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Orthosilicate-Mediated Esterification of Monosubstituted Phosphinic Acids

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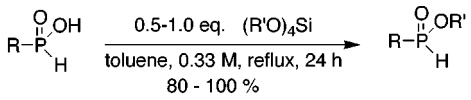
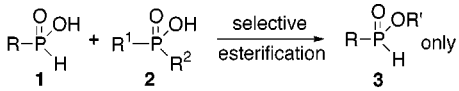
ABSTRACT



Monosubstituted phosphinic acids are esterified with orthosilicates in excellent yields. Phosphinylidene-containing acids react selectively under these conditions, while disubstituted phosphinic acids and phosphonic acids remain unchanged. One-pot procedures are also described for the preparation of phosphinate esters from an alcohol. This novel method provides a convenient and general alternative to more commonly employed conditions such as diazomethane or carbodiimide.

Existing methods for the esterification of phosphinic acids commonly use diazomethane and related diazoalkanes,[1] carbodiimide/ alcohol,[2] RCOCl/alcohol,[3] and to a lesser extent other reagents.[4] However, these methods are not selective for phosphinylidene-containing compounds and are often either inconvenient or limited in the range of esters that can be obtained. A largely overlooked exception is the esterification with an alcohol under continuous water removal.[5] Unfortunately, this reaction is still limited to the preparation of esters derived from high-boiling alcohols. Accordingly, the general and selective esterification of monosubstituted phosphinic acids **1** in the presence of other phosphorus acids such as **2** is still difficult to achieve (Scheme 1).

Scheme 1



In connection with studies related to the synthesis of biologically active phosphinate compounds, we developed a method to convert monosubstituted phosphinic acids into the corresponding esters. Esters **3** (Scheme 1) are important synthetic intermediates and final targets.[6] In addition, a method for selectively esterifying monosubstituted acids **1** over disubstituted acids **2** is especially valuable since most

(1) (a) Tokutake, N.; Hiratake, J.; Katoh, M.; Irie, T.; Kato, H.; Oda, J. *Bioorg. Med. Chem.* **1998**, *6*, 1935. (b) Lloyd, J.; Schmidt, J. B.; Hunt, J. T.; Barrish, J. C.; Little, D. K.; Tymiak, A. A. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1323. (c) Martin, M. T.; Angeles, T. S.; Sugasawara, R.; Aman, N. I.; Napper, A. D.; Darsley, M. J.; Sanchez, R. I.; Booth, P.; Titmas, R. C. *J. Am. Chem. Soc.* **1994**, *116*, 6508. (d) Baillie, A. C.; Cornell, C. L.; Wright, B. J.; Wright, K. *Tetrahedron Lett.* **1992**, *33*, 5133.

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(4) $P(OAlk)_3$: (a) Allen, M. C.; Fuhrer, W.; Tuck, B.; Wade, R.; Wood, J. M. *J. Med. Chem.* **1989**, *32*, 1652. (b) Elepina, L. T.; Balakhontseva, V. N.; Nifant′ev, E. E. *J. Gen. Chem. USSR* **1973**, *43*, 1795. $(AlkO)_2SO_2$: (c) Hatt, H. H. *J. Chem. Soc.* **1933**, 776. PCl_5: (d) Natchev, I. A. *Liebigs Ann. Chem.* **1988**, 861. PyBOP/*i*-Pr_2NEt: (e) Chen, S.; Lin, C.-H.; Walsh, C. T.; Coward, J. K. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 505.

(5) (a) Nifant'ev, E. E.; Kil'disheva, V. R.; Nasonovskii, I. S. *Zh. Prikl. Khim.* **1969**, *42*, 2590. (b) Cherbuliez, E.; Weber, G.; Rabinowitz, J. *Helv. Chim. Acta* **1963**, *46*, 2464. (c) Dumond, Y. R.; Baker, R. L.; Montchamp, J.-L. Unpublished results.

(6) Many examples can be found in refs 1−4.

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reactions used for the preparation of **1** produce varying amounts of **2** ($R^1 = R^2 = R$) as a contaminant which cannot be easily removed. Therefore, selective esterification would allow easy purification of such mixtures by simple extraction, leaving in the aqueous phase the unreacted impurity **2**. In contrast with adamantanamine and other salts which are commonly used to purify **1**, the ester product **3** is also immediately available for further functionalization.

We now report a novel, selective, and high-yielding method, which employs orthosilicates to esterify phosphinic acids **1** and addresses the limitations outlined above. In a typical procedure (conditions A), a phosphinic acid (5 mmol) in toluene (15 mL) is treated with an orthosilicate (2.5−5.0 mmol), and the reaction mixture is refluxed for 24 h under N_2. At that time, the yield is determined by ^{31}P NMR. The solution is then concentrated under reduced pressure and purified.[7] Results are presented in Table 1.

Table 1. Esterification of Monosubstituted Phosphinic Acids with Orthosilicates (Method A)[a]

entry	R	R′	equiv of $(R'O)_4Si$	^{31}P NMR yield, % (unreacted acid, %)	RP(O)(OR′)H isolated yield, %
1	Ph	Et	0.25	48 (52)	
2	Ph	Et	0.5	82 (18)	
3	Ph	Et	1.0	90 (10)	83
4	Ph	Et	2.0	82 (18)	
5	Ph	Me	1.0	100 (0)	85
6	Ph	Bu	1.0	93 (7)	93
7	Ph	Bu	0.5	94 (6)	
8	Ph	Allyl	1.0	97 (3)	94
9	Ph	Ph	1.0	100 (0)	
10	$Ph(CH_2)_4$	Me	1.0	94 (0)	81
11	$Ph(CH_2)_4$	Et	1.0	84 (7)	70
12	$Ph(CH_2)_4$	Bu	1.0	100 (0)	98
13	$Ph(CH_2)_4$	Allyl	1.0	91 (3)	80
14	Oct	Me	1.0	96 (0)	
15	Oct	Allyl	1.0	97 (3)	87
16	Oct	Ph	1.0	98 (2)	
17	$C_9H_{19}CHOH$	Bu		85 (0)	65

[a] All reactions were conducted in refluxing toluene for 24 h.

While orthosilicates are available cheaply, and employed extensively in the sol−gel process,[8] a literature survey showed a paucity of applications in organic synthesis. Under conditions A, diphenyl phosphinic acid (**2**, $R^1 = R^2 = Ph$) and phenyl phosphonic acid (**2**, $R^1 = Ph$, $R^2 = OH$) did not give any detectable quantity of the corresponding esters, while phenyl phosphinic acid (**1**, R = Ph) gave ethyl phenyl phosphinate in 90% yield (Table 1, entry 3), under otherwise identical conditions. This selectivity was further established by conducting a competition experiment in which an equimolar mixture of phenyl phosphinic acid, phenyl phosphonic acid, diphenyl phosphinic acid, and $(EtO)_4Si$ was refluxed in toluene. After 24 h, ^{31}P NMR analysis of the reaction mixture revealed the formation of ethyl phenyl phosphinate (88%) as the only ester product. In 1956, Sumrell and Ham reported the successful esterification of carboxylic acids with 0.5 equiv of an alkyl orthosilicate, without a solvent.[9] As a result, we also tested the reactivity of carboxylic acids under our conditions. Interestingly, when benzoic acid and hydrocinnamic acid were treated with 1 equiv of $(EtO)_4Si$ under conditions A, the corresponding esters were obtained in <2% and 16% yields, respectively. These experiments indicate that monosubstituted phosphinic acids are selectively esterified and that the presence of a phosphinylidene group is required for efficient esterification to occur.

The number of transferrable groups from $(EtO)_4Si$ was studied next by examining the influence of the orthosilicate stoichiometry on the yield of phenyl phosphinate ester (Table 1, entries 1−4). It was found that the first two substituents on silicon can both be transferred to phosphorus within 24 h, while the third and fourth substituents require heating for an extended period of time. In entry 1, the yield went from 48% after 24 h, to 67% after 48 h, to 72% after 72 h. Using 2 equiv (entry 4) instead of 1 (entry 3) did not provide any improvement. An equimolar equivalent of $(R'O)_4Si$ and RP(O)(OH)H was therefore routinely employed, although 0.5 equiv of $(R'O)_4Si$ also proved satisfactory (Table 1, compare entries 3 vs 2 and 6 vs 7).

Reactions were typically conducted with 0.33 M phosphinic acid in toluene; yet the influence of the concentration was also briefly studied. Doubling the concentration from 0.33 M (Table 1, entry 3, R′ = Et, 90%) to 0.66 M gave the ester in 93% yield. When the reaction was conducted neat, the yield was also 93%. Finally, the reaction in entry 3 was scaled up to 100 mmol without any difficulty, to provide ethyl phenyl phosphinate in 88% yield.

Once these reaction parameters were established, the influence of the alkoxy residue in $(R'O)_4Si$ was investigated. It was found that R′ = Me, Bu, Allyl, Ph gave the corresponding esters in 91−100% yields (Table 1, entries 5−9), while R′ = Et gave a slightly lower yield. Orthosilicate reactivity appears proportional to the boiling point of R′OH released in the medium.[10] Due to the easy accessibility of its silicon atom, $(MeO)_4Si$ escapes this trend and is the most reactive.

The scope of the esterification was then probed with a few other monosubstituted phosphinic acids. For example, (4-phenylbutyl) phosphinic acid,[2c] octyl phosphinic acid,[2c] and (α-hydroxydecyl) phosphinic acid[11] all reacted smoothly with various orthosilicates (Table 1, entries 10−15). Once

(7) Purification typically involves radial or flash chromatography on silica gel. However, in favorable cases, a simple partitioning of the crude product between CH_3CN and hexane is sufficient to provide almost pure phosphinate. The hexane layer contains the nonpolar silicon-derived impurities, while the polar phosphinate ester remains in the CH_3CN layer.

(8) For example, see: Loy, D. A.; Shea, K. J. *Chem. Rev.* **1995**, *95*, 1431, and references cited.

(9) Sumrell, G.; Ham, G. E. *J. Am. Chem. Soc.* **1956**, *78*, 5573. To our knowledge, these conditions have not been employed since.

(10) Indeed, ^{1}H NMR analysis of the reaction mixture obtained from entry 7 revealed the presence of 2 mmol of BuOH.

(11) Albouy, D.; Brun, A.; Munoz, A.; Etemad-Moghadam, G. *J. Org. Chem.* **1998**, *63*, 7223.

again, isolated yields were good to excellent. The facile preparation of methyl phosphinates with method A is particularly noteworthy as an alternative to the use of diazomethane.

Since method A is limited by the availability of the orthosilicate reagents, we then devised a more general process which would directly employ an alcohol, based on the observation that the phenyl esters were formed in nearly quantitative yields (Table 1, entries 9 and 16) but were unstable and could not be isolated as pure compounds.[12] This reactivity suggested that the phenyl esters could serve as activated esters for the esterification of alcohols, and in fact, related transesterifications of phenyl phosphates, phenyl phosphonates, and phenyl phosphite are well-known to proceed, but usually under basic conditions.[13]

A one-step esterification with alcohols for which the corresponding orthosilicate is not readily available could indeed be developed (method B). The results are presented in Table 2 (entries 1−4). In this reaction, the phenyl ester is first formed using method A and then transesterified in situ with an alcohol under neutral conditions. Typically, a phosphinic acid (5 mmol) and tetraphenoxysilane (3 mmol) are refluxed in toluene (15 mL) for 24 h, then an alcohol (5−10 mmol) is added, and the mixture is refluxed for an additional 2−4 h (method B). The crude product obtained after evaporation of the solvent is purified by chromatography. All runs were usually clean, with the desired esters being formed almost exclusively. On occasion, small amounts of unreacted acid and/or phenyl ester could be detected.[14] As expected, when a small amount of phenyl ester remained, addition of more R′OH typically resulted in complete consumption of that reactive intermediate with a proportional increase in yield.

Table 2. One-Pot Esterification of R−P(O)(OH)H with Alcohols

entry	R	R′	equiv of R′OH	SiX_4	yield, %[a] (acid, %)
1	Ph	Bu	1.0	0.55 equiv of $Si(OPh)_4$	86 (7)
2	Ph	Bn	2.0	0.6 equiv of $Si(OPh)_4$	92 (0)
3	$Ph(CH_2)_4$	3-pentyl	2.0	0.6 equiv of $Si(OPh)_4$	100 (0)
4	Oct	cinnamyl	2.0	0.6 equiv of $Si(OPh)_4$	100 (0)
5	Ph	Bu	2.0	0.5 of $SiCl_4$ + 2.2 of Pyr	85 (15)
6	Ph	*i*-Pr	4.0	1.0 of $SiCl_4$ + 4.4 of Pyr	73 (14)[b]

[a] Determined by ^{31}P NMR. [b] Isolated yield was 73%.

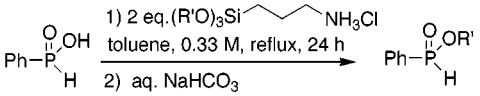
Butyl phenyl phosphinate was obtained in 86% yield, using only 1 equiv of 1-butanol and 0.55 equiv of $(PhO)_4Si$ (Table 2, entry 1). Compared to method A, method B is only slightly lower yielding but allows the formation of esters directly from the corresponding alcohol. Since tetraphenoxysilane is commercially available, or prepared very cheaply from phenol and either $(EtO)_4Si$ or $SiCl_4$,[15] this one-pot procedure provides an easy solution to selectively esterify monosubstituted phosphinic acids with various alcohols.

Also in order to circumvent the need for a purified orthosilicate in method A, another approach to directly employ an alcohol was briefly investigated (method C, Table 2, entries 5, 6) where the orthosilicate is formed in situ. Once again we focused on a straightforward one-pot process in order to simplify the experimental procedure. Accordingly, a toluene solution of $SiCl_4$ (2.5−5.0 mmol), pyridine, and R′OH (in a 1/4.4/4 ratio) is refluxed for 1 h, then treated with the acid (5 mmol), and refluxed for 24 h (method C). Once again, even with only 0.5 equiv of the reagent, butyl phenyl phosphinate was obtained in good yield (Table 2, entry 5, 85%). Secondary esters were also formed without complications (Table 2, entries 4 and 6). On the other hand, tertiary esters could not be obtained in useful yields with any of the methods employed.

Finally, the generality of the orthosilicate-promoted esterification was explored with other alkoxysilanes. Trialkoxysilanes $(R'O)_3SiR''$ were capable of esterifying monosubstituted phosphinic acids, although at least 2 equiv was necessary to reach a useful yield in 24 h. On the other hand, the reaction of dialkoxysilanes proved very sluggish, even when a large excess was employed. For example, reacting phenyl phosphinic acid with 5 equiv of diethoxydimethylsilane for 24 h afforded the corresponding ester in only 44% yield, and byproducts were also formed.

In terms of usefulness, trialkoxysilanes may still find some applications, if for example the use of hazardous tetramethyl orthosilicate must be avoided. While the yields were generally a little lower (ca. 60−80%) using these reagents, the only phosphorus-containing compound other than the desired ester was the unreacted acid starting material. This suggested a protocol which both provides a replacement for tetramethyl orthosilicate and simplifies product purification (Scheme 2).

Scheme 2



R' = Et, NMR: 68%, isolated 58%
R' = Me, NMR: 100%, isolated 72%

(12) Some phenyl esters (R′ = Ph) have been prepared previously in low or unreported yields and purity: (a) see ref 6a (R = Bu). (b) Foss, V. L.; Kudinova, V. V.; Lutsenko, I. F. *J. Gen. Chem. USSR* **1979**, *49*, 489 (R = *t*-Bu). (c) Johnson, M. K. *Biochem. Pharmacol.* **1988**, *37*, 4095 (R = Ph). (d) Yamashita, M.; Long, P. T.; Shibata, M. *Carbohydr. Res.* **1980**, *84*, 35 (R = Ph). These esters are particularly sensitive to hydrolysis and decompose on silica gel.

(13) (a) Kers, A.; Kers, I.; Stawinski, J.; Kraszewski, A. *Synthesis* **1995**, 427. (b) Billington, D. C.; Baker, R.; Kulagowski, J. J.; Mawer, I. M. *J. Chem. Soc., Chem. Commun.* **1987**, 314. (c) Ogilvie, K. K.; Beaucage, S. L. *Tetrahedron Lett.* **1976**, 1255. (d) Ogilvie, K. K.; Beaucage, S. L. *J. Chem. Soc., Chem. Commun.* **1976**, 443. (e) Slotin, L. A. *Synthesis* **1977**, 737. (f) van Boom, J. H.; Burgers, P. M. J.; van Deursen, P.; Reese, C. B. *J. Chem. Soc., Chem. Commun.* **1974**, 618. (g) Jones, G. H.; Moffatt, G. *J. Am. Chem. Soc.* **1968**, *90*, 5337.

When 3-aminopropyl trimethoxysilane hydrochloride[16] **4** was heated with phenyl phosphinic acid, a nearly quantitative yield of ester was observed by ^{31}P NMR.[17] After aqueous workup, the ester was obtained cleanly in 72% yield. The esterification with trialkoxysilane derivatives also opens up new opportunities, for example, in the development of polymer-supported reagents. These promising leads will be the subject of future developments.

In conclusion, we have developed several protocols for the selective esterification of monosubstituted acids in one pot. The methods based on orthosilicate reagents provide the esters in good to excellent yields under mild conditions. Compared to other existing methodology for the synthesis of monosubstituted phosphinate esters, our reaction offers several advantages. The process has a broad scope and is experimentally straightforward, cheap, scalable, selective, and high yielding. For the preparation of methyl esters, tetramethyl orthosilicate offers significant advantages over diazomethane, and when the toxicity of $(MeO)_4Si$ is an issue, alternate procedures relying on alkyl trimethoxysilanes have also been developed. Further developments of this chemistry, its application to the preparation of biologically active organophosphorus compounds, and mechanistic studies will be reported in due course.

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Supporting Information Available: Spectroscopic data and representative proton and carbon spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) The esterification also proceeded satisfactorily when all the reagents were mixed together from the start (i.e., the phenyl ester was not preformed first), even though in this case these two compounds often remained in small amounts at the end of the reaction.

(15) For example, see: (a) Ismail, R. M.; Koetzsch, H. J. *J. Organomet. Chem.* **1967**, *10*, 421 and references cited. (b) Malatesta, L. *Gazz. Chim. Ital*. **1948**, *78*, 750.

(16) Hydrochloride **3** was most conveniently prepared from the commercially available amine by exchange with NH_4Cl. See: Speier, J. L.; Roth, C. A.; Ryan, J. W. *J. Org. Chem.* **1971**, *36*, 3120.

(17) The reason for the high yield obtained with **4** compared to, for example, propyltrimethoxysilane is unclear.