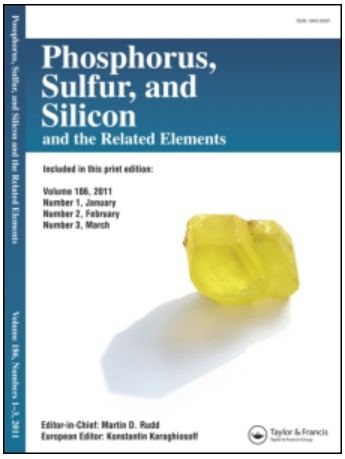

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A FACILE ROUTE TO SUBSTITUTED DIMETHOXY PHOSPHONOTHIONATES USING DIMETHYL THIOPHOSPHITE

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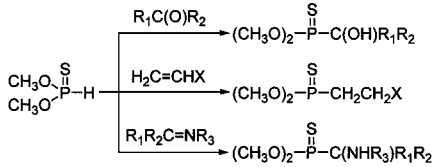
Dimethyl thiophosphite reacts with aliphatic aldehydes and ketones, Michael acceptors, and N-benzyl imines to afford excellent yields of α-hydroxy phosphonothionates, β-substituted phosphonothionates and α-amino phosphonothionates, respectively. Dealkylation of α-amino phosphonothionates affords N-benzyl α-amino phosphonothioic acids. Dimethyl thiophosphite reacts with electrophiles at a significantly greater rate than dimethyl phosphite.



Keywords: α-Amino phosphonothionates; α-amino phosphonothioic acids; α-hydroxy phosphonothionates; β-substituted phosphonothionates; dimethyl thiophosphite

INTRODUCTION

Much attention has been given to the preparation of α-hydroxy phosphonates[1,2]and α-amino phosphonates[3–8] largely because of their structural resemblance to the corresponding α-hydroxy- and α-amino acids.[9] The phosphoryl group (P═O) is an important isostere of the carbonyl group and can serve as a transition state mimic owing to the additional ligand allowed by sp^3 hybridization. α-Substituted phosphonates

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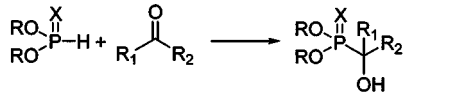
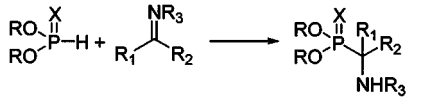
have been conveniently prepared by addition reaction of a dialkyl phosphite (H-phosphinate) to a carbonyl compound (Eq. 1) or imine (Eq. 2).[10] This reaction type was envisioned for adaptation to the corresponding α-substituted phosphonothionates in which a P=S group is installed. The presence of the thiophosphoryl (P=S) would enable the formation of a center of asymmetry at phosphorus, an important variation to the reaction. Interestingly, the corresponding addition of dimethyl thiophosphite to electrophiles has not been thoroughly explored, and therefore is the objective of this work.



α-hydroxy phosphonate (1)



α-amino phosphonate (2)

X = O or S
R = Me, Et, etc.

RESULTS AND DISCUSSION

Numerous improvements in addition reactions of phosphites have been reported including asymmetric routes that afford products enantioenriched at the α-carbon. As noted, installing a thiophosphoryl (P=S) group in substituted phosphonates could greatly expand the number of potential reactions and resultant chemical properties. In a prior report[11] from this lab, stereoisomers of N-phospholeucinamides (phosphoramidothioates) were prepared by dealkylating a thiophosphoryl methyl ester (MeO–P=S) to form phosphorothioic acids which bear a center of asymmetry at phosphorus. Our initial strategy, therefore, sought to convert the P=O group of readily available N-protected α-amino phosphonates to the corresponding thiophosphoryl (P=S) compounds.

Unfortunately, all attempts to form the thiophosphoryl (P=S) compounds from the phosphoryl (P=O) analogs failed including numerous conditions using Lawesson's reagent [$(Ar_2PS_2)_2$][12] or P_4S_{10}. Changing the nitrogen protecting group (benzyl, trityl, phthalimide, etc.) did not improve the outcome. Formation of the thioic acid (–P(=O)SH) directly from the phosphonate diester or reaction of either phosphorus methyl or ethyl esters with NaSH[13] or Na_2S failed. A more direct method of

constructing the thiophosphonates was needed. α-Substituted phosphonothionates were prepared by addition of dialkyl thiophosphites [$(RO)_2P(S)H$] to carbonyl compounds and imines in reactions analogous to the known dialkyl phosphite additions (Eq. 1 and 2; X = S).[14–16] Surprisingly, the addition of dimethyl thiophosphite is absent from most reports. This may be due, in part, to the undesirable preparation, handling and unpredictable reactions[17,18] of dimethyl thiophosphite. We reexamined this reagent with the hope of directly accessing α-substituted dimethoxy phosphonothionates. Dimethyl thiophosphite was obtained by the reaction of dimethyl phosphite with Lawesson's reagent.[19] Filtration and fractional distillation of the crude reaction afforded dimethyl thiophosphite ($^{31}P\{^1H\}$ NMR; δ = ppm; greater than 95% pure) that was used directly in reactions with various electrophiles. The reaction of dimethyl thiophosphite with carbonyl compounds, imines, and Michael acceptors are summarized in Table I.

As indicated in Table I, aldehydes, ketones, Michael acceptors, and imines undergo reaction with dimethyl thiophosphite in high conversion (by $^{31}P\{^1H\}$ NMR) at room temperature and without catalysts to afford phosphonothionate products. The results contrast the reaction of dialkyl phosphites which require elevated temperatures, long reaction times and/or catalysts. Also notable was the chemoselective 1,4-addition to 2-butenal (entry 6).

In some cases, isolated yields were lower due to product volatility and chromatographic instability. The best yields were observed when the reactions were conducted neat or in methylene chloride and lower yields and slower reaction rates occurred when tetrahydrofuran was used as solvent.

The progress of reaction and net conversion was monitored by $^{31}P\{^1H\}$ NMR for the production of product thionate that generally appeared between 98–106 ppm consistent with the phosphonothionate (tetrahedral $^{V}P{=}S$) signal.[20,21] The products of entries 1–3, 5, 6, 9, 10, and 13–16 afford an asymmetric center at the α-carbon which causes the ^1H NMR of methoxy groups to appear as diastereotopic doublets. An example of the influence of a chiral auxiliary (*S*-α-methyl benzylamine) in the imine addition was explored. The product diastereomers formed in a ratio of 3:2 (entry 15) and 3:1 (entry 16) at room temperature. Further exploration of the diastereoselectivity of thiophosphite addition to imines is underway.

Given these successes, we briefly compared the relative reactivity of dimethyl thiophosphite to dimethyl phosphite. Acetaldehyde, butyraldehyde and benzaldehyde reacted with dimethyl phosphite in 14 h to afford 64%, 56%, and 87% conversion, respectively. In contrast, dimethyl thiophosphite gave near quantitative formation to the

TABLE I Outcome of Reactions Between Dimethyl Thiophosphite and Electrophiles (Eq. 1 and 2; R = Me)

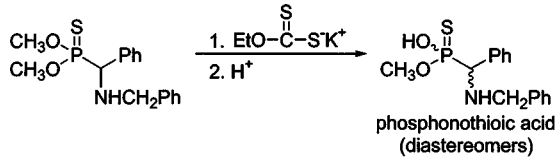
Entry	Electrophile	Product	Yield (%)[a]		Product
			crude[b]	isolated	$^{31}P\{^1H\}$ (δ)[c]
1	CH_3CHO	$(CH_3O)_2P(S)CH(OH)CH_3$	98	46	101.3
2	PhCHO	$(CH_3O)_2P(S)CH(OH)Ph$	100	93	98.0
3	$CH_3CH_2CH_2CHO$	$(CH_3O)_2P(S)CH(OH)CH_2CH_2CH_3$	100	71	101.0
4	$(CH_3)_2C{=}O$	$(CH_3O)_2P(S)C(OH)(CH_3)_2$	100	73	105.0
5	$CH_3CH_2C(O)CH_3$	$(CH_3O)_2P(S)C(OH)(CH_3)CH_2CH_3$	75	64	105.3
6	$H_3C{-}CH{=}CH{-}CHO$	$(CH_3O)_2P(S)CH(CH_3)CH_2CHO$	100	67	101.7
7	$H_2C{=}CH{-}C(O)CH_3$	$(CH_3O)_2P(S)CH_2CH_2C(O)CH_3$	100	65	103.6
8	$H_2C{=}CH{-}C(O)CH_2CH_3$	$(CH_3O)_2P(S)CH_2CH_2C(O)CH_2CH_3$	95	72	103.9
9	$Ph{-}CH{=}CH{-}C(O)Ph$	$(CH_3O)_2P(S)CH(Ph)CH_2C(O)Ph$	100	68	102.8
10	$PhC(O)CH_3$	$(CH_3O)_2P(S)C(OH)(CH_3)(Ph)$	90	75	101.7
11	$H_2C{=}CH{-}CN$	$(CH_3O)_2P(S)CH_2CH_2CN$	90	71	97.7
12	$H_2C{=}CH{-}CO_2{}^tBu$	$(CH_3O)_2P(S)CH_2CH_2CO_2{}^tBu$	70	53	102.7
13	$CH_3CH{=}NCH_2Ph$	$(CH_3O)_2P(S)CH(CH_3)NHCH_2Ph$	88	74	105.2
14	$PhCH{=}NCH_2Ph$	$(CH_3O)_2P(S)CH(Ph)NHCH_2Ph$	75	53	98.8
15	(*S*)-$CH_3CH{=}NCH(CH_3)Ph$	$(CH_3O)_2P(S)CH(CH_3)NHCH(CH_3)Ph$	75	53	104.6/104.7[d]
16	(*S*)-$PhCH{=}NCH(CH_3)Ph$	$(CH_3O)_2P(S)CH(Ph)NHCH(CH_3)Ph$	100	72	101.8/99.0[d]

[a] Product identity was confirmed by spectral, chromatographic and/or elemental analyses.
[b] Crude conversion estimated by $^{31}P\{^1H\}$ NMR.
[c] Relative to H_3PO_4 in $CDCl_3$.
[d] Diastereomers.

corresponding thiophosphoryl products in 1h or less. More stark was the finding that ketones and imines gave poor conversion to products with dimethyl phosphite at 14 h whereas dimethyl thiophosphite reacted quickly to afford α-substituted phosphonothionates.

A 1:5 mixture of dimethyl phosphite to dimethyl thiophosphite (confirmed by $^{31}P\{^{1}H\}$ NMR integration) was used to explore the relative rate. The fractional concentration of dimethyl phosphite was unchanged in the reaction (versus internal standard) and no phosphonate product was detected by $^{31}P\{^{1}H\}$ NMR. These results indicate that dimethyl thiophosphite is far more reactive than dimethyl phosphite in these addition reactions although more precise kinetic analyses and relaxation values are needed to further support this finding.

Now that a reliable sequence is available for production of α-substituted phosphonothionates, we explored the use of the phosphonothionate (P=S) group. One highly useful conversion is dealkylation of the phosphorus methyl ester which would afford stereoisomeric phosphorothioic acids.[22–24] Phosphorothioic acids can also be alkylated (at sulfur or oxygen), resolved into stereoisomers and converted to thiophosphoryl halides,[25] the latter which can react with nucleophiles. Selective monodemethylation of an α-amino thiophosphonate (Table I; entry 14) with potassium ethyl xanthate ($EtOC(S)S^{-}K^{+}$) afforded a mixture of thioacid diastereomers ($^{31}P\{^{1}H\}$ δ 75.5 and 74.7 in a ratio of 47:53 (80% yield) (Eq. 3). Diastereomeric phosphonothioacids can be separated by fractional crystallization or alkylation at sulfur.[11]



(3)

CONCLUSION

Dimethyl thiophosphite not only undergoes the same range of reactions as dimethyl phosphite but also does so at improved rates, overall yield and with chemoselectivity. The incorporation of a dimethoxy thiophosphoryl group will enable further product diversity and permit access to asymmetric organophosphorus compounds.

EXPERIMENTAL

Unless otherwise noted, reactions were run in flame-dried apparatus under argon atmosphere. Anhydrous reagent grade solvents

and reagents were purchased from Aldrich Chemical Co. in sure-sealed bottles and used without further purification. Analytical thin-layer chromatography (TLC) was performed on silica gel (Whatman) aluminum-backed plates. Compounds were detected using UV absorption at 254 nm and/or stained with ninhydrin or 2,6-dibromoquinonechlorimide. Flash chromatography was performed with silica gel 60 (Merck, 230–240 mesh). A Varian 400 MHz Unity Plus spectrometer was used to determine the ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz), and ^{31}P NMR (171 MHz) spectra. Chemical shifts are reported in parts per million (ppm, δ) using $CHCl_3$ (7.26 ppm for ^{1}H), $CDCl_3$ (77 ppm for ^{13}C) or H_3PO_4 (0 ppm for ^{31}P) as references. High resolution mass spectra (HRMS) were obtained using electrospray ionization (ESI) Micromass LCT connected with Waters 2790 HPLC with C-18 reversed phase column (2.1 mm i.d., 5 cm long). Elemental analyses for C, H, and N were performed by Midwest Microlab (Indianapolis, IN).

General Procedure

To a 5 mL flask containing an electrophile (carbonyl, Michael acceptor or imine; 0.95 mmol) in toluene (800 μL) at rt under argon atmosphere was added dimethyl thiophosphite (100 μL; 0.95 mmol). The reaction was stirred at rt until $^{31}P\{^{1}H\}$ NMR indicated no further reaction progress (usually >90% complete). The solvent was removed in vacuo and the product purified by column chromatography (hexane/ether). All new compounds showed satisfactory elemental and/or spectral data following purification by flash column chromatography. *Caution*: Several preparations of dialkyl thiophosphites report uncontrollable exothermic reaction and/or loss of malodorous material.[18]

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