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Mild and efficient Cs_2CO_3-promoted synthesis of phosphonates

Richard J. Cohen, Daniel L. Fox, Jarrod F. Eubank and Ralph Nicholas Salvatore*

Department of Chemistry, Western Kentucky University, 1 Big Red Way, Bowling Green, KY 42101-3576, USA

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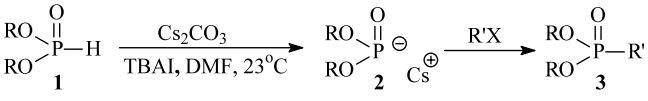
Abstract—A mild and convenient synthesis for phosphonates using cesium carbonate (Cs_2CO_3), tetrabutylammonium iodide (TBAI) and DMF was developed at room temperature. Numerous dialkyl phosphites were screened using a diverse array of alkyl halides and these reaction conditions were found to be highly efficient producing various phosphonates exclusively in moderate to high yields.

New or improved methods for phosphonate synthesis continue to attract much attention because phosphonates display a multitude of robust biologically important properties serving as natural products,[1] analogues of phosphates,[2] phosphonopeptides,[3] amino acid analogues,[4] and as pro-drugs.[5] Given their ubiquitous use as pharamacological agents[6] and as crucial synthetic intermediates[7] (e.g. Wadsworth–Emmons and related reactions), construction of the P–C bond still remains a formidable challenge. Traditionally, organophosphonates are prepared via a Michaelis–Arbuzov[8] or a Michaelis–Becker reaction[9] utilizing the nucleophilic properties of tervalent P(III) compounds (e.g. trialkyl phosphites or alkali metal salts of dialkyl phosphites) in the presence of alkyl halides. Depending on the method of choice, these conventional reaction conditions are often not convenient requiring elevated temperature,[10] the use of strong anhydrous base,[11] and very long reaction times.[12] Moreover, these procedures often lead to a complicated mixture of side products or result in poor yield of the phosphonate.[13] Therefore, to circumvent these aforementioned chronic problems, numerous other methods have been investigated.[14] Nonetheless, each of these methods lack in generality prompting us to embark on a milder and improved procedure better suited toward the synthesis of phosphonopeptides and phosphonotyrosine (pTyr)-containing peptidomimetics. Such mimetics are widely used for designing biological probes to modulate aberrant cellular signaling for the treatment of cancer and other diseases.

In the presence of cesium carbonate and tetrabutylammonium iodide (TBAI) at room temperature H-phosphonate anion **2**, was smoothly generated from dialkyl phosphite (**1**) in-situ. Subsequent alkylation of anion **2** with an alkyl halide produced the corresponding phosphonate **3** exclusively using anhydrous *N*,*N*-dimethylformamide (DMF) as the solvent of choice (Scheme 1).

Initially, we undertook an optimization study using dimethyl phosphite (**4**) and benzyl chloride as model coupling partners. At the outset of this work, we began our approach by screening a variety of different bases for the efficient synthesis of phosphonate **5**. Numerous alkali metal carbonates were probed including lithium, sodium, potassium, rubidium and cesium carbonate. Of the various alkali metal carbonates examined, cesium carbonate was the most successful base (Table 1, entry 5) delivering dimethyl benzylphosphonate (**5**) in highest yield.[15] Other carbonate bases were not as effective for the same transformation (Table 1, entries 1–4). We attribute this high selectivity to the unprecedented 'cesium effect'.[16] Cesium bases have enjoyed much success in facilitating numerous alkylations efficiently.[17] This methodology therefore, we believe, further contributes to existing cesium base promoted transformations.[17] As further indication, we found that cesium hydroxide in the presence of activated molecular sieves,



Scheme 1.

Keywords: phosphonate; dialkyl phosphite; cesium carbonate; tetrabutylammonium iodide.

* Corresponding author. Tel.: +1-270-745-3271; fax: +1-270-745-5361; e-mail: ralph.salvatore@wku.edu

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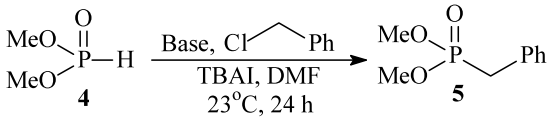
Table 1. Use of various bases in Cs_2CO_3-promoted alkylation of **4** with benzyl chloride

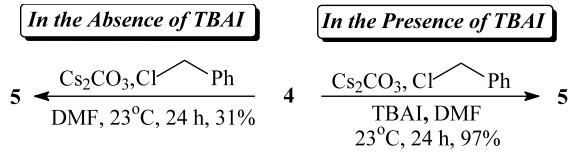


entry	base (3 eq.)	yield of **5**
1	Li_2CO_3	16%
2	Na_2CO_3	50%
3	K_2CO_3	77%
4	Rb_2CO_3	85%
5	***Cs_2CO_3***	***97%***
6	CsOH /4 Å MS	68%

also proved to be suitable, however, a lower product yield was noticed (entry 6). Although not shown in the table, the use of organic bases such as Et_3N and DBU displayed poor conversions mimicking product yields very similar to the starting entry.

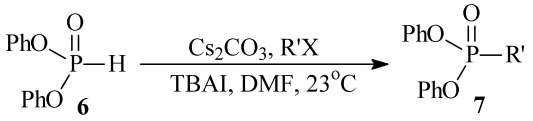
Interestingly, the inclusion of tetrabutylammonium iodide (TBAI) as a phase transfer catalyst was found to have a marked effect on producing high product yields. Therefore, to gain further insight the crucial role TBAI plays on the course of the reaction, we decided to pursue an important comparative study. As shown in Scheme 2, in the presence of TBAI, the desired phosphonate **5** was acquired in nearly quantitative yield after 24 h.[18] However, using the same reaction conditions in the absence of TBAI, the reaction appeared sluggish to consume **4**, resulting in a poor 31% yield of **5** after the same time period.

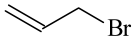
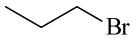
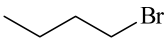
As delineated in Table 2, various primary and secondary bromides were examined and found to be generally applicable. As depicted in entry 1, allyl bromide coupled with diphenyl phosphite (**6**) efficiently to provide the unsaturated phosphonate **7** in 77% yield (entry 1). Likewise, an unactivated halide, 1-bromopropane was equally prosperous (entry 2). In addition, extension of the alkyl chain on the halide-coupling partner also proved fruitful (entries 3–5). Therefore, we next directed our efforts toward the synthesis of a complex phosphonate analog of biological importance, geranyl phosphate. Using the aforementioned techniques, **6** underwent alkylation with geranyl bromide preparing the phosphonate analog **7** in 52% yield after



Scheme 2.

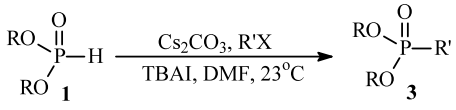
Table 2. Phosphonate formation of **6** utilizing various alkyl halides



entry	R'X	time (h)	yield of **7**
1		40	77%
2		49	64%
3		49	52%
4	1-chloropentane	49	65%
5	1-bromoheptane	6 d	53%
6	geranyl bromide	72	52%
7	isobutyl bromide	48	66%
8	2-bromobutane	66	75%
9	2-iodopropane	40	55%
10	$C_6H_{11}Cl$	70	47%

72 h (entry 6). In addition, we found introduction of the isobutyl moiety also proved successful (entry 7). Furthermore, other sterically demanding secondary bromides including isopropyl bromide, 2-bromobutane and cyclohexyl chloride also followed similar suite delivering the corresponding phosphonate products **7** exclusively (entries 8–10). Tertiary substrates, as expected, were resistant to alkylation employing these procedures. It is noteworthy to highlight no side products stemming from elimination or hydrolysis were detected in any case.[19]

Table 3. Phosphonate formation using dialkyl phosphites, and alkyl halides in the presence of Cs_2CO_3 and TBAI

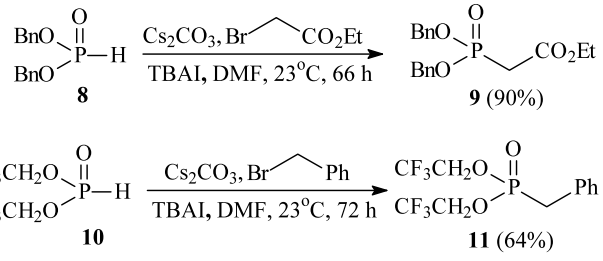


entry	phosphite **1**	halide (R'X)	time (h)	yield of **3**
1	$(BnO)_2P(O)H$	BnBr	29	75%
2		*n*-BuBr	72	95%
3		1-bromo-3-phenylpropane	74	65%
4		2-bromobutane	50	50%
5	$(EtO)_2P(O)H$	BnBr	28	82%
6		(2-bromoethyl)benzene	29	54%
7	$(PrO)_2P(O)H$	BnBr	25	59%
8		4-methoxybenzyl chloride	48	76%
9	$(BuO)_2P(O)H$	BnCl	45	84%
10	$(LaurylO)_2P(O)H$	BnCl	6 d	81%
11	$(i\text{-}PrO)_2P(O)H$	BnBr	72	95%
12		1-bromo-3-phenylpropane	80	91%

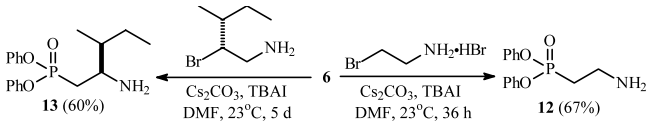
Using the conditions described, we next screened various dialkyl phosphites. As shown in Table 3, numerous primary aliphatic bromides were united with dibenzyl phosphite in moderate to high yields (entries 1–3). As represented in entry 4, a sterically hindered secondary bromide, 2-bromobutane, also underwent consolidation offering **3** in 50% yield using the disclosed protocol. In a continuing study, we explored the effect of alkyl chain length on the dialkyl phosphite. Diethyl phosphite reacted smoothly with both benzyl bromide and 2-(bromoethyl)benzene after approximately 29 h (entries 5 and 6). Also, dipropyl phosphite was found to behave similarly using benzyl bromide (entry 7). In contrast, an electron-rich halide (PMBCl) furnished a higher yield of the desired phosphonate **3** (entry 8). Whereas, $(BuO)_2P(O)H$ was also successfully transformed into the coupled product in 84% isolated yield after 45 h (entry 9). In addition, a lipophilic phosphite, dilauryl phosphite, was converted to **3**, in excellent yield (entry 10). Similarly, $(^iPrO)_2P(O)H$, a sterically congested phosphite, which fails to undergo reaction using conventional methods, proved particularly satisfactory with both BnBr and 1-bromo-3-phenylpropane (entries 11 and 12).

As demonstrated in Scheme 3, this improved phosphorylation method was also effective in the synthesis of unique substituted phosphonates that contain sensitive functional groups. Employing our mild Cs_2CO_3-promoted conditions, dibenzyl phosphite (**8**) united with ethyl bromoacetate after 66 h affording the substituted phosphonate **9** in high yield. Since fluoroalkyl phosphonates have attracted attention,[20] we next endeavored toward the construction of the P–C bond which contain the electron-withdrawing trifluoro-moiety. Employing similar reaction conditions, commercially available bis(2,2,2-trifluoroethyl)phosphite (**10**) smoothly coupled with benzyl bromide. Neither ester or phosphonate hydrolysis were detected in either example.

After screening various classes of dialkyl phosphites with numerous alkyl halides establishing the scope and limitation of our procedure, we next embarked on the synthesis of phosphonates that hold important applications in synthesis. As shown in Scheme 4, diphenyl phosphite (**6**) underwent alkylation with unprotected 2-bromoethylamine·HBr to afford a derivative of the biologically important 2-aminoethylphosphonic acid (AEPA), **12** in 67% isolated yield. It is crucial to note, no direct *N*-alkylation products were detected, which demonstrates our methods are highly chemoselective in tuning



Scheme 3.

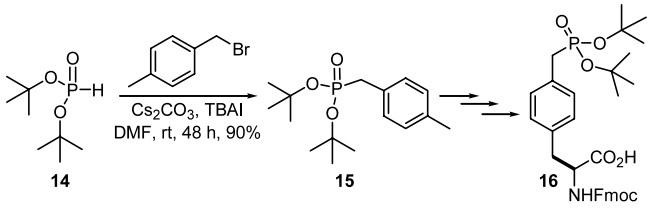


Scheme 4.

alkylations. Furthermore, the use of protecting groups was completely avoided providing shortened synthetic sequences. With this important result in hand, as well as keeping the synthesis of phosphonopeptides[3,21] in mind, we envisioned the use of a bare β-amino bromide, as a synthon might also prove facile. Therefore, after construction of the β-amino bromide derived from isoleucinol using a similar reported bromination protocol,[22] we subjected this chiral template to our conditions. Phosphite **6** successfully conjugated with the aforementioned β-amino bromide to generate rearranged product **13** cleanly, and in satisfactory yield. Moreover, racemization was not detected during the alkylation of this chiral substrate while complications stemming from hydrolysis or *N*-alkylation were not observed to a noticeable extent.[23]

Finally, we applied this methodology to the synthesis of a phosphonate which is a crucial intermediate in the synthesis phosphonomethylphenylalanine (L-Pmp), a mimetic that exhibits similar properties to phosphotyrosine.[24] As shown in Scheme 5, the synthesis of (4-methylbenzyl)phosphonic acid di-*tert*-butyl ester (**15**) was carried out by reaction of 4-methylbenzylbromide with cesium di-*tert*-butyl phosphite generated in-situ from $(^tBuO)_2P(O)H$ (**14**) in DMF at room temperature in high yield (90%). Subsequent reactions on building block **15** can lead to the synthesis of protected Fmoc-L-$Pmp(Bu^t)_2$-OH **16**, which is a very useful synthon for the synthesis of Pmp-containing peptides and peptidomimetics.[24]

In summary, we report a mild and efficient method for the preparation of phosphonates using cesium carbonate and tetrabutylammonium iodide offering a general synthetic protocol. These improved procedures augmented by the use of mild base and ambient reaction temperature proved suitable for use with a wide variety of dialkyl phosphites and alkyl halides. Moreover, the synthesis of extremely hindered phosphonates otherwise difficult to prepare using conventional methods was particularly noteworthy. Furthermore, our procedures discussed herein were superior to known methods, since chiral templates encompassing amino acid derivatives and labile functionalities proved compatible. Applications of this methodology toward the preparation of



Scheme 5.

higher order phosphonopeptides and phoshonotyrosine-containing peptidomimetics are currently in progress and will be reported in due course.

Acknowledgements

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15. *Representative experimental procedure*: To a solution of dimethyl phosphite (**4**) (0.50 g, 0.42 mL, 4.54 mmol, 1 equiv.) in anhydrous DMF (23 mL) was added cesium carbonate (4.44 g, 13.6 mmol, 3 equiv.) and tetrabutylammonium iodide (5.03 g, 13.6 mmol, 3 equiv.) with vigorous stirring for 1 hour at room temperature under a nitrogen atmosphere. After this time period, benzyl chloride (1.73 g, 1.6 mL, 13.6 mmol, 3 equiv.) was added and stirred for an additional 24 h. The resulting milky white suspension was then poured into water (30 mL) and extracted with EtOAc (3×30 mL). The combined organic layers were washed with water (2×30 mL), brine (30 mL), and dried over anhydrous sodium sulfate. The filtrate was concentrated in vacuo, and subjected to flash chromatography (hexanes–EtOAc, 9:1 v/v) affording dimethyl benzylphosphonate (**5**) as a clear yellow oil (0.88 g, 97%). ^{1}H NMR (270 MHz, $CDCl_3$) δ_{ppm} 3.09 (d, $^{2}J_{PH}=21.7$ Hz, 2H), 3.59 (d, $^{3}J_{POCH}=11$ Hz, 6H), 7.23 (br s, 5H). ^{13}C NMR (70 MHz, $CDCl_3$) δ_{ppm} 32.76 ($^{1}J_{PC}=138.0$ Hz), 52.83 ($^{2}J_{POC}=7.1$ Hz), 126.94 ($^{5}J_{PC}=3.5$ Hz), 128.59 ($^{4}J_{PC}=3.0$ Hz), 129.65 (d, $^{3}J_{PC}=6.6$ Hz), 131.16 (d, $^{2}J_{PC}=9.6$ Hz).
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