Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 2003–2004

Convenient microwave-assisted synthesis of 1-chloroethyl phosphates

Hanna Kumpulainen,[a,*] Raimo Saari,[a] Marko Lehtonen,[a] Jarkko Rautio,[a] Tomi Järvinen[a] and Jouko Vepsäläinen[b]

[a]*Department of Pharmaceutical Chemistry, University of Kuopio, PO Box 1627, FI-70211 Kuopio, Finland*
[b]*Department of Chemistry, University of Kuopio, PO Box 1627, FI-70211 Kuopio, Finland*

Received 29 November 2005; revised 28 December 2005; accepted 13 January 2006
Available online 2 February 2006

Abstract—An efficient microwave-assisted synthesis of 1-chloroethyl phosphates was developed. Protected vinyl chlorophosphates undergo a fast conversion to the chloroethylidene phosphates in the presence of HCl with excellent yields up to 900 times faster than at the standard NTP conditions.

1-Chloroethyl phosphates are excellent building blocks for the synthesis of ethylidene-linked phosphate prodrugs to enhance water solubility[1] and clinical usefulness of a parent drug.[2–4] By adding a phosphate group to the parent drug via an ethylidene spacer group instead of an oxymethyl spacer, the release of toxic formaldehyde can be avoided. Previously, we described the first method for synthesizing 1-chloroethyl phosphates and phosphoramidates.[5] However, the reaction times required to synthesize some of the products were extremely long and the synthesis required HCl bubbling through the solution from days to weeks to obtain 1-chloroethyl phosphates in reasonable yields. In order to determine whether the microwave-assisted synthesis would provide significant benefits compared to the previously described method, the addition reaction of HCl to the vinyl ester of phosphates was studied under microwave conditions (Scheme 1).

We selected six vinyl phosphates (**1**–**6**) whose times varied between 24 and 912 h under NTP conditions.[5] Furthermore, one of the molecules, diphenylvinyl phosphate (**6**) did not react at all under standard conditions.

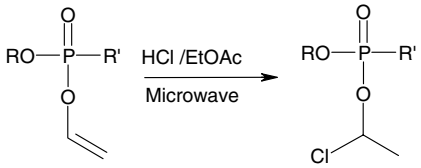
To understand the impact of microwave irradiation on the present procedure, the synthesis was investigated using bis-trichloroethylvinyl phosphate, which had the longest reaction time at NTP conditions. Bis-trichloroethylvinyl phosphate **2** was dissolved in ethyl acetate saturated with dry HCl gas.[†] The mixture was heated at 176 °C at 20 bar in a microwave oven. After 30 min, approximately 81% of the vinyl phosphate was converted to the corresponding 1-chloroethyl phosphate (**8**) according to the ^{1}H and ^{31}P NMR spectra. By extending the reaction time to 60 min the reaction proceeded to 95%.

Keywords: Microwave-assisted synthesis; 1-Chloroethyl phosphates.
* Corresponding author. Tel.: +358 44 303 7577; fax: +358 17 162 456; e-mail: Hanna.Kumpulainen@uku.fi

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.01.063

[†] *A general method for the synthesis of chloroethylidene phosphates*: Ethyl acetate was saturated with dry HCl gas by bubbling HCl through the solution for 15 min. Trichloroethylvinyl phosphate (100 mg, 0.26 mmol) was dissolved in 4 ml of saturated HCl–ethyl acetate solution. The mixture was heated at 176 °C at 20 bar for 60 min in a Biotage Initiator microwave reactor. The progress of the HCl addition was monitored by measuring ^{1}H and ^{31}P NMR spectra from the reaction mixture during the reaction course. After the appropriate reaction time, the solvents were evaporated to dryness. The NMR spectra, GC–MS and CHNS analysis were consistent with those published previously,[5] except **12**.

Phosphoric acid 1-chloro-ethyl ester diphenyl ester **12**: Yield 98% (without purification), colorless, viscous oil. Chromatography eluent hexane/EtOAc 1:1. ^{1}H NMR[6] ($CDCl_3$, 500 MHz) δ 7.38–7.16 (10H, m), 6.39 (1H, dq, $^{3}J_{HP} = 7.63$, $^{3}J_{HH} = 5.61$ Hz), 1.75 (3H, dd, $^{3}J_{HH} = 5.61$, $^{4}J_{HP} = 1.22$ Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 150.24[¶] (d, $^{2}J_{CP} = 7.4$ Hz), 150.07[¶] (d, $^{2}J_{CP} = 7.4$ Hz), 129.85 (d, $^{2}J_{CP} = 7.9$ Hz), 125.74 (d, $^{2}J_{CP} = 8.6$ Hz), 120.26[¶] (d, $^{3}J_{CP} = 4.8$ Hz), 120.17[¶] (d, $^{3}J_{CP} = 4.4$ Hz), 86.41 (d, $^{2}J_{CP} = 6.5$ Hz), 27.41 (d, $^{3}J_{CP} = 8.4$ Hz); ^{31}P NMR ($CDCl_3$) δ −13.81. GC–MS *m*/*z* 312 (M^{+}), 277 (M−Cl). Anal. Calcd for $C_{14}H_{14}ClO_4P * 0.1$ hexane: C, 54.58; H, 4.83. Found: C, 54.45; H, 4.58. [¶]Due to chiral center and prochirality, there are two ^{13}C chemical shifts for ipso- and ortho-carbons.



1,**7**: R=Et; R^1=OEt
2,**8**: R=Cl_3CCH_2; R^1=OCH_2CCl_3
3,**9**: R=Me; R^1=OPh
4,**10**: R=(2,6-Me_2)C_6H_3; R^1=O-(2,6-Me_2)C_6H_3
5,**11**: R,R^1=$(CH_2)_3O$
6,**12**: R=Ph; R^1=OPh

Scheme 1.

Table 1.

Compd	R	R′	rt Conditions		Microwave-assisted			
			Yield (%)[a]	Time[b] (h)	Yield (%)[a]	Time[b] (h)	Temp (°C)	Pressure (bar)
7	Et	OEt	91	24 (7)	99	0.25	100	6
8	Cl_3CCH_2	OCH_2CCl_3	66	912 (195)	95	1	176	20
9	Me	OPh	87	500 (50)	95	0.75	100	6
10	(2,6-Me_2)C_6H_3	O-(2,6-Me_2)C_6H_3	92	480 (90)	96	0.5	170	20
11	–$CH_2CH_2CH_2O$–		98	30 (12)	99	0.125	120	6
12	Ph	OPh	—[c]	—[c]	98	1	173	20

[a] Yield without purification (Some of the products partially decomposed during the purification procedure and in the case of some products the purification needed to be repeated a few times to get analytically pure products. Since the crude products from the synthesis of 1-chloroethyl phosphates did not contain any major impurities according to ^1H, ^{13}C, and ^{31}P NMR, these building blocks should be used without further purification. Thus the yields of **1**–**6** presented in Table 1 are reported without purification and are estimated from the actual chemical yields according to the purity of the ^1H and ^{31}P NMR spectra.)
[b] The reaction times are the total reaction times, with the times of HCl bubbling (rt) in parenthesis.
[c] No reaction.

By comparison, the synthesis under NTP conditions gave a yield of 66% after 195 h of bubbling (Table 1).

After these promising results, the microwave-assisted reaction was carried out with diphenylvinyl phosphate **6**, which did not react at all using the previously described method, even if catalysts or higher pressure were used. However, with microwave-assisted heating for 60 min at 173 °C at 20 bar 98% of diphenylvinyl phosphate was converted to the corresponding 1-chloroethyl phosphate **12**. Also, the other four vinyl phosphates reacted under microwave conditions (Table 1) to give excellent yields (>95%) in significantly shorter reaction times. For example, while the synthesis of diethyl 1-chloroethyl phosphate **1** took 24 h at NTP, the microwave-assisted reaction at 100 °C was completed after only 15 min to yield 99% of **7**.

In summary, the present study describes an effective microwave-assisted synthetic approach for the preparation of 1-chloroethyl phosphates with various protecting groups via addition of HCl to the double bond of vinyl phosphates. The present method not only provided increased yields and shortened reaction times but also enabled the synthesis of the otherwise unavailable reaction products.

Acknowledgements

This study was financially supported by the Graduate School of Bioorganic and Medicinal Chemistry, the National Technology Agency of Finland and the Academy of Finland (grants #204905, JR; #105975, JV).

References and notes

1. Fleisher, D.; Bong, R.; Stewart, B. H. *Adv. Drug Deliv. Res.* **1996**, *19*, 115–130.
2. Chang, S.; Griesgraber, G. W.; Southern, P. J.; Wagner, C. R. *J. Med. Chem.* **2001**, *44*, 223–231.
3. Egron, D.; Imbach, J. L.; Gosselin, G.; Aubertin, A. M.; Perigaud, C. *J. Med. Chem.* **2003**, *46*, 4564–4571.
4. Freel Meyers, C. L.; Borch, R. F. *J. Med. Chem.* **2000**, *43*, 4319–4327.
5. Kumpulainen, H.; Järvinen, T.; Saari, R.; Lehtonen, M.; Vepsäläinen, J. *J. Org. Chem.* **2005**, *70*, 9056–9058.
6. The ^1H NMR parameters were solved precisely with the PERCHit iterator[7] using PERCH software.[8]
7. Laatikainen, R.; Niemitz, M.; Weber, U.; Sundelin, J.; Hassinen, T.; Vepsäläinen, J. *J. Magn. Reson. Series A* **1996**, *120*, 1–10.
8. PERCH Software, Version 2004.1 ed.; PERCH Solutions Ltd: Kuopio, Finland, 2004.