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Z-Selective ring opening of vinyl oxetanes with dialkyl dithiophosphate nucleophiles†

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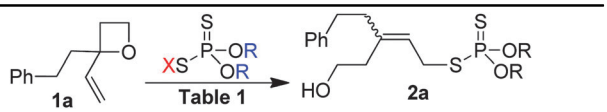
Dialkyl dithiophosphates selectively ring open vinyl oxetanes in excellent yields under mild reaction conditions to form useful allylic thiophosphate products with high *Z*-selectivity.

Vinyl oxetanes are a neglected class of substrates that provide exciting opportunities to study new ring expansions and ring openings. We have reported two catalytic ring expansion approaches (Fig. 1), one employing a carbene, the other a Lewis or Brønsted acid.[1] We wondered whether a dialkyl dithiophosphate could be used to divert an acid catalyzed ring expansion pathway to a nucleophilic ring opening pathway. Larock[2] has shown that C, O, and N-nucleophiles could be used with the help of a palladium catalyst to ring open vinyl oxetanes. Yields are generally good and the products are enriched in the *E*-olefin isomer. Although we could not find any examples of ring expansions of vinyl oxetanes with sulfur nucleophiles, we were encouraged by a report detailing an oxetane ring opening with dialkyl esters of dithiophosphoric acids.[3]

We chose vinyl oxetane **1a** as the test substrate for our reaction optimization studies (Table 1). We were delighted to learn of how efficiently and selectively dithiophosphate esters ring opened **1a**. We only observed attack at the olefin terminus (S_N2'-type attack) and the resulting trisubstituted allylic thiophosphates were afforded as primarily *Z*-olefin isomers. In our search for the optimal reaction conditions we varied the ester group (*R*), counterion (X), solvent, and temperature. These studies revealed that chlorinated solvents were most suitable, resulting in a faster reaction and slightly higher isolated yields. We selected dichloromethane (DCM) as our solvent of choice for further studies. Interestingly, lowering the temperature (entries 7–9) did not impact yield or *Z*/*E*-selectivity in a significant way, which is why we chose to run all ensuing reactions at room temperature. Replacement of the hydrogen with a counterion (X) resulted in longer reactions times and less reproducible results (entries 10–12).[4] Finally we looked at the size of the ester group (*R*). Although the results in Table 1 (entry 8 *vs.* entries 13–14) do not reveal a clear preference between methyl, ethyl and isopropyl, we learned when we investigated other substrates that the isopropyl esters gave the best *Z*/*E*-selectivity and yields.

We have subjected the seventeen vinyl oxetane compounds shown in Table 2 to our standard reaction conditions

Table 1 Vinyl oxetane ring opening optimization studies



Entry	(X, R)	Solvent	*T* (°C)	*t* (h)	*Z*/*E* ratio	Yield (%)
1	(H, Me)	Toluene	rt	2.0	4.9 : 1	62
2	(H, Me)	Benzene	rt	2.0	4.7 : 1	75
3	(H, Me)	THF	rt	2.5	3.2 : 1	80
4	(H, Me)	Ether	rt	3.0	3.5 : 1	78
5	(H, Me)	DCE	rt	0.5	4.0 : 1	86
6	(H, Me)	Chloroform	rt	0.5	4.1 : 1	82
7	(H, Me)	DCM	rt	0.5	4.0 : 1	85
8	(H, Me)	DCM	0	0.7	4.2 : 1	88
9	(H, Me)	DCM	−78	1.2	4.4 : 1	90
10	(NH_4, Me)	DCM	40	4.0	2.5 : 1	75
11	(Na, Me)	DCM	40	24.0	5.8 : 1	32
12	(TMS, Me)	DCM	rt	0.5	2.0 : 1	81
13	(H, Et)	DCM	rt	0.5	4.1 : 1	83
14	**(H, iPr)**	**DCM**	**rt**	**0.5**	**4.3 : 1**	**87**

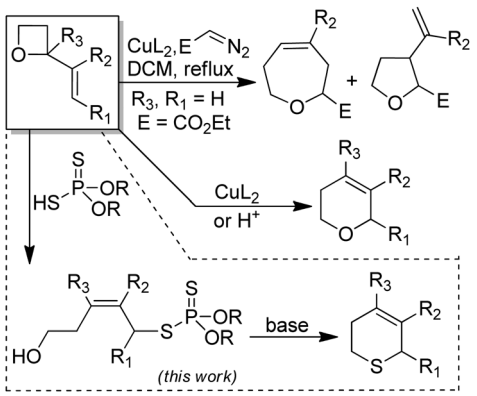


Fig. 1 Njardarson group vinyl oxetane based reactions.

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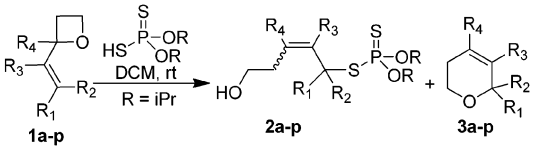
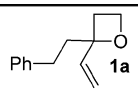
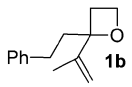
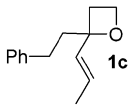
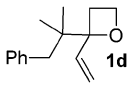
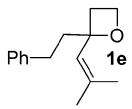
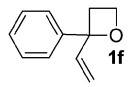
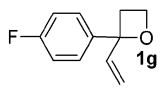
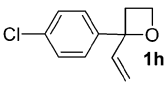
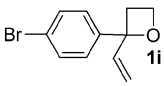
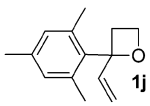
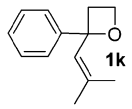
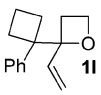
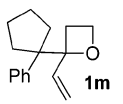
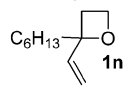
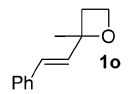
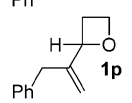
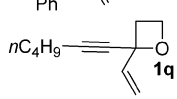
† Electronic supplementary information (ESI) available: Experimental details and spectral data for all new compounds. See DOI: 10.1039/c3cc46660d

Table 2 Vinyl oxetane ring opening scope

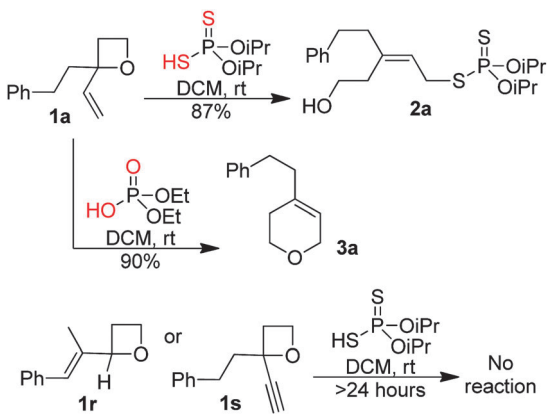


	Time (h)	Yield (%)	2/3 ratio	2 *E*/*Z* ratio
 **1a**	0.5	87	**2** only	1 : 4.3
 **1b**	0.5	92	**2** only	1 : 2.5
 **1c**	1.5	78	4.9 : 1	1 : 6.7
 **1d**	0.5	95	**2** only	*Z* only
 **1e**	10	86	**3** only	NA
 **1f**	0.5	90	**2** only	1 : 5.8
 **1g**	0.7	93	**2** only	1 : 7.1
 **1h**	0.7	92	**2** only	1 : 7.9
 **1i**	0.7	96	**2** only	1 : 7.5
 **1j**	0.5	86	**2** only	1 : 3.8
 **1k**	8	90	**3** only	NA
 **1l**	0.5	91	**2** only	*Z* only
 **1m**	0.5	95	**2** only	*Z* only
 **1n**	0.5	80	**2** only	1 : 4.4
 **1o**	2.0	65	5.4 : 1	1 : 5.1
 **1p**	0.5	48	**2** only	1 : 1.5
 **1q**	0.5	86	**2** only	1 : 8.2

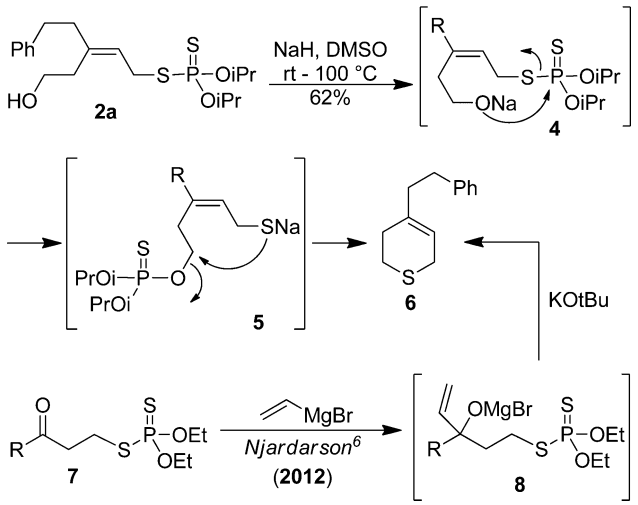
(1.2 equiv. diisopropyl dithiophosphate, DCM, rt). Almost all of the substrates proceeded to form ring opening products in excellent yields and generally high *Z*-selectivity. Sterics play a key role for this new reaction, with substituents at the olefin terminus retarding (**1c** and **1o**) or inhibiting (**1e** and **1k**) nucleophilic ring opening. For substrates containing very large 2-alkyl substituents (**1d**, **1l** and **1m**) the *Z*-olefin selectivity was excellent. The most drastic erosion of *Z*-selectivity was observed for **1b** and **1p**, both of which contain an internally substituted olefin (methyl or benzyl substitution). Vinyl oxetane substrate **1q** is particularly noteworthy, as it presents an opportunity for forming either an olefin or an allene depending on which unsaturation the nucleophile attacks. For this substrate, the diisopropyl dithiophosphate selectively attacked the olefin forming an allylic thiophosphate product with high *Z*-selectivity.

It is interesting to contrast the orthogonal reaction outcomes when vinyl oxetanes such as **1a** are treated separately with a diisopropyl dithiophosphate *vs.* diethyl phosphoric acid[1b] (Scheme 1). These two nearly structurally identical reagents are about equal when it comes to acidity (pK_a),[5] but differ most significantly in terms of the relative nucleophilicity of their respective heteroatoms (O *vs.* S). As a result, in one case, a nucleophilic ring opening to form **2a** proceeds, while in the other, the vinyl oxetane cleanly ring expands to a six membered ring (**3a**). Of course, as we learned from the examples presented in Table 2, these reaction outcomes can be altered by changing the vinyl oxetane substitution patterns. For example, nucleophilic attack can be completely blocked by substituting both positions of the olefin terminus, thus forcing the dithiophosphate to act only as an acid and afford a 3,6-dihydro-2*H*-pyran instead (substrates **1e** and **1k**). Beyond the reactivity trends presented in Table 2, we have also learned that alkynyl oxetanes (**1s**) do not react under the normal reaction conditions. Furthermore, nucleophilic ring opening can also be shut down when a vinyl oxetane substrate containing a single terminal olefin substituent and a less reactive oxetane (*mono*-substituted) is employed as exemplified by **1r**.

The *Z*-olefin products obtained from this new ring opening reaction provided us with an opportunity to investigate the 8-membered ring S → O hopping capacity of the thiophosphate group. Our hope was that treatment of **2a** with the appropriate



Scheme 1 Nucleophilicity *vs.* acidity.



Scheme 2 Anionic hopping – thiopyran formation.

base would facilitate a thiophosphate transfer from **4** to **5** (Scheme 2) followed by 6-*exo-tet* cyclization to form 3,6-dihydro-*2H*-thiopyran **6**. This would represent a new approach for accessing such sulfur heterocycles and a complementary one to our vinyl nucleophile initiated approach (**7** → **6**),[6] which proceeds *via* a 6-membered ring S → O hopping step. Screening of bases, solvents, and temperature revealed that this anionic cascade (**2a** → **6**) could be realized by treating **2a** with sodium hydride in a polar aprotic solvent (DMSO) at elevated temperatures (100 °C).[7] These are more forcing conditions than those we required for converting **8** to **6** (room temperature and THF), which we contribute primarily to the more challenging 8-membered ring thiophosphate hop *versus* a 6-membered ring.

In summary, we have developed a mild vinyl oxetane ring opening reaction that affords *Z*-substituted allylic thiophosphate products in excellent yields. The reaction is impacted by the electronics and sterics of the vinyl oxetane, with electronic stabilization of potential tertiary cation being favorable while substitution of the olefin terminus deterring or fully inhibiting the reaction. We have furthermore demonstrated for the first time that these allylic thiophosphates[8] can be converted to 3,6-dihydro-*2H*-thiopyrans upon treatment with base. Efforts are currently underway to expand the scope of this strategy, elucidate the exact mechanism and better understand the limits of S → O thiophosphate hopping.

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Notes and references

1 (*a*) D. J. Mack, L. A. Batory and J. T. Njardarson, *Org. Lett.*, 2012, **14**, 378–381; (*b*) B. Guo, G. Schwarzwalder and J. T. Njardarson, *Angew. Chem., Int. Ed.*, 2012, **51**, 5675–5678.
2 (*a*) R. C. Larock and S. K. Stolz-Dunn, *Tetrahedron Lett.*, 1988, **29**, 5069–5072; (*b*) R. C. Larock and S. K. Stolz-Dunn, *Tetrahedron Lett.*, 1989, **30**, 3487–3490.
3 B. A. Arbuzov, O. N. Nuretdinova, F. F. Guseva, R. G. Gainullina and L. Z. Nikonova, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1973, **22**, 2285–2287, translated from B. A. Arbuzov, O. N. Nuretdinova, F. F. Guseva, R. G. Gainullina and L. Z. Nikonova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1973, 2342–2345.
4 K, Cs, Ca, Mg, Ti, Pd, Pb, Cu(I) and Ni thiolates were also screened, but in all cases reactions very slow and conversions low.
5 (*a*) W. D. Kumler and J. J. Eiler, *J. Am. Chem. Soc.*, 1943, **65**, 2355–2361; (*b*) M. I. Kabachnik, T. A. Mastrukova, A. E. Shipov and T. A. Melentyeva, *Tetrahedron*, 1960, **9**, 10–28.
6 F. Li, D. Calabrese, M. Brichacek, Y. Lin and J. T. Njardarson, *Angew. Chem., Int. Ed.*, 2012, **51**, 1938–1941.
7 Conversion of thiophosphate **2a** to thiopyran product **6** also serves as a confirmation of the *Z*-olefin geometry of **2a**.
8 For recent allylic thiophosphate transformations, consult: (*a*) A. Goswami, *J. Chem. Res., Synop.*, 2000, 554–555; (*b*) X. Han, Y. Zhang and J. Wu, *J. Am. Chem. Soc.*, 2010, **132**, 4104–4106; (*c*) A. M. Lauer, F. Mahmud and J. Wu, *J. Am. Chem. Soc.*, 2011, **133**, 9119–9123; (*d*) A. M. Lauer and J. Wu, *Org. Lett.*, 2012, **14**, 5138–5141.

