER DRX-500 AVANCE spectrometer at 500 and 125.8 MHz, respectively. Mass spectra were recorded on a Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer.

General procedure for synthesis of alkyl 2-(3-acetyl-2-oxotetrahydro-3-furanyl)acrylate and alkyl 3-[2-oxodihydro-3(*2H*)furanyliden]propanoate (exemplified by 5a and 7a).

To a magnetically stirred solution of methyl propiolate (0.1644 ml, 2 mmol) and 2-acetylbutyrolactone (0.215 ml, 2 mmol) in CH_2Cl_2 (10 ml) was added, dropwise, a mixture of triphenylphosphine (0.524 g, 2 mmol) in CH_2Cl_2 (3 ml) at –10 °C over 10 min. The reaction mixture was allowed to stand at room temperature and stirred for a week. The solvent was removed under reduced pressure and the viscous residue was purified by silica gel (Merck silica gel 60, 230–400 mesh) column chromatography using ethyl acetate and hexane (30:70). The products **5a** and **7a** were obtained.

Methyl 2-(3-acetyl-2-oxotetrahydro-3-furanyl) acrylat (5a). Yellow oil, yield 30%; IR (ν_{max}/cm^{-1}): 1755 and 1733 (C=O), 1663 (C=C); ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 2.22 (3H, s, CH_3), 3.19–3.21 (2H, m, CH_2), 3.74 (3H, s, OCH_3), 4.3–4.41 (2H, m, OCH_2), 5.99 and 6.54 (2H, 2s, 2=CH); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ_C 26.14 (CH_2), 31.43 (CH_3), 52.61 (OCH_3), 63.36 (OCH_2), 66.19 (quatrenary carbon of the butyrolactone moiety), 128.89 and 137.52 (olefinic carbons), 165.67 and 172.75 (2C=O, esters), 199.57 (C=O, ketone); MS: *m/z* (%) 213 (M^+ + 1, 42), 181 (M^+– OCH_3, 17), 170 (M^+ + 1 – CH_3CO, 29), 138 [M^+–(CH_3CO + OCH_3), 100], 110 [M^+–(CH_3CO + CO_2Me), 44], 43 (CH_3CO, 18); Anal. Calcd. for $C_{10}H_{12}O_5$ (212.20); C, 56.6; H, 5.70%. Found: C, 56.37; H, 5.68%.

Ethyl 2-(3-acetyl-2-oxotetrahydro-3-furanyl) acrylat (5b). Yellow oil, yield 35%; IR (ν_{max}/cm^{-1}): 1756, 1726 (C=O), 1663 (C=C); ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 1.25 (3H, t, $^3J_{HH}$ = 7.1 Hz, CH_3), 2.25 (3H, s, CH_3CO), 2.13–2.20 and 2.90–3.00 (2H, 2m, CH_2), 4.19–4.25 (4H, m, $2OCH_2$), 5.99 and 6.56 (2H, 2s, 2=CH); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ_C 13.96 (CH_3), 26.19 (CH_2), 31.44 (CH_3CO), 61.87 (OCH_2), 64.11 (OCH_2), 66.18 (quatrenary carbon of the butyrolactone moiety), 128.54 and 137.76 (olefinic carbons), 165.14 and 172.81 (2C=O, esters), 199.64 (C=O, ketone); MS: *m/z* (%) 227 (M^+ + 1, 11), 184 (M^+ + 1–CH_3CO, 29), 181 (M^+ – OEt, 13), 138 [M^+–(CH_3CO + OEt), 100], 110 [M^+–(CH_3CO + CO_2Et), 37], 43 (CH_3CO, 36); Anal. Calcd. for $C_{11}H_{14}O_5$ (226.23): C, 58.40; H, 6.24%. Found: C, 58.17; H, 6.22%.

Methyl 3-[2-oxodihydro-3(2H)furanyliden]propanoate (7a). Yellow oil, yield 55%; IR (ν_{max}/cm^{-1}): 1727 and 1685 (C=O), 1654 (C=C); ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 2.88 (2H, m, CH_2), 3.2 (2H, d, $^3J_{HH}$ = 7.4 Hz, CH_2), 3.69 (3H, s, OCH_3), 4.36 (2H, t, $^3J_{HH}$ = 7.4 Hz, OCH_2), 6.82 (1H, tt, $^3J_{HH}$ = 7.4 Hz and $^4J_{HH}$ = 2.9 Hz, =CH); ^{13}C NMR (125.8 MHz, $CDCl_3$) : δ_C 25.14 (CH_2), 35.29 (CH_2), 51.99 (OCH_3), 65.33 (OCH_2), 128.67 and 131.10 (olefinic carbons), 169.81 and 170.41 (2C=O, esters); MS: *m/z* (%) 171 (M^+ + 1, 13), 139 (M^+ – OCH_3, 21), 138 (M^+ –CH_3OH, 100), 111 (M^+–CO_2Me, 36), 97 (M^+–CH_2CO_2Me, 8), 67 [M^+–(CO_2Me + OCH_2CH_2), 60], 59 (CO_2Me, 57), 53 [M^+–(CH_2CO_2Me + OCH_2CH_2), 85); Anal. Calcd. for $C_8H_{10}O_4$ (170.16): C, 56.47; H, 5.92%. Found: C, 56.24; H, 5.90%.

Ethyl 3-[2-oxodihydro-3(2H)furanyliden]propanoate (7b). Yellow oil, yield 65%; IR (ν_{max}/cm^{-1}): 1735 and 1686 (C=O), 1654 (C=C); ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 1.26 (3H, t, $^3J_{HH}$ = 7.1 Hz, CH_3), 2.88 (2H, m, CH_2), 3.21 (2H, d, $^3J_{HH}$ = 7.4 Hz, CH_2), 4.16 (2H, q, $^3J_{HH}$ = 7.1 Hz, OCH_2), 4.38 (2H, t, $^3J_{HH}$ = 7.4 Hz, OCH_2), 6.87 (1H, tt, $^3J_{HH}$ = 7.4 Hz and $^4J_{HH}$ = 2.9 Hz, =CH); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ_C 14.07 (CH_3), 25.12 (CH_2), 35.45 (CH_2), 61.22 (OCH_2), 65.37 (OCH_2), 128.55 and 131.26 (olefinic carbons), 169.41 and 170.47 (2C=O, esters); MS: *m/z* (%) 185 (M^++1, 100), 139 (M^+–OEt, 29), 138 (M^+ –EtOH, 70), 111 (M^+ –CO_2Et, 24), 97 (M^+ –CH_2CO_2Et, 11), 67 [M^+ –(CO_2Et + OCH_2CH_2), 41], 53 [M^+ –(CH_2CO_2Me + OCH_2CH_2), 34]; Anal. Calcd. for $C_9H_{12}O_4$ (184.19): C, 58.69; H, 6.57%. Found: C, 58.46; H, 6.55%.

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Povzetek

Pri reakciji trifenilfosfina z nesimetričnimi elektrofili, kot so alkil propiolati, v prisotnosti 2-acetilbutirolaktona, dobimo alkilne derivate 2-(3-acetil-2-oksotetrahidro-3-furanil)akrilata in a-metilen-g-butirolaktona.