Pergamon

Tetrahedron Letters, Vol. 38, No. 16, pp. 2791-2794, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00491-7

A Novel Esterification Procedure Applied to Synthesis of Biologically Active Esters of Foscarnet

Boris I. Gorin, Colin G. Ferguson, and Gregory R.J. Thatcher*

Department of Chemistry, Queen's University,
Kingston, Ontario, K7L 3N6, CANADA

Abstract: The high reactivity of the phosphonoformate moiety requires development of a novel synthesis for esters of phosphonoformate, which is reported together with preliminary data on the antiviral activity of these esters. © 1997 Elsevier Science Ltd.

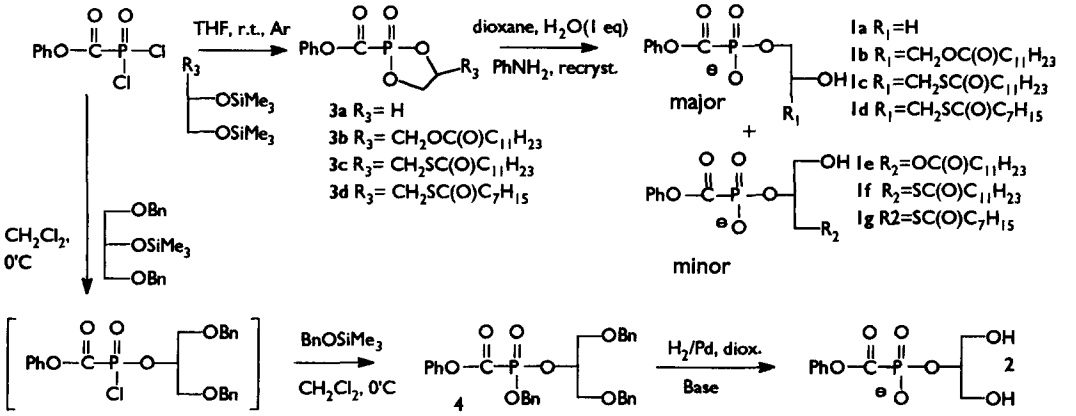
The synthesis of a series of esters of the AIDS drug Foscarnet (phosphonoformate, PFA), **1a-d, 2,** is reported. A novel esterification procedure has been required to circumvent problems associated with the high and special reactivity features of the phosphonoformate functionality. This procedure permits access to synthesis of a large variety of PFA triesters, diesters and monoesters. Preliminary data on inhibition of Herpes Simplex Virus (HSV) for one PFA diester surpasses that of the parent compound Foscarnet, although it is unclear whether PFA esters act as Foscarnet prodrugs.

Foscarnet (trisodium PFA) is effective in AIDS chemotherapy as an antiviral agent with activity against HIV, HSV and human cytomegalovirus (HCMV).[1] The polyanionic nature of Foscarnet causes significant bioavailability problems which may potentially be alleviated by a prodrug approach employing PFA esters.[2,3] Indeed, the first investigation of PFA esters, by Noren *et al.*, showed anti-HSV activity in esters possessing an aryl group at the C and/or P.[4] However, studies with a more mechanistic focus have begun to elucidate peculiar and complex reactivity patterns associated with the PFA functionality, including very high reactivity at phosphorus and facile P-C bond cleavage.[2,3,5,6,7,8] Although of substantial interest, this reactivity causes problems in prodrug stratagems and in synthesis of PFA esters.

Traditional phosphate and phosphonate esterification procedures have been extended to synthesis of PFA esters. The three prevalent strategies are: (i) via Arbuzov reaction of preformed chloroformate and phosphite moities[4]; (ii) coupling of a nucleophilic PFA silver salt with an alkyl halide[9]; (iii) coupling of a nucleophilic

alcohol with a PFA phosphonodichloridate.[2,3,10] Each strategy has significant limitations, but the last procedure has proven of most general utility for preparation of PFA triesters and the phosphonodichloridate is easily prepared from the corresponding *bis*-trimethylsilyl ester by reaction with $SOCl_2$ or PCl_5. The problems specific to this strategy are twofold and caused by the special reactivity of the PFA functionality in the reaction of the phosphonodichloridate with alcohol. Firstly, the unusually high reactivity of the P towards nucleophiles, orders of magnitude greater than for simple alkyl phosphonates,[8] hinders the selectivity required in synthesis of mixed diesters (e.g. **4**). Sequential substitution of the two chlorides by two different alcohols is not possible. Furthermore, reaction with *vic*-diols leads to mixtures of both cyclic and acyclic PFA triesters as products. Secondly, we have observed that the high reactivity of the carbonyl C towards nucleophiles and a propensity for migration between C and P may result in displacement of the phenolic group at C and some migration to P.[2]

Our approach to this problem is to attenuate the reactivity of the nucleophile by use of a trimethylsilylether, which greatly improves selectivity.[11] The added benefit of this procedure is the ease of isolation of the highly reactive PFA di- or triester product, primarily through eschewing the nitrogen base required in the reaction with simple alcohol. Thus, the first and second phosphonodichloridate chlorides may be displaced selectively and sequentially in synthesis of **4.** Furthermore, quantitative yields for synthesis of the cyclic PFA triesters, contrast to the low selectivity of the traditional procedure in which cyclic and acyclic triesters are produced on reaction with *vic*-diols.



Scheme 1

Silyl ether and phosphonodichloridate precursors were synthesized by conventional methods. Coupling of disilyl ethers with equimolar phosphonodichloridate gave cyclic PFA triesters, **3** , in quantitative yield by ^{31}P NMR, after removal of Me_3SiCl under vacuum. The cyclic triesters, **3**, possessed distinctive downfield shifted ^{31}P NMR signals, with two signals for the diastereomeric glycerol derivatives (Table 1). The highly labile cyclic esters were not further purified, but ring-opened directly with a molar equivalent of water in dioxane, with work-up in base to prevent further reaction. Using aniline as base, the product salts thus isolated were isomeric mixtures of 1- and 2-glycerol esters, **1** , which could be distinguished by the ^{31}P-splitting of the

relevant ^1H NMR methylene or methine signals. In all cases, the 1-glycerol isomer was substantially favoured (90-95% by ^{31}P NMR). The major isomer was isolated, in each case, from the isomeric mixture, by recrystallization of the anilinium salt from diethyl ether (Table 2).

Table 1 ^{31}P NMR shift data for intermediates and products[a]

	1e	**1f**	**1g**	**3a**	**3b**	**3c**	**3d**	**4**
δ	-7.05	-7.27	-7.41	12.08	11.77	11.22	11.25	-4.95
δ[b]	-	-	-	-	11.67	10.96	11.00	-

a. At 162 MHz, in THF, ref. 85% H_3PO_4. b. Diastereomer.

Table 2 Analytical data for PFA diesters as anilinium salts[a]

	^{31}P	^{13}C NMR[c]				FAB/MS
	NMR[b]	C(P)	C1	C2	C3	-m/z
1a	-6.58	171.53	67.22	60.98	-	245
1b	-6.41	171.44	66.60	67.71	65.03	456
1c	-6.46	171.47	68.43	68.76	43.36	471
1d	-6.61	171.47	68.50	68.77	43.40	416
2	-4.80	171.60	61.10	74.10	61.10	274

a. Satisfactory elemental analysis was obtained for all compounds listed.
b. At 162 MHz in DMSO, ref. 85% H_3PO_4.
c. At 100 MHz in $DMSOd_6$, ref. TMS, C1-3 are glycerol (or glycol) carbons.

In order to provide a more satisfactory route to the 2-glycerol isomers of **1** and explore the utility of this synthesis for assymetric and acyclic esters, the synthesis of the mixed PFA triester **4** was completed. Sequential *in situ* addition of two different silyl ethers to the phosphonodichloridate allows synthesis of **4** without need for isolation of the phosphonomonochloridate intermediate. The first silyl ether (1eq.) was added dropwise, under Ar, to the dichloridate in CH_2Cl_2, cooled in an ice bath. The reaction mixture was stirred for a further 4 hr. before addition of the second silyl ether (1eq.) under the same conditions. After removal of volatiles and solvent, the product **4** was obtained in 90% yield as assessed by ^{31}P NMR (Table 1). The lability of *C*-aryl PFA triesters on chromatography dictated direct hydrogenation to the diester **2**, using Pd/C. Work up with $NaHCO_3$ gave the desired product **2** as the sodium salt. However, work up with aniline is again preferable because of the ease of recrystallization of the product **2** as the anilinium salt (Table 2).

In order to test the potential of these PFA diesters as anti-viral agents, preliminary assays on HSV1 infected confluent human lung fibroblast cells were performed.[12] Antiviral activity was determined for the sodium salts of **1,b,e** and **1,c,f**, preliminary data being obtained for inhibition by the isomeric mixtures. In separate assays: (i) the activity of **1,c,f** (EC_{50}=155μM) was found to be greater than that of Foscarnet itself (218μM); and (ii) **1,b,e** showed no activity (EC_{50}>800μM).

Interestingly, the potential hydrolysis product of **1b,e** (Scheme 1: **1b,e** with Na in place of Ph) also possessed greater activity (EC_{50}=137μM; toxicity at 400μM) than Foscarnet itself (EC_{50}=177μM). All compounds showed minimal conversion (<10%) to Foscarnet in liver and intestinal homogenates as deteced by hplc.[13] Thus whether such diesters indeed act as Foscarnet prodrugs is problematic.

A novel, practical and efficient synthetic strategy for PFA esters has been developed, suited to the high and peculiar reactivity of PFA and allowing access to a broad family of PFA derivatives. Regardless of whether the PFA diesters thus synthesized act as Foscarnet prodrugs, the full antiviral spectrum of such derivatives is promising and remains to be fully explored.

Acknowledgements The financial support of Astra Arcus (Sweden) and NSERC (Canada) is gratefully acknowledged, in addition to the encouragement of Dr Brian Pring (Astra).

References

1. Oberg, B., *Pharmac. Ther.*, **1989**, *40*, 213.
2. Freeman and co-workers were first to report the anomalous migration of a benzyl group between P and C in phosphonoformates: Mitchell, A.G.; Nicholls, D.;Walker, I.; Irwin, W.J.; Freeman, S. *J. Chem. Soc. Perkin Trans. 2*, **1991**, 1297.
3. Mitchell, A.G.; Nicholls, D.; Irwin, W.J.; Freeman, S. *J. Chem. Soc. Perkin Trans. 2*,**1992**, 1145.
4. Noren, J.O.; Helgstrand, E.; Johansson, N.G.; Msiorny, A.; Stening, G. *J. Med. Chem.*, **1983**, *26*, 264.
5. Warren, S.; Williams, M.R. *J. Chem. Soc. (B)*, **1971**, 618.
6. Thatcher, G.R.J.; Krol, E.S.; Cameron, D.R. *J. Chem. Soc. Perkin Trans. 2*, **1994**, 683.
7. Krol, E.S.; Davis, J.M.; Thatcher, G.R.J. *J. Chem. Soc. Chem. Commun.*, **1991**, 118.
8. Krol, E.S.; Thatcher, G.R.J. *J. Chem. Soc. Perkin Trans. 2*, **1993**, 793.
9. Iyer, R.P.; Phillips, L.R.; Biddle, J.A.; Thakker, D.R.; Egan, W. *Tetrahedron Lett.*, **1989**, 7141.
10. Vaghefi, M.M.; McKernan, P.A.; Robins, R.K. *J. Med. Chem.*, **1986**, *29*, 1389.
11. The only report of any similar synthetic strategy in synthesis of cyclic phosphate triesters did not report extension of the method to synthesis of acyclic unsymmetric esters [Schwarz, R., Ugi, I. *Angew. Chem. Int. Ed. Engl.*, **1981**, *20*, 789]. Further exploration, by us, of this coupling procedure has shown that it is not universally applicable to simple unactivated phosphoro- and phosphono-dichloridates, because the attenuated reactivity of the silyl ether allows side reactions to become competitive in these less reactive systems..
12. Cells were incubated with drugs (3-800μM) at 37°C in a humidified atmosphere of 5% CO_2 in air until control wells showed characteristic cytopathic effects (24-48h). Cells were lysed with Triton X- 100 and viral antigen content of the supernatants measured by ELISA.
13. Petterson, K.J.; Nordgren, T.; Westerlund, D. *J. Chromat.*, **1989**, *488*, 447.

(*Received in USA* 14 *January* 1997; *accepted* 4 *March* 1997)