

Vinyl Diazophosphonates as Precursors to Quaternary Substituted Indolines and Cyclopentenones

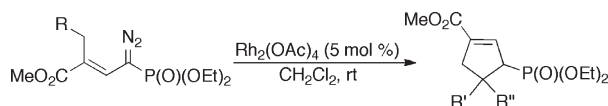
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Received December 3, 2010

ABSTRACT



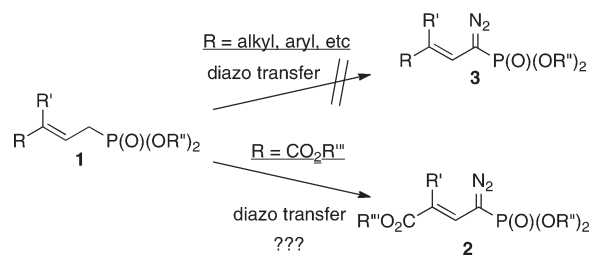
Vinyl diazophosphonates can be stereoselectively synthesized and, depending upon their substitution pattern, undergo intramolecular C–H insertion reactions or sulfonium ylide rearrangements when exposed to Rh₂(OAc)₄.

Despite the important role that phosphonates play in synthetic and medicinal chemistry,^{1,2} vinyl diazophosphonates have received relatively little attention from the chemical synthesis community.³ We believe that this has been at least partly due to the inability of simple vinyl and allyl phosphonates to undergo diazo transfer chemistry (Scheme 1). From an interest in utilizing vinyl diazophosphonates as precursors to more elaborate structures, we became fascinated by the possibility that phosphonocrotonates might enable us to overcome the diazo transfer limitation. Our initial results in this area are described here.

After finding that the parent diethylphosphonocrotonate **4** does not undergo selective diazo transfer chemistry when treated with *p*-acetamidobenzenesulfonyl azide (ABSA)

and base,⁴ we turned to the corresponding substituted variants.

Scheme 1. Diazophosphonates from Diazotransfer?



The 2002 report by Solberghe and Marko of the stereoselective synthesis of a number of monoalkyl substituted phosphonocrotonates from the anionic alkylation of phosphonocrotonate **4** was critical to the success of this work.⁵ As indicated in Table 1, by subjecting **4** to LiHMDS and primary alkyl halides and triflates, we were able to generate

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(3) For previously reported syntheses of vinyl diazophosphonates, see: (a) Marmor, R. S.; Seyferth, D. J. *J. Org. Chem.* **1971**, *36*, 128–136. (b) Theis, W.; Regitz, M. *Tetrahedron* **1985**, *41*, 2625–2634. (c) Davies, H. M. L.; Houghland, P. W.; Cantrell, W. R., Jr. *Synth. Commun.* **1992**, *22*, 971–978.

(4) We suspect diazirine formation and decomposition.

(5) Solberghe, G. F.; Marko, I. E. *Tetrahedron Lett.* **2002**, *43*, 5061–5065.

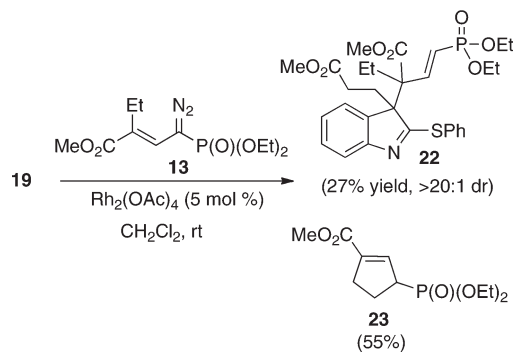
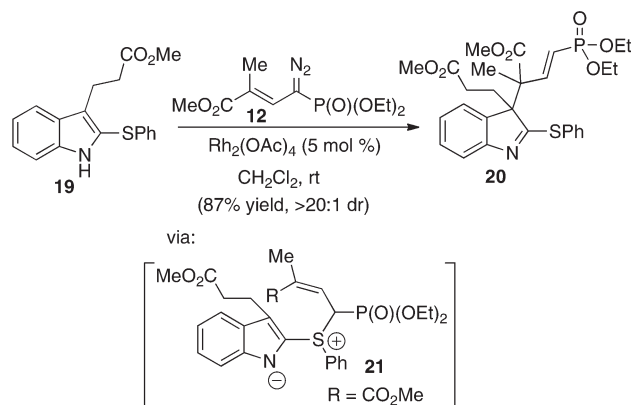
Table 1. Vinyl Diazophosphonate Synthesis

$\text{MeO}_2\text{C}-\text{CH}=\text{CH}-\text{P}(\text{O})(\text{OEt})_2 \xrightarrow[\text{RX}]{\text{LiHMDS, THF}} \text{MeO}_2\text{C}-\text{CH}(\text{R})=\text{CH}-\text{P}(\text{O})(\text{OEt})_2 \xrightarrow[\text{CH}_3\text{CN, rt}]{\text{ABSA, DBU}} \text{MeO}_2\text{C}-\text{CH}(\text{R})=\text{CH}-\text{N}_2-\text{P}(\text{O})(\text{OEt})_2$						
entry	RX	R	phosphonocrotonate	yield	diazo	yield
1	CH ₃ I	CH ₃	5	75%	12	60%
2	CH ₃ CH ₂ I	CH ₃ CH ₂	6	33%	13	75%
3	CH ₃ CH ₂ CH ₂ I	CH ₃ CH ₂ CH ₂	7	35%	14	78%
4	(CH ₃) ₂ CHCH ₂ I	(CH ₃) ₂ CHCH ₂	8	20%	15	74%
5	PhCH ₂ CH ₂ OTf	PhCH ₂ CH ₂	9	50%	16	75%
6			10	46%	17	76%
7			11	50%	18	83%

monoalkylated phosphonocrotonates **5–11**. Although the yields for the alkylation reactions generally fell in the low to moderate range, the relatively facile separation of **5–11** from the major byproduct of the reaction, the corresponding dialkylated phosphonocrotonates, made these transformations synthetically useful. Of additional note is that phosphonocrotonates **5–11** were isolated exclusively as the *E*-enoate isomer having the alkyl substituent α to the ester. Having ready access to **5–11**, we were prepared to examine their conversion to the corresponding vinyl diazo substrates. We were delighted to find this conversion to be uneventful under standard diazo transfer conditions (DBU and ABSA, Table 1).⁶

With the requisite diazo substrates in hand, we next explored their reactivity. From our interest in the synthesis of quaternary substituted indolines from the coupling of 2-thioindoles with vinyl diazoesters,⁷ we initially examined the coupling of thioindole **19** with methyl-substituted phosphonate **12**. The addition of **12** to a solution of **19** and Rh₂(OAc)₄ at rt resulted in the formation of vicinal quaternary-

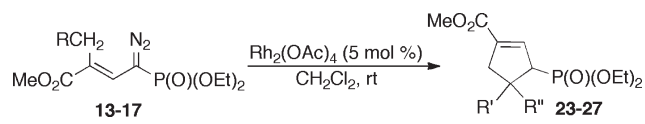
substituted indoline **20** in 87% isolated yield as a single diastereomer (Scheme 2). As we have described previously for the diazoester couplings,⁷ we believe that the reaction to **20** proceeds via sulfonium ylide intermediate **21** and a subsequent [3,3] sigmatropic rearrangement. We were impressed that the diazophosphonate coupling of **12** compares favorably with the related diazoester reaction with respect to yield and selectivity.

Scheme 3. Competitive C–H Insertion of **13****Scheme 2.** Diazophosphonate–Thioindole Coupling

In contrast to the results with **12**, when ethyl-substituted diazophosphonate **13** was exposed to Rh₂(OAc)₄ and indole **19** we not only isolated the desired quaternary substituted indoline **22** but also a significant quantity of cyclopentenyl phosphonate **23** that presumably resulted from a competitive intramolecular C–H insertion reaction (Scheme 3).

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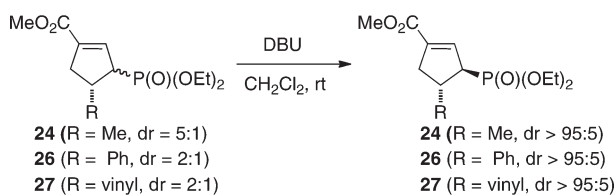
(7) (a) Boyarskikh, V.; Nyong, A.; Rainier, J. D. *Angew. Chem., Int. Ed.* **2008**, *47*, 5374. (b) Nyong, A.; Rainier, J. D. *J. Org. Chem.* **2005**, *70*, 746. (c) Novikov, A. N.; Kennedy, A. R.; Rainier, J. D. *J. Org. Chem.* **2003**, *68*, 993–996. (d) Kennedy, A. R.; Taday, M. H.; Rainier, J. D. *Org. Lett.* **2001**, *3*, 2407.

Table 2. C–H Insertion Reactions of Vinyl Diazophosphonates


entry	R	R'	R''	cyclopentene	dr	yield (%)
1	CH ₃	H	H	23		67
2	CH ₃ CH ₂	Me	H	24	5:1 ^a	89
3	(CH ₃) ₂ CH	CH ₃	CH ₃	25		87
4	Bn	Ph	H	26	2:1 ^b	78
5	allyl	vinyl	H	27	2:1 ^a	82

^a Determined by ¹H NMR of the crude reaction mixture; ^b Determined by HPLC of the crude reaction mixture

The conversion to cyclopentene **23** could be improved to 67% yield by simply carrying out the reaction in the absence of thioindole **19** (Table 2, entry 1).

Scheme 4. Equilibration to *trans*-Phosphonates

While intramolecular C–H insertions of Rh carbenes are well-known,⁸ to the best of our knowledge very few of these transformations have utilized vinyl diazo substrates as precursors.^{7c,8,9} Additionally, very few C–H insertion reactions of diazophosphonates have been reported.¹⁰ In contrast, intermolecular C–H insertions of vinyl diazoesters and O–H and N–H insertions of diazophosphonates have been demonstrated to be powerful synthetic transformations.^{11–13} In light of this and because this transformation, if

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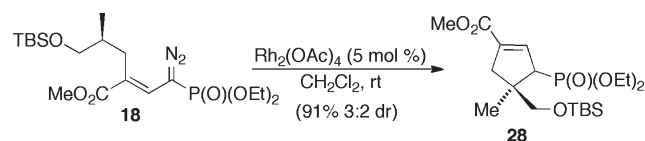
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general, would represent a powerful entry into structurally rich cyclopentenyl phosphonates we opted to study its scope. As illustrated in Table 2, alkyl, benzyl, and even homoallyl diazophosphonates undergo C–H insertion reactions in high yields to give the corresponding cyclopentenyl phosphonates when exposed to catalytic Rh₂(OAc)₄.

The mixture of *cis*- and *trans*-phosphonates **24**, **26**, and **27** were equilibrated to the *trans* diastereomer by simply subjecting the mixture to DBU for 30 min (Scheme 4).

Scheme 5. Stereoselective C–H Insertion to **28**

Optically active phosphonocrotonate **18** also underwent a C–H insertion reaction resulting in the generation of cyclopentene **28** in 91% yield as a 3:2 mixture of diastereomers (Scheme 5). We were pleased to find that the major **28** diastereomer existed as a single enantiomer. Based on Taber's precedent,¹⁴ we presume that the C–H insertion reaction proceeded with retention of absolute configuration.

In summary, we have demonstrated both the synthesis and the reactivity of vinyl diazophosphonates in C–H insertions and sulfonium ylide transformations. Both reactions deliver relatively complex substrates from simple starting material. Our future efforts in this area will be focused on examining the scope of vinyl diazophosphonate reactivity and the application of the products from these efforts in the synthesis of complex substrates including natural products.

Acknowledgment. We are grateful to the National Science Foundation for support of this work (CHE 1012670). We thank the support staff at the University of Utah and especially Dr. Peter Flynn (NMR) and Dr. Jim Muller (mass spectrometry) for help in obtaining data. We also thank Professor Douglass F. Taber (University of Delaware) for insightful discussions.

Supporting Information Available. Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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