Tetrahedron 71 (2015) 5538–5546

Contents lists available at ScienceDirect

Tetrahedron

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

New ω-ketovinyl phosphonates: inexpensive synthesis, isomerization studies and route for functionalized 1,3-butadienes

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ARTICLE INFO

Article history:
Received 1 May 2015
Received in revised form 3 June 2015
Accepted 16 June 2015
Available online 21 June 2015

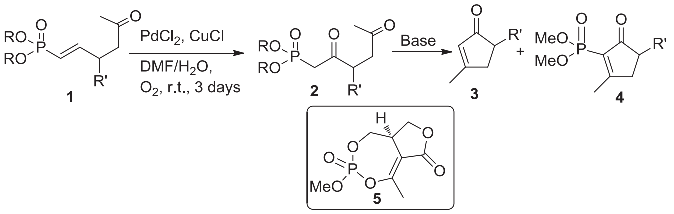
Keywords:
Phosphonates
1,3-Diketones
Iron(III) chloride
Isomerization
1,3-Butadienes

ABSTRACT

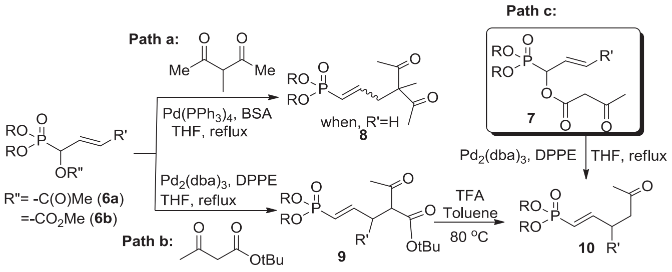
A straightforward and inexpensive synthetic protocol to access new ω-ketovinyl phosphonates is established from the Lewis or Brønsted acid mediated reactions of α-hydroxy allylic phosphonates with aromatic 1,3-diketones. Predominantly, $FeCl_3$ or $FeCl_3 \cdot 6H_2O$ has been preferred as easily available, inexpensive and efficient Lewis acid under solvent-free conditions. With experimental and theoretical support, we have demonstrated that some of the substituted open chain 1,3-diketones may exist predominantly in the keto form. Mild base mediated isomerization reactions for ω-ketovinyl phosphonates were carried out to generate corresponding allylic phosphonates. Utility of one of the allylic phosphonates in Horner–Wadsworth–Emmons (HWE) reactions facilitated access to variety of densely substituted 1,3-butadienes attached with 1,3-diketone functionality at the terminal carbon.

1. Introduction

In the family of organophosphonates, vinyl and keto phosphonates are recognized as useful classes of compounds in the field of organic synthesis[1] and material sciences.[2] Phosphonates with both vinyl and keto functionalities[3] have also revealed their utility to obtain natural products having cyclopentenone ring system like Jasmone[3a] and an effective antitumor agent, sarkomycin was produced using several steps starting from similar kind of phosphonates.[4] Further, the research work on ω-ketovinyl phosphonate **1** by Spilling et al.[5] brings special attention where these compounds are used in Wacker oxidation to obtain diketophosphonate **2**, a novel precursor to generate cyclopentenone **3** (via intramolecular HWE reaction) along with phosphonocyclopentenone **4** (Scheme 1).[5a] The compound **4** was also obtained from diketophosphonate **2** at room temperature in the presence of silica gel. Additionally, ω-ketovinyl phosphonate was utilized to synthesize the first phosphonate analogue of cyclophostin **5** (Scheme 1), a natural acetyl cholinesterase inhibitor.[5b] Hence, an easy synthesis of ω-ketovinyl phosphonates followed by their applications is desirable. In this direction, the original approach for synthesizing ω-ketovinyl phosphonate **8** (Scheme 2) includes the $Pd(PPh_3)_4$-catalyzed reactions of α-acetoxy allylic phosphonate **6a** with 1,3-diketone via umpolung[6] in allylic phosphonates (path a, Scheme 2).[6a]



Scheme 1. Reported applications of ω-ketovinyl phosphonates.



Scheme 2. Reported synthetic routes for ω-ketovinyl phosphonates.

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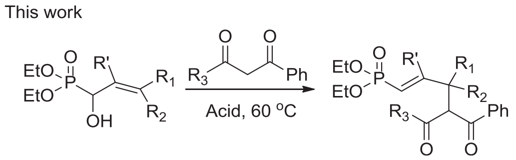
http://dx.doi.org/10.1016/j.tet.2015.06.064

Later, modified method was reported from the reaction of phosphono allylic carbonate **6b** with *t*-butylacetoacetate using Pd/DPPE as catalyst (via compound **9**) and then successive trifluoroacetic acid (TFA) mediated hydrolysis of **9** led to the formation of ω-ketovinyl phosphonate **10** (path b, Scheme 2).[5a] The Pd-catalyzed decarboxylative rearrangement of phosphono allylic acetoacetate **7** also led to the formation of ω-ketovinyl phosphonate (path c, Scheme 2).[5a] Although these are undoubtedly useful processes, these synthetic strategies suffer from drawbacks such as necessity of expensive palladium/ligand, synthesis of starting materials (**6** or **7**) using environmentally hazardous pyridine, methylchloroformate or unstable diketene. The other potential pitfalls include less yield, decomposition of starting material on prolonged storage and competitive unavoidable formation of phosphonodiene along with the desired ketophosphonate (in case of path c). Nevertheless, Pd-catalyzed methods allow for transfer of chirality and a much wider substrate scope.

With the interest on organophosphonates,[7] we report here a simple, efficient and inexpensive acid mediated approach to generate new ω-ketovinyl phosphonates starting directly from α-hydroxy allylic phosphonates and *aromatic* 1,3-diketones that are known to be used as UVA sunscreens.[8]



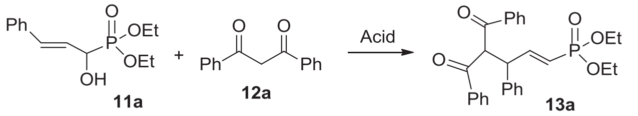
In addition, we demonstrate both acid and base mediated isomerization studies for new ω-ketovinyl phosphonates to its allylic isomers with support from theoretical calculations and utilized one of these allylic phosphonates in HWE reactions to access new conjugated 1,3-butadienes attached with 1,3-diketone functionality at the terminal carbon. A relevant work on base catalyzed isomerization of simple vinyl phosphonate to allylic phosphonate was utilized to generate valuable *trans*-retinoic acid.[9] Moreover, this isomerization also helped to generate allylic phosphonium and phosphoryl ylides[10] that can undergo both conventional as well as vinylogous Wittig/HWE reactions to afford a range of multisubstituted 1,3-butadienes.[11] Notably, the regio- and stereoselective synthesis of multisubstituted conjugated 1,3-butadienes with proximal functionalities is challenging although these dienes are valuable building blocks for several products and advanced materials.[12]

2. Results/discussion

(i) Synthesis of ω-ketovinyl phosphonates

In this work, the reported issues related to the synthesis of essential starting materials for ω-ketovinyl phosphonates were avoided by the direct use of α-hydroxy allylic phosphonates as precursors. Initially, the phosphonate **11a** and 1,3-diketone **12a** were used to obtain the new type of ω-ketovinyl phosphonate **13a** in high yield by varying different acids (both Lewis or Brønsted) under several reaction conditions (Table 1). Encouraged by our previous results,[7a] Fe(III) was selected as one of the effective Lewis acids for these studies. In fact, the reaction was more satisfactory under solvent-free conditions upon heating at 60–70 °C (entry 1). Compared to other Lewis acids such as the Cu(II) and Zn(II) used herein, $Bi(OTf)_3$ worked well for this reaction (entry 10, Table 1). Among the selected Brønsted acids, *p*-toluenesulfonic acid (*p*-TSA) and triflic acid (TfOH) were effective to afford **13a** in higher yields (entries 15 and 16, Table 1) in the presence of DCE as solvent. However, being inexpensive and easily accessible, Fe(III) was preferred for all other reactions to make this protocol solvent—free and utilized successfully to obtain a range of ω-ketovinyl phosphonates in high yields.

Table 1
Screening of reaction conditions to synthesize **13a**[a]



Entry	Acid	Solvent	Time (h)	Isolated yield of **13a** (%)
1	$FeCl_3\cdot 6H_2O$	Neat	12	73[b]
2	$FeCl_3\cdot 6H_2O$	1,2-Dichloroethane	10	60
3	$FeCl_3\cdot 6H_2O$	Nitromethane	12	60
4	$FeCl_3$	Neat	14	0
5	$FeCl_3$	Nitromethane	12	0
6	$Cu(OTf)_2$	1,2-Dichloroethane	12	10[c]
7	$Cu(OAc)_2$	1,2-Dichloroethane	12	0[c]
8	$CuCl_2\cdot 2H_2O$	1,2-Dichloroethane	14	20
9	$Fe(acac)_3$	Dichloromethane	14	0[c]
10	$Bi(OTf)_3$	1,2-Dichloroethane	8	80
11	$ZnCl_2$	1,2-Dichloroethane	36	50[c]
12	AcOH	Dichloromethane	12	0
13	CF_3CO_2H	1,2-Dichloroethane	12	0[c]
14	CH_3SO_3H	1,4-Dioxane	12	0
15	*p*-TSA	1,2-Dichloroethane	14	80
16	TfOH	1,2-Dichloroethane	14	85

[a] Reactions were performed with **11a** (1 mmol) and **12a** (1.2 mmol) using acid (1 mmol) at 60–65 °C (oil bath temperature); only for entries 7 & 9 the reaction was heated under reflux.

[b] The ^{31}P NMR for the reaction mixture showed another peak at δ 28.5 (~20%) but could not be isolated in pure form. The NMR (^{31}P ^{1}H &^{13}C) spectra partly support presumably the formation of α-substituted product.

[c] Starting material was recovered.

In literature, fruitful reactions of allylic alcohols and acetylacetone were reported by using In(III),[13a] Fe(III)[13b–c] or Brønsted acids,[13d] to obtain the *C*-alkylated product and the products were isolated as regioisomeric mixture in case of unsymmetrically substituted allylic alcohols. In those reports, except aromatic 1,3-diketones, all other active methylene compounds including β-ketoester and diester were used. Reaction of cinnamyl alcohol with dibenzoylmethane (aromatic 1,3-diketone) was reported only with 52% isolated yield in the presence of expensive $La(OTf)_3$.[14] Gratifyingly, we could generate a range of valuable regio- and stereoselective ω-ketovinyl phosphonates in good yields by acid mediated direct reactions of aromatic 1,3-diketones with α-hydroxy allylic phosphonates. Considering the availability, cost and reactivity, we have selected the allylic hydroxy phosphonates **11a–d** and aromatic 1,3-diketones **12a–d** (Table 2) for the current study. The newly synthesized ω-ketovinyl phosphonates **13b–i** are listed in Table 2.

The compound **13b** was formed as 1:1 diastereomeric mixture from the reaction of **11a** and **12b**. We could isolate one of the diastereomers in pure isomeric form and the other diastereomer was separated only with ~80% pure isomeric form. Both *p*-TSA and $FeCl_3\cdot 6H_2O$ worked satisfactorily to generate compound **13b** in high yield (90%). With the interest on fluorinated organophosphonates,[1g] ω-ketovinyl phosphonate **13c** was synthesized in pure form with moderate yield. Furthermore, the reaction of another thiophene containing fluorinated aromatic 1,3-diketone **12d** and phosphonate **11a** generated desired compound **13d** with good diastereoselectivity (dr 1:0.2) in excellent yield (85%) only in the presence of $FeCl_3\cdot 6H_2O$ (entry 3, Table 2). In this case, the use of *p*-TSA or TfOH was not satisfactory. The phosphonate **11b** furnished very promising result to obtain **13e** (entry 4, Table 2) as expected single isomer and **13f** (entry 5, Table 2) as mixture of diastereomers (1:1) from the reactions with **12a** and **12b**, respectively.