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Ti(*O-iso*Pr)$_4$ Catalyzed hydrophosphonylation of activated alkenes by diphenyl H-phosphonate

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Abstract—Diphenyl 2-(alkoxycarbonyl)alkylphosphonates were synthesized via a titanium alkoxide catalyzed Pudovik reaction under mild conditions. Methacrylates or acrylates were selectively hydrophosphonylated by diphenyl H-phosphonate even in the presence of a dialkyl phosphite.

Formation of P–C bonds is of considerable importance in organophosphorus chemistry.[1] The hydrophosphonylation of C=C by H-phosphonates is doubtlessly the most atom-economic method to form P–C bonds. Historically, the free radical addition of H-phosphonates to alkenes[2] has been the method of choice. However, the electrophilic nature of phosphoryl radicals essentially excludes the use of electron-deficient alkenes;[3,4] thus acrylates and methacrylates are not suitable substrates for the free radical hydrophosphonylation. On the other hand, these electron-deficient alkenes are activated by the adjacent carboxyl group, and are subject to the base or Lewis acid catalyzed Pudovik reaction.[5,6] Although a number of examples of Pudovik reaction of dialkyl H-phosphonates have been documented, the hydrophosphonylation of (meth)acrylate-type activated alkenes by diaryl H-phosphonates has witnessed few reports.[7]

In our ongoing program to develop organophosphorus polymer additives, we aimed to synthesize diaryl phosphonates.[8] These compounds are attractive not only because the variation of ester groups on the phosphonates changes their many physical and chemical properties such as toxicity,[9] volatility, and stereochemistry outcomes[10,11] in Horner–Wadsworth–Emmons reaction, but also because they have largely been ignored, probably because of the lack of good synthetic methods to access them. Due to their relatively high molecular weights and thus low volatility compared with the dialkyl 2-(alkoxycarbonyl)alkylphosphonates, diaryl 2-(alkoxycarbonyl)alkylphosphonates caught our attention in our search of a new type of organophosphorus additives. Naturally, the Pudovik reaction is our first choice to synthesize diaryl 2-(alkoxycarbonyl)alkylphosphonates from diaryl H-phosphonates and carbonyl-activated alkenes. However, it has been long recognized that diaryl and dialkyl H-phosphonates often follow a different reaction pathway and the reaction conditions which are suitable for dialkyl H-phosphonates often fail to apply to diaryl H-phosphonates.[12,13] This dissimilarity presents a synthetic challenge to utilize diaryl H-phosphonates.

In this Letter, we report an efficient method with high selectivity to synthesize diphenyl 2-(alkoxycarbonyl)-alkylphosphonates from diphenyl H-phosphonate, the most important and readily available diaryl H-phosphonate, and a variety of (meth)acrylate-type activated alkenes under mild conditions.

We began with the traditional easily handled base catalysts such as triethylamine and 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU), which have been proven to be successful in the Pudovik reaction of dialkyl H-phosphonates, and Lewis acids in an attempt to synthesize methyl 2-(diphenylphosphono)propionate from diphenyl H-phosphonate and methyl acrylate. Unfortunately, although both the tested base catalysts

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Table 1. Catalyst screening for the hydrophosphonylation of methyl acrylate by diphenyl H-phosphonate[a]

Entry	Catalyst	Yield[b] (%)
1	Triethylamine	8
2	DBU	13
3	$AlCl_3$	0
4	$TiCl_4$	0
5	Ti(*O-iso*Pr)$_4$	95[c]

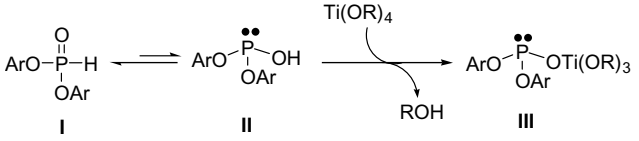
[a] Reactions were run at a mol ratio of diphenyl H-phosphonate/methyl acrylate:catalyst = 1.64/1/0.10 with diphenyl H-phosphonate = 0.100 mol at room temperature for 30 min.
[b] ^{31}P NMR yield.
[c] 5% (*iso*-PrO)(C_6H_5O)P(=O)CH_2CH_2C(O)OCH_3.

gave the targeted product, the yields were very low (Table 1, entries 1 and 2), and Lewis acids such as $AlCl_3$ and $TiCl_4$ were totally ineffective (Table 1, entries 3 and 4).

Since the attacking species diaryl phosphite exits in two tautomeric forms, the phosphite (**II**, Scheme 1) and the H-phosphonate (**I**, Scheme 1) with the latter predominating under neutral conditions, [14] We speculated that catalysts that aid to shift the reaction to the right may accelerate the reaction; therefore, we tested titanium *iso*-propoxide which is reported to undergo the transesterification with the hydrogen phosphite to form a metallo-phosphite (**III,** Scheme 1),[15,16] a species which has a lone pair of electrons and thus is a potential attacking species. The result was very satisfactory. Methyl 2-(diphenylphosphono)propionate was obtained in 95% yield at room temperature (Table 1, entry 5).

Titanium *iso*-propoxide was subsequently applied to a variety of (meth)acrylate-type alkenes. Most of the tested compounds produced the targeted diphenyl 2-(alkoxylcarbonyl)alkylphosphonates at high yields (Table 2, entries 1–5 and 7). For example, ethyl and *tert*-butyl 2-(diphenylphosphono)propionates were formed quantitatively from diphenyl H-phosphonate and the corresponding acrylates at the 10 mol % catalyst loading under the mild reaction conditions.

It is noted that the carboxylic ester groups considerably affected the reaction course. The bulky ester groups significantly retard the reaction. Changing the methyl to *tert*-butyl or phenyl group of the acrylates required much high temperatures and/or long reaction times in order to achieve a satisfactory conversion (Table 2, entries 1, 3, and 4). The results in Table 2 show that methyl acrylates readily reacted with diphenyl H-phosphonate at room temperature in the presence of 10 mol % titanium *iso*-propoxide but *tert*-butyl acrylate needed an elevated temperature (65 °C) and a prolonged reaction time (5 h) in order to complete the reaction. Phenyl acrylate has an intermediate reactivity. The similar pattern was also observed in the methacrylate series where methyl methacrylate is more reactive than phenyl methacrylate (Table 2, entries 5 and 6).



Scheme 1. Formation of the Ti–phosphite.

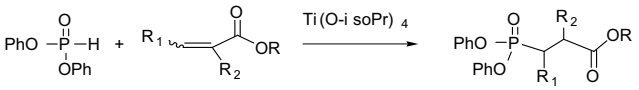
The presence of substituents at α or β position of the activated alkenes also substantially reduces the reaction rate. For instance, methyl acrylate was much more easily subject to the phosphonylation than methyl methacrylate or ethyl crotonate/cinnamate (Table 2, entries 1, 5, 7, and 8). Obviously, steric hindrance and the changing of the electron density of C=C caused by the substituents accounted for these differences.

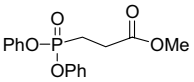
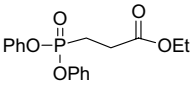
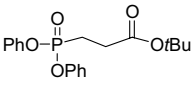
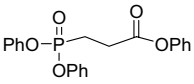
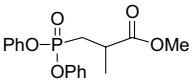
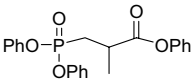
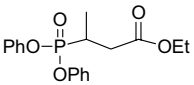
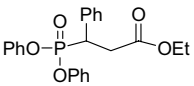
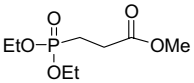
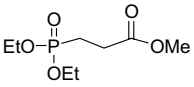
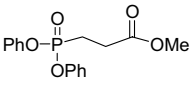
Interestingly, a high selectivity was observed between diphenyl H-phosphonate and *iso*-propyl phenyl/di(*iso*-propyl) H-phosphonates produced by the transesterification of diphenyl H-phosphonate and *iso*-propanol (Scheme 2, top right part). Under the reaction conditions used, the products mainly arose from diphenyl H-phosphonate ($\geqslant$95%). The selectivity among the phosphonylating agents can be controlled at higher than 98% by adjusting the feed ratio. In fact, when diphenyl H-phosphonate and diethyl H-phosphonate were mixed with methyl acrylate and Ti(*O-iso*Pr)$_4$ at a mole ratio of 2/2/1/0.1 (Table 2, entry 10), the only phosphonate product observed was methyl 2-(diphenylphosphono)propionate. Therefore, titanium *iso*-propoxide provides an excellent way to selectively hydrophosphonylate the (meth)acrylate-type alkenes by diphenyl H-phosphonate.

The high selectivity observed between diaryl and dialkyl (or alkyl aryl) H-phosphonates can be attributed to their different acidities. High acidity facilitates the formation of Ti–phosphite (**III**, Scheme 1). Although diethyl H-phosphonate reacts with titanium alkoxide too[15,16] and forms methyl 2-(diethylphosphono)propionate when methyl acrylate was present (Table 2, entry 9), it cannot compete with diphenyl H-phosphonate because of the latter's higher acidity. Therefore, the reaction selectively uses diphenyl H-phosphonate as the hydrophosphonylating agent.

A possible mechanism of the titanium alkoxide catalyzed Pudovik reaction of diaryl H-phosphonate is shown in Scheme 2. Transesterification produces a Ti–phosphite (**I**, Scheme 2) that attacks C=C to form **II** (Scheme 2). While **II** could extract a proton from H-phosphonates[18] followed by the tautomerization to an ester intermediate (**III**, Scheme 2) that is subject to the further reaction at the metal center (Path a), the negative effect of the bulky ester groups on the reactivity regardless of their electron-donating or electron-withdrawing nature seems to disfavor this path since Path (a) would exhibit a normal reactivity order; that is, phenyl (meth)acrylate > methyl (meth)acrylate due to the phenoxy group's activation on C=C.[19] An alternative path (Path b) involves the direct attack of the O^- nucleophile (**II**, Scheme 2) on the metal via a seven-membered ring in the transition stage to generate a phosphonate

Table 2. The hydrophosphonylation of (meth)acrylates by diphenyl H-phosphonate in the presence of Ti(*O-iso*Pr)$_4$[a,17]

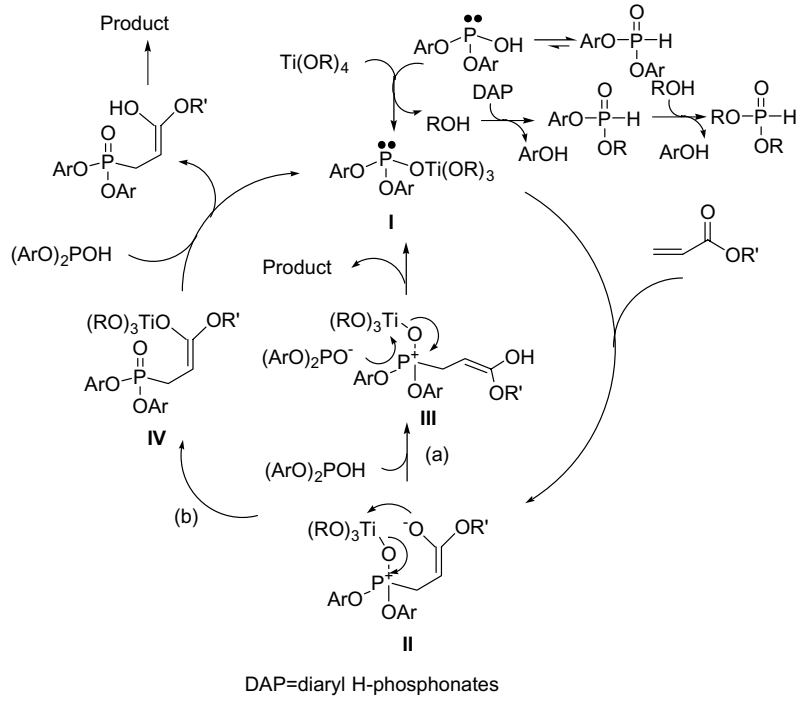


Entry	Mol ratios[b] DPP/C=C/[Ti]	Temperature (°C) & Time (h)	Product	Yield[c] (%)
1	1.64/1/0.060 1.64/1/0.10 2.00/1/0.10	25, 0.5 25, 0.5 25, 0.5		84[d] 95[e] 100 (82)
2	2.00/1/0.10	25, 0.5		100 (87)
3	1.64/1/0.10 2.00/1/0.10	25, 0.5 65, 5		20[d] 97[d] (72)
4	1.64/1/0.10	25, 0.5 25, 72		30[d] 92[d] (61)
5	1.64/1/0.10 1.64/1/0.15 2.77/1/0.26	25, 0.5 25, 0.5 60, 0.5		12 22 100 (88)
6	1.64/1/0.15	25, 0.5 25, 240		0 50[d] (40)
7	1.64/1/0.10 2.77/1/0.26	25, 0.5 105, 3		50[d] 85[d] (70)
8	1.64/1/0.10 2.77/1/0.26	65, 8 105, 3		60 60[d] (52)
9	2.00/1/0.10	25, 168		100
10	DEP/DPP /MA/[Ti][f]= 2.00/2.00 /1/0.10	25, 24	 	0 100

[a] Reactions were run at diphenyl H-phosphonate = 0.0500–0.100 mol. Results were the average of two runs.
[b] DPP = diphenyl H-phosphonate, C=C=alkenes, [Ti] = Ti(*O-iso*Pr)$_4$.
[c] ^{31}P NMR yields based on the activated alkenes. The isolated yields were in the parenthesis. Purification was not optimized.
[d] Selectivity ⩾98% from the ^{31}P NMR results.
[e] Selectivity = 95% from the ^{31}P NMR results.
[f] DEP = diethyl H-phosphonate, MA = methyl acrylate.

intermediate (**IV**, Scheme 2). Apparently, any bulky groups either in the carboxylic ester part or at the α/β positions of carboxylic esters will introduce ring strain in the transition stage and reduce the reactivity. Intermediate **IV** subsequently undergoes a transesterification at the metal center and consequently forms the product and regenerates the catalyst.

In conclusion, we developed a method to synthesize diphenyl 2-(alkoxylcarbonyl)alkylphosphonates from diphenyl H-phosphonate and (meth)acrylates under mild conditions. The method relies on the titanium alkoxide catalyzed Pudovik reaction. It is efficient and highly selective among different types of hydrogenphosphonylating agents.



Scheme 2. A possible mechanism of the $Ti(OR)_4$ catalyzed Pudovik reaction of diaryl H-phosphonates.

Acknowledgments

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Supplementary data

General experimental procedures, ^{1}H, ^{31}P, and ^{13}C NMR data and spectra of compound **1**–**8** in Table 2. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.02.055.

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17. *A typical experimental procedure for Ti(O-isoPr)$_4$ catalyzed Pudovik reaction*: Diphenyl phosphite (DPP, 95%, 16.300 g, 0.0661 mol) and methyl acrylate (2.860 g, 0.0332 mol) were mixed in a vial. To this mixture was then added titanium(IV) propoxide (0.940 g, 0.00331 mol) at room temperature. A strong exotherm was observed. The reaction was stopped after half hour. The mixture was then diluted with toluene and washed by aqueous HCl followed by caustic washes and water washes then dried in a Rotavapor®. The product methyl 2-(diphenylphosphono)propionate was further recrystallized from the ether solution. Mp: 41–43 °C; ^{1}H NMR ($CDCl_3$): 7.1–7.36 (m, 10H), 3.70 (s, 3H), 2.74–2.87 (m, 2H), 2.35–2.51 (m, 2H); ^{13}C NMR: 171.698 (d, $J^{3}_{PC} = 19.32$ Hz), 149.915

(d, $J^2_{PC} = 9.05$ Hz), 129.627, 125.077, 120.232 (d, $J^3_{PC} = 4.60$ Hz), 52.024, 27.115 (d, $J^2_{PC} = 3.70$ Hz), 21.378 (d, $J^1_{PC} = 145.10$ Hz); ^{31}P NMR: 23.53 ($J^2_{PH} = 17.80$ Hz, $J^3_{PH} = 11.87$ Hz).

18. One can draw a mechanism based on the proton abstraction from alcohols that shares the same intermediate (**II**) in Scheme 2. However, the fact that Ti(*O*-*iso*Pr)$_4$ also works for diethyl H-phosphonate suggests the proton abstraction from EtOH unlikely because EtOH has weaker acidity than diethyl H-phosphonate.
19. Phenyl acrylate has been shown to be more reactive than methyl acrylate in the base-catalyzed Michael addition. For example, Shi, M.; Chen, L. H.; Li, C. Q. *J. Am. Chem. Soc.* **2005**, *127*, 3790–3800.