Taylor & Francis
Taylor & Francis Group

Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: http://www.tandfonline.com/loi/lsyc20

A simple route to synthesize (E)-3 propyl-4-oxo-2-butenoic acid esters through the Z isomer

Cristiano Bolchi, Gabriella Roda & Marco Pallavicini

To cite this article: Cristiano Bolchi, Gabriella Roda & Marco Pallavicini (2017): A simple route to synthesize (E)-3 propyl-4-oxo-2-butenoic acid esters through the Z isomer, Synthetic Communications, DOI: 10.1080/00397911.2017.1390587

To link to this article: http://dx.doi.org/10.1080/00397911.2017.1390587

A simple route to synthesize (*E*)-3 propyl-4-oxo-2-butenoic acid esters through the *Z* isomer

Cristiano Bolchi*

Dipartimento di Scienze Farmaceutiche, Università degli Studi di Milano, Milano, Italia

Gabriella Roda

Dipartimento di Scienze Farmaceutiche, Università degli Studi di Milano, Milano, Italia

Marco Pallavicini

Dipartimento di Scienze Farmaceutiche, Università degli Studi di Milano, Milano, Italia

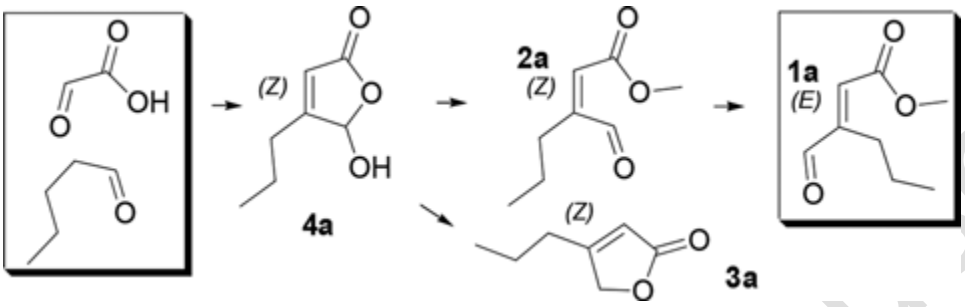
Address correspondence to Cristiano Bolchi. E-mail: cristiano.bolchi@unimi.i

ABSTRACT

Esters of 3-alkyl-2-oxo-2-butenoic acid, which are very important synthons, are not equally accessible in both *E* and *Z* configuration. The *Z* isomers can be easily obtained from 3-alkyl-4-hydroxybutenolides, in turn prepared by aminoalkylation of aliphatic aldehydes with glyoxylic acid. The *E* isomers, on the contrary, result from laborious procedures: the condensation of aldehydes with glyoxylic acid, followed by separation from γ-hydroxybutenolide by-product and esterification, or of aldehydes enamines with glyoxylic esters, followed by *Z* ester by-product conversion into γ-aminobutenolide and purification. Here, we describe a straightforward route to the title compounds, applied to methyl (*E*)-3-propyl-4-oxo-2-butenoate, avoiding any problematic

by-product or isomer chromatographic separation: pentanal and glyoxylic acid are condensed to 3-propyl-4-hydroxybutenolide, which is converted to methyl (*Z*)-3-propyl-4-oxo-2-butenoate and then isomerized to the *E* ester under acidic conditions.

GRAPHICAL ABSTRACT



KEYWORDS: 3-alkyl-4-hydroxybutenolide, 3-alkyl-4-oxobutenoic acid ester, 3-alkylbutenolide, *e* configuration, isomerization, *z* configuration

Introduction

Esters of (*E*)- and (*Z*)-3-alkyl-4-oxo-2-butenoic acid (**1** and **2**) and 3-alkyl substituted butenolides (**3**) are very useful intermediates in organic synthesis, in particular as dienophiles and α,β-unsaturated substrates of conjugate reduction or addition reactions giving access to either racemic or enantiomerically enriched saturated derivatives (**Figure 1**).[1–6] α,β-Unsaturated-γ-lactones, chiral γ-lactones possessing a β-stereocenter and γ-hydroxybutenolids are constituents of a wide number of naturally occurring and/or biologically active compounds.[3,7,8]

A vast literature has focused on the preparation of **3** and great attention has been devoted to a condensation/reduction strategy to make it ready available.[3,9–11] Aldol condensation of glyoxylic acid with aliphatic and cyclic ketones provides α-hydroxy-γ-oxo carboxylic acids and γ-oxo-α,β-unsaturated carboxylic acids,[12] but it is virtually unsuccessful with aliphatic aldehydes

mainly because of self-aldolization. On the other hand, G.G. Wermuth has reported that Mannich-type aminoalkylation of enolizable aldehydes with equimolar glyoxylic acid and morpholine hydrochloride, namely under acidic conditions, directly affords γ-hydroxybutenolides **4** in high yields suggesting a mechanism involving the spontaneous elimination of morpholine from the corresponding α-morpholino-γ-hydroxybutanolides (**Figure 2**).[13] As more recently reported, piperidine hydrochloride can be used in place of morpholine hydrochloride.[3,13]

γ-Hydroxybutenolides **4** are easily converted into **3** by reduction with sodium borohydride[3,14,15] or into *Z* methyl or ethyl esters **2** by treatment with a base and methyl iodide or triethyloxonium tetrafluoborate respectively.[6,16]

More problematic is to obtain *E* esters **1**. Indeed, aldol condensation of glyoxylic acid with an aliphatic aldehyde in basic medium gives the corresponding *E* α,β-unsaturated γ-oxo carboxylic acid, but besides the undesired γ-hydroxy butenolide **4** and, as previously underlined, large amount of self-condensed aldehyde.[17] Therefore, although the *E* acid can be isolated from the other products and easy converted into ester **1**, the procedure is inefficient. However, according to A. Guingant, formation of **4** and self-aldolization can be avoided by condensation of glyoxylic esters with aliphatic aldehydes morpholinenamine, followed by acid treatment.[17] The resulting mixtures of *E* and *Z* esters, with **1** as a major component and **2** as a minor component, are not resolvable by chromatography and neither by distillation, as elsewhere reported.[18] Nevertheless, if neutral, instead of acidic, conditions are adopted for the final hydrolysis, the *Z* isomers are quantitatively converted into γ-morpholinobutenolides and the unchanged *E* isomers can be recovered from the (*E*)-**1**/morpholinobutenolide mixture by chromatography.

Results and Discussion

It is evident that the reported routes to esters **1** or to their acid precursors are penalised by the side formation of **4** or of **2**, which has to be converted into butenolides to allow the separation from **1**. Therefore, we planned an alternative strategy to obtain **1**, relying on the isomerization of readily accessible **2** to **1** rather than on its discharge as an undesired by-product through conversion into butenolides. Such *Z* to *E* isomerization is not described for the 4-oxo-2-butenoic acid esters having an alkyl substituent at C(3). Instead, it is reported for the unsubstituted 4-oxo-2-butenoic acid ester: maleinaldehydic acid methyl ester is quickly and quantitatively converted to fumaraldehydic acid methyl ester by light exposure in the presence of traces of iodine or by acidic catalysis.[19] We thus decided to verify whether **2**, in particular the methyl ester of (*Z*)-3-propyl-4-oxo-2-butenoic acid **2a**, can be quantitatively isomerized to **1a** (Alk = *n*-propyl). If so, a unique straightforward way would be followed to prepare all the three compounds, butenolide and *E* and *Z* γ-oxo-α,β-unsaturated esters. From glyoxylic acid and pentanal we would be able to prepare, in the order, **4a**, **3a**, **2a** and, above all, **1a** (Scheme 1).

The condensation of glyoxylic acid with valeraldehyde was accomplished by treatment with little more than stoichiometric piperidine hydrochloride in boiling dioxane/water. At variance with literature reports, simple extraction procedures allowed pure γ-hydroxybutenolide **4a** to be recovered in 55% yield without chromatographic separation. In fact, by-products were removed by washing the reaction mixture, previously diluted with 2 M aqueous HCl, with diisopropyl ether and **4a** was successively extracted with dichloromethane. The subsequent reduction of **4a** with sodium borohydride in methanol afforded **3a** in quantitative yield, while **2a** was obtained from **4a** by treatment with NaH and CH_3I in HMPA in 82% yield after chromatographic purification. The same reaction, accomplished with NaH and CH_3I in DMSO, quantitatively afforded a 7/5 mixture of **2a** and **1a**, which was directly converted into pure **1a** by stirring in dichloromethane at room

temperature for 1 hour in the presence of few millilitres of 4 M HCl dioxane solution. No conversion into **1a** was observed by light exposure in the presence of iodine. The isomerization of **2a** to **1a** could be easy monitored by TLC, where **2a** gives, under 1/1 cyclohexane/DCM elution, a slow running spot, completely separated from the faster running spot of **1a**. Furthermore, the two isomers could be clearly distinguished and relatively quantified, when in mixture, by H NMR spectroscopy on the basis of the aldehyde proton resonance. Consistently with what is reported in the literature for the *Z* and *E* isomers of the analogous 3-methyl, 3-ethyl and 3-isopropyl substituted 4-oxo-2-butenoates,[17,20] the *Z* aldehyde proton resonance appears, as expected, downfield relative to the resonance frequency of the *E* isomer. In particular, the chemical shifts of the aldehyde proton singlet of **2a** (10.56 δ) and of **1a** (9.50 δ) are the same reported, respectively, for the *Z* and *E* isomer of the 3-isopropyl substituted analogue.[17]

The acid catalysed isomerization in dichloromethane successfully completed the synthetic sequence opening a direct and simple route to esters **2**, otherwise poorly available and through laborious procedures. Furthermore, the esterification in DMSO allowed us not only to avoid the use of HMPA but also to accomplish the *Z* to *E* isomerization on a mixture containing a considerable percentage of *E* isomer in advance. In case of large-scale preparation of **2** from **4**, HMPA must be obviously replaced by another solvent, which will be selected depending on the 3-alkyl substituent and the chosen esterifying R group. Conversion of γ-hydroxybutenolides into *Z* esters under conditions different for reagents and solvent is fairly exemplified in literature.[6,8,21–24] Trimethyloxonium tetrafluoborate and NaH in THF under anhydrous conditions are not the only alternative; iodomethane and bases, such as DIPEA or potassium carbonate, in dipolar aprotic solvents, such as DMSO, DMF or aceton, are widely used. Furthermore, for the other reactions, undesirable solvents, such as dioxane, DCM and di-isopropyl ether, whose substitution is advisable

or requested, could be replaced by 'green' ethers (MeTHF, TAME, CPME) according to the continuously updated suggestions of the current solvent selection guides.

Conclusions

In summary, we have developed a straightforward route from ready available glyoxylic acid and pentanal to both the *E* and *Z* isomers of 3-propyl-4-oxobutenoic acid methyl ester, which are very useful synthetic intermediates. In order to avoid laborious and inefficient isomers separations, we exploited the much easier accessibility of the *Z* isomer of this kind of esters from the corresponding 4-hydroxybutenolides and tried subsequent isomerization to *E* form. According to such an approach, we first prepared methyl (*Z*)-3-propyl-4-oxobutenoate and then quantitatively isomerized it to *E* butenoate. By this simple way, we succeeded in making the *E* isomer, otherwise arduous to synthesize, as available as the *Z* isomer.

Experimental

3-Propyl-4-hydroxybutenolide (4a)

Glyoxilic acid monohydrate (4.55 g, 49.42 mmol) and piperidine hydrochloride (6.30 g, 51.80 mmol) were added to a solution of pentanal (5 mL, 47.02 mmol) in 7/1 dioxane/water (25 mL) under nitrogen. The mixture was heated at reflux for 18 h and, after cooling to room temperature, diluted with 2 M HCl (100 mL) and extracted with diisopropyl ether (3×30 mL). The first extract was discharged, while the other two were combined and extracted with 2 M HCl (3×30 mL). These three acidic extracts were combined with the reaction mixture, which had been previously diluted 2 M HCl and washed with diisopropyl ether, and the whole aqueous layer was extracted with DCM (3×80 mL). The DCM were concentrated to give **4a** (3.68 g, 55%) as an oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.00 (s, 1H), 5.84 (t, *J* = 1.8 Hz, 1H), 4.65 (bs, 1H, exchange with D_2O), 2.25-2.52 (m, 2H), 1.52-1.77 (m, 2H), 1.00 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 170.3, 117.2, 99.4, 29.6, 19.9, 13.7. Anal. Calcd for $C_7H_{10}O_3$: C, 59.14; H, 7.09. Found: C, 58.98; H, 7.13.

3-Propylbutenolide (3a)

Sodium borohydride (2.0 g, 52.86 mmol) was portionwise added to a solution of **4a** (3.62 g, 25.47 mmol) in methanol (50 mL). After stirring at room temperature for 1 h, the reaction mixture was concentrated and 2 M HCl (100 mL) was added. The aqueous phase was extracted with DCM (40 mL). The organic extract was dried over Na_2SO_4 and concentrated to give **3a** in quantitative yield as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.83 (s, 1H), 4.73 (s, 2H), 2.38 (t, *J* = 7.6 Hz, 2H), 1.55-1.70 (m, 2H), 1.00 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 170.3, 117.2, 99.4, 29.6, 19.9, 13.7. Anal. Calcd for $C_7H_{10}O_2$: C, 66.65; H, 7.99. Found: C, 66.48; H, 8.03.

Methyl (Z)-3-propyl-4-oxo-2-butenoate (2a)

A solution of **4a** (10 g, 70.35 mmol) in HMPA (40 mL) was added dropwise to a suspension of sodium hydride (1.69 g, 70.35 mmol) in HMPA (40 mL) at 0 °C. After stirring at 0 °C for 1 h, iodomethane (6.6 mL, 105.53 mmol) was added dropwise. The mixture was stirred at room temperature for 15 min and then cooled to 0 °C again. Water (100 mL) was slowly added and the resulting solution was extracted with diethyl ether (3×80 mL). The organic extracts were dried over Na_2SO_4 and concentrated. The resultant residue was purified by chromatography on silica gel (petroleum ether/ethyl acetate 95/5) to give **2a** (8.96 g, 82%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.56 (s, 1H), 6.47 (t, *J* = 1.2 Hz, 1H), 3.80 (s, 3H), 2.30 (td, *J* = 7.6, 1.2 Hz, 2H), 1.47 (sextet,

J = 7.6 Hz, 2H), 0.93 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.0, 165.3, 154.0, 129.2, 52.1, 32.4, 21.3, 13.7. Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.40; H, 7.78. The above procedure was repeated by replacing HMPA with DMSO: **4a** (10 g, 70.35 mmol) was converted into a 7/5 mixture (10.64 g, 97%) of **2a** and **1a**, which was directly used in the subsequent isomerization step without chromatographic purification.

Methyl (E)-3-propyl-4-oxo-2-butenoate (1a)

A 4 M solution of HCl in dioxane (5 mL) was added to a solution of a 7/5 mixture of **2a**/**1a** (10.64 g, 68.12 mmol) in DCM (80 mL). After stirring for 70 min, DCM (70 mL) was added and two washings were performed with saturated aqueous Na_2CO_3 solution (2×50 mL). The organic phase was dried over Na_2SO_4 and concentrated. The residue was distilled in a Kugelrohr apparatus (60 °C, 0.3 mbar) to give **1a** (7.86 g, 74%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.50 (s, 1H), 6.46 (s, 1H), 3.81 (s, 3H), 2.66 (t, *J* = 7.6 Hz, 2H), 1.44 (sextet, *J* = 7.6 Hz, 2H), 0.92 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.4, 165.7, 154.8, 134.9, 51.9, 26.6, 22.1, 14.1. Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.39; H, 7.77.

Supporting Information: ^{1}H and ^{13}C NMR spectra. This material can be found via the "Supplementary Content,, section of this article's webpage.

References

[1] Tayaka, Y.; Senda, T.; Kurushima, H.; Ogasawara, M.; Hayashi, T. *Tetrahedron: Asymmetry* **1999**, 10, 4047–4056.
[2] Asami, M.; Mukaiyama, T. *Chem. Lett.* **1979**, 569–572.
[3] Hughes, G.; Kimura, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11253–11258.
[4] Zhou, J. H.; Cai, S. H.; Xu, Y. H.; Loh, T. P. *Org. Lett.* **2016**, *18*, 2355–2358.
[5] Corey, E. J.; Desai, M. C.; Engler, T. A. *J. Am. Chem. Soc.* **1985**, *107*, 4339–4341.
[6] (a) Solladié, G.; Girardin, A. *J. Org. Chem.* **1989**, *54*, 2620–2628; (b) Solladié, G.; Berl, V. *Synlett* **1991**, 795–796.

[7] Egi, M.; Ota, Y.; Nishimura, Y.; Shimizu, K.; Azechi, K.; Akai, S. *Org. Lett.* **2013**, I15, 4150–4153.
[8] Miura, H.; Tacheuchi, K.; Shishido, T. *Angew. Chem. Int. Ed.* **2016**, *55*, 278–282.
[9] Inhoffen, H. H.; Kreiser, W.; Nazir, M. *Liebigs Ann. Chem.* **1972**, *755*, 1–11.
[10] Kreiser, W.; Nazir, M. *Liebigs Ann. Chem.* **1972**, *755*, 12–16.
[11] Sum, F. W.; Weiler, L. *J. Org. Chem.* **1979**, *44*, 1012–1013.
[12] Bielefeld, M. A.; Kurath, M. *J. Org. Chem.* **1969**, *34*, 237–240.
[13] Bourguignon, J. J.; Wermuth, C. G. *J. Org. Chem.* **1981**, *46*, 4889–4894.
[14] Citron, C. A.; Junker, C.; Schulz, B.; Dickshat, J. S. *Angew. Chem. Int. Ed.* **2014**, *53*, 4346–4349.
[15] Bourguignon, J. J.; Schoenfelder, A.; Schmitt, M.; Wermuth, C. G.; Hechler, V.; Charlier, B.; Maitre, M. *J. Med. Chem.* **1988**, *31*, 893–897.
[16] Raber, D. J.; Gariano, P. Jr.; Brod, A. O.; Gariano, A.; Guida, W. C.; Guida, A. R.; Herbst, M. D. *J. Org. Chem.* **1979**, *44*, 1149–1154.
[17] Laugraud, S.; Guingant, A.; D'Angelo, J. *J. Org. Chem.* **1987**, *52*, 4788–4790.
[18] Merger, F.; Juergen, F. EP 421271 A2, 1991.
[19] Schroeter, S. H.; Appel, R.; Brammer, R.; Schencl, G. O. *Liebigs Ann. Chem.* **1966**, *697*, 42–61.
[20] Curley, R. W. Jr.; Ticoras, C. J. *J. Org. Chem.* **1986**, *51*, 256–258.
[21] Kakushima, M.; Das, J.; Reid, G. R.; White, P. S.; Valenta, Z. *Can. J. Chem.* **1979**, *57*, 3356–3358.
[22] Das, J.; Dickinson, R. A.; Kakushima, M.; Kingston, G. M.; Reid, G. R.; Sato, Y.; Valenta, Z. *Can. J. Chem.* **1984**, *62*, 1103–1111.
[23] Tanaka, K.; Kamatani, M.; Mori, H.; Fujii, S.; Ikeda, K.; Hisada, M.; Itagaki, Y.; Katsumura, S. *Tetrahedron* **1999**, *55*, 1657–1686.
[24] Kajikawa, T.; Aoki, K.; Iwashita, T.; Niedzwiedzki, D. M.; Frank, H. A.; Katsumura, S. *Org. Biomol. Chem.* **2010**, *8*, 2513–2516.

Figure 1. 3-Alkyl substituted 4-oxobutenoic acid esters and butenolides.

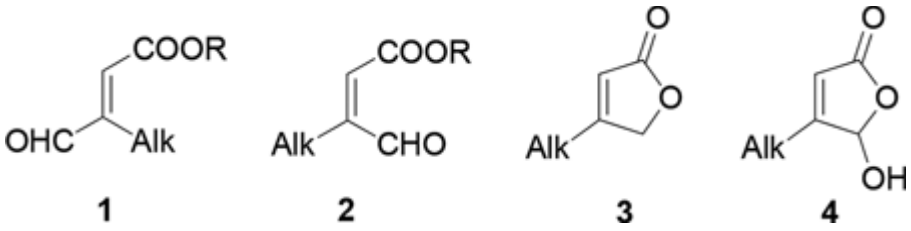
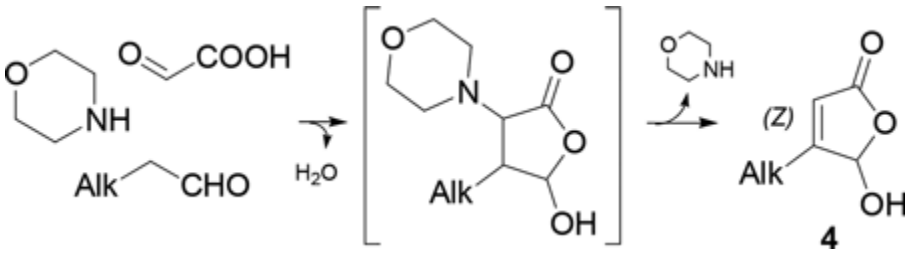


Figure 2. Reaction pathway proposed for the glyoxylic acid-aliphatic aldehyde condensation to **4** in the presence of morpholine under acidic conditions.



Scheme 1. Reaction conditions: (a) piperidine hydrochloride, dioxane/water, reflux, 18 h; (b) NaBH4, methanol, rt, 1 h; (c) NaH, CH3I, HMPA, rt, 15 min; (d) HCl in dioxane/DCM, rt, 70 min (from **2a** prepared in DMSO rather than in HMPA).