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Synthesis of dialkyl and diaryl benzylphosphonates through a ZnI_2-mediated reaction

Rebekah M. Richardson, Rocky J. Barney, David F. Wiemer *

Department of Chemistry, The University of Iowa, Iowa City, Iowa 52242-1294, United States

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This paper is dedicated in honor of Professor Henri-Jean Cristau on the occasion of his 70th birthday.

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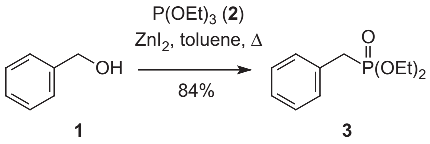
ABSTRACT

Several trialkyl and two triaryl phosphites have been tested for their reactivity in the zinc iodide mediated conversion of benzyl alcohol to the corresponding phosphonates. Most react smoothly to afford the desired phosphonate diesters, including hindered and nonracemic phosphites. The implications of this reactivity on the reactions involved in the transformation are discussed.

For many years the Horner–Wadsworth–Emmons (HWE) condensation has remained a popular reaction for the synthesis of α,β-unsaturated esters.[1,2] In its original incarnation,[3] the condensation of an α-phosphonoester with an aldehyde was shown to favor the formation of the trans olefin isomer. More recent modifications, including those reported by Breuer,[4] Savignac,[5] Stille,[6] and perhaps especially Ando,[7] have allowed preferential formation of the cis olefin isomer in a variety of cases when specific phosphonate esters are employed. This stereocontrol has only increased the value of the phosphonate reagents and the popularity of this strategy for the synthesis of α,β-unsaturated esters. Furthermore, other applications of phosphonates in carbon-carbon bond formation have been reported as well.[1,2] For example, the applications of benzylic phosphonates in stilbene synthesis have been recognized for many years,[8] and this strategy has been particularly useful to us in the synthesis of natural stilbenes such as the schweinfurthins[9] and pawhuskins.[10]

In contrast to the many studies on the scope and stereochemistry of the HWE condensation, strategies for phosphonate synthesis have not changed a great deal over the years.[1,2] The Arbuzov reaction is easily the most commonly employed strategy, but recent reports have described a Lewis acid mediated approach to the preparation of diethyl phosphonates (Scheme 1).[11,12] Our studies[11] have suggested that this is a general reaction for benzylic and allylic alcohols, and offered some mechanistic insight. However, limitations with respect to the nature of the phosphite component remained unclear. Given the increasing application of more hindered phosphonate esters in HWE reactions and our longstanding interest in phosphonate chemistry,[13] the potential use of this process toward the preparation of other phosphonate esters was of interest.

Benzyl alcohol was selected as the test compound because it gave good yields under relatively mild conditions in reactions with $ZnI_2/P(OEt)_3$.[11] Several other trialkyl and triaryl phosphites now have been examined under standard reaction conditions (Table 1, entries 2–8). Attempted preparation of bis(1,1,1-trifluoroethyl) benzylphosphonate (entry 2) from the corresponding phosphite (**4**) through this methodology was not successful under the standard conditions, which may be due to the strong electron withdrawing nature of the 1,1,1-trifluoroethyl substituents combined with the steric hindrance these substituents engender. In somewhat surprising contrast, the reaction of triisopropyl phosphite



Scheme 1. Conversion of benzyl alcohol to diethyl benzylphosphonate.

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* Corresponding author. Tel.: +1 319 335 1365; fax: +1 319 335 1270.
E-mail address: david-wiemer@uiowa.edu (D.F. Wiemer).

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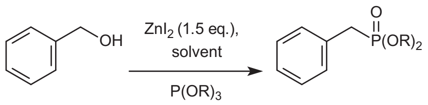
Table 1
Synthesis of varied esters of benzylphosphonate through a ZnI_2 mediated reaction

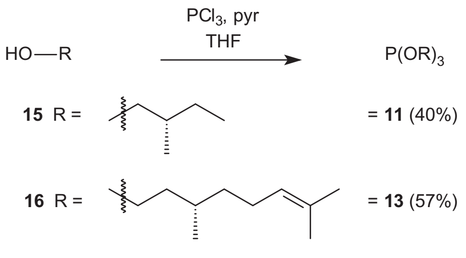


Entry	R (phosphite/ phosphonate)	Solvent	Rx temp (°C)	Isolated yield (%)
1[11]	CH_2CH_3 (**2**/**3**)	Toluene	80	84
2	CH_2CF_3 (**4**/-)	DMF	120	–
3	$(CH)(CH_3)_2$ (**5**/**6**)	THF	66	59
4	$(CH)(CH_3)_2$ (**5**/**6**)	DMF	80	97
5	C_6H_5 (**7**/**8**)	DMF	120	81
6	*o*-Tolyl (**9**/**10**)	Toluene	111	34
7	*S*-2-Methylbutyl (**11**/**12**)	THF	66	81
8	*S*-Citronellyl (**13**/**14**)	THF	66	76

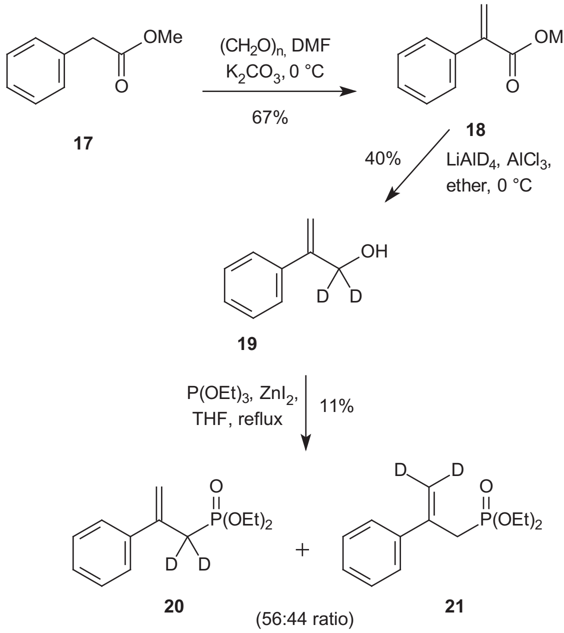
(**5**) with benzyl alcohol in THF gave a moderate yield of diisopropyl benzylphosphonate (**6**, entry 3), and in DMF at a higher temperature the transformation became virtually quantitative (entry 4). Even triphenyl phosphite (**7**) in DMF gave an attractive yield of diphenyl benzylphosphonate (**8**, entry 5). While the ZnI_2-mediated reaction of benzyl alcohol with *o*-tolylphosphite (**9**) proceeded in poor yield in DMF, and the product proved very difficult to isolate even when toluene was utilized, a 34% yield of the very sterically hindered *o*-tolyl phosphonate **10** was achieved (Table 1, entry 6).

Because phosphonate esters prepared from nonracemic alcohols have been employed in a number of studies,[14] the applicability of this methodology in the preparation of such compounds was also examined. Synthesis of one nonracemic phosphite was accomplished through the reaction of (*S*)-2-methyl-1-butanol (**15**) with PCl_3 in the presence of pyridine to give the new trialkylphosphite **11** in modest yield (Scheme 2). Through a parallel process the reaction of (*S*)-citronellol (**16**) with PCl_3, gave the new trialkylphosphite **13** in moderate yield. Both these nonracemic phosphites reacted smoothly with benzyl alcohol under the standard reaction conditions. When heated at reflux in THF with benzyl alcohol and ZnI_2, phosphite **11** gave the desired phosphonate **12** in 81% yield. Phosphite **13**, derived from citronellol, also reacted smoothly to afford phosphonate **14** in comparable yield (76%). These results certainly suggest that nonracemic phosphites derived from other primary alcohols would undergo parallel reactions.

Of the examples listed in Table 1, perhaps most surprising are the attractive results obtained in the isopropyl and phenyl series, as well as observation of even modest yields of product with the *o*-tolyl phosphite. The bulky nature of these nucleophiles implies that a standard Arbuzov mechanism is unlikely, both because these phosphites are relatively poor nucleophiles and because after formation of a tetrasubstituted phosphorus intermediate, the ester substituents are not readily susceptible to an S_N2 attack by a halide ion. For example, when benzyl bromide was treated under Arbuzov conditions with triphenyl phosphite and variations in solvent, temperature, and reaction duration, only traces of the diphenyl benzylphosphonate product were observed based on the analysis of the ^{31}P NMR spectra. While the preparation of diisopropyl benzylphosphonate has been reported in 70% yield under standard Arbuzov conditions,[15] the phenyl analogue required a nickel catalyst to be obtained in good yield (92%),[16] and the *o*-tolyl has not been reported prior to this study.



Scheme 2. Synthesis of nonracemic trialkyl phosphites.



Scheme 3. A deuterium labeling experiment.

It has been suggested[11] that this transformation might involve the formation of a tetracoordinate zinc species[17] which undergoes C–P bond formation and the loss of ZnO through an S_N1-like process. The observed loss of stereochemistry in the reaction with (*S*)-1-phenylethanol supports an S_N1-like process,[11] and a final Arbuzov-like reaction would afford the observed product **2**. To study this reaction sequence in more detail, a number of additional experiments have been conducted.

To examine further the first component of this transformation, an isotopic labeling experiment was envisioned with a deuterated alcohol (Scheme 3). After preparation of the acrylate **18**[18] through a Knoevenagel condensation of methyl phenylacetate (**17**) and formaldehyde, the allylic alcohol could be obtained easily through the reduction of ester **18** with $LiAlH_4$ or DIBAL, albeit in low yield. When the resulting allylic alcohol was treated under the standard reaction conditions, the expected phosphonate was obtained. Even though the product phosphonate was obtained in low yield, this system offered a reasonable test of the reaction sequence. Therefore, reduction of ester **18** was conducted with $LiAlD_4/AlCl_3$ to obtain the desired isotopically labeled alcohol **19** (Scheme 3). Subsequent treatment with zinc iodide and triethyl phosphite in THF provided a mixture of both the methylene deuterated (**20**) and the vinyl deuterated (**21**) phosphonates, and analysis of the NMR spectra suggested a 56:44 ratio of **20**, **21** (Scheme 3). Formation of these products might be explained by a mixture of S_N2 and S_N2' reactions, but an S_N1-like mechanism may be a more fitting explanation.

The observed reactivity of the aryl phosphites in this transformation sheds some light on the second half of the reaction sequence. For the diethyl phosphonates and perhaps for the diisopropyl phosphonates, formation of a tetracoordinate zinc species (**22**), loss of zinc oxide, and a direct Arbuzov reaction on an intermediate such as **23** would explain formation of phosphonate

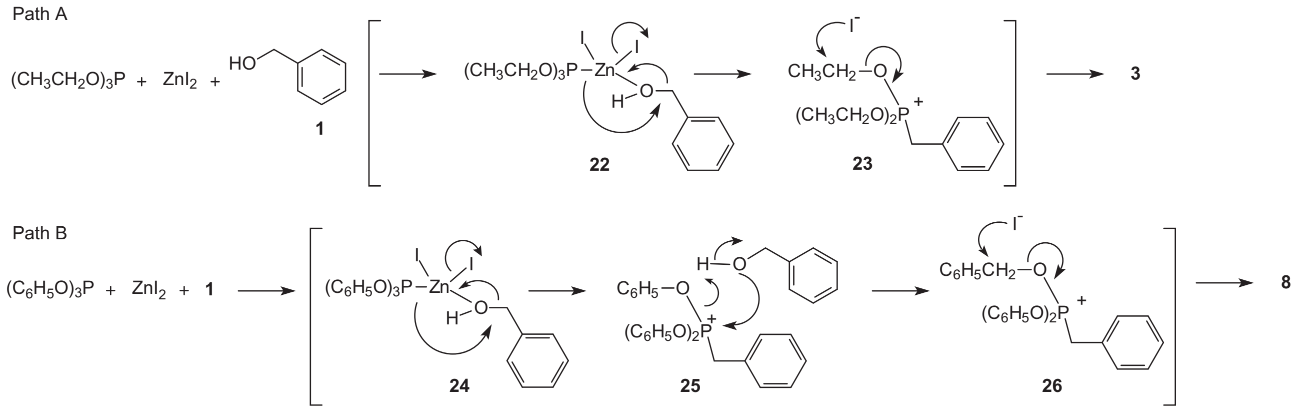


Figure 1. A possible reaction sequence for the zinc-mediated transformations.

3 (Fig. 1, Path A). However, loss of an aryl iodide through a simple S_N2 mechanism is unlikely, and the low yields for the formation of compound **8** under traditional Arbuzov conditions support that view. Instead (Path B), after the formation of a parallel zinc complex (**24**) from the aryl phosphite and loss of zinc oxide to generate the C–P bond (**25**), it is possible that exchange with unreacted benzyl alcohol affords an intermediate (**26**) that is capable of a final Arbuzov reaction to afford phosphonate **8**. However, if this type of exchange were involved the exchange process would have to be catalytic in terms of the benzyl alcohol, because an excess of this reagent was not employed and yields are well above the 50% that might be expected if an equivalent were needed for the second step. Thus there are mechanistic aspects of this transformation that still would benefit from further studies.

In conclusion, these studies have determined that the zinc iodide mediated transformation of benzylic alcohols to phosphonates is viable with both trialkyl and triaryl phosphites. Because it allows access to the hindered phosphonate esters that have been employed in newer variations of the Horner-Wadsworth-Emmons condensation, including both hindered and nonracemic esters, the reaction is relatively broad in scope and may be useful in preparation of a variety of reagents.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures and/or spectral data for compounds **6**, **8**, **10**–**14**, and **18**–**21**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.09.114.

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