Pergamon

Tetrahedron Letters 39 (1998) 1465–1468

TETRAHEDRON LETTERS

Substituent Effects in the Reaction of Allyl Trichloroacetimidates with N-Halosuccinimides: Cyclization Vs Aza-Claisen Rearrangement.

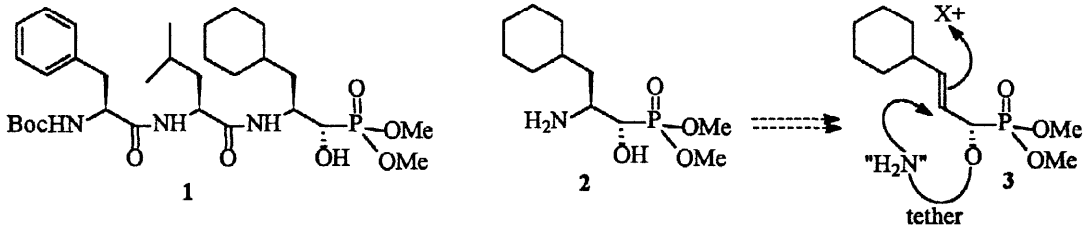
Hossein Shabany and Christopher D. Spilling*

Department of Chemistry, University of Missouri-St. Louis
8001 Natural Bridge Road, St. Louis Missouri 63121

Received 7 November 1997; revised 11 December 1997; accepted 12 December 1997

Abstract: **We report a novel substituent effect in the reaction of allylic trichloroacetimidates with N-halosuccinimides. Reaction of *E* allylic trichloroacetimidates bearing phosphonate or cyano substituents with NBS in $CHCl_3$ results in a [3.3] sigmatropic rearrangement. In contrast, the *Z* allylic phosphonate or phenyl substituted allylic trichloroacetimidate undergo halocyclization.**

The last five years have witnessed a rapid advance in methods for the enantioselective synthesis of hydroxyphosphonates.[1-5] Recent advances include the use of homochiral phosphonate anion equivalents,[1] enzymatic resolution,[2] asymmetric reduction,[3] asymmetric hydroxylation,[4] and in particular chiral metal catalysts,[5] which have given access to hydroxyphosphonates of high enantiomeric purity. We have begun to explore applications of this new technology to the asymmetric synthesis of structurally more complex, and biologically interesting molecules.



Phosphonopeptides **1**, containing the hydroxyphosphonates **2**, were as identified by Patel *et. al* as potent inhibitors of the human aspartyl protease enzyme renin.[6] Analogous phosphonopeptides can be prepared by asymmetric phosphonylation[5] of unsaturated aldehydes,[7] and introduction of an amino group at the β carbon (alkene). It was expected that high levels of stereocontrol could be gained by tethering the nitrogen nucleophile to the α-hydroxyl.[8] The β-amine can then be introduced by halocyclization of the tethered nitrogen nucleophile, and reduction of the resulting halide with tributyltin hydride.[9] We had previously described[10a] (as was reported independently by Ohler et. al)[10b] that allylic hydroxyphosphonates would react with trichloroacetonitrile and DBU to give the corresponding trichloroacetimidates, which rearranged upon heating[10b] or treatment with $Pd(PhCN)_2Cl_2$ in toluene[10a] to give γ-amido vinylphosphonates. Since the

0040-4039/98/$19.00
PII: S0040-4039(97)10837-1

trichloroacetimidates contain a tethered nitrogen nucleophile, they appeared to be ideal candidates for introduction of an amine group by halocyclization.[9]

A series of racemic hydroxyphosphonates **4a-e** were prepared by the Et_3N catalyzed reaction of dimethyl phosphite with unsaturated aldehydes.[11] DBU catalyzed addition of the hydroxyphosphonate to trichloroacetonitrile (Scheme 1) gave the trichloroacetimidates **5a-e** in high yield (>90%).[10]

Scheme 1

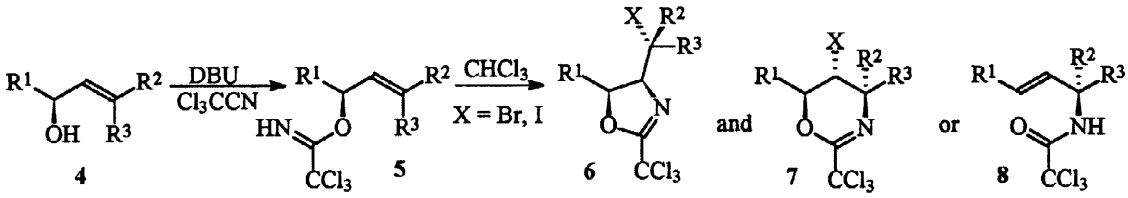


Table 1. Reaction of Allylic Trichloroacetimidates with N-Halosuccinimides

Cmpd #	R^1	R^2	R^3	halide/solvent/time	Yield, crude % (isolated%)[a]		
					5-exo **6**	6-endo **7**	amide **8**
a	$(MeO)_2P(O)$-	Ph	H	NBS/$CHCl_3$/24 hrs	—	—	91 (91)[b]
b	$(MeO)_2P(O)$-	Me	H	NBS/CH_2Cl_2:CH_3CN, 6:1, 24 hrs	—	—	98 (82)
b	$(MeO)_2P(O)$-	Me	H	NBS/$CHCl_3$/36 hrs			86 (53)[c]
c	$(MeO)_2P(O)$-	cyc-C_6H_{11}	H	NBS/$CHCl_3$/24 hrs	—	—	(89)
d	$(MeO)_2P(O)$-	2-furanyl	H	NIS/CH_2Cl_2/24 hrs	—	—	65 (65)[d]
e	$(MeO)_2P(O)$-	n-C_5H_{11}	H	NBS/$CHCl_3$/24 hrs	—	—	88 (55)
f	CN	Ph	H	NBS/$CHCl_3$/24 hrs	—	—	100 (71)
g	Ph	Ph	H	NBS/CH_2Cl_2:CH_3CN, 6:1, 24 hrs	1 : 9 ratio (86%)		—
h	$(MeO)_2P(O)$-	H	n-C_5H_{11}	NBS/$CHCl_3$/5 days	86 (71)[e]	—	—

a) recrystallized from ether, b) crude product consists of pure amide, c) 4g scale, d) the furans decomposed slowly at room temperature complicating isolation, e) yield after hydrolysis to hydroxy amide.

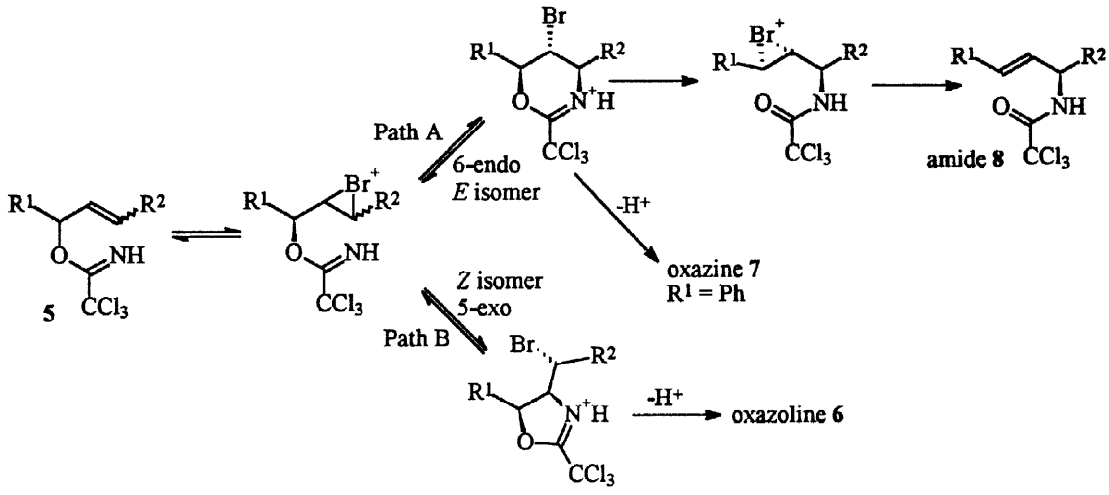
The trichloroacetimidates **5a-e** were reacted with NBS or NIS in $CHCl_3$ solution at room temperature. However, rather than the expected halocyclized products, the ^1H NMR spectra showed that the major product (>85%) was the γ-amido vinyl phosphonate **8** (Table 1). Further investigation showed that the final outcome of the reaction of the imidates **5a-e** with NBS was dependent upon the solvent used and the reaction time. For example, prolonged exposure to NBS in acetonitrile resulted in the initially formed amide **8** undergoing some further halocyclization via addition of the carbonyl oxygen into the vinyl phosphonate.[12] However, under standard conditions (NBS 1eq., $CHCl_3$, 24 hrs.) the rearrangement was high yielding and was observed with both alkyl and aryl allylic phosphonates.

The vinyl phosphonates **8a-e** show a characteristic coupling pattern in the ^1H NMR spectra (e.g. **8c**) for the α (5.71 ppm, J_{HH} = 17.4, J_{HH} = 1.8, J_{HP} = 18.9 Hz),and the β (6.67 ppm, J_{HH} = 17.4, J_{HH} 5.7, = J_{HP} = 22.2 Hz) protons, and signals in the ^{31}P NMR spectra in the range δ 19-21 ppm.[10] The precursor imidates **5a-e** show signals in the ^{31}P NMR spectra 0.2-0.75 ppm upfield of the vinylphosphonates **8a-e**, whereas the products of further cyclization are upfield of the imidates by 2-3 ppm.[12]

The unusual reactivity of imidates **5a-e** can be rationalized on the basis of the stereoelectronic effect the electron withdrawing phosphonate group. Three additional imidates **5f-h** were prepared to test this hypothesis.[13] Reaction of the allylic nitrile system **5f** mirrored that of the phosphonates and gave the rearranged product **8f**. The diphenylpropenyl imidate **5g** underwent the halocyclization to give a mixture of oxazoline **6g** (5-exo) and oxazine **7g** (6-endo) in a 1:9 ratio. The *Z* allylic phosphonate **4h** provided a critical result. Reaction of the imidate **5h** with NBS in chloroform was exceedingly slow, but gave a single oxazoline diastereoisomer **6h** resulting from 5 exo cyclization, and provides a new synthesis of an analog of the known renin inhibitor **1**. This is in complete contrast to the related *E* allylic phosphonate **5e** which gave rearrangement product **8e**.

The observed results can be rationalized by a mechanism (Scheme 2) which is comparable to that of the metal ion catalyzed [3.3] rearrangements.[14] Alkene geometry has been shown to have a major effect on the halocyclization of imidates; *E* Olefins generally give oxazines (endo cyclization, path A), due to destabilization of the incipient β cation by the electron withdrawing imidate group, whereas, the *Z* olefin suffers from a severe steric interaction in the 6 endo cyclization prefers to form oxazolines (exo cyclization, path B) by attack at the β position.[9b] The additional inductive electron demand of the phosphonate and nitrile groups enforce this effect, but also increase the electrophilicty of the α-carbon enhancing susceptibility to neighboring group attack by the halide, leading to rearrangement.

Scheme 2



In summary, we have discovered a novel, efficient, and stereospecific[15] method for the [3.3] sigmatropic rearrangement of *E* allylic trichloroacetimidates bearing electron withdrawing groups. This reaction is complimented by the cyclization of the *Z*-allylic imidate which, under similar conditions, gave a single oxazoline diastereoisomer resulting from 5 exo cyclization, providing a novel synthesis of a renin inhibitor analog.

Acknowledgments

We are grateful to the University of Missouri Research Board and the National Science Foundation (CHE 9628820) for financial support of this project, and the National Science Foundation (CHE-9318696), the U.S. Department of Energy (DE-FG02-92-CH10499) and the University of Missouri Research Board for grants to purchase the NMR spectrometers.

References and Notes

1. a) Blazis, V. J.; Koeller, K. J.; Spilling, C. D. *J. Org. Chem.* **1995**, *60*, 931 and references cited therein; b) Blazis, V. J.; Koeller, K. J.; Spilling, C. D. *Tetrahedron Asymm.* **1994**, *5*, 499; c) Gordon, N. J.; Evans, Jr., S. A. *J. Org. Chem.* **1993**, *58*, 5293; d) Cain, M. J.; Baird, C. A.; Kee T. P. *Tetrahedron Lett.* **1994**, *35*, 8671; e) Sum, V: Kee T. P.; Thornton-Pett, M. *J. Chem. Soc., Chem. Commun.* **1994**, 743; f) Sum, V.; Kee T. P. *J. Chem. Soc. Perkin 1* **1993**, 1369; g) Sum, V.; Davies, A. J.; Kee T. P. *J. Chem. Soc., Chem. Commun.* **1992**, 1771.
2. a) Drescher, M.; Li F-Y.; Hammerschmidt, F. *Tetrahedron* **1995**, *51*, 4933; b) Li Y.-F.; Hammerschmidt F. *Tetrahedron Asymm.* **1993**, *4*, 109; c) Heisler, A.; Rabiller, C.; Douillard, R.; Goalou, N.; Hägele, G.; Levayer, F. *Tetrahedron Asymm.* **1993**, *4*, 959.
3. a) Gajda, T. *Tetrahedron Asymm.* **1994**, *5*, 1965; b) Meier, C.; Laux, W. H. G. *Tetrahedron Asymm.* **1995**, *6*, 1089.
4. Pogatchnik, D. M.; Wiemer, D. F. *Tetrahedron Lett.* **1997**, *38*, 3495; Yokomatsu, T.; Yoshida, Y.; Suemune, K.; Yamagishi, T.; Shibuya, S. *Tetrahedron Asymm.* **1995**, *6*, 365.
5. a) Rath, N. P; Spilling, C. D. *Tetrahedron Lett.* **1994**, *35*, 227: b) Yokomatsu, T.; Yamagishi, T.; Shibuya, S. *Tetrahedron Asymm.* **1993**, *4*, 1783; c) Yokomatsu, T.; Yamagishi, T.; Shibuya, S. *Tetrahedron Asymm.* **1993**, *4*, 1779; d) Wynberg, H.; Smaardijk, A. A. *Tetrahedron Lett.*, **1983**, *24*, 5899; Sasai, H.; Arai, S.; Tahara, Y.; Shibisaki, M. *J. Org. Chem.* **1995**, *60*, 6656; Yokomatsu, T.; Yamagishi, T.; Shibuya S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1527; Sasai, H.; Bougauchi, M.; Arai, T.; Shibasaki, M. *Tetrahedron Lett.* **1997**, *38*, 2717 and references cited therein.
6. Patel, D. V.; Rielly-Gauvin, K.; Ryono, D. E. *Tetrahedron Lett.* **1990**, *31*, 5587; Patel, D. V.; Rielly-Gauvin, K.; Ryono, D. E. *Tetrahedron Lett.* **1990**, *31*, 5591; Patel, D. V.; Rielly-Gauvin, K.; Ryono, D. E.; Free, C. W.; Rogers, W. L.; Smith, S. A.; DeForrest, J. M.; Oehl, R. S.; Petrillo, Jr., E. W. *J. Med. Chem.* **1995**, *38*, 4557; see also Dellaria, J.F., Jr.; Maki, R.G. *Tetrahedron Lett.* **1986**, *27*, 2337.
7. Katsuki, T.; Lee, A. W. M.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Tuddenham, D.; Walker, F. J. *J. Org. Chem.*, **1982**, *47*, 1373; Patois, C.; Savignac, P. *Tetrahedron Lett.* **1991**, *32*, 1317 and references cited therein.
8. Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307; Hoffman R. W. *Chem. Rev.* **1989**, *89*, 1841.
9. a) Calter, M.; Hollis, T. K.; Overman, L. E.; Ziller, J.; Zipp, G. G. *J. Org. Chem.* **1997**, *62*, 1449 and references cited therein; b) Bongini, A.; Cardillo, G.; Orena, M.; Sandri, S.; Tomasini, C. *J. Org. Chem.* **1986**, *51*, 4905; c) Cardillo, G. in "*Methods of Organic Chemistry*" Vol. E21 pp 4746-4759, Thieme Veralag, Stuttgart, 1995 and references cited therein.
10. a) Blazis, V. J.; De la Cruz, A.; Koeller, K. J.; Spilling, C. D. "*The Preparation and Reactions of Chiral, Non Racemic, 1-Hydroxy Phosphonates*" Abstracts, 206th National Meeting of the American Chemical Society, Chicago, IL, Aug. 22-27, 1993, **ORGN 164**; b) Öhler, E.; Kotzinger, S. *Synthesis* **1993**, 497
11. Baraldi, P. G.; Guarneri, M.; Moroder, F.; Pollini, G. P.; Simoni, D. *Synthesis* **1982**, 653.
12. The cyclization of the amide has been verified by taking the isolated amide and reacting it with excess NBS in acetonitrile solution. Whereas, the trichloroacetamide reacts slowly, the monochlroracetamide (prepared by Zn/HOAc reduction) cyclizes much more efficeintly. See reference 9c.
13. 1,3-Diphenyl-2-propenyl imidate **5g** and 1-cyano-3-phenyl-2-propenyl imidate **5f** were prepared by reaction of the known alcohols with trichloroacetonitrile and DBU in CH_2Cl_2. The *Z* allylic hydroxyphosphonate **4h** was prepared by Lindlar reduction of the corresponding propargylic hydroxy phosphonate and was reacted as described to give the imidate **5h**. All new compounds were characterized by IR and NMR spectroscopy and elemental analysis. 1-cyano-3-phenyl-2-propenol, Belokon, Y.; Ikonnikov, N.; Moscalenko, M.; North, M.; Orlova, S.; Tararov, V.; Yashkina, L. *Tetrahedron Asymm.* **1996**, *7*, 851; hydroxy propargylic phosphonates, Benayoud, F.; deMendonca, D. J.; Digits, C.A.; Moniz, G.A.; Sanders, T.C.; Hammond, G. B. *J. Org. Chem.* **1996**, *61*, 5159.
14. Overman, L. E. *Ang. Chem. Int. ed. Engl.* **1984**, *23*, 579; Overman L. E. *J. Am. Chem. Soc.* **1976**, *98*, 2901; Overman L. E. *J. Am. Chem. Soc.* **1974**, *96*, 597; Overman, L. E. *Acc. Chem. Res.* **1980**, *13*, 218.
15. The *E* imidate **5a** was prepared with 60% enantiomeric excess, rearrangment with NBS in $CHCl_3$ gave only the *E* amide **8a** with 60% e.e.