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A concise method for synthesis of diaryl aryl- or alkylphosphonates

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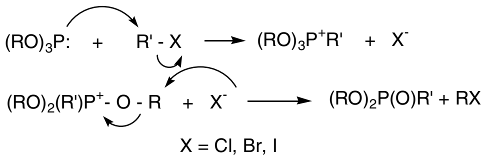
Abstract—A convenient method has been developed to synthesize diaryl arylphosphonates from triaryl phosphites, triethyl phosphite, and aromatic halides. The new method relies on the triethyl phosphite assisted nickel catalyzed Arbuzov reaction and can be applied to synthesize certain diaryl alkylphosphonates without catalysts.

Phosphonates have important applications in flame retardancy,[1,2] organic synthesis,[3] and biological applications.[4,5] The Arbuzov reaction is regarded as the premier synthetic method in the preparation of phosphonates from phosphites and halides.[6] The mechanism of the Arbuzov reaction has been shown to involve two nucleophilic attacks, that is, the formation of a quasi-phosphonium salt and the dealkylation of this salt, accompanied by rearrangement to a phosphonate (Scheme 1).[7]

However, due to the aryl groups' resistance to nucleophilic attack, the classic Arbuzov reaction was essentially limited to the preparation of alkylphosphonates ($R' =$ alkyl in Scheme 1). The synthesis of arylphosphonates ($R' =$ aryl in Scheme 1) represents one early challenge. In this regard, the transition-metal catalyzed Arbuzov reaction has gained remarkable success.[8–12] Tavs's seminal work on nickel catalyzed phosphonylation of aryl halides by trialkyl phosphites extends the classic Arbuzov reaction to the synthesis of dialkyl arylphosphonates.[8] In spite of these advances, the transition-metal catalyzed Arbuzov reaction faces the same challenge when directly applied to the synthesis of diaryl arylphosphonates (R, $R' =$ aryl in Scheme 1) from triaryl phosphites, because it would require the nucleophilic displacement on an aryl group in the rearrangement step of the Arbuzov reaction.[13]



Scheme 1. Mechanism of the Arbuzov reaction.

In our project to evaluate the performance of organophosphorus additives in polymers, we set a goal to develop industrially feasible synthetic methods for diaryl arylphosphonates, which have been only accessible through tedious and expensive routes, that is, Friedel–Crafts reaction of aromatic compounds by PCl_3 followed by the oxidation of aromatic dichlorophosphines and the subsequent esterification of arylphosphonic dichlorides with aromatic alcohols.[14,15] Since the Arbuzov reaction requires the presence of at least one alkylating group in a quasiphosphonium structure to satisfy the subsequent dealkylation to phosphonates, we envisioned that triaryl arylphosphonium salts may transform to diaryl arylphosphonates in the presence of an alkylating agent, which is able to first transesterify the quasiphosphonium salt and subsequently allow the rearrangement step of the Arbuzov reaction. We now find that diaryl arylphosphonates can indeed be formed from triaryl phosphites, aromatic halides, and alkylating agents, and the new method can be easily extended to certain diaryl alkylphosphonates as well.

In the first attempt, triphenyl phosphite was mixed with iodobenzene in the presence of nickel chloride. Methanol was then used to assist the Arbuzov rearrangement. Entry 1 of Table 1 shows that diphenyl phenylphospho-

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Keywords: Triaryl phosphite; Triethyl phosphite; Diaryl arylphosphonate; Diaryl alkylphosphonate; Arbuzov reaction.

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Table 1. Diphenyl phenylphosphonate from triphenyl phosphite (TPPi) and iodobenzene in the presence of an alkylating agent[a]

Entry	Alkylating agent	Yield (%)[b]
1[c]	CH_3OH	77
2[d]	$(EtO)_3P$	98

[a] 0.06 mol TPPi, 160 °C/4 h, the amount of $NiCl_2$ (5 mol %) was based on iodobenzene.

[b] ^{31}P NMR results.

[c] TPPi/idobenzene/CH_3OH = 1/1/1.3, phenol was formed.

[d] TPPi/idobenzene/triethyl phosphite (TEPi) = 2/3/1.1, no phenol was generated.

nate was obtained in a good yield (77%). However, diphenyl methylphosphonate (23%) and a theoretical quantity of phenol together with methyl iodide were also simultaneously produced. From the point of atom economy,[16] this route has a disadvantage. Since we speculated that the rearrangement may be preceded by a transesterification, we then resorted to triethyl phosphite, which undergoes ester exchange with triphenyl phosphite.[17] To our delight, diphenyl phenylphosphonate was obtained in a high yield (98%) with ethyl iodide as the major by-product.

This triethyl phosphite assisted method was extended to a variety of aryl halides and triaryl phosphites. Most of the diphenyl arylphosphonates were obtained in excellent yields (Table 2, entries 1–6, 8, 10, and 12). While a detailed kinetic study was not performed, it was observed that the electron donating groups on the aromatic ring of the aryl halide usually facilitated the reaction while electron withdrawing groups suppressed the reaction.[18] Thus, while diphenyl 4-methoxybenzenephosphonate (Table 2, entry 5) was obtained in 97% yield at 163 °C in 2.5 h, ethyl diphenylphosphonobenzoate (Table 2, entry 6) required 6.5 h to reach a similar conversion at even higher temperature, and diphenyl 4-tolylphosphonate and diphenyl phenylphosphonate (Table 2, entries 4 and 3) were synthesized under intermediate conditions.

Aryl iodides generally reacted faster than aryl bromides, while non-activated aryl chlorides were inert under similar reaction conditions (Table 2, entries 1, 3, 7, and 9). The functional groups in aryl iodides may interfere with the nickel halide catalyst. Formation of a few percent of diphenyl methylphosphonate was noted when 4-methoxyiodobenene was used instead of 4-methoxybromobenzene (Table 2, entry 2). Apparently, methylphosphonate was formed via methyl iodide, which stemmed from the cleavage of the 4-methoxy group on the benzene ring.

Steric hindrance significantly affects the course of the reaction. It has been observed in the classic Arbuzov reaction that the presence of a β branch in the alkyl halide retards the reaction. Thus, it was not too surprising that the reaction of triphenyl phosphite and methyl *o*-iodobenzoate went very slowly (Table 2, entry 11). A sterically demanding phosphite also significantly lowered the yield (Table 2, entry 15).

This synthetic method can be easily applied to the activated alkyl halides where the catalyst is not necessary. For example, diphenyl benzylphosphonate was readily obtained quantitatively (Table 2, entry 13). However, the attempt to make diphenyl pentylphosphonate only met limited success (Table 2, entry 14).

The $NiCl_2$-catalyzed Arbuzov reaction of trialkyl phosphites with aryl halides involves in situ reduction of $NiCl_2$ to tetrakis(trialkyl phosphite) nickel(0).[18] We propose a reaction mechanism based on the oxidative addition and reductive elimination on nickel(0) with an additional transesterification step, which generates the mixed phosphites (Scheme 2).[19–22]

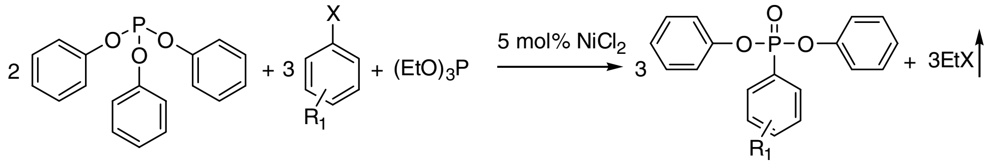
When triphenyl phosphite was mixed with triethyl phosphite, an equilibrium was established between starting materials and ethyl diphenyl and diethyl phenyl phosphites, which were formed via ester exchange. Obviously, those phosphites with alkylating ability induce the formation of arylphosphonates **I**, **II**, and **III** in the presence of aryl halides under the influence of a nickel(0) catalyst (Scheme 2, left circle). Indeed, in the course of the reaction, not in the final products, we found the formation of both diethyl arylphosphonates and ethyl aryl arylphosphonates in the ^{31}P NMR. However, the absence of di/mono-ethyl arylphosphonates (**II** and **III** in Scheme 2) in the final products suggests they act as alkylating agents (Scheme 2, right circle).

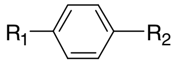
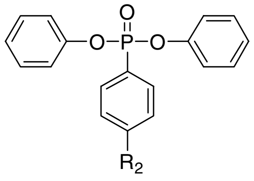
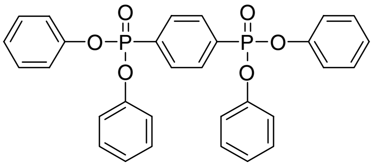
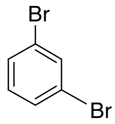
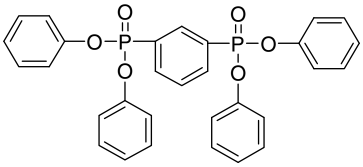
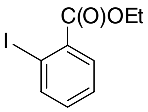
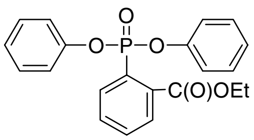
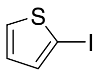
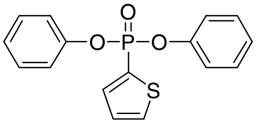
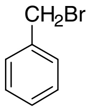
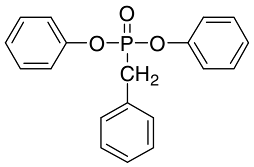
That **II** and **III** act as alkylating agents is supported by the fact that the change of the addition order did not alter the reaction products. For example, immediately after diethyl phenylphosphonate (**III** in Scheme 2, $R_1 = H$) was synthesized from triethyl phosphite/iodobenzene/$NiCl_2$, adding triphenyl phosphite and iodobenzene to the reaction solution yielded the same final products, diphenyl phenylphosphonate (**I** in Scheme 2, $R_1 = H$ and $Ar = Ph$) and ethyl iodide, as those obtained by adding triethyl phosphite to the solution of triphenyl phosphite/iodobenzene/$NiCl_2$. The intermediate ethyl phenyl phenylphosphonate was observed in the ^{31}P NMR in both cases. The mechanism leading to the formation of diaryl alkylphosphonates is likely to be similar to the above mechanism except that the P–C bond is directly formed without the metal being involved.

In contrast to the transition-metal-catalyzed carbon–carbon bond formation of aromatic halides where electron-withdrawing groups usually facilitate the reactions by activating the benzene ring and thus the oxidative addition step,[23] the retardation of electron-withdrawing groups on phosphonylation may suggest that the reductive elimination of arylphosphonates from the presumed nickel complex is the rate-determining step.

In conclusion, we have developed a triethyl phosphite assisted method to synthesize diaryl aryl- or alkylphosphonates from triaryl phosphites and aryl or activated alkyl halides. This new method easily extends the classic Arbuzov reaction to cover the otherwise difficultly synthesized diaryl aryl- or alkylphosphonates. Its

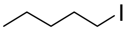
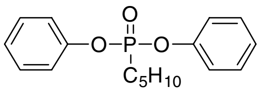
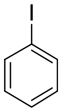
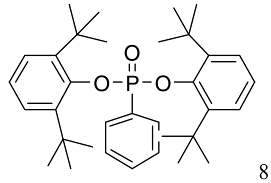
Table 2. Diaryl phosphonates from triaryl phosphites and aromatic or alkyl Halides[a]



Entry	Halide		Product		Yield (%)[b]
	R_1	R_2	Temperature (°C)	Time (h)	
					
1	I	H	160	4	93 (98)
2	I	OMe	155	2	(95)
3[c]	Br	H	173	6	(98)
4[c]	Br	Me	170	6	94 (98)
5[c]	Br	OMe	163	2.5	87 (97)
6	Br	C(O)OEt	173	6.5	87 (97)
7	Cl	H	180	8	0
					
8	Br	Br	178	2.5	97 (99)
9	Cl	Cl	180	8	0
10			 163	5	85 (98)
11			 180	8	(12)
12			 160	4	89 (97)
13[d]			 175	5	92 (97)

(continued on next page)

Table 2 (*continued*)

Entry	Halide		Product		Yield (%)[b]
	R_1	R_2	Temperature (°C)	Time (h)	
14[d]			 180	8	(35)
15[e]			 180	8	(32)

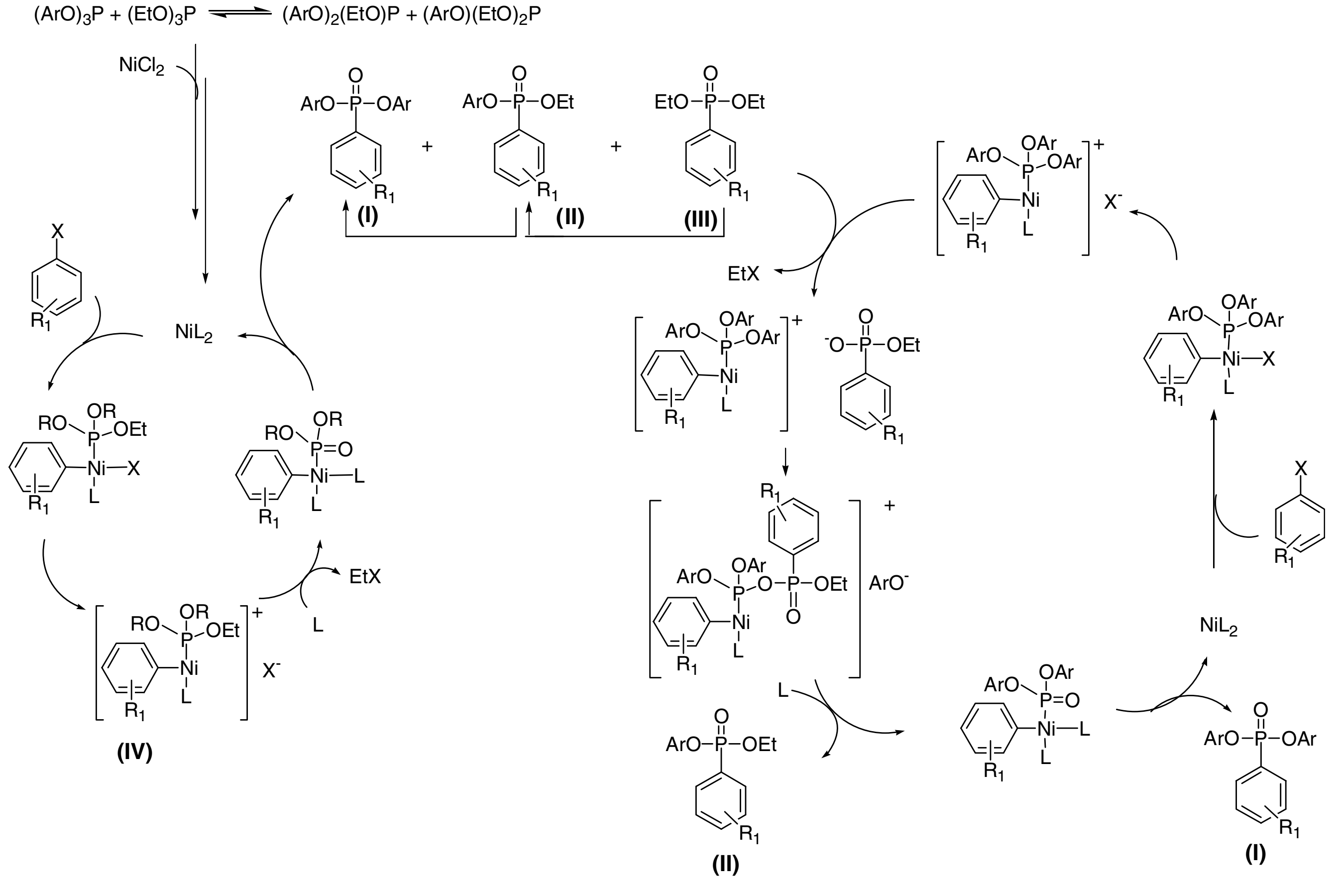
[a] 0.06 mol TPPi, TPPi/halide/TEPi/$NiCl_2$ = 2/3/1.1/0.15, $NiCl_2$ was used, unless otherwise specified.

[b] Isolated yield with ^{31}P NMR yield in parentheses.

[c] $NiCl_2$ and $NiBr_2$ were compared, no difference in the yield and rate was observed.

[d] No catalyst used.

[e] Tris(2,4-di-*tert*-butylphenyl)phosphite used.



L= triaryl phosphite, triethyl phosphite, and mixed phosphites, R=Ar or Et

Scheme 2. Plausible mechanism of the formation of diaryl arylphosphonates.

simplicity and general utility should find wider application in the synthesis of diaryl arylphosphonates or activated alkylphosphonates. In the future, we will study the possibility of using non-activated aryl chlorides and alkyl halides for this type of reaction.

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Supplementary data

General experimental procedures, ^{1}H, ^{31}P, and ^{13}C NMR data and spectra of compound **1**, **3**, **4**, **6**, **8–10**, and **13**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.11.028.

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