Organic LETTERS

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Facile Synthesis of γ-Ketophosphonates by an Intermolecular Stetter Reaction onto Vinylphosphonates

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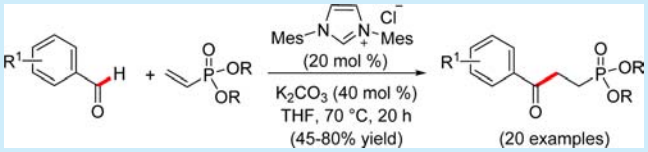
S *Supporting Information*

ABSTRACT: The atom-economic and practical N-heterocyclic carbene (NHC) catalyzed Stetter reaction for the synthesis of γ-ketophosphonates by the reaction of aromatic aldehydes with vinylphosphonates is reported. The NHC derived from *N*-mesitylimidazolium salt (IMes) was an effective catalyst for this transformation, and the products were formed in moderate to good yields.



Organophosphorus compounds are an important class of molecules having potential application in various areas of chemistry including materials chemistry, pharmaceuticals, agrochemicals, and in catalysis.[1] Among the various organophosphorus compounds, phosphonates in general and γ-ketophosphonates in particular are associated with diverse biological properties.[2] For instance, the triazole-containing γ-ketophosphonate (**A**) is important due to its herbicide and fungicide activity,[3] and the pyrrole-linked compound (**B**) is used in the treatment of osteoporosis (Figure 1).[4] Moreover, the biphenyl-derived γ-ketophosphonate (**C**) shows activity as inhibitors of matrix-metalloprotease (MMP-2),[5] and the amino acid-derived compound (**D**) exhibits 5-alanine levulinic acid dehydratase inhibitor activity.[6]

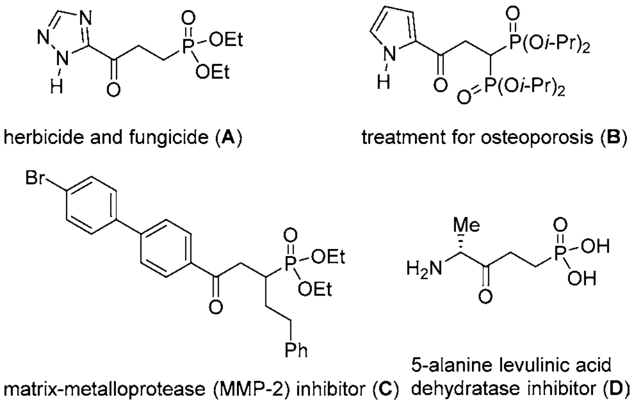
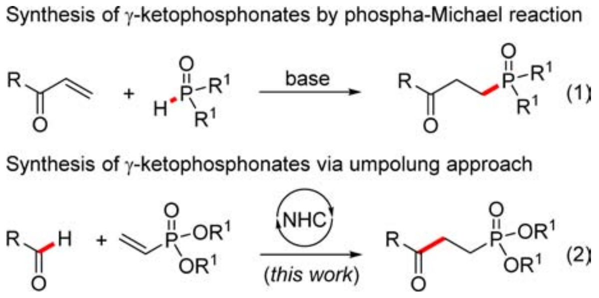


Figure 1. Selected biologically active γ-ketophosphonates.

One of the versatile and powerful methods for the synthesis of γ-ketophosphonates is via the phospha-Michael reaction by the addition of phosphorus nucleophiles to *α*,*β*-unsaturated ketones.[7] This method forms the unique P−C bond, and different variations of this reaction including the asymmetric version are known (Scheme 1, eq 1).[8] In this context, we envisioned a new approach to the synthesis of γ-ketophosphonates by generating the acyl anion equivalents by the umpolung of aldehydes under N-heterocyclic carbene (NHC) catalysis,[9] followed by its subsequent interception with *α*,*β*-unsaturated phosphonates. If successful, this can constitute the NHC-catalyzed intermolecular Stetter reaction[10,11] onto vinyl phosphonates. Notably, the intramolecular Stetter reaction of vinylphosphine oxides and vinylphosphonates has been demonstrated by Rovis and co-workers.[12] Herein, we demonstrate the NHC-organocatalyzed reaction of aromatic aldehydes with vinyl phosphonates leading to the synthesis of biologically important γ-ketophosphonates (eq 2).[13] The present reaction can be considered as a hydroacylation to moderately electron-poor C−C double bond of vinylphosphonates.[14]

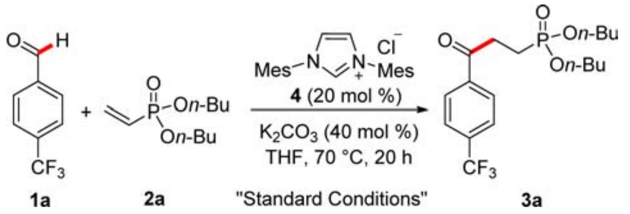
Scheme 1. Synthesis of γ-Ketophosphonates



We began our present studies by treating 4-(trifluoromethyl)benzaldehyde **1a** with the vinylphosphonate **2a** in the presence of the imidazolium salt **4** and K_2CO_3 in THF as the solvent. Interestingly, under these conditions, a facile reaction occurred leading to the formation of the γ-ketophosphonate **3a** in 80% isolated yield (Table 1, entry 1). The carbene generated from **4** is well-known for the homoenolate generation from enals[15] and its subsequent reactivity compared to the generation of acyl anion equivalents from aldehydes. In

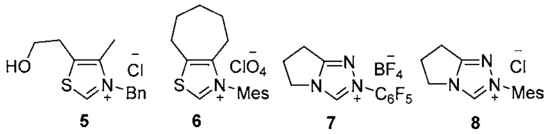
Received: July 30, 2014
Published: September 5, 2014

Table 1. Optimization of the Reaction Conditions[a]



entry	variation from the standard conditions[a]	yield of **3a** (%)[b]
1	none	82 (80)[c]
2	**5** instead of **4**	<5
3	**6** instead of **4**	<5
4	**7** instead of **4**	19
5	**8** instead of **4**	<5
6	DBU instead of K_2CO_3	14
7	Et_3N instead of K_2CO_3	<5
8	KO*t*-Bu instead of K_2CO_3	39
9	1,4-dioxane instead of THF	21
10	DME instead of THF	24
11	toluene instead of THF	44
12	CH_2Cl_2 instead of THF	19
13	reaction run at 50 °C	42
14	1.0 equiv of **1a** instead of 1.5 equiv	49
15	10 mol % of **4** instead of 20 mol %	50

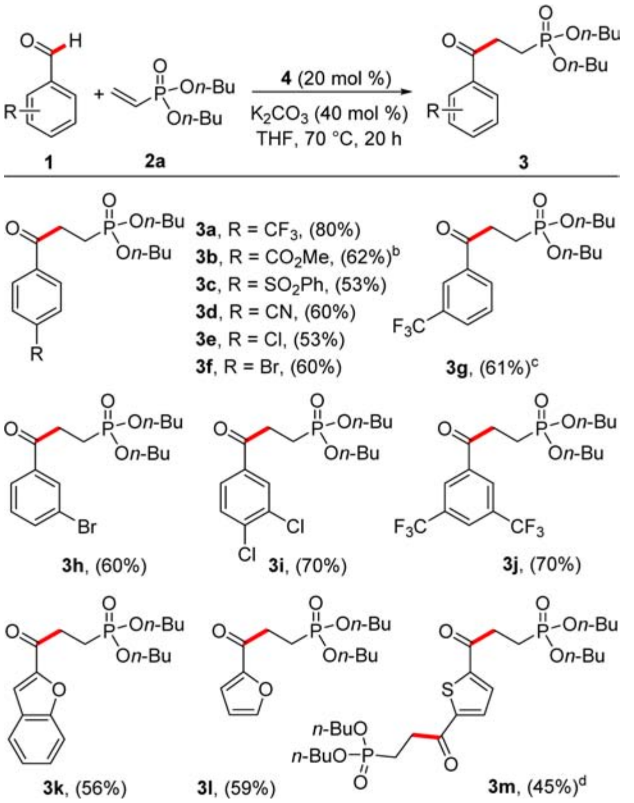
[a] Standard conditions: **1a** (0.38 mmol), **2a** (0.25 mmol), NHC·HX (20 mol %), K_2CO_3 (40 mol %), THF (1.5 mL), 70 °C and 20 h. [b] The yields were determined by ^1H NMR analysis (in $CDCl_3$) of crude products using CH_2Br_2 as the internal standard. [c] Isolated yield in parentheses.



comparison to carbene generated from **4**, other carbene precursors **5**−**8**, which are known for benzoin and Stetter reactions, as well as the hydroacylation reactions, are far less reactive in this case (entries 2−5). Screening of different bases for the generation of free carbenes indicated that K_2CO_3 is the optimal base for this transformation, and reactions carried out using other bases such as DBU, Et_3N, and KO-*t*-Bu furnished inferior results (entries 6−8). We also tested the effect of solvent in this Stetter reaction, which indicated that THF is the solvent of choice and the reactions performed in other solvents afforded the *γ*-ketophosphonate **3a** in low yields (entries 9−12). The reaction returned only 42% of **3a** when the temperature was lowered to 50 °C indicating the role of 70 °C for this Stetter reaction (entry 13). Moreover, decreasing the amount of either the aldehyde **1a** or the carbene precursor **4** resulted in reduced yield of the product (entries 14 and 15). Thus, the use of imidazolium salt **4** (20 mol %) and K_2CO_3 as base (40 mol %) in THF at 70 °C was found to be the condition for the satisfactory yield of the desired product **3a** (the standard condition in entry 1).[16] Additionally, **3a** was formed in the same yield when the reaction was performed on a 5.0 mmol scale demonstrating the scalable nature of the present reaction.

Next, we examined the scope and limitations of the present NHC-catalyzed Stetter reaction for the synthesis of *γ*-ketophosphonates (Scheme 2). A series of aromatic aldehydes with an electron-withdrawing group at the 4-position of the ring underwent smooth coupling reaction leading to the formation of the expected *γ*-ketophosphonates in moderate to good yields (**3a**−**e**).[17] Moreover, 4-bromo substitution is well-tolerated, and the corresponding bromophosphonate **3f** was isolated in 60% yield. Disappointingly, the parent benzaldehyde and aldehydes containing an electron-releasing group at the 4-position of the ring afforded only traces of the desired *γ*-ketophosphonates. Additionally, 3-substituted benzaldehydes as well as disubstituted benzaldehydes worked well to furnish the target product in good yields (**3g**−**j**). Furthermore, heteroaromatic aldehydes can also be used as the aldehyde component in this umpolung approach providing access to various heterocyclic *γ*-ketophosphonates in moderate yields (**3k**,**l**). Interestingly, thiophene-2,5-dicarbaldehyde underwent double Stetter reaction with excess of vinylphosphonate to form the phosphonate **3m** in 45% yield.[18] It may be mentioned that our preliminary studies showed that aliphatic aldehydes and *α*,*β*-unsaturated aldehydes[19] did not afford the desired *γ*-ketophosphonates under the optimized reaction conditions.

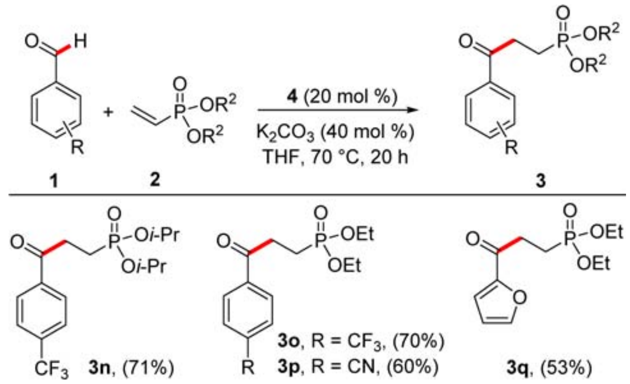
Scheme 2. NHC-Catalyzed Synthesis of *γ*-Ketophosphonates: Variation of the Aldehydes[a]



[a] General conditions: **2a** (0.50 mmol), **1** (0.75 mmol), **4** (20 mol %), K_2CO_3 (40 mol %), THF (3.0 mL), 70 °C, and 20 h. Yields of isolated products are given. [b] Reaction was run for 36 h. [c] Reaction was run for 24 h. [d] Reaction was run for 30 h using **2a** (1.25 mmol), the dialdehyde (0.50 mmol), **4** (40 mol %), K_2CO_3 (80 mol %).

We further examined the scope of this reaction using various vinylphosphonate derivatives (Scheme 3). The reaction of 4-(trifluoromethyl)benzaldehyde **1a** with diisopropyl vinylphosphonate afforded the expected *γ*-ketophosphonate **3n** in 71% yield. Moreover, diethyl vinylphosphonate also furnished the desired product in moderate to good yield (**3o**−**q**). Disappointingly, preliminary experiments revealed that *β*-

Scheme 3. Variation of the Vinylphosphonate Moiety[a]

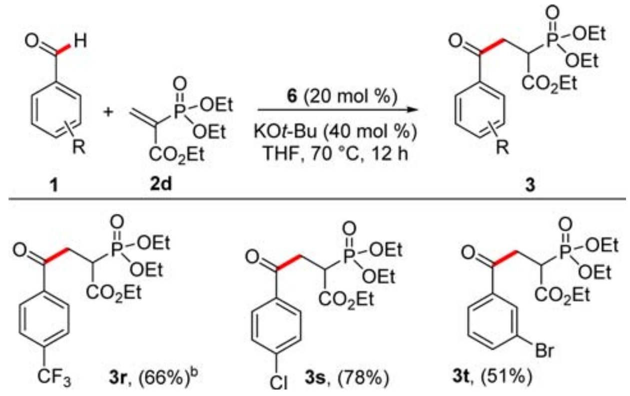


[a] General conditions: **2** (0.50 mmol), **1** (0.75 mmol), **4** (20 mol %), K_2CO_3 (40 mol %), THF (3.0 mL), 70 °C, and 20 h. Yields of isolated products are given.

substituted *α*,*β*-unsaturated phosphonates failed to undergo this transformation under the optimized reaction conditions.

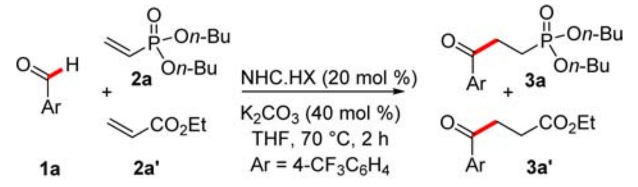
We also tested the feasibility of this reaction with *α*,*α*-disubstituted olefins (Scheme 4). The reaction of **1a** with ethyl 2-(diethoxyphosphoryl)acrylate **2d** using carbene derived from **4** afforded only reduced yield of the *γ*-ketophosphonate **3r**. Interestingly, when the reaction was performed using the carbene generated from **6**,[20] an efficient reaction occurred leading to the formation of **3r** in 66% yield. Analogous reactivity was achieved using halogenated aldehydes, and the desired product was isolated in moderate to good yields (**3s**,**t**).

Scheme 4. Stetter Reaction Using Phosphoryl Acrylate[a]



[a] General conditions: **2d** (0.50 mmol), **1** (0.75 mmol), **6** (20 mol %), KO*t*-Bu (40 mol %), THF (2.0 mL), 70 °C, and 12 h. Yields of isolated products are given. [b] Product **3r** contained small amounts of an impurity.

Scheme 5. Competition Experiment between Vinylphosphonate and Acrylate

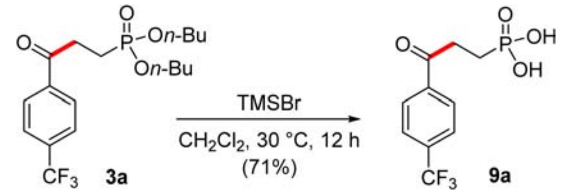


When NHC.HX = **4**, **3a** (10%), **3a'** (27%)
When NHC.HX = **6**, **3a** (<5%), **3a'** (44%)

To get insight into the relatively poor reactivity of vinylphosphonate compared to other Michael acceptors, we carried out intermolecular competition experiments using **2a** and the acrylate **2a′**. Interestingly, upon performing the reaction under optimized conditions and quenching after 2 h, the acrylate-derived Stetter product **3a′** was isolated in 27% yield, whereas the phosphonate-derived product **3a** was isolated in 10% yield only (Scheme 5).[16] Moreover, executing the reaction using carbene derived from **6**, **3a′** was isolated in 44% yield, and only traces of **3a** were observed. When this reaction was run for 20 h, **3a′** was observed in 95% and **3a** in 10% yield. These experiments shed light on the moderately electron-poor carbon−carbon double bond in vinylphosphonates.

The *γ*-ketophosphonate **3a** can easily be converted into the free *γ*-ketophosphonic acid derivative. Bromotrimethylsilane-mediated hydrolysis of **3a** followed by quenching with methanol resulted in the formation of the phosphonic acid **9a** in 71% yield (Scheme 6).

Scheme 6. Synthesis of *γ*-Ketophosphonic acid



In summary, we have developed the NHC-catalyzed cross-coupling of aromatic aldehydes with *α*,*β*-unsaturated phosphonates. This Stetter reaction using moderately electron-poor Michael acceptor afforded the *γ*-ketophosphonates in moderate to good yields. Given the importance of *γ*-ketophosphonates in crop protection and medicinal chemistry, the protocol demonstrated herein is likely a practical method for accessing these compounds.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures as well as characterization data of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support to this work was generously provided by the Science and Engineering Research Board, DST, Government of India (Grant No. SR/S1/OC/12/2012). A.P. and A.B. thank CSIR-New Delhi for the award of research fellowships. We thank Dr. P. R. Rajamohanan (CSIR-NCL) for the excellent NMR support and Ms. B. Santhakumari (CSIR-NCL) for the HRMS data.

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(16) For details, see the Supporting Information.

(17) Notably, benzaldehyde afforded the expected product in ∼10% yield, and 2-naphthaldehyde furnished 23% yield of the desired product.

(18) The moderate yield in some cases may be due to the polymerization of the vinylphosphonate under the reaction conditions. In most of the cases, the vinylphosphonates are completely consumed, and the aldehyde is converted into the corresponding benzoin. It may be noted the aldehyde−Breslow intermediate−benzoin formation is reversible under the NHC-catalyzed reaction conditions.

(19) It may be mentioned that α,β-unsaturated aldehydes afforded the γ-lactone derivative resulting from the homocoupling of enals with complete recovery of vinylphosphonates under optimized conditions.

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