Pergamon

Tetrahedron Letters 41 (2000) 7327–7331

TETRAHEDRON LETTERS

Phosphonodithioformates as heterodienophiles: synthesis of (3,6-dihydro-2*H*-thiopyran-2-yl)phosphonates

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Received 20 June 2000; accepted 18 July 2000

Abstract

Phosphonodithioformates are shown to be good heterodienophiles in [4+2] cycloadditions with open chain and cyclic dienes. Lewis acids efficiently catalyze this hetero Diels–Alder reaction and a selective radical desulfanylation of the cycloadducts using Bu_3SnH leads to new (3,6-dihydro-2*H*-thiopyran-2-yl) phosphonates. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: dithioester; phosphonate; thiocarbonyl; hetero Diels–Alder; thiopyran.

The [4+2] cycloaddition involving heterodienophiles is a powerful method for the synthesis of six-membered heterocycles.[1] The ability of the thiocarbonyl group to participate as dienophile in these reactions has been shown in several examples involving thioaldehydes, thioketones or dithioesters and was in particular used to trap unstable thiocarbonyl derivatives.[2a,b] These cycloadditions, which lead to dihydrothiopyran derivatives, have found a few interesting applications for the synthesis of natural products or their analogues.[3a–c] Compared to thioaldehydes, dithioesters are less reactive[4] but their stability make them more easy to handle as synthetic intermediates. Moreover, when they are α-substituted by an electronwithdrawing group (CN,[5a,b] COOEt,[6a,b] CF_3,[7] SO_2R)[8] which lowers the LUMO of the thiocarbonyl, dithioesters become efficient heterodienophiles and can be used to obtain, in smooth conditions, functionalised 2-alkylsulfanyl dihydrothiopyrans. These heterocycles can find applications in the synthesis of thiaglycoside derivatives particularly via the possible dihydroxylation of their double bonds.[3b,9a,b]

In connection with our studies related to the use of easy accessible phosphonodithioformates as intermediates for the synthesis of new sulfur substituted phosphonates,[10a–d] we report here our first results related to the reactivity of methyl phosphonodithioformate **1** as heterodienophile, the influence of Lewis acids on the rate of the reaction and the desulfanylation of the cycloaddition products.

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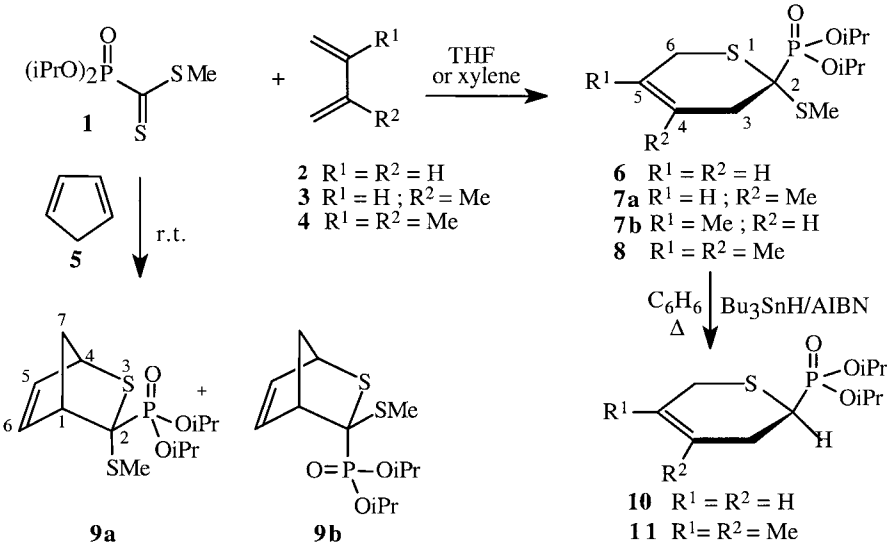
PII: S0040-4039(00)01221-1

We found that methyl diisopropylphosphonodithioformate **1** respectively reacts with an excess (5 equiv.) of butadiene **2**, methylbutadiene **3** or dimethylbutadiene **4** in methylene chloride (conditions indicated in Table 1) to give the corresponding (3,6-dihydro-2-methylsulfanyl-2*H*-thiopyran-2-yl)phosphonates **6**, **7a–b** and **8** (Scheme 1). A complete disappearance of the red color of the dithioformate indicates the end of the reaction. Compounds **6**, **7a–b** and **8** were isolated in nearly quantitative yield after purification by flash chromatography on silica gel.[11] Dihydrothiopyran **6** was also prepared by refluxing a solution of **1** with 3 equiv. of sulfolene in xylene for 20 min. However, probably due to some degradation at this higher temperature, yield of **6**, after purification, was only 63%. From the non-symmetrical 2-methyl-1,3-butadiene **3**, regioisomers **7a** and **7b** have not been separated. However, an NMR study of their mixture allowed us to determine a low regioselectivity (40:60) in favor of the 5-methyl substituted thiopyran (the 'para' derivative). This is in agreement with previous hetero Diels–Alder reactions involving this diene and dithioesters,[5b,6a]

Table 1

Diene	Conditions (a)	Cycloadduct	^{31}P NMR δ ppm ($CDCl_3$)	Yield % (ratio **a/b**) (c)
2	r.t., 24 h (b)	**6**	20.2	95
3	r.t., 24 h	**7a/7b**	18.1/18.5	93 (40/60)
4	50°C, 6 h	**8**	20.5	95
5	r.t., 1 h	**9a/9b**	20.8/20.5	90 (70/30)

(a) 0.4 mmol of **1** is mixed with 2mmol of diene in 1.5 ml of CH_2Cl_2; (b) reaction in a sealed tube; (c) after chromatography on silica gel (eluent: Petroleum ether/AcOEt, 80:20).



Scheme 1.

When **1** was treated by an excess (10 equiv.) of freshly dedimerized cyclopentadiene **5**, decoloration was observed after 1 h. A 70:30 mixture of two isomeric thia-norbornene derivatives **9a** (SMe-*endo*) and **9b** (SMe-*exo*) was obtained. When the reaction was prolonged for at least 30 min, the ratio of the two isomers evolves to 40:60 indicating that **9a** is the kinetic product and **9b** the thermodynamic one. This equilibration very probably came through a retro Diels–Alder reaction which was already mentioned for such bicyclic derivatives[12] and presently observed during concentration of the solution of **9a–b** under reduced pressure, even at room temperature (appearance of a pink coloration due to the generation of starting dithioester **1**). Structures of isomers **9a** and **9b** were deduced from NMR spectra. The shielding effect of the double bond on the SMe-*endo*-protons was observed (δ SMe-*endo* = 2.33; δ SMe-*exo* = 2.51). Moreover, by irradiation of the SMe-*endo* protons of **9a**, a NOE effect was observed on the signals of bridgehead protons H_1,H_4 and ethylenic protons H_5,H_6.

As shown in Table 2 for the reaction of **1** with dimethylbutadiene **4**, we found that the cycloadditions can be catalysed by Lewis acids such as $ZnCl_2$ and $BF_3{\cdot}Et_2O$, the last one being the more efficient. Since, to our knowledge, no example of a Lewis acid catalysis of a hetero Diels–Alder reaction involving a thiocarbonyl group as dienophile has so far been observed, we think it is mainly due to a chelation with the oxygen of the phosphinyl group which increases its electrowithdrawing effect on the thiocarbonyl. This is in accordance with the decrease of the δ observed in ^{31}P NMR and also with the similar effect observed in ^{13}C NMR for the signal of the thiocarbonyl carbon.[13,14] A secondary chelation involving sulfur is also possible, especially with the softer Zn cation.

Table 2
Lewis acid-catalysed reaction of **1** with diene **4***

Entry	**4** (eq.)	**Lewis acid** (eq.)	React. time	**8** Yield %
1	5	none	24 h	93
2	1.5	none	36 h	74
		$ZnCl_2$		
3	5	1	45 min.	97
4	5	0.1	5 h	98
5	1.5	0.1	24 h	96
		$BF_3.Et_2O$		
6	5	0.1	5 min.	95
7	1.5	1	1 min.	94
8	1.5	0.1	15 min.	86

* the diene is mixed with 2.4 mmol of **1** in 5 ml of CH_2Cl_2.

Of the two methods previously used for the selective desulfanylation of a 2-acetyl-3,6-dihydro-2-methylthio-2*H*-thiopyran ($Ph_3P/C_2H_5OH/CH_3CO_2H$ or *p*-$CH_3C_6H_4S^-$/DMF),[6a] we found that neither were efficient with the phosphono-substituted analogue **6**. More recently,[15] it has been shown that Bu_3SnH/AIBN in refluxing toluene can be used to replace one or two SR groups of phosphonodithioacetals by an hydrogen. However, from a mixed SMe, SPh dithioacetal a moderate selectivity is observed. We have tested this reaction on the dihydrothiopyrans **6** and **8.** The desulfanylation was found totally selective, the methylsulfanyl group being removed, without noticeable opening of the thiopyran ring. This reaction provided (3,6-dihydro-2*H*-thiopyran-2-yl)-phosphonates **10** and **11** in 80 to 85 % yield after purification.[16] These compounds are the

dihydrothiopyrans which could have been obtained from the unknown and probably very unstable phosphonothioformaldehyde.

In conclusion, the sequence hetero Diels–Alder cycloadditions and selective desulfanylation described in this Letter shows that a phosphonodithioformate, used as masked phosphonothioformaldehyde, is an interesting heterodienophile for the synthesis of new phosphono-substituted dihydrothiopyrans. With the aim of applications of these heterocycles to the synthesis of phosphorylated thiaglycoside derivatives, studies related to the dihydroxylation of their double bond and to the reactivity of phosphonodithioformates towards functionalized butadienes (in particular by OR groups) are presently in progress.

References

1. Weinreb, S. M.; Staib, R. R. *Tetrahedron* **1982**, *38*, 3087–3128.
2. For recent reviews, see: (a) Kirby, G. B. *Phosphorus, Sulfur, and Silicon* **1993**, 1–4, 17–29. (b) Metzner, P. *Organosulfur Chemistry I, Topics in Current Chemistry*; Page, P. B., Ed.; Springer-Verlag, 1999; Vol. 204, pp. 128–181.
3. (a) Herczegh, P.; Zsely, M.; Bognar, R.; Szilagyi *Tetrahedron Lett*. **1986**, *27*, 1509–1512. (b) Freer, A. A.; Isaacs, N. W.; Kirby, G. B.; Littlejohn, A.; Rhaman, M. S. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1261–1264. (c) Vedejs, E.; Galante, R. J.; Goekjian, P. G. *J. Am. Chem. Soc*. **1998**, *120*, 3613–3622.
4. Beslin, P.; Metzner, P. *Tetrahedron Lett*. **1980**, *21*, 4657–4658.
5. (a) Vyas, D. M.; Hay, G. W. *Can. J. Chem*. **1971**, *49*, 3755–3758. (b) Vyas, D. M.; Hay, G. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 180–186.
6. (a) Vedejs, E.; Arnost, M. J.; Dolphin, J. M.; Eustache, J. *J. Org. Chem*. **1980**, *45*, 2601–2604.(b) Kirby, G. W.; Lochead, A. W.; Williamson, S. *J. Chem. Soc., Perkin Trans. 1* **1996**, 977–984.
7. Portella, C.; Shermolovich, Y. G.; Tschenn, O. *Bull. Soc. Chim. Fr*. **1997**, *134*, 697–702.
8. Boerma, J. A.; Nilsson, N. H.; Senning, A. *Tetrahedron* **1974**, *30*, 2735–2740.
9. (a) Vyas, D. M.; Hay, G. W. *J. Chem. Soc., Chem. Commun*. **1971**, 1411–1412. (b) Vyas, D. M.; Hay, G. W. *Can. J. Chem*. **1975**, *53*, 1362–1366.
10. (a) Bulpin, A.; Masson, S.; Sene, A. *Tetrahedron Lett*. **1989**, 30, 3415–3418; (b) Bulpin, A.; Masson, S. *J. Org. Chem*. **1992**, 57, 4507–4512; (c) Levillain, J.; Masson, S.; Hudson, A. *J. Am. Chem. Soc*. **1993**, 115, 8444–8446; (d) Makomo, H.; Masson, S.; Saquet, M. *Tetrahedron* **1994**, 50, 10277–10288; (d) Bulpin, A.; Le Roy-Gourvennec, S.; Masson, S. *Phosphorus, Sulfur, and Silicon*, **1994**, *89*, 119–132.
11. ^{1}H and ^{13}C NMR data (δ ppm, J Hz) of a typical example of cycloadduct: Diisopropyl (3,6-dihydro-2-methylsulfanyl-2*H*-thiopyran-2-yl)phosphonate **6** (pale yellow oil). ^{31}P NMR ($CDCl_3$): 20.2; ^{1}H NMR ($CDCl_3$): $\delta = 1.06$ (d, $^{3}J = 6.3$, 3H), 1.086 (d, $^{3}J = 5$, 3H), 1.087 (d, $^{3}J = 6.4$, 3H), 1.10 (d, $^{3}J = 5.7$, 3H), 1.95 (dd, $^{2}J = 18.5$, $^{3}J = 1.8$, 1H, H_3), 2.05 (s, 3H, SCH_3), 2.58–2.72 (m, 1H, H_3), 2.62 (br. d, $^{2}J = 16$, 1H, H_6), 3.05 (dd, $^{2}J = 16$, $^{3}J = 2.4$, 1H, $H_{6'}$), 4.61–4.86 (m, 2H), 5.41–5.46 and 5.56–5.62 (2 m, 2H, H_4 and H_5); ^{13}C NMR ($CDCl_3$): 14.8 (s, **S**CH_3), 22.7 (d, $^{3}J_{CP} = 5.4$, **C**H_3), 23.5 (d, $^{3}J_{CP} = 6.3$, C_6), 23.6 (d, $^{3}J_{CP} = 5.4$, **C**H_3), 24.1 (d, $^{3}J_{CP} = 2.7$, **C**H_3), 24.4 (d, $^{3}J_{CP} = 2.7$, **C**H_3), 31.3 (d, $^{2}J_{CP} = 2.3$, C_3), 49.8 (d, $^{1}J_{CP} = 160.6$, C_2), 71.8 (d, $^{2}J_{CP} = 7.2$, **C**HO-), 72.7 (d, $^{2}J_{CP} = 8.1$, **C**HO-), 122.7 (d, $^{4}J_{CP} = 1.8$, C_5), 124.6 (d, $^{3}J_{CP} = 9.9$, C_4). Microanalysis: $C_{12}H_{23}0_3PS_2$ calcd: C, 46.43; H, 7.47; found: H, 46.21; H, 7.56.
12. Vedejs, E.; Eberlein, T. H.; Wilde, R. G. *J. Org. Chem*. **1988**, *53*, 2220–2226.
13. δ ^{31}P NMR of phosphonodithioformate **1** in THF/$CDCl_3$: neat (–3.69 ppm); with 1 equiv. of $ZnCl_2$ (–7.51 ppm); with 1 equiv. of $BF_3{\cdot}Et_2O$ (–12.63 ppm).
14. δ ^{13}C NMR of C=S of phosphonodithioformate **1** in THF/$CDCl_3$ (doublet $J_{CP} = 177$ Hz): neat (231.7 ppm); with 1 equiv. of $ZnCl_2$ (224.5 ppm); with 1 equiv. of $BF_3{\cdot}Et_2O$ (220.7 ppm)
15. Balczewski, P. *Phosphorus, Sulfur, and Silicon* **1995**, *104*, 113–121.
16. Experimental procedure for the desulfanylation of **6** and **8**: To a refluxing solution of dihydrothiopyran (1 equiv.) and azoisobutyronitrile (AIBN) (0.07 equiv.) in benzene (10 ml/mmol) under N_2, a solution of Bu_3SnH (2 equiv.) and AIBN (0.22 equiv.) in the same solvent (2 ml/mmol) was added in a few min. Reflux was maintained for 2 h after the end of the addition. After evaporation of the solvent, a flash chromatography on silica gel (eluent:

petroleum ether:AcOEt, 70:30) gave pure **10** and **11** in 85 and 79% yield. NMR data of a typical example of desulfanylated dihydrothiopyran: Diisopropyl (3,6-dihydro-2H-thiopyran-2-yl)phosphonate **10** (colorless oil): ^{31}**P** NMR ($CDCl_3$): 22.9; ^{1}H NMR ($CDCl_3$): 1.28 (d, $^{3}J = 6.1$, 12H), 2.42–2.49 (m, 2H, H_3), 2.98 (ddd, $^{2}J_{HP} = 18.8$, $^{3}J_{H2-H3} = 7.3$, $^{3}J_{H2-H3'} = 6.7$, 1H, H_2), 3.11 (~d, $^{2}J = 16.8$, 1H, H_6), 3.21 (~d, $^{2}J = 16.8$, 1H, $H_{6'}$), 4.67 (dsept, $^{3}J_{HP} = 6.4$, $^{3}J_{HH} = 6.1$, 1H), 4.70 (dsept, $^{3}J_{HP} = 6.4$, $^{3}J = 6.1$, 1H), 5.78–5.81 (m, 2H, H_4 and H_5); ^{13}C NMR ($CDCl_3$): 24.0 and 24.1, (2d, $^{3}J_{CP} = 5.4$, 2×**C**H_3), 24.2 and 24.3 (2d, $^{3}J_{CP} = 7.2$, 2×**C**H_3), 25.7 (d, $^{3}J_{CP} = 6.3$, C_6), 25.8 (d, 1.8, C_3), 34.0 (d, $^{1}J_{CP} = 151.7$, C_2), 71.1 and 71.5 (2d, $^{2}J_{CP} = 7.2$, **C**H-O), 123.7 (C_5), 126.7 (d, $^{3}J_{CP} = 10.8$, C_4). Microanalysis: $C_{11}H_{21}0_3PS$: calcd C, 49.98; H, 8.01; found: C, 49.61; H, 7.82.