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Reactivity of Vinyl Phosphonate Containing Diazoesters: Formation, Reactivity, and Utility

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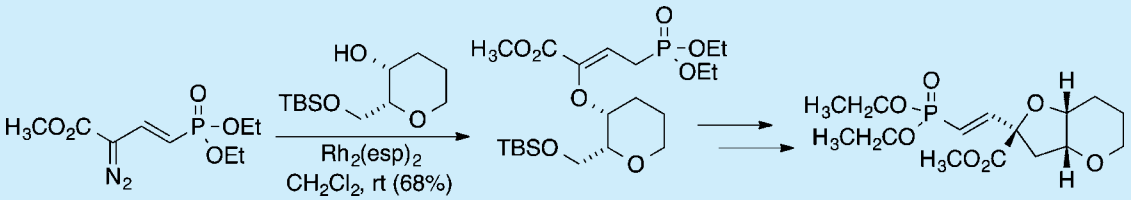
Supporting Information



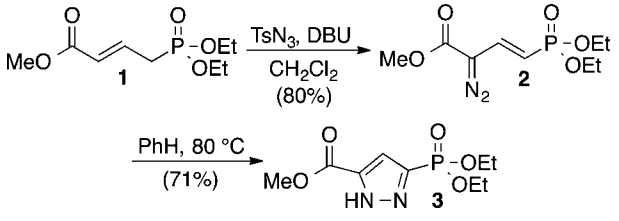
ABSTRACT: Treatment of diazo vinyl phosphonate with alcohols, amines, and thiols in the presence of Rh(II) results in the chemo- and stereoselective generation of enol ethers, enamines and vinyl sulfides via an X−H insertion process. The utility of the products from these reactions was demonstrated through their conversion into quaternary substituted heterocycles including furans and oxetanes as highlighted by the generation of a bicyclic phosphonate analogue of neodysiherbaine.

The ability to harness the reactivity of metal carbenoids has led to both the efficient generation of interesting architectures and a better understanding of the role of electronics and sterics on reactivity.[1] As a result of studies that have come predominantly from the Davies group, it has been established that donor−acceptor metal carbenoids from vinyl diazoacetates show high levels of chemo- and stereoselectivity in a number of interesting and important transformations including intermolecular cyclopropanations, ylide-initiated processes, and O−H, N−H, and C−H insertion reactions.[2]

In contrast to the results with donor−acceptor carbenoids, the corresponding diacceptor vinyl metal carbenoid analogues have received less attention.[3] We contend that the development of methods and substrates that would result from the use of diacceptor vinyl metal carbenoids in synthetic chemistry would be valuable. Of particular interest to us was a diacceptor carbenoid that paired a phosphonate with an ester, cf. **2**.[4] Not only would the successful use of this system lead to the generation of products that contained useful functionality for synthetic chemistry, but it would represent a novel entry into unique phosphonates that could be used directly in a variety of applications.[5,6] Precedent for the development of vinyl diazo phosphonates in this context exists: Davies has used Rh carbenoids from donor−acceptor vinyl diazophosphonates in cyclopropanation reactions and overall [4 + 3] cycloadditions,[7] Park and co-workers also used a donor−acceptor vinyl diazophosphonate and $Rh_2(esp)_2$ in a cascade with a 2*H*-azirine to build a phosphonate substituted pyridine,[8] Lonzi and López utilized a diazo vinylphosphonate in a [3 + 2] cycloaddition to generate a pyrrole,[9] and we recently reported the use of substituted vinyl diazophosphonates in Rh-catalyzed intramolecular C−H insertion reactions to cyclopentenes and in thionium ylide rearrangements to quaternary substituted indolines.[10] Contained herein are our continued contributions to this area through the demonstration of vinyl phosphonate containing diazoester **2** in intermolecular O−H, N−H, and S−H insertion reactions.

While our overriding concerns were focused on the reactivity and selectivity of the metal carbenoid, it was unclear to us whether diazo transfer with our substrate of interest, namely **1**, would lead to the diazo adjacent to the ester, the phosphonate, or a mixture of both. Our concerns were mitigated to some extent by the high levels of selectivity that were observed in the anionic alkylation chemistry of **1** and our belief that similar levels of selectivity would be seen in the diazo-transfer reaction.[11] Although our initial attempts to perform a diazo transfer to **1** using ABSA (4-acetamidobenzenesulfonyl azide) resulted in the generation of a mixture of products, this problem was easily overcome by turning to TsN_3 to give diacceptor vinyl diazoester **2** as the exclusive product in 80% yield (Scheme 1).[12] Diazo **2** is stable to storage for at least 1 month at −30 °C and decomposes within hours upon heating to diazene **3**.

Scheme 1. Diazo Vinylphosphonate 2



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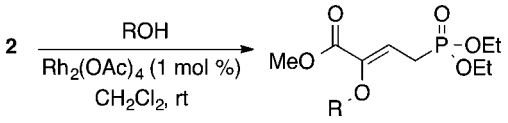
With a route to **2** in hand, we next examined its O−H insertion chemistry by subjecting it to alcohols in the presence of catalytic $Rh_2(OAc)_4$ (Table 1). At the outset, it was not clear

Table 1. O−H Insertion Reactions of 2



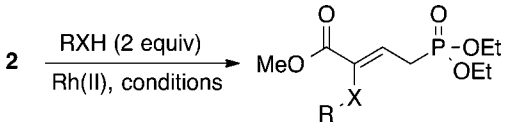
entry	R	product	yield (%)
1	Bu	**4**	82
2	*i*-Pr	**5**	82
3	CH_2CHCH_2	**6**	83
4	CH_2CCH	**7**	74
5	CH_2CH_2I	**8**	78
6	$CH_2CH_2CH_2Br$	**9**	74
7	Ph	**10**	56

to us whether allyl ether or enol ether products would be the result from these reactions: the glutaconic acid diacceptor system gave enol ethers when exposed to simple alcohols and Rh(II) while donor−acceptor carbenoids gave allyl ethers.[13] As with the chemistry of **1** that was discussed above, it was not obvious to us that the reaction would necessarily occur adjacent to the ester.[14]

Keeping the above considerations in mind, we treated **2** with $Rh_2(OAc)_4$ and 1-butanol and found it to undergo an efficient O−H insertion reaction to give *Z*-enol ether **4** having the new C−O bond proximal to the ester (Table 1). Similar reactivity was observed with both 2-propanol to give **5** and with more elaborate alcohol substrates to give allyl ether **6**, propargyl ether **7**, and phenyl ether **10**, respectively. Of note was the lack of products from [3,3]- or [2,3]-sigmatropic rearrangements as had been observed by others with substituted propargyl and allyl ethers.[15−17] Further evidence for the selectivity of this diacceptor system came from the O−H insertion reactions of halohydrins to give **8** and **9**.

Amides, sulfonamides, and carbamates also react with **2** when exposed to Rh(II) to generate enamides **11**−**13** (Table 2).

Table 2. N−H and S−H Insertion Reactions with 2

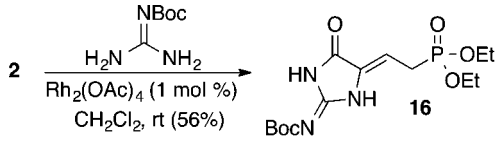


entry	RX	conditions[a]	product	yield (%)
1	NHBoc	A	**11**	78
2	NHAc	B	**12**	58
3	NHTs	A	**13**	49
4	NHPh	A	**14**	71
5	SPh	A	**15**	81

[a](A) $Rh_2(OAc)_4$ (1 mol %), CH_2Cl_2, rt, 4 h. (B) $Rh_2(esp)_2$ (1 mol %), $PhCH_3$, 60 °C, 2 h.

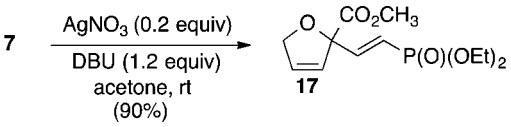
While $Rh_2(OAc)_4$ was superior for the generation of **11** and **13**, the Dubois−Espino catalyst $Rh_2(esp)_2$ worked best in our hands for the generation of **12**.[18] It is worth noting that **11**−**13** are structurally related to potent glutamate receptor agonists.[19] The use of aniline and thiophenol gave enamine **14** and vinyl sulfide **15**, respectively. As with the alcohol reactions, the products existed as the *Z*-alkene isomer and incorporated the heteroatom adjacent to the ester. Finally, we did not isolate N−H insertion products when butylamine was used in the reaction but instead recovered vinylphosphonate **2**.

The use of *N*-Boc-guanidine resulted in the isolation of the interesting imidazolidinone **16**, where both N−H insertion and imidazolidine formation had occurred (eq 1).



(1)

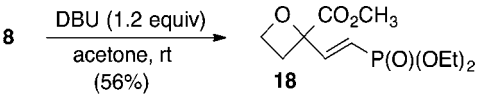
As was mentioned above, the products from the insertion reactions of **2** have the potential to be valuable precursors to more elaborate systems. As an example of this, we isolated dihydrofuran **17** from a 5-*endo-dig* cyclization when we subjected propargyl enol ether **7** to $AgNO_3$ in acetone (eq 2). This reaction is noteworthy in that cyclization occurred



(2)

adjacent to the ester to give the more hindered quaternary center. It is interesting that related substrates and conditions have been reported to give 5-*exo-dig* cyclization products.[20−22]

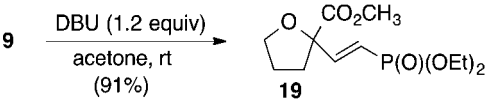
The ability to selectively insert into the O−H bond of halohydrins to generate **8** and **9** gave us the opportunity to explore the generation of cyclic ethers via intramolecular substitution reactions (eq 3). Toward this goal, we subjected



(3)

iodoether **8** to DBU and isolated oxetane **18** in 56% yield. As with the cyclization to **17**, the reaction occurred exclusively at the carbon atom adjacent to the ester.

In a fashion similar to the reaction of **8**, bromoether **9** gave quaternary-substituted furan **19** in 91% yield when subjected to DBU (eq 4).[23]



(4)

The overall insertion and cyclization sequence to cyclic ethers having quaternary centers is exciting as it presents us with the opportunity to synthesize a number of structurally complex substrates that have this architectural motif. Illustrated in Scheme 2 is the synthesis of novel neodysiherbaine analogue **23** from readily available pyran **20**.[24] Insertion of the Rh carbenoid from **2** into the secondary alcohol in **20** led to the generation of **21** in 68% yield. Following the two-step conversion of **21** into the corresponding tosylate **22**, we were pleased to find that we could convert **22** into bicyclic ether **23** as a single diastereomer by simply subjecting it to DBU. The presence of quaternary-substituted ethers that are structurally

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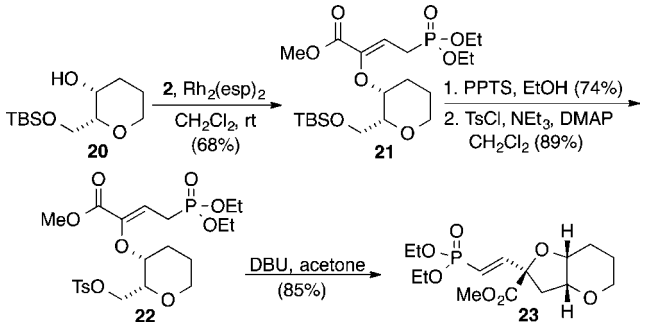
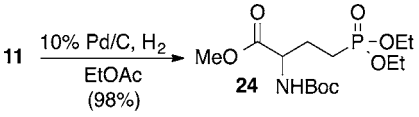
Scheme 2. Bicyclic Fused Ether Formation



related to **23** in important kainate receptor agonists and antagonists makes this methodology potentially impactful.[25]

As a final illustration of the utility of the insertion products, we have generated the protected variant of the glutamate receptor agonist AP4 by subjecting *N*-Boc-enamide **11** to hydrogenation conditions to give **24** (eq 5).[26]



(5)

In conclusion, we have utilized acceptor−acceptor diazophosphonate **2** in chemo- and stereoselective O−H, N−H, and S−H insertion reactions to give the corresponding enol ether, enamine, and vinyl sulfide products. We have also demonstrated the utility of the products from these transformations by carrying out subsequent cyclizations and reductions. We anticipate that these novel substrates and reactions will enable us to efficiently access heretofore unavailable phosphonate-containing substrates.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and spectral data for compounds **2**−**24**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(17) Compound **6** undergoes a Claisen rearrangement upon heating (see the Supporting Information).

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