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One-pot formation of 2,4-di- or 2,4,6-tri-olefinic monocarboxylic acids by straight chain C4-extension

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Abstract

We report a one-pot formation of 2,4-diolefinic or 2,4,6-triolefinic monocarboxylic acids, R-$(CH{=}CH)_{2or3}$-COOH, by decarboxylative condensation of an optionally α,β-unsaturated aldehyde with glutaconic acid, HOOC-CH_2-CH=CH-COOH as straight chain C4-extender. The reaction is broadly applicable to saturated and unsaturated aldehydes and opens up a simple gateway to valuable organic products and reactive intermediates.

Keyword: Organic chemistry

1. Introduction

We are here concerned with the direct formation of α,β-unsaturated carboxylic acids by carbon chain extension of aldehydes. Previous reactions of this kind are limited to C2-extension: Peterson olefination [1], Wittig-Horner type reaction [2, 3], extension by (trimethylsilyl)ketene [4] or its acetal [5] and Knoevenagel extension with malonic acid [6, 7]. We now report a reaction which extends the carbon skeleton by a straight chain unit of four carbon atoms, thereby simultaneously introducing two conjugated olefinic bonds and a free carboxylic acid group. Specifically, we performed a one-pot decarboxylative condensation of

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aldehydes **2a-f** with trans-glutaconic acid **1** in the presence of a nitrogen base. Our reaction is related to the Knoevenagel reaction [6], encouraged by the principle of vinylogy [8, 9] (Fig. 1).

2. Results and discussion

The reaction is favored by tetrahydrofuran (THF) as solvent, by an elevated reaction temperature of preferably 65 to 70 °C, and by 4-dimethylamino-pyridine (DMAP) as a catalytic nitrogen base. The reaction also proceeds with pyridine alone, or with pyridine in combination with pyrrolidine, piperidine or diethylamine, albeit with reduced yields.

The two conjugated double bonds that are introduced by the C4-extender have mainly *E*-configuration as shown by NMR analysis. If an α,β-unsaturated aldehyde is used, the product, a 2,4,6-triolefinic monocarboxylic acid, acquires an additional conjugated double bond with retention of its stereo configuration. Educt aldehydes **2a-f** and products **3a-f** are shown in Fig. 2. Reaction yields for all products determined after ethyl acetate extraction are about 20%. GC/MS yields and stereo selectivities are listed in Table 1. For example, 2*E*,4*E*,6-heptatrienoic acid **3a** was obtained with a stereo selectivity of 93%. The reaction appears to proceed by condensation, followed by decarboxylation as evidenced by non-decarboxylated byproducts. All mass data and NMR spectra (^{1}H, ^{13}C, COSY, HSQC, HMBC) including signal assignments for products **3a-f** are given in the Supplemental Information section.

Our reaction conditions are related to those previously employed in the Knoevenagel reaction with malonic acid [7]. Compared to the conventional C2-extension, the here reported C4-extension reshuffles the synthetic burden between aldehyde and extender. Because the extender adds four carbon atoms, the aldehyde can be correspondingly shortened. Moreover, because the extender introduces an extra double bond into the final molecule, the aldehyde structure is correspondingly unburdened. A simplified aldehyde structure means a correspondingly simplified aldehyde synthesis. In this manner, the overall synthesis is characterized by a favorable reaction step economy.

The now presented reaction yields unsaturated free carboxylic acids, without a saponification step, which would be necessary in a reaction with glutaconic diester

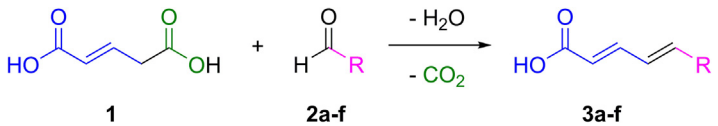

Fig. 1. Formation of α,β-unsaturated carboxylic acids **3a-f** by decarboxylative condensation of aldehydes **2a-f** with glutaconic acid **1**.

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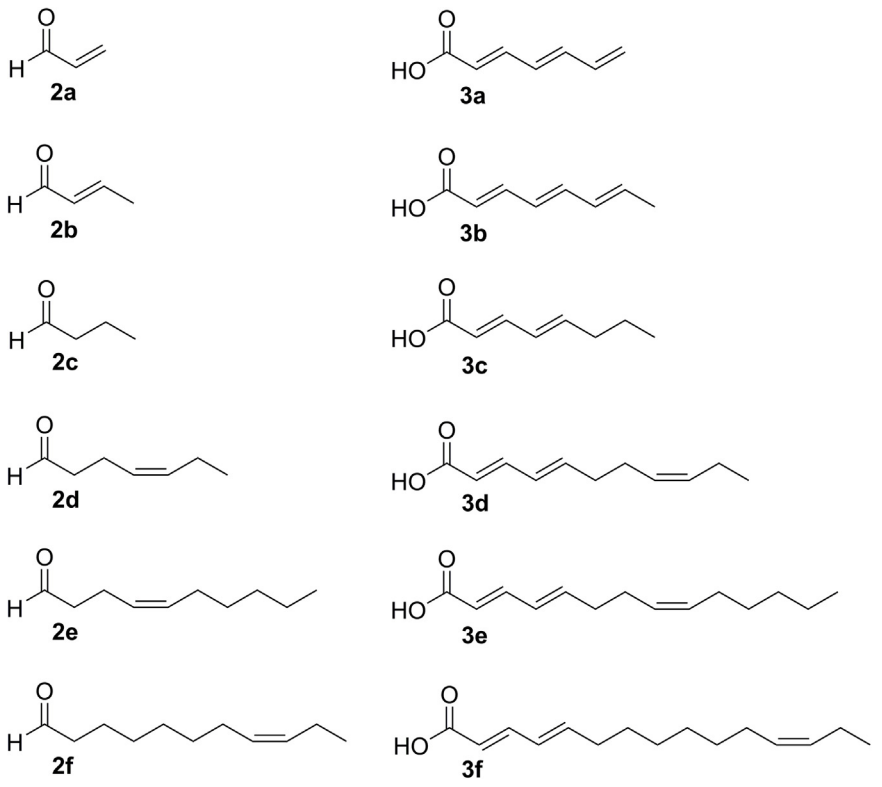

Fig. 2. Educt aldehydes **2a-f** and resulting unsaturated monocarboxylic acid **3a-f** by C4 extension.

[10, 11, 12]. Low yields are mainly caused by fast decarboxylation of glutaconic acid to butenoic acid at enhanced temperatures in the presence of DMAP. Aldol condensation of the aldehyde is also observed. As shown earlier for similar

Table 1. Conversion of aldehydes **2a-2f** to 2,4-diolefinic and 2,4,6-triolefinic monocarboxylic acids **3a-3f** by condensation with glutaconic acid and DMAP as catalyst in THF.

Aldehyde	Product	Stereo selectivity[#]	GC-MS Yield [%][*] of the *2E,4E* isomer
2a	**3a**	93:7	18.4
2b	**3b**	58:42	10.4
2c	**3c**	72:28	14.7
2d	**3d**	55:45	15.4
2e	**3e**	60:40	9.3
2f	**3f**	66:34	10.4

[*]Yields of 2*E*,4*E*-isomers, quantified by GC-MS with the following standards: 3-heptenoic acid for **3a**; 3-octenoic acid for **3b**,**c**; 3-dodecanoic acid for **3d**; 3-pentadecanoic acid for **3e** and **f**.

[#] Stereo selectivity of the 2*E*,4*E* products.

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reactions [7], the yields might be improved by varying the reaction conditions. However, this was not the aim of our proof-of-principle study.

Pending further optimization in terms of productivity and selectivity, the here reported reaction opens an efficient gateway to classes of valuable polyunsaturated monocarboxylic acids and their derivatives with potential utility in commercial products. These would include a host of natural products with a wide range of biological effects as well as their chemically modified analogs. We mention here specifically 2,4,6-octatrienoic acid (**3b** in Table 1) that may be used as tanning promoter and antioxidant in skin care products [13]. Moreover, a large class of natural polyunsaturated monocarboxylic acid amides [14, 15, 16, 17, 18] of the formula R-CH=CH-CH=CH-CO-NH-isobutyl, wherein R signifies a saturated or an unsaturated aliphatic group may now come into facile synthesis. They exhibit a wide range of biological properties and a corresponding range of possible utilities, notably as modulators or enhancers for the immune system [14, 15, 16] or as insecticides [17, 18].

3. Material and methods

All chemicals were purchased from Sigma Aldrich GmbH (Steinheim, Germany) in the highest purity available. All organic solvents were purchased from VWR International GmbH (Darmstadt, Germany) in the highest purity available. Commercial aldehydes were used without purification.

In a typical experiment, 65.0 mg of trans-glutaconic acid (0.5 mmol, 1 eq.) was dissolved in a mixture of 244 mg of 4-dimethylaminopyridine (DMAP) (2.0 mmol, 4 eq.) and 1.60 ml of tetrahydrofuran (THF) and stirred at 40 °C for 15 min. The solution was cooled down to room temperature and the aldehyde (3 eq.) was added. The reaction mixture was warmed up to 65–70 °C and stirred for 12 h. The reaction was finished by the addition of 1 ml of ethylacetate and aqueous H_2SO_4 (until slightly acidic pH) at room temperature. After phase separation the aqueous phase was extracted two more times using 1 ml of ethylacetate. The organic phases were combined and dried over Na_2SO_4. For analysis by GC-MS, 25 µl of the organic phase was derivatized with 75 µl *N-tert*-butyldimethylsilyl-*N*-methyltrifluoroacetamide for 30 min at 70 °C.

GC-MS analysis was performed with the Shimadzu instrument GC-17A and QP-5000 (Duisburg, Germany) using a 30 m x 0.25 mm x 0.25 µm fused silica capillary column (Equity ^{TM}-5, Supelco, Bellefonte, PA, USA) and AOC-20i auto injector. Temperature program and settings: 0–6 min at 60 °C, 6–25 min at 60–280 °C, 10 °C/min; 25–28 min at 280 °C; injector temperature: 260 °C; detector temperature: 260 °C; column flow rate: 1 mL/min; scan interval: 0.5 sec; detector voltage 1.5 kV. Quantification was performed by external calibration using known concentrations of commercially available reference compounds (for details see footnotes of Table 1).

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The product structures were also confirmed by one and two-dimensional NMR-spectroscopy using a Bruker AV-HD 500 instrument (Rheinstetten, Germany).

Declarations

Author contribution statement

Jessica Sobotta: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Maximilian Schmalhofer, Thomas M. Steiner: Performed the experiments.

Wolfgang Eisenreich: Contributed reagents, materials, analysis tools or data; Wrote the paper.

Günter Wächtershäuser: Conceived and designed the experiments; Wrote the paper.

Claudia Huber: Conceived and designed the experiments;Analyzed and interpreted the data; Wrote the paper.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

Supplementary content related to this article has been published online at http://dx.doi.org/10.1016/j.heliyon.2017.e00368

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References

[1] P.A. Grieco, C.-L.J. Wang, S.D. Burke, Trimethylsilylacetic Acid Dianion: Application to Organic Synthesis, J. Chem. Soc. Chem. Commun. (1975) 537.

[2] G.A. Koppel, M.D. Kinnick, Carboxyvinylation; A one-step synthesis of α,β-unsaturated acids, Tetrahedron Lett. (1974) 711.

[3] H.J. Bestmann, R. Dostalek, R. Zimmermann, Phosphanalkenyle, 52. Umsetzung von [1-(Trimethylsilyl)alkyliden]triphenylphosphoranen mit Kohlendioxid und Folgereaktionen, Chem. Ber. 125 (1992) 2081.

[4] A.B. Concepcion, K. Maruoka, H. Yamamoto, Organoaluminum-promoted cycloaddition of trialkylsilylketene with aldehydes: A new, stereoselective approach to *cis*-2-oxetanones and 2(Z)-alkenoic acids, Tetrahedron 51 (1995) 4011.

[5] M. Bellassoued, M. Gaudemar, Stereoselective synthesis of (E)-α,β-unsaturated acids from C,O, O-tri(trimethylsilyl) ketene acetal and aldehydes, Tetrahedron Lett. 29 (1988) 4551.

[6] G. Jones, The Knoevenagel Condensation, Org. React. 15 (1967) 204.

[7] S.T. Kemme, T. Šmejkal, B. Breit, *Catal*. Practical Synthesis of (E)-α,β-Unsaturated Carboxylic Acids Using a One-Pot Hydroformylation/Decarboxylative Knoevenagel Reaction Sequence, Adv. Synth. 350 (2008) 989.

[8] R.C. Fuson, The Principle of Vinylogy, Chem. Rev. 16 (1935).

[9] S.J. Krishnamurthy, The Principle of Vinylogy, Chem. Edu. 59 (1982) 543.

[10] F. Henrich, Zur Kenntnis des Glutaconsäureesters, Chem. Ber. 35 (1902) 1663.

[11] P.R. Nandaluru, G.J. Bodwell, Multicomponent Synthesis of 6*H*-Dibenzo[*b, d*]pyran-6-ones and a Total Synthesis of Cannabinol, Org. Lett. 14 (2012) 310.

[12] B. Pezzati, M.F. Chellat, J.J. Murphy, C. Besnard, G. Reginato, J.C. Stephens, A. Alexakis, Organocatalytic Asymmetric Annulation of 1,3-Bis(alkoxycarbonyl)buta-1,3-dienes and Aldehydes, Org. Lett. 15 (2013) 2950.

[13] E. Flori, A. Mastrofrancesco, D. Kovacs, Y. Ramot, S. Briganti, B. Bellei, R. Paus, M. Picardo, 2,4,6-Octatrienoic acid is a novel promoter of melanogenesis and antioxidant defence in normal human melanocytes via PPAR-γ activation, Pigment Cell Melanoma Res. 24 (2011) 618.

http://dx.doi.org/10.1016/j.heliyon.2017.e00368

[14] Z. Qiang, C. Hauck, J.A. McCoy, M.P. Widrlechner, M.B. Reddy, P.A. Murphy, S. Hendrich, *Echinacea sanguinea* and *Echinacea pallida* extracts stimulate glucuronidation and basolateral transfer of Bauer alkamides 8 and 10 and ketone 24 and inhibit P-glycoprotein transporter in Caco-2 cells, Planta. Med. 79 (2013) 266.

[15] R. Bauer, P. Remiger, TLC and HPLC Analysis of Alkamides in *Echinacea* Drugs 1,2, Planta. Med. 55 (1989) 367.

[16] G.C.L. Ee, C.M. Lim, M. Rahmani, K. Shaari, C.F. Bong, Pellitorine, a potential anti-cancer lead compound against HL6 and MCT-7 cell lines and microbial transformation of piperine from Piper Nigrum, Molecules 15 (2010) 2398.

[17] H. Greger, Alkamides structural relationships, distribution and biological activity, Planta. Med. 50 (1984) 366.

[18] M. Miyakado, I. Nakayama, H. Yoshioka, N. Nakatani, The *Piperaceae* Amides I: Structure of Pipercide, A New Insecticidal Amide from Piper nigrum L, Agric. Biol. Chem. 43 (1979) 1609.

http://dx.doi.org/10.1016/j.heliyon.2017.e00368