Tetrahedron Letters 53 (2012) 243–246

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

One-pot synthesis of phosphate diesters and phosphonate monoesters via a combination of microwave-CCl_3CN–pyridine coupling conditions

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ARTICLE INFO

Article history:
Received 8 September 2011
Revised 1 November 2011
Accepted 7 November 2011
Available online 15 November 2011

Keywords:
Microwave chemistry
Phosphorylation
Phosphate alcohol coupling
Glycophospholipid

ABSTRACT

Simple and convenient one-pot synthesis of a phosphorus–oxygen bond in phosphate diesters and phosphonate monoesters using trichloroacetonitrile as an activating agent and pyridine as a solvent under microwave irradiation conditions was described. This method is useful for the preparation of various biologically interesting glycophospholipids and also phosphate diesters or phosphonate monoesters containing diverse moieties such as alkyl, prenyl, and benzyl substituents.

Numerous biologically interesting natural products possess a phosphate diester moiety.[1] For example, β-D-mannosyl phosphomycoketide (MPM), isolated from the cell walls of *Mycobacterium tuberculosis* or *Mycobacterium avium*, is a CD1c-presented antigen for T cells. Phosphatidylglucoside (PtdGlc), isolated from *Staphylococcus aureus* and mammalian cell, plays an important role in glial cell development and differentiation. β-D-Arabino-furanosyl-1-monophosphoryl-decaprenol (DPA) is a key substrate for arabinogalactan (AG) and lipoarabinomannan (LAM) in mycobacterium cell wall biosynthesis (Fig. 1).

One of our research interests is to synthesize key bacterial or mycobacterial cell wall components, such as DPA or Lipid II, and study their biological functions.[2] Based on the preliminary literature study, our model glycophospholipid **3** might be prepared through the phosphoramidite–phosphotriester approach.[1a] However, this reagent, 2-cyanoethyl *N*,*N*-diidopropylchlorophosphoramidite, is quite expensive so this method is limited to scale up. General esterification of phosphoric acids with alcohols by coupling reagents under thermal conditions has been extensively studied; however, our initial attempts to utilize these known coupling reagents such as dicyclohexylcarbodiimide (DCC) or triisopropylbezenesulfonyl chloride (TPSCl) to prepare glycophospholipid **3**, one of the phosphate diesters (Scheme 1, Table 1) from protected sugar **1** and long chain alcohol **2** were not satisfactory because of low yields (<10%) and elongated reaction

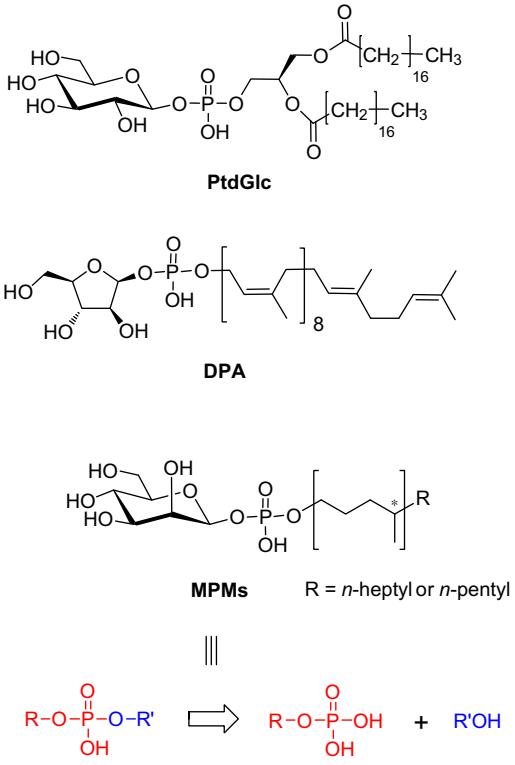

Figure 1. Natural products containing a phosphate diester and its retrosynthesis.

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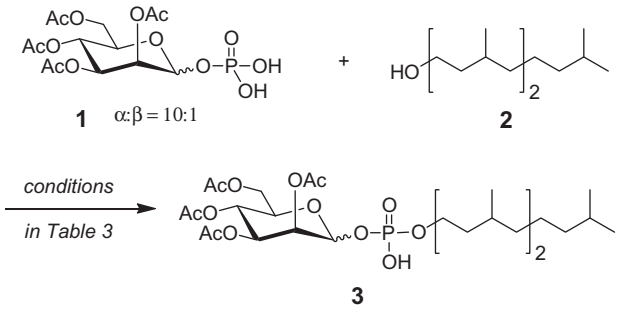
doi:10.1016/j.tetlet.2011.11.032



Scheme 1. Model reaction used for the screening of coupling conditions.

Table 1
Examination of coupling conditions for the preparation of glycophospholipid **3**[a]

Entry	Reagents and conditions	*T* (°C)	Time	Yield[b] (%)
1	TPSCl/py.	80	>72 h	64
2	DCC/py.	80	>72 h	9
3	PPh_3/DIAD/py.	80	>72 h	5
4	CCl_3CN/py.	90	48 h	47
5	TPSCl/py. (μw 120 W)	80	60 min	41
6	PPh_3/DIAD/py. (μw 120 W)	80	60 min	—[c]
7	DCC/py. (μw 120 W)	90	60 min	13
8	CCl_3CN/py. (μw 120 W)	90	15 min	89

[a] Reagents and conditions: **1** (0.4 mmol), **2** (1.5 equiv) and coupling reagents (3.0 equiv) in pyridine.
[b] Isolated yield.
[c] Not detected.

times required (>72 h).[1,3] These poor results urged us to develop a more practical method for the preparation of glycophospholipids.

Recently, Kalek and Stawinski have reported the synthesis of mono- and di-arylphosphinic acids via microwave-assisted palladium-catalyzed cross coupling.[4] Their work inspired us to evaluate microwave conditions to prepare our target molecules. Theoretically, a phosphorus–oxygen bond formation by the coupling of phosphates or phosphonates to alcohols might be suitable under microwave irradiation because these molecules can absorb the microwave energy more efficiently through the ionic conduction mechanism.[5] Over the last two decades, microwave-assisted organic synthesis (MAOS) has become a powerful technique to boost the reaction rates and to reduce the reaction time with an improvement in the yield and quality of the product.[5] However, to the best of our knowledge, a microwave-assisted phosphorus oxygen bond formation in a one-pot manner has not been studied yet. Herein, we report the development of simple and convenient method for the synthesis of structurally diverse glycophospholipids, phosphate diesters, and phosphonate monoesters via microwave irradiation with specific coupling conditions.

Our investigation was started from evaluating the efficiency of coupling reagents for the assembly of mannopyranosidyl monophosphate (**1**)[6] with 3,7,11-trimethyl-dodecan-1-ol (**2**) under thermal and microwave-assisted conditions (Scheme 1 and Table 1).

As shown in Table 1, under thermal conditions (entries 1–4), better yields were given by using TPSCl and CCl_3CN as coupling reagents instead of DCC or PPh_3/DIAD but a longer time (>48 h) was required in all reactions. With the assistance of microwave irradiation, the yields were still too low (<13%) and messy results were showed in either DCC-mediated conditions or Mitsunobu reaction (entries 6 and 7).[3,7] Fortunately, when CCl_3CN-mediated conditions[8] were applied with pyridine as the solvent, the yield was dramatically improved to 89% within 15 min at 120 W (Table 1, entry 8). Presumably, the mechanism of this one-pot synthesis could be proposed to generate an iminophosphate as a key intermediate.[8]

Table 2
Examination of reaction factors (solvent and time)[a]

Entry	Solvent	*T* (°C)	Time (min)	Yield[b] (%)
1	Toluene	100	60	13
2	Acetone	100	60	7
3	1,4-Dioxane	100	60	6
4	THF	100	60	17
5	Acetonitrile	100	60	28
6	DMF	100	60	45
7	Pyridine	90	15	89
8[c]	Pyridine (80 W)	90	60	11

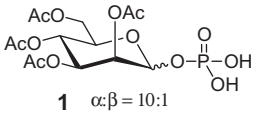
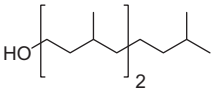
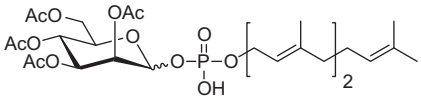
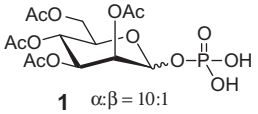
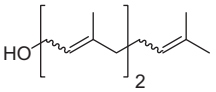
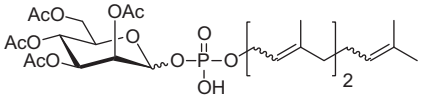
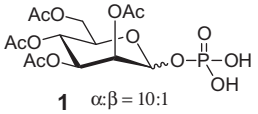
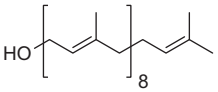
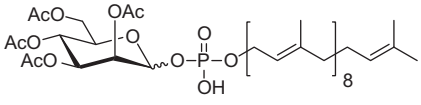
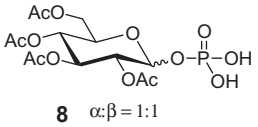
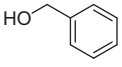
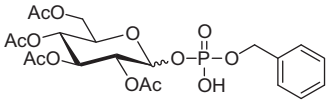
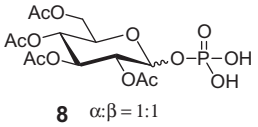
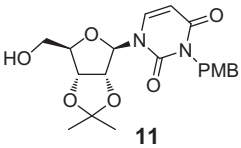
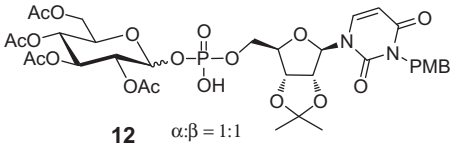
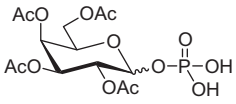
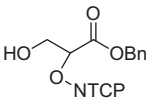
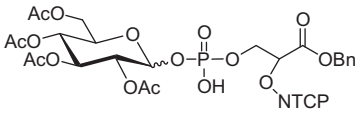
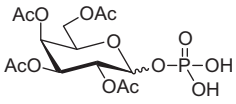
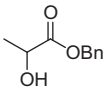
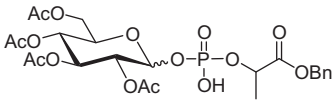
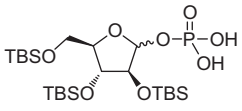
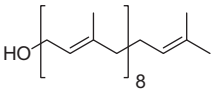
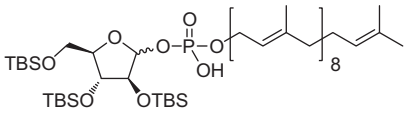
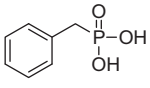
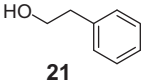
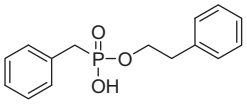
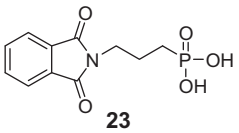
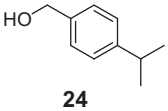
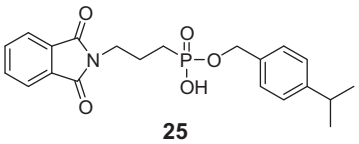
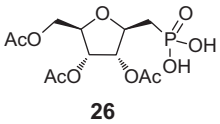
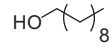
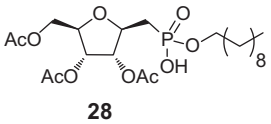
[a] Reagents and conditions: **1** (0.4 mmol), **2** (1.5 equiv) and CCl_3CN (2 mL) in the desired solvent (entries 1–7) was irradiated at 120 W in a sealed tube.
[b] Isolated yield.
[c] The reaction was irradiated at 80 W.

This encouraging observation promoted us to further investigate various solvent systems, and the results were shown in Table 2. Polar aprotic solvents such as DMF, pyridine and acetonitrile (Table 2, entries 5–7) gave better yields than less polar ones. These results can be rationalized by higher dielectric constants of solvents and easy charge separation of the phosphate anion from its counter ion in polar solvents. Notably, pyridine was the best solvent in our study to prepare glycophsopholipid **3** under microwave irradiation (120 W, 90 °C, 15 min, Table 2, entry 7). In contrast, changing irradiation power from 120 to 80 W, a significant decrease in reaction yield was obtained (Table 2, entry 7 vs 8).

To demonstrate the efficiency and the scope of the microwave-assisted synthesis, various sugar phosphates and alcohols were chosen to investigate the reaction feasibility to form glycophospholipids or phosphate diesters using CCl_3CN as an activating reagent in weak basic conditions (pyridine). As shown in Table 3, the reaction's progress was strongly dependent on the electronic or steric property of the alcohol. For example, farnesol (**4**, entry 2) was converted to the corresponding glycophospholipid **5** at 80 W within 15 min, but solanesol (**6**, $C_{45}H_{73}OH$, entry 3) required a longer time (60 min) to consume all the starting materials. Presumably, this long-chain lipid in **6** did not make the reaction mixture homogeneous to perform a uniform heating pattern. Besides, uridine-5′-monophosphate glucopyranoside (**12**) could also be prepared by microwave-assisted conjugation of **8** and **11** in 71% within 15 min (Table 3, entry 5). Notably, when an alcohol such as **14** containing a labile tetrachlorophthalic (TCP) moiety was coupled with a phosphate (entry 6), the reaction conditions should be milder (70 °C, 60 W) in order to obtain a reasonable yield (62%, entry 6). Secondary alcohols such as benzyl 2-hydroxypropanoate (**16**) and 1-phenylpropan-2-ol (**29**) were also applied to successfully generate desired adducts **17** and **30**, respectively (entries 7 and 12). Excitingly, diverse phosphonate monoesters could also be smoothly prepared via this method (Table 3, entries 9–11). As we know, during the preparation of glycophospholipids via a typical glycosylation reaction from activated sugars and lipid-phosphates, the neighboring participation could affect the anomeric selectivity. Thus, more synthetic steps might be required to prepare specific sugar building blocks in order to control the desired anomeric selectivity.[12] In contrast, the fixed ratio of anomers in our starting glycophosphates such as **1**, **8**, and **13** would directly convert to the corresponding glycophospholipid products without changing their anomeric ratio (see in Table 3).

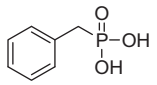
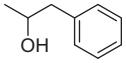
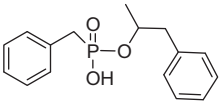
Next, D-arabinofuranosyl-1-monophosphorylsolanesol (**31**, DPA analogue), a key natural product-like compound for mycobacterium cell wall biosynthesis, was synthesized to demonstrate the efficiency of our methodology (Scheme 2). The TBS protected D-arabinose-monophosphate **18**[10] was chosen as our starting material to conjugate with a polyisoprenol, solanesol **6**, at 90 °C for 60 min under 80 W irradiation, followed by global desilylation

Table 3
Microwave assisted one-pot synthesis of phosphate diester and phosphonate monoester analogues[9]

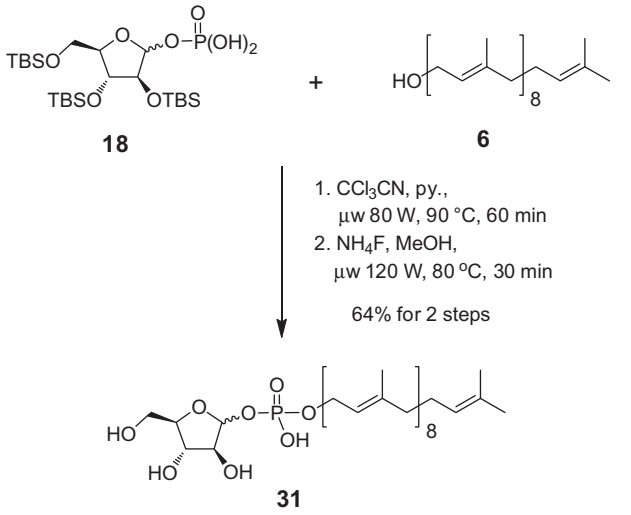
Entry	Phosphate/Phosphonate	Alcohol	Conditions (°C/W/min)	Products	Yield[a] (%)
1	 **1** α:β = 10:1	 **2**	90/120/15	 **3** α:β = 10:1	89
2	 **1** α:β = 10:1	 *Z*,*E*-farnesol **4**	80/80/15	 **5** α:β = 10:1	86
3	 **1** α:β = 10:1	 solanesol **6**	80/80/60	 **7** α:β = 10:1	82
4	 **8** α:β = 1:1	 **9**	80/80/15	 **10** α:β = 1:1	89
5	 **8** α:β = 1:1	 **11**	90/120/15	 **12** α:β = 1:1	71
6[b]	 **13** α:β = 1:20	 **14**	70/60/60	 **15** α:β = 1:20	62
7	 **13** α:β = 1:20	 **16**	80/120/15	 **17** α:β = 1:20	78
8	 **18** α:β = 2:1	 solanesol **6**	80/80/60	 **19** α:β = 1.8:1	84
9	 **20**	 **21**	90/120/15	 **22**	73
10	 **23**	 **24**	80/80/15	 **25**	68
11	 **26**	 *n*-decanol **27**	90/120/15	 **28**	83

(*continued on next page*)

Table 3 (*continued*)

Entry	Phosphate/Phosphonate	Alcohol	Conditions (°C/W/min)	Products	Yield[a] (%)
12	 **20**	 **29**	90/120/15	 **30**	81

[a] Isolated yield.
[b] Compound was decomposed at 90 °C.



Scheme 2. Microwave-assisted synthesis of **31**.

under fluoride-mediated microwave conditions to directly generate the desired product **31** in a 64% overall yield for two steps.[11]

In summary, we have successfully developed a simple and convenient method for the formation of phosphorus–oxygen bond to prepare various glycophospholipids, phosphate diesters, and phosphonate monoesters under the assistance of microwave irradiation. The optimized conditions we discovered were to utilize trichloroacetonitrile as an activating reagent and pyridine as a solvent for the conjugation of a phosphate or phosphonate with an alcohol. In addition, the fixed ratio of anomers in our starting glycophosphates would directly convert to the corresponding glycophospholipids without changing their anomeric ratio. Structurally diverse functional groups, including an electron-withdrawing and electron-donating moiety, can be applied in these clean and economic microwave-assisted reactions.

Acknowledgment

This work was supported by the National Science Council and Academia Sinica.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.11.032.

References and notes

1. (a) Lee, R. E.; Mikusova, K.; Brennan, P. J.; Besra, G. S. *J. Am. Chem. Soc.* **1995**, *117*, 11829–11832; (b) de Jong, A.; Arce, E. C.; Cheng, T. Y.; van Summeren, R. P.; Feringa, B. L.; Dudkin, V.; Crich, D.; Matsunaga, I.; Minnaard, A. J.; Moody, D. B. *Chem. Biol.* **2007**, *14*, 1232–1242; (c) van Summeren, R. P.; Moody, D. B.; Feringa, B. L.; Minnaard, A. J. *J. Am. Chem. Soc.* **2006**, *128*, 4546–4547; (d) Greimel, P.; Lapeyre, M.; Nagatsuka, Y.; Hirabayashi, Y.; Ito, Y. *Bioorg. Med. Chem.* **2008**, *16*, 7210–7217.
2. Shih, H. W.; Chen, K. T.; Cheng, T. J.; Wong, C. H.; Cheng, W. C. *Org. Lett.* **2011**, *13*, 4600–4603.
3. (a) Warren, C. D.; Liu, I. Y.; Herscovics, A.; Jeanloz, R. W. *J. Biol. Chem.* **1975**, *250*, 8069–8078; (b) Dinev, Z.; Gannon, C. T.; Egan, C.; Watt, J. A.; McConville, M. J.; Williams, S. J. *Org. Biomol. Chem.* **2007**, *5*, 952–959; (c) Zhou, D.; Staake, M.; Patterson, S. E. *Org. Lett.* **2008**, *10*, 2179–2182.
4. Kalek, M.; Stawinski, J. *Tetrahedron* **2009**, *65*, 10406–10412.
5. (a) Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225–9283; (b) Gabriel, C.; Gabriel, S.; Grant, E. H.; Halstead, B. S. J.; Mingos, D. M. P. *Chem. Soc. Rev.* **1998**, *27*, 213–223; (c) Polshettiwar, V.; Varma, R. S. *Acc. Chem. Res.* **2008**, *41*, 629–639; (d) Wolkenberg, S. E.; Shipe, W. D.; Lindsley, C. W.; Guare, J. P.; Pawluczyk, J. M. *Curr. Opin. Drug Discov. Devl.* **2005**, *8*, 701–708.
6. Sim, M. M.; Kondo, H.; Wong, C. H. *J. Am. Chem. Soc.* **1993**, *115*, 2260–2267.
7. (a) Jacob, A. M.; Moody, C. J. *Tetrahedron Lett.* **2005**, *46*, 8823–8825; (b) Lampariello, L. R.; Piras, D.; Rodriquez, M.; Taddei, M. *J. Org. Chem.* **2003**, *68*, 7893–7895.
8. (a) Cherbuliez, E.; Rabinowitz, J. *Helv. Chim. Acta.* **1956**, *39*, 1461–1467; (b) Myers, T. C. *Ann. N.Y. Acad. Sci.* **1969**, *159*, 221–233.
9. General procedure for generation of phosphate diester and phosphonate monoester analogues. Discover™ Focused Microwave Synthesis (CEM Corporation) was used for focused microwave irradiations. A vessel containing phosphate (or phosphonate) (0.4 mmol), alkyl alcohol (0.6 mmol, 1.5 equiv), CCl_3CN (2 mL) and dried pyridine (2 mL) was sealed with Teflon septum and irradiated in microwave reactor (the microwave power, reaction temperature and time was shown in Table 3). After cooling, the reaction mixture was evaporated to dryness and purified by flash column chromatography.
10. Liav, A.; Brennan, P. J. *Tetrahedron Lett.* **2005**, *46*, 2937–2939.
11. Typical procedure for generation of D-arabinofuranosyl-1-monophosphorylsolanesol (**31**). In a vessel, **18** (0.23 g, 0.4 mmol), **6** (0.46 g, 0.6 mmol, 1.5 equiv) and CCl_3CN (2 mL) were added to dried pyridine (2 mL). The tube was sealed and irradiated in microwave reactor (80 W) for 60 min at 90 °C. After cooled to rt, the reaction was evaporated to dryness and treated with ammonium fluoride (0.15 g, 4 mmol) and methanol (4 mL), and irradiated again in microwave reactor (120 W) for 30 min at 80 °C. The mixture after cooling was evaporated to dryness and purified by flash column chromatography to afford **31** (0.25 g, 64%).
12. Martin, T. J.; Dufner, G.; Kratzer, B.; Schmidt, R. R. *Glycoconjugate J.* **1996**, *13*, 547–553.