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Preparation of unsymmetrical dialkyl acetylenedicarboxylates and related esters by enzymatic transesterification

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ABSTRACT

An unexpected highly selective mono-transesterification of symmetrical acetylenedicarboxylates with various alcohols occurred in the presence of *Candida rugosa* lipase. This reaction allows an efficient preparation of unsymmetrical acetylenedicarboxylates and related α,β-acetylenic esters.

1. Introduction

7-Oxanorborna-2,5-diene-2,3-dicarboxylates obtained by Diels–Alder reaction of furans with dialkyl acetylenedicarboxylates are useful masked forms of the acetylenic partner.[1] Such compounds have been used in Michael additions or [3+2] cycloadditions followed by a retro-Diels–Alder reaction to prepare ethylenic[2] or heterocyclic[2c,3–5] products. To increase the scope of these sequences, an efficient access to unsymmetrical acetylenedicarboxylates would be of great interest. In a literature example, the allyl methyl acetylenedicarboxylate was prepared in low yield by the reaction of methyl chloroformate with the lithium derivative of allyl propiolate.[6] In a patent, related to epothilone derivatives, the synthesis of an unsymmetrical acetylenedicarboxylate was reported by the reaction of acetylenedicarboxylic acid monomethyl ester with a triazolo-thiazole.[7] Flash vacuum pyrolysis at 500 °C of 1,2,4-trioxo-3-triphenylphosphoranylidenebutane derivatives, obtained by the reaction of alkyl oxalyl chlorides with alkoxycarbonylmethylenetriphenylphosphoranes, has allowed the preparation of unsymmetrical acetylenedicarboxylates in moderate yields by extrusion of Ph_3PO.[8,9] Acetylenedicarboxylates could also be obtained by esterification of dibromofumaroyl dichloride followed by elimination of the bromine atoms with zinc.[10] This strategy was proposed to overcome the difficulties related to the use of acetylenedicarbonyl dichloride. Treatment of dibromofumaroyl dichloride with 1 equiv of one alcohol and subsequent addition of a small excess of a second alcohol allowed the preparation of acetylenedicarboxylates with different substituents in the ester groups, but a statistical ratio of the three possible diesters was obtained.[11]

For 30 years, enzymes, and particularly lipases, have become important reagents in organic synthesis.[12] In various examples, lipase-catalyzed transesterification of diesters with an alcohol gave a new diester with different alkoxy groups, but this selectivity was generally driven by the enzyme recognition of a stereogenic center or a bulky substituent.[13] A plant extract could catalyze a formal transesterification of caffeate derivatives (3-(3,4-dihydroxyphenyl)prop-2-enoates),[14] and it was soon recognized that α,β-ethylenic esters could be prepared by transesterification of activated acrylate derivatives with alcohols in the presence of hydrolases.[15] Numerous examples of lipase-catalyzed preparation of such esters have been described in the literature.[16] To our knowledge, few enzyme-catalyzed reactions with α,β-acetylenic acid derivatives were reported. Treatment of ethyl propiolate with aromatic amines afforded Michael addition products while, in the presence of the *Candida rugosa* lipase,[17] propargylamides were formed.[18] In an earlier report, formation of the monoethyl ester of acetylenedicarboxylic acid was described by hydrolysis of diethyl acetylenedicarboxylate in the presence of α-chymotrypsin.[19] The yield of the monoethyl ester was 24% after 1.6 h and the reaction slowed down markedly thereafter. Addition of nucleophiles to the triple bond was proposed to explain the enzyme inhibition.

This Letter is dealing with a one step method to prepare unsymmetrical acetylenedicarboxylates by lipase-catalyzed mono-transesterification of symmetrical acetylenedicarboxylates with an alcohol.

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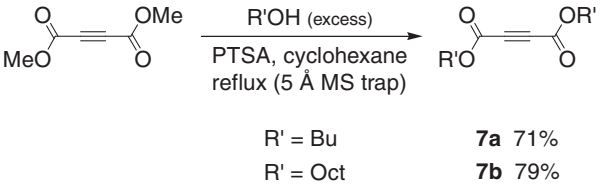
2. Results and discussion

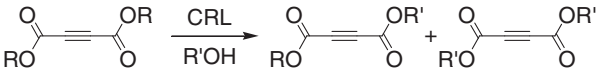
Preliminary experiments were run with 1.2/1 mixtures of 2,2-dimethylpropanol (neopentyl alcohol) and dimethyl acetylenedicarboxylate (DMAD) in the presence of various lipase-containing preparations. After 20 h at 20 °C in *tert*-butyl methyl ether, ^{1}H NMR spectra show no reaction in the presence of porcine pancreatic lipase (PPL), *Pseudomonas cepacia* lipase (lipase PS Amano) or *Pseudomonas fluorescens* lipase (lipase AK Amano). With *Candida rugosa* lipase (CRL) or an immobilized form of the *Rhizomucor miehei* lipase (Lipozyme), conversions were 18 and 3%, respectively. Thus, we focused our attention on the *Candida rugosa* lipase, and the influence of various parameters in the reactions of ethylfurylsilylmethanol **2** (Fig. 1)[20,21] with commercially available dimethyl and diethyl acetylenedicarboxylates, and with the corresponding dibutyl and dioctyl esters **7a** and **7b** has been studied.

Dibutyl and dioctyl acetylenedicarboxylates **7a** and **7b** were easily prepared by treatment of DMAD with butan-1-ol and octan-1-ol, respectively, in the presence of a catalytic amount of *para*-toluenesulfonic acid in refluxing cyclohexane and a 5 Å molecular sieves trap was used to remove the produced methanol (Scheme 1).



Scheme 1. Preparation of symmetrical acetylenedicarboxylates.

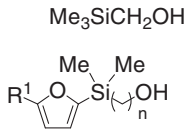
Transesterification reactions catalyzed by *Candida rugosa* lipase (CRL) were performed at 35 °C. After the indicated reaction time, the silylmethyl ester/alcohol **2** ratio was determined by ^{1}H NMR spectroscopy (by integration of signals of the alcohol and the esters at 3.56 and 4.13 ppm, respectively). A priori, these reactions could give an unsymmetrical acetylenedicarboxylate **6** and a symmetrical diester **7** with two ethylfurylsilylmethyl groups (Scheme 2, Table 1).



R = Me	BuOH	**6a**	**7a**
R = Me	OctOH	**6b**	**7b**
R = Me	$PhCH_2CH_2OH$	**6c**	**7c**
R = Me	Me_3CCH_2OH	**6d**	**7d**
R = Me	**1**	**6e**	**7e**
R = Me	**2**	**6f**	**7f**
R = Me	**3**	**6g**	**7g**
R = Me	**4**	**6h**	**7h**
R = Me	**5**	**6i**	**7i**
R = Et	**2**	**6j**	**7f**
7a	**2**	**6k**	**7f**
7b	**2**	**6l**	**7f**

Scheme 2. Lipase-catalyzed transesterifications.

In all our experiments, analyses of the crude reaction mixtures by ^{1}H NMR and gas chromatography showed the formation of an unsymmetrical diester **6** and no evidence of the presence of the di-transesterified ester **7** (see below). Optimization of the reaction conditions was mainly realized with diethyl acetylenedicarboxylate (entries 7–15) in order to obtain high conversion of the starting alcohol **2**. Initially, we have determined the conversions after 24 h with 1.15/1 mixtures of the dicarboxylate and silylmethanol **2**. In *tert*-butyl methyl ether, the presence of 5 Å or 13 Å molecular sieves (MS) gave an increase of the conversion from 60% to 75–77% (compare entries 7–9). The drying effect of molecular sieves might explain the increase of the conversion, however we did not observe any detectable hydrolysis of the diethyl acetylenedicarboxylate in the experiment without molecular sieves. No beneficial influence of triethylamine[22] was noticed in this reaction. The conversion after 24 h was about 40% and various unidentified products have appeared under these conditions (entry 10). In the presence of 13 Å molecular sieves, the use of toluene (entry 15) or petroleum ether (entry 12) as the solvent instead of *tert*-butyl methyl ether gave, respectively, a decrease (66%) and an increase (85%) of the conversion. An appreciable enhancement of the conversion was noticed increasing the reaction time to two days (entry 13) or increasing the initial ratio of the acetylenedicarboxylate to alcohol **2** to 1.5/1 (entry 14). In petroleum ether, the replacement of 13 Å molecular sieves by 5 Å molecular sieves further accelerates the reaction (compare entries 11 and 12). The beneficial influence of molecular sieves in *tert*-butyl methyl ether was also evident in the case of dimethyl acetylenedicarboxylate (compare entries 1–3) and with



Me_3SiCH_2OH **1**

n = 1, R^1 = Et **2**

n = 1, R^1 = H **3**

n = 2, R^1 = Et **4**

n = 3, R^1 = Et **5**

Figure 1. Silylalkanols used in the transesterifications.

dibutyl ester **7a** (compare entries 16–18). With dioctyl ester **7b**, a lower influence of the molecular sieves was observed (compare entries 21–23). Use of petroleum ether as the solvent gave also a higher reaction rate in the case of DMAD (compare entries 2–5) but no influence was observed with the dibutyl and the dioctyl esters (compare entries 17–20 and 22–25). The increased conversion noticed in the presence of molecular sieves could be related to their ability to adsorb low molecular weight alcohols. For the reactions in petroleum ether in the presence of 5 Å molecular sieves, ^{1}H NMR spectra of the reaction mixtures before evaporation of the solvent showed the absence of signals of methanol (entry 4) or ethanol (entry 11), the presence of butanol (entry 19) in a lower proportion than expected (29%), and the expected amount of octanol (entry 24). Under the same conditions in the presence of 13 Å molecular sieves, a similar trend was noticed but with a decreased ability to adsorb low molecular weight alcohols: a tiny signal of methanol was still present in the ^{1}H NMR spectrum (entry 5) and 29% of the expected ethanol and 89% of the expected butanol remained in solution (entries 12 and 20, respectively).[23] Under similar reaction conditions, the reaction rate order is: diethyl ≈ dimethyl > dibutyl > dioctyl ester. To achieve generally high conversions, we selected the experimental conditions hereafter: petroleum ether as the solvent, 35 °C, 5 Å MS, 1.5/1 ratio of acetylenedicarboxylate to alcohol, 4 days reaction time. Under these conditions, 94% of alcohol **2** was converted in the reaction with DMAD (entry 6).

In order to determine the scope of this reaction, DMAD was treated with various alcohols in the presence of *Candida rugosa* lipase under the optimized conditions cited above. A preparative experiment was also run with diethyl acetylenedicarboxylate. Table 2 summarizes the conversions of the alcohols, the ratios of mono- to di-transesterified products and the yields of the isolated unsymmetrical diesters.

Ratios **6**/**7** were measured by gas chromatography on the crude reaction mixtures. The retention times of the dibutyl, dioctyl, di(2,2-dimethylpropyl) and di(trimethylsilylmethyl) acetylenedicarboxylates were previously determined, and the presence or

Table 1
Lipase-catalyzed transesterification of acetylenedicarboxylates with alcohol 2[a]

Entry	R	Solvent	Additive	Ratio **6**/**2**	Entry	R	Solvent	Additive	Ratio **6**/**2**
1	Me	*t*-BuOMe	—	51/49	14[b]	Et	Petroleum ether	13 Å MS	93/7
2	Me	*t*-BuOMe	5 Å MS	80/20	15	Et	Toluene	13 Å MS	66/34
3	Me	*t*-BuOMe	13 Å MS	81/19	16	Bu	*t*-BuOMe	—	45/55
4	Me	Petroleum ether	5 Å MS	90/10	17	Bu	*t*-BuOMe	5 Å MS	68/32
5	Me	Petroleum ether	13 Å MS	88/12	18	Bu	*t*-BuOMe	13 Å MS	64/36
6[b,c]	Me	Petroleum ether	5 Å MS	94/6	19	Bu	Petroleum ether	5 Å MS	67/33
7	Et	*t*-BuOMe	—	60/40	20	Bu	Petroleum ether	13 Å MS	66/34
8	Et	*t*-BuOMe	5 Å MS	75/25	21	Oct	*t*-BuOMe	-	22/78
9	Et	*t*-BuOMe	13 Å MS	77/23	22	Oct	*t*-BuOMe	5 Å MS	27/73
10	Et	*t*-BuOMe	NEt_3 (1 equiv)	41/59[d]	23	Oct	*t*-BuOMe	13 Å MS	25/75
11	Et	Petroleum ether	5 Å MS	96/4	24	Oct	Petroleum ether	5 Å MS	27/73
12	Et	Petroleum ether	13 Å MS	85/15	25	Oct	Petroleum ether	13 Å MS	26/74
13[e]	Et	Petroleum ether	13 Å MS	91/9					

[a] Unless otherwise noted, reactions were carried out at 35 °C for 24 h with 1.15/1 mixtures of acetylenedicarboxylate and alcohol **2**, in the presence of *Candida rugosa* lipase.
[b] A 1.5/1 mixture of acetylenedicarboxylate and alcohol **2** was used.
[c] Reaction time was 4 days.
[d] Unidentified by-products were also observed by ^1H NMR.
[e] Reaction time was 2 days.

absence of these symmetrical esters in the lipase-catalyzed reactions was easily checked (entries 1, 2, 4 and 5). For the reaction of alcohol **2** with diethyl acetylenedicarboxylate and the reactions of alcohols **3** and **4** with DMAD (entries 7, 8 and 9), a very small peak with a higher retention time than that of the unsymmetrical diester was observed in the chromatograms. Gas chromatography/mass spectrometry analysis of these samples has shown the expected molecular mass of the di-transesterified compounds for these minor products. In the other cases (entries 3, 6 and 10), no peak with a retention time higher than that of the unsymmetrical diester was present in the chromatograms. Mono-transesterified products were generally isolated in yields in the range of 71–93% after evaporation of the starting acetylenedicarboxylate under reduced pressure and silica gel chromatography. The moderate yield of butyl methyl acetylenedicarboxylate **6a** (entry 1) is mainly due to a tedious chromatography to separate the DMAD and the product (under reduced pressure, the unsymmetrical diester **6a** was also partially evaporated).

For comparison, we have checked the transesterification of DMAD with butanol, octanol or silylmethanol **2** in petroleum ether at 35 °C in the presence of *para*-toluenesulfonic acid (10%) using a 1.5/1 ratio of ester to the alcohol. After 4 days, about 78% conversions of butanol and octanol were noticed. In these reactions, 88/12 and 81/19 mixtures, respectively, of mono- and di-transesterified esters **6** and **7** were obtained. Under the same conditions, addition of 5 Å molecular sieves decreased significantly the conversion rates (e.g. 23% conversion of octanol after 4 days). Silylmethanol **2** was totally consumed, but the products were mainly 2-ethylfuran and the Diels–Alder adduct of this furan derivative with DMAD. Clearly, the lipase-catalyzed transesterifications were faster and more selective than the acid-catalyzed reactions. Moreover, this lipase allows efficient transesterification with acid sensitive alcohols.

Table 2
Preparation of unsymmetrical dicarboxylates **6**[a]

Entry	Alcohol	Conv. (%)	Ratio **6/7**	Diester **6** Yield[b] (%)	
1	BuOH	95	93/7	**6a**	51
2	OctOH	98	100/0	**6b**	92
3	$PhCH_2CH_2OH$	94	100/0	**6c**	80[c]
4	Me_3CCH_2OH	97	98/2	**6d**	92
5	**1**	95	98/2	**6e**	93
6	**2**	94	100/0	**6f**	78
7	**2**[d]	95	99.5/0.5	**6j**	80
8	**3**	99	98.5/1.5	**6g**	71
9	**4**	97	96/4	**6h**	82
10	**5**	96	100/0	**6i**	84

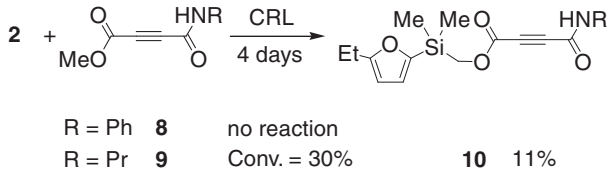
[a] Unless otherwise noted, reactions were carried out for 4 days with a 1.5/1 ratio of DMAD to the alcohol in the presence of 5 Å molecular sieves and a crude extract containing the *Candida rugosa* lipase in petroleum ether at 35 °C.
[b] Unless otherwise noted, yields of unsymmetrical diesters after silica gel column chromatography.
[c] Yield after distillation of reactants.
[d] In this reaction, diethyl acetylenedicarboxylate was used.

During the lipase-catalyzed transesterification of DMAD with the 3-hydroxypropylsilane **5** in the presence of a new batch of 5 Å molecular sieves,[24,25] formation of 2-ethylfuran and various products resulting from [4+2] cycloaddition of this furan with acetylenedicarboxylate derivatives was noticed. These by-products decreased using 5 Å molecular sieves of another supplier[26] and were absent in the presence of an old sample of 5 Å molecular sieves of a third supplier.[27] Clearly, silane **5** was unstable in petroleum ether in the presence of the new batch of molecular sieves[24] and 1,1-dimethyl-1-sila-2-oxacyclopentane was obtained with release of 2-ethylfuran. Degradation of hydroxypropylsilane **5** was avoided when the new batch of 5 Å molecular sieves[24] was previously washed with an aqueous NaOH solution followed by water before air drying and reactivation (280 °C, 0.1 torr, 4 h).

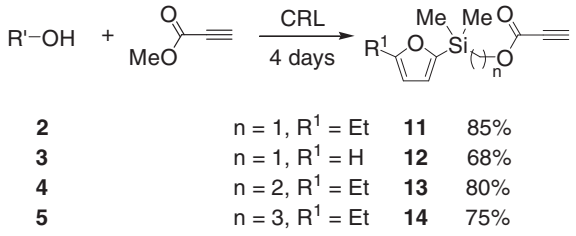
The enzymatic preparation recovered after the reaction of alcohol **2** with DMAD has been reused twice in similar experiments. The same selectivity was obtained, but each reaction showed about 10% decrease of the conversion with regard to the precedent transesterification. In Contrast to α-chymotrypsin,[19] the *Candida rugosa* lipase does not seem to be inhibited by the acetylenedicarboxylates.

Lipase-catalyzed transesterification of the unsymmetrical diester **6f** with the alcohol **2** was also attempted, but no symmetrical diester **7f** was detected. Under the same reaction conditions with methyl 3-(*N*-phenylcarbamoyl)propiolate **8** and alcohol **2**, no conversion was noticed after 4 days in contrast to the analogous *N*-propylamidoester **9** for which 30% conversion was obtained (Scheme 3). The low yield (11%) of the isolated corresponding silylmethyl ester **10** was mainly due to the difficulties to separate the product from the reactants.

The *Candida rugosa* lipase seems unsuitable to accept an acetylenedicarboxylic acid derivative with a too sterically demanding substituent in the group away from the reactive center. It is well known that the highly flexible saturated long chain carboxylates are good substrates of this lipase and they could bind to the active site in quite different conformations.[28] So, the size of the substituent in the non-reactive part of these acetylenedicarboxylic acid derivatives should play a very important role in the active site because of the rigidity of the acetylenic framework.



Scheme 3. Transesterification of amidoesters.



Scheme 4. Preparation of propiolates.

From a synthetic point of view, the ability of this lipase to catalyze the transesterification of methyl propiolate with alcohols **2–5** is also interesting, because of the particularly mild reaction conditions: no activation of the propiolic acid required, neutral conditions, near to room temperature (Scheme 4).

3. Conclusion

Transesterification of acetylenedicarboxylates with alcohols occurred in the presence of *Candida rugosa* lipase. Unexpectedly, a highly selective mono-transesterification was noticed and unsymmetrical acetylenedicarboxylates could be prepared in high yields. This selectivity was due to the inability of this lipase to accept, in the reactive site, propiolate ester derivatives with a too bulky substituent in the β position.

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Supplementary data

Supplementary data (general procedure for the lipase-catalyzed transesterification and spectroscopic data of the symmetrical diesters **7a–b**, unsymmetrical diesters **6a–j**, amidoester **10** and propiolates **11–14**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.04.103.

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