ORGANIC LETTERS

2010
Vol. 12, No. 18
3990−3993

Room-Temperature Alternative to the Arbuzov Reaction: The Reductive Deoxygenation of Acyl Phosphonates

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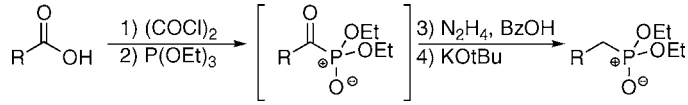
Received July 6, 2010

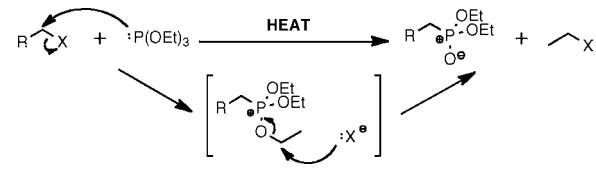
ABSTRACT



The reductive deoxygenation of acyl phosphonates using a Wolff−Kishner-like sequence is described. This transformation allows direct access to alkyl phosphonates from acyl phosphonates at room temperature. The method can be combined with acyl phosphonate synthesis into a one pot, four-step procedure for the conversion of carboxylic acids into alkyl phosphonates. The methodology works well for a variety of aliphatic acids and shows a functional group tolerance similar to that of other hydrazone-forming reactions.

Phosphonates are a key functional group in both organic synthesis and biological chemistry.[1] In synthesis, they are a direct precursor of olefins through the Horner−Wadsworth−Emmons reaction.[2] In biological chemistry, their unique structure and charge distribution give them an important role in pharmaceuticals[3] and phosphoester mimicry.[4] Phosphonates have traditionally been accessed through the Arbuzov reaction:[5,6] a double S_N2 process between an alkyl halide and a trialkylphosphite (Scheme 1), and this remains the most commonly employed route today. Notable exceptions include aryl/vinyl phosphonates,[7] whose corresponding halides cannot readily participate in S_N2 reactions, and α-hydroxyl/α-amino phosphonates,[8] whose corresponding halides are unstable.

Scheme 1. The Arbuzov Reaction



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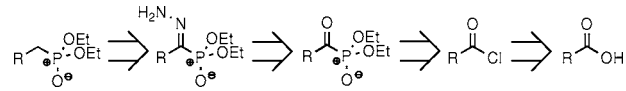
(5) Also known as the Michaelis−Arbuzov reaction.

10.1021/ol1015493
Published on Web 08/20/2010

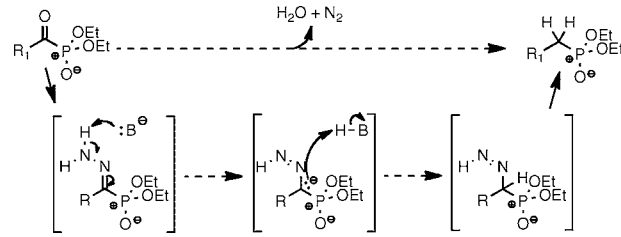
Despite its prevalence, the Arbuzov reaction has two key drawbacks. First, the elevated temperatures typically required limit the scope of substrates suitable for the reaction. Second, the reaction generates one equivalent of alkyl halide, which can react with the phosphite under the reaction conditions to reduce yield and reaction efficiency. A modification using dialkylphosphite salts instead of trialkylphosphites eliminates the problem of new alkyl halide generation, but the yields are typically poorer, and this strategy is much less used.[9] A number of other strategies for alkyl phosphonate synthesis have been developed,[10,11] most notably the transition metal-mediated hydrophosphonylation of olefins with cyclic five-membered hydrogen phosphonates.[12] Yet even this reaction is limited by the phosphite component scope and prolonged heating. Here we present a room-temperature alternative to the Arbuzov reaction that allows for the synthesis of phosphonates from carboxylic acids.

We began with the observation that the Arbuzov reaction of acyl halides is strikingly mild in comparison to the alkyl variant, often going to completion in several minutes at room temperature.[13] Second, we noted that these acyl phosphonates can form isolable hydrazones,[14] in contrast to most other carboxylic acid derivatives. This led us to consider the possibility that such acyl phosphonates could be deoxygenated through a Wolff−Kishner-type reduction to give alkyl phosphonates. Such a reaction would allow alkyl phosphonates to be readily accessed from carboxylic acid precursors (Scheme 2). At first glance, such a proposal may seem unattractive, given that Wolff−Kishner conditions are quite harsh (the frequently used Huang-Minlon modification calls for ethylene glycol and potassium hydroxide at 200 °C).[15,16] However, we reasoned that the electron-withdrawing phosphonate group could stabilize the carbanionic character of the presumed key intermediate (Scheme 3). The attendant transition state stabilization would allow this reaction variant to be much milder.

Scheme 2. Retrosynthesis of Alkyl Phosphonates from Carboxylic Acids



Scheme 3. Electron-Withdrawing Phosphonate Stabilizes the Carbanionic Character of the Key Intermediate



To test this proposal, we synthesized the hydrazone of diethyl propionylphosphonate. Guided by several reports of low temperature (≤100 °C) Wolff−Kishner reductions,[17] we slowly added the hydrazone to a rapidly stirring mixture of 10 equiv of potassium *tert*-butoxide in dimethyl sulfoxide at room temperature. Pleasingly, a trace amount of diethyl propylphosphonate could be detected in the crude reaction mixture by ^{31}P NMR. After exploring a variety of reaction conditions with the screening robot in the Caltech Center for Catalysis and Chemical Synthesis, we found that good (≥70%) yields of diethyl propylphosphonate could be obtained at room temperature using potassium *tert*-butoxide in a 50% *v*/*v* tetrahydrofuran:*tert*-butanol solvent mixture.

We then turned our attention toward the hydrazone-formation step, seeking conditions that would allow the crude hydrazone to be used directly in the base-promoted reduction step. Using propionyl phosphonate as the model substrate, we found that moderately acidic conditions worked best: strongly acidic conditions led to no reaction, while pH-neutral and basic conditions led to decomposition of the starting

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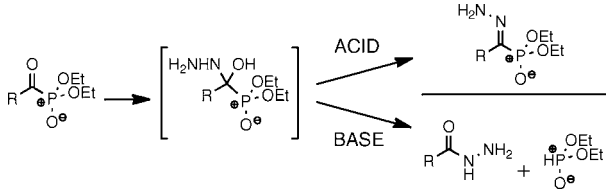
material into propionyl hydrazide and diethylphosphite (Scheme 4). These observations are consistent with the trends observed in the formation of Schiff bases and related structures,[18] except—in this case—higher pHs lead to decomposition rather than merely slower rates. The observed decomposition products are consistent with elimination of the phosphite from the presumed tetrahedral intermediate, indicating that the elimination of phosphite is favored under basic or neutral conditions, while the elimination of water is favored under acidic conditions.

Scheme 4. Reaction Course of Acyl Phosphonates with Hydrazine is pH-Dependent



We next sought to combine the hydrazone-formation and -reduction steps. Since hydrazone formation is a reversible process, we anticipated that the direct addition of base to the water-containing hydrazone-formation reaction would lead to the same decomposition products observed previously (dialkylphosphite and propionyl hydrazide). This prediction was confirmed in practice under a variety of conditions. Similarly, when one equivalent of water was added to the reduction reaction of the purified hydrazone, the yield was dramatically reduced. Therefore, water must be removed from the hydrazone-forming reaction prior to its treatment with base. Adding desiccants to the reaction mixture (e.g., $MgSO_4$, molecular sieves, etc.) gave low and inconsistent yields of the propyl phosphonate, even when the desiccant was filtered off prior to base addition. Evaporation of the liquid reactions under hi-vacuum failed to remove all the water, and the resultant oils gave poor yields of phosphonate when the reduction conditions were applied. However, when benzene was used as solvent in combination with a solid acid additive such as benzoic acid, the reaction mixture could be flash-frozen and placed under hi-vacuum to effectively remove all water, leaving behind a powdery solid matrix of hydrazone and benzoic acid. Applying the reduction conditions to the residual lyophilized powder gave the phosphonate in consistently satisfactory yields.

Having arrived at a two-step, one-pot deoxygenation of propionyl phosphonate, we set out to explore the substrate scope of this transformation, only to realize that the starting acyl phosphonates could be purified only by distillation (in our hands, these compounds would not crystallize as solids, and they decomposed during chromatography). Fortunately, the "acyl-Arbuzov" reaction is quite clean, and the crude

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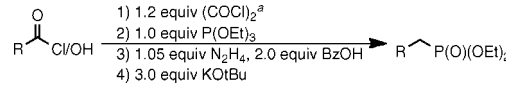
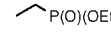
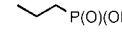
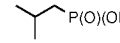
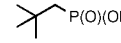
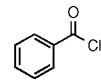
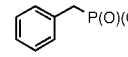
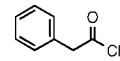
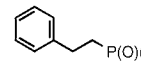
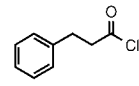
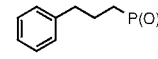
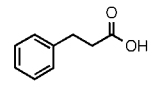
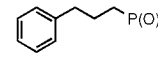
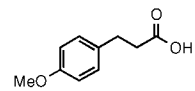
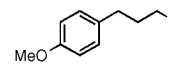
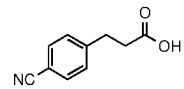
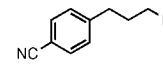
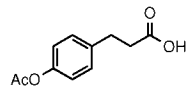
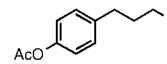
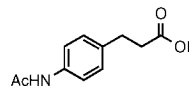
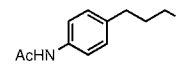
Table 1. Investigation of Substrate Scope



entry	substrate	product	yield (%)[b]
1			58 (83)
2			74 (90)
3a 3b[c]			35 (70) 45 (77)
4			< 5
5a 5b[d]			21 (59) 30 (67)
6			65 (87)
7			74 (90)
8			69 (91)
9			65 (90)
10			58 (87)
11			< 5
12			< 5

[a] Oxalyl Chloride used where the acyl chloride was not commercially available. [b] Isolated yields; values in parentheses represent average per-step yields for the 3-or 4-step sequence. [c] Four equivalents of benzoic acid used in hydrazone formation. [d] Two equivalents of *ortho*-bromobenzoic acid used in hydrazone formation.

product can be used directly after the *in vacuo* removal of the volatile chloroethane, eliminating any possible side reactions involving this byproduct. This led us to a one-pot, three-step (or four-step, in cases where the acid chloride is formed *in situ*) sequence for the direct conversion of acid chlorides/carboxylic acids to diethyl phosphonates. The optimized sequence is as follows. First, the acid is treated with oxalyl chloride and catalytic dimethylformamide in

dichloromethane. After removal of solvent and excess reagent *in vacuo*, the acid chloride is redissolved in dichloromethane and treated with one equivalent of triethylphosphite at 0 °C. Solvent and byproduct are again removed *in vacuo*; then, benzene and two molar equivalents of benzoic acid are added to the residue. Dropwise addition of a slight molar excess of commercially available 1.0 M hydrazine in THF solution yields the hydrazone in several minutes. This solution is then lyophilized to give a finely dispersed solid mixture of benzoic acid and the hydrazone. The solid is then dissolved in 50% *v/v* tetrahydrofuran/*tert*-butanol and treated with three equivalents of 0.6 M potassium *tert*-butoxide in 50% *v/v* tetrahydrofuran/*tert*-butanol at room temperature. Solid potassium benzoate immediately precipitates, and typical reactions turn yellow in color; gas evolution can be observed immediately. The reaction is then quenched with water, washed with saturated sodium bicarbonate, and purified by flash column chromatography to yield the pure phosphonate.

This reaction works well for simple carboxylic acids, yielding ≥58% for the sequence, corresponding to nearly 90% per step (Table 1). However, yields fall significantly for alpha-branched substrates (entries 3−5). NMR analysis of the reaction of isobutyryl chloride indicated that the acyl phosphonate is formed in high yield, but much of it decomposed to diethylphosphite and isobutyryl hydrazide during the hydrazone formation step. These are the same side products that we observed when trying to form the hydrazone of propionyl phosphonate under basic conditions (Scheme 4). Given that alpha branching leads to a more sterically crowded tetrahedral intermediate, we postulate that this steric crowding increases the effective nucleofugality of the bulky phosphite substituent relative to water. Having previously established that acid biases the tetrahedral intermediate toward the elimination of water over phosphite, we performed the same reaction using slightly more acidic conditions. Consistent with our hypotheses, this adjustment led to a small improvement in yield but a much slower reaction (entry 3b). Benzoyl chloride also gave poor yields (entry 5). Alpha branching may contribute to the low yield, but there are likely some electronic factors also in play, as benzoyl phosphonate is much less reactive than other acyl phosphonates under the hydrazone-forming reaction conditions (reaction times are 100−1000-fold longer).

Functional groups such as ethers (entry 9) and nitriles (entry 10) are well tolerated by the reaction, while amides (entry 11) and esters (entry 12) give poor yields, presumably due to the reaction of the carboxyl group with the hydrazine. While there are thus some limitations to the scope of this reaction sequence, it compares favorably to the conventional Arbuzov reaction in many cases.

In conclusion, we have developed a one-pot protocol for the Wolff−Kishner-type reductive deoxygenation of acyl phosphonates. We have further adapted this reaction to develop a one-pot sequence for the synthesis of alkyl phosphonates from carboxylic acids. We anticipate that this new reaction will offer a low-temperature alternative to the Arbuzov reaction for the synthesis of this important class of compounds.

Acknowledgment. We gratefully acknowledge the Caltech Center for Catalysis and Chemical Synthesis for screening and its director Dr. Scott Virgil for helpful discussions. This work was supported by the NIH (NS 34407) and an NIH training grant for S.K. (NRSA 5-T32-GM07616).

Supporting Information Available: Full experimental procedures, characterization data, and copies of ^{1}H, ^{13}C, and ^{31}P NMR spectra for all synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL1015493