Tetrahedron 71 (2015) 8876–8884

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Straightforward synthesis of functionalized (*E*)-3-acylacrylic acids

Ivan Sivák, Jakub Václav, Dušan Berkeš, Andrej Kolarovič *

Institute of Organic Chemistry, Catalysis and Petrochemistry, Slovak University of Technology, Radlinského 9, 81237 Bratislava, Slovakia

ARTICLE INFO

Article history:
Received 8 July 2015
Received in revised form 14 September 2015
Accepted 1 October 2015
Available online 9 October 2015

Keywords:
Horner–Wadsworth–Emmons reaction
Phosphonate
3-Oxoalk-2-enoic acid
Glyoxylic acid

ABSTRACT

An experimentally simple, mild and straightforward synthetic route towards diversely functionalized (*E*)-3-acylacrylic acids is described, with Horner–Wadsworth–Emmons (HWE) reaction as the key step. The substrate scope and limitations of the HWE reaction were investigated with a range of β-ketophosphonates. Glyoxylic acid monohydrate was demonstrated to be fully compatible with the HWE reaction conditions, thus avoiding a troublesome hydrolysis of the corresponding 3-acylacrylates in the last step and providing a valuable synthetic shortcut.

1. Introduction

The (*E*)-3-acylacrylic moiety can be found in numerous natural products of diverse structural complexity and biological properties (Fig. 1).[1]

Moreover, due to its dense functionality, compounds bearing the (*E*)-3-acylacrylic subunit exhibit interesting combinations of miscellaneous reactivities. These provide a multitude of synthetic options for further structural modifications, e.g., Michael and Michael-type additions,[2,3] Friedel–Crafts, Rauhut–Currier and Diels–Alder reactions,[4–6] decarboxylative couplings[7] or multicomponent reactions.[8] 3-Acylacrylic acids and esters have proven to be valuable synthetic precursors in syntheses of various heterocyclic derivatives[9] and compounds with therapeutic potential in general.[10] A broad applicability of 3-acylacrylic building blocks came hand in hand with the development of several complementary synthetic routes to access them. The classical methods are represented by either Friedel–Crafts acylation or condensation reactions of ketones with glyoxylic acid, targeting predominantly 3-aroylacrylic derivatives.[11] More advanced synthetic approaches towards 3-acylacrylates comprise, e.g., multistep construction strategies,[12] isomerization reactions,[13] acylations with *trans*-vinylogous ester anion equivalent,[14] allylic oxidations,[15] oxidative opening of 2-substituted furans[16] and Horner–Wadsworth–Emmons (HWE) reaction of glyoxylic esters.[17] Due to our long-term interest in studies of crystallization-induced asymmetric transformations (CIAT) involving 3-acylacrylic acids as substrates,[3c,18] we looked for a general, straightforward and simple access to this class of compounds. A synthetic route relying on HWE reaction as a key step appeared to be attractive, since it starts from easily available esters of carboxylic acids **1** and allows for a very broad structural variability of the acyl chain (Scheme 1).

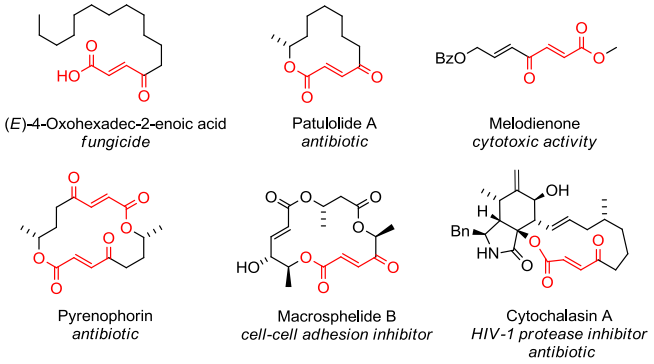
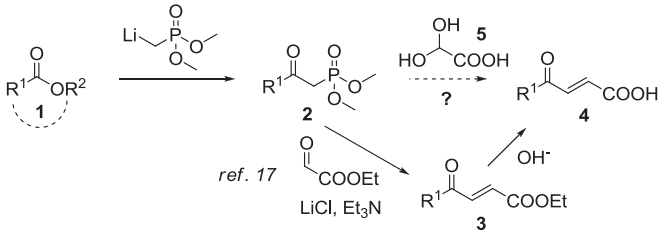


Fig. 1. Examples of natural compounds bearing 3-acylacrylic subunit.



Scheme 1. Considered synthetic strategies towards 3-acylacrylic acids **4**.

* Corresponding author. E-mail address: and.kolarovic@gmail.com (A. Kolarovič).

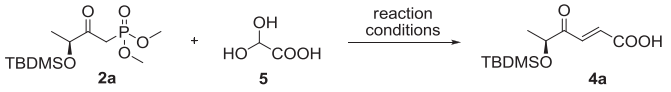
http://dx.doi.org/10.1016/j.tet.2015.10.003
0040-4020/

On the other hand, the necessity of a base-promoted hydrolysis in the final step could be regarded as a serious drawback since consideration of protection strategies might be inevitable.[12c] Despite the highly reactive nature of 3-acylacrylates **3**, alkaline hydrolysis was reported to be applicable to simple and unfunctionalized 3-acylacrylate esters, providing the corresponding acids **4** in average yields.[15a,19] However, the hydrolysis protocols might turn incompatible with more sensitive substrates and, importantly, constitute an extra step towards the target compounds. Therefore we were intrigued by the possibility of performing HWE reactions directly with monohydrate of glyoxylic acid **5**, which would entail a simple, yet valuable synthetic shortcut (Scheme 1).

2. Results and discussion

As a model substrate for our initial investigations, we chose a readily available β-ketophosphonate **2a** (Table 1).[20]

Table 1
Reactivities of β-ketophosphonate **2a** and glyoxylic acid monohydrate **5** under different reaction conditions[a]



Entry	Reaction conditions	Conversion (%)[b]	Yield (%)[b]
1	2.6 equiv Et_3N, 1.0 equiv LiCl	36	32
2	2.6 equiv DBU, 1.0 equiv LiCl	65	61
3	2.6 equiv DBU	73	72
4	2.6 equiv DBU[c]	91	88

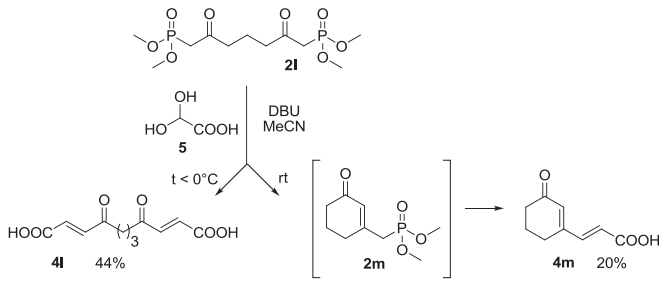
[a] General reaction conditions: 1.5 equiv **5** (0.3 M solution in MeCN), 0 °C, 30 min. DBU=1,8-diazabicyclo[5.4.0]undec-7-ene.
[b] Determined by ^{1}H NMR analysis with internal standard.
[c] A solution of **5** in MeCN was stored over 4 Å molecular sieves for 24 h.

Our brief screening of reaction conditions started with a protocol that had been successfully applied to esters of glyoxylic acid (entry 1).[17] We were pleased to find that despite using a free acid reagent **5**, the target 3-acylacrylic acid **4a** was formed in a yield of 32% within 30 min. Masamune and Roush have reported a significant acceleration of HWE reactions in the presence of DBU, presumably due to its increased basicity.[21] Indeed, application of DBU to our reaction system significantly improved reactivity of **2a** (entry 2). Although lithium cation is expected to increase the acidity of phosphonates via 1,3-dioxocomplexation,[21] we envisioned that under protic reaction conditions it might not be applicable (entry 3). With respect to the sensitive nature of 3-acylacrylates towards, e.g., retro aldol and condensation reactions, we reduced water content in the reaction media by predrying a solution of **5** in MeCN over 4 Å molecular sieves for a period of 24 h. Apart from that, in situ generation of free glyoxylic acid was supposed to result in a more readily reacting system. Indeed, this procedure resulted in a faster conversion and a very good yield of acid **4a** (entry 4).

With the optimized conditions defined, applicability to a broader scope of phosphonate substrates was explored. For the purpose of our studies, a variety of diversely functionalized β-ketophosphonates **2b**–**m** was prepared (Table 2), utilizing a combination of slightly modified published protocols based on dimethyl methylphosphonate (DMMP).[22] In general, the target phosphonates were easily accessible and obtained in good yields. In agreement with the data published for related perfluoroalkylated β-ketophosphonates,[23] β-ketophosphonate **2k** (entry 11) was obtained as a mixture of oxo and enol tautomers in a ratio of 77:23, respectively, as determined by means of ^{1}H NMR.

Next, reactivity of β-ketophosphonates **2b**–**m** in HWE reaction with a predried solution of glyoxylic acid monohydrate **5** was explored (Table 3). We were pleased to find that with the exception of **2k**, the investigated phosphonates were smoothly converted to the corresponding (*E*)-3-acylacrylic acids in modest to excellent yields of 36–95%. Importantly, due to mild reaction conditions, side chains decorated with a variety of functional groups were very well tolerated.

The observed unreactivity of phosphonate **2k** in the reaction system can be plausibly attributed to a strongly electron withdrawing nature of the perfluoropropyl substituent. The existence of **2k** as a mixture of oxo/enol tautomers is indicative of a relatively high stability and thus lowered nucleophilicity of the corresponding enolate, generated in situ upon deprotonation with DBU. As the most problematic turned out to be the sequence **1d**→**2d**→**4d**, providing rather unsatisfactory yields of 37% and 36%, respectively. Presumably due to increased reactivity of the methylene bridge, being additionally activated by the adjacent phenyl group, these compounds were more prone to side reactions. As anticipated, depending on the reaction conditions, diphosphonate **2l** can cyclize spontaneously to form phosphonate **2m** and thus serve as a precursor both for the acids **4l** and **4m** (Scheme 2).



Scheme 2. HWE reaction of diphosphonate **2l** and glyoxylic acid monohydrate **5** under different temperature conditions.

However, a careful control of the reaction temperature enables to obtain the diacid **4l** in an acceptable yield of 44% (Table 3, entry 12).

3. Conclusion

In summary, we have described a simple and straightforward synthetic route leading to diversely functionalized (*E*)-3-acylacrylic acids as synthetically versatile building blocks. The scope and limitation of the HWE reaction were studied with a range of substrates. We have demonstrated that glyoxylic acid monohydrate is fully compatible with the HWE reaction conditions, thus sparing a troublesome hydrolysis of the corresponding 3-acylacrylates in the last step. We are currently exploring applicability of this synthetic method to the preparation of ω-substituted fytoceramide derivatives.

4. Experimental section

4.1. General information

Melting points were measured on BÜCHI Melting Point B-540 and were uncorrected. ^{1}H and ^{13}C NMR spectra were recorded either on a Varian VXR-300 (300 and 75 MHz, respectively) or a Varian INOVA 600 spetrometer (600 and 151 MHz, respectively), with TMS as an internal standard. Chemical shifts are reported in parts per million (ppm). Optical rotations were measured on a JASCO P-1020 or a POLAR L-mP (IBZ Messtechnik) polarimeter