Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 2445–2447

TETRAHEDRON LETTERS

Synthesis of phosphonocinnamic thioesters, substrate analogues of cinnamoyl-CoA reductase, a key enzyme in the lignification process

Caroline Lapeyre, Florence Bedos-Belval, Hubert Duran,* Michel Baltas and Liliane Gorrichon

SPCMIB, UMR CNRS 5068, Université Paul Sabatier, 118 route de Narbonne, 31062 Toulouse, France

Received 17 January 2003; revised 23 January 2003; accepted 6 February 2003

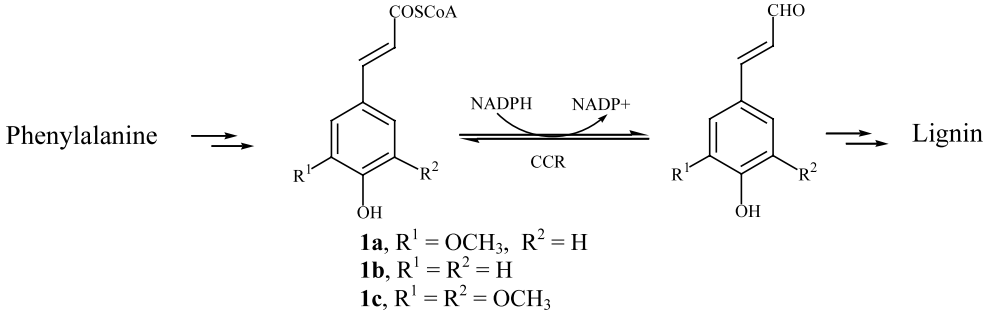
Abstract—The one-pot transesterification of diethylarylvinylphosphonates with *N*-acetylcysteamine has been achieved using phosphonochloridates as intermediates. Reaction of phosphonodiesters with $(COCl)_2$ gave the corresponding chlorinated compounds, which were coupled with *N*-acetylcysteamine in presence of Et_3N. © 2003 Published by Elsevier Science Ltd.

Lignins are complex aromatic polymers resulting from the oxidative polymerisation of hydroxycinnamyl alcohols, i.e. *p*-coumaryl, coniferyl, sinapyl alcohols.[1] Their biosynthesis begins with the common phenylpropanoid pathway, starting by the deamination of phenylalanine which affords *p*-hydroxylated cinnamic acids and next cinnamoyl-CoA esters. They are common precursors of a wide range of products which play important roles in plant development and defense.[2] Cinnamoyl-CoA esters are then channelled into the lignin branch pathway to produce the aldehydes through a reductive step involving the cinnamoyl-CoA reductase (CCR).[3] The CCR has been shown to occupy a key position as a control point in order to regulate the carbon flux towards lignins (Scheme 1).

An original way to the cinnamoyl-CoA esters has already been proposed, in which cinnamic acids were activated as iminium salts before transesterification.[4] In order to investigate the mechanism and the behaviour of the CCRs versus the three substrates (**1a**, **1b**, **1c**), we have undertaken the synthesis of phosphorylated substrates analogues.

Herein, we report a new and efficient synthetic approach of thiophosphonates analogues **4a–d** (Schemes 2 and 3) built from the cinnamoyl pattern and a shortened CoA frame.

Diester phosphonates (**2a–2d**) were obtained as previously described.[5] Deprotonation of tetraethyl methylenediphosphonate by LDA in THF gave the corresponding anions which were condensed with the *p*-hydroxycinnamic aldehydes. Thermal treatment of the diphosphorylated intermediate gave exclusively *trans*-vinylic phosphonates. The monophosphonic acids

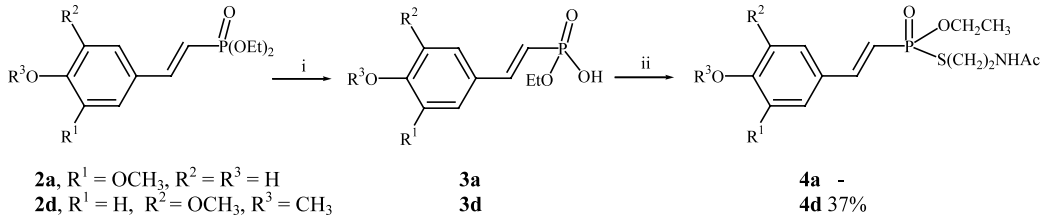


Scheme 1. Lignin biosynthesis pathway.

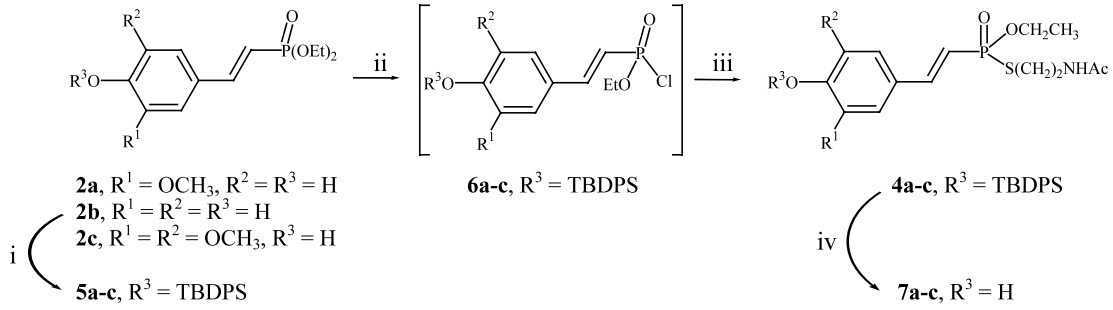
Keywords: lignification; thioesters; phosphonothioesters; cinnamoyl-CoA reductase.

* Corresponding author. Fax: +33(0)5 61 55 60 11; e-mail: huduran@chimie.ups-tlse.fr

0040-4039/03/$ - see front matter © 2003 Published by Elsevier Science Ltd.
doi:10.1016/S0040-4039(03)00349-6



Scheme 2. *Reagents and conditions*: (i) Ref. 5; (ii) **3d**, $(COCl)_2$, then Et_3N, *N*-acetylcysteamine, (37%).



Scheme 3. *Reagents and conditions*: (i) TBDPSCl, DMAP, imidazole, DMF, 16 h, rt, (67–91%); (ii) $(COCl)_2$, CH_2Cl_2, 20 h, rt, quantitative; (iii) Et_3N, *N*-acetylcysteamine, 16 h, rt, (49–67%); (iv) Et_3N–HF, THF, 15 min (23–50%).

(**3a**, **3d**) have next been obtained by treatment of the diesters (**2a**, **2d**) in a basic medium (NaOH/EtOH) under reflux (75–80% yield).

Thioesterification of **3a** according to the usual carbonyl coupling methods (EDC, HCl, DMAP, CH_2Cl_2)[6] was unsuccessful. Thus, several chlorination reagents including $POCl_3$ or $(COCl)_2$[7] were used in order to produce phosphonochloridates as intermediates before coupling reactions.

Treatment of phosphonodiester **2a** by phosphorous oxychloride, a reagent known to transform in one-step under mild conditions functionalised phosphonates[8] provided a complex mixture of phosphorylated compounds, as evidenced by ^{31}P NMR spectroscopy. On the contrary, the phosphono monoacid **3d** reacted with oxalyl chloride to lead quantitatively to the corresponding phosphonochloridate. This reaction was monitored by ^{31}P NMR spectroscopy (δ_P 30.63 ppm). Further reaction with *N*-acetylcysteamine using triethylamine afforded after purification the phosphonothioester **4d** in 37% yield, despite a critical purification step.[9]

Consequently, it appeared necessary to protect the *p*-hydroxy group on the aromatic moiety to obtain the phosphonothioester. The phosphonate diesters **2a**–**c** were protected by reaction with *tert*-butyldiphenylchlorosilane using imidazole, DMAP in DMF to give compounds **5a**–**c** in good yields (91, 67, 79%, respectively).[10]

The silylated phosphonodiesters **5a**–**c** were then converted to the corresponding phosphonochloridates by treatment with oxalyl chloride in dichloromethane. All reactions have been monitored by ^{31}P NMR spectroscopy and in each case a single product was identified as the corresponding phosphonochloridate **6a** (δ_P 27.2 ppm), **6b** (29.0 ppm), **6c** (23.3 ppm). Condensation with *N*-acetylcysteamine in the presence of triethylamine, in dichloromethane, gave the phosphonothioesters **4a**–**c** (67, 49, 62%, respectively).[11] Final cleavage of the silyl protective group has been carefully carried out using triethylamine-HF to provide the expected phosphonothioesters **7a**–**c**.[12]

In conclusion, the methodology described in this communication leads to phosphonothioesters under mild conditions, offering easy access to various thiol substitutions. Efforts are underway to test the potential inhibitor activity of these cinnamoyl-CoA analogues versus the cinnamoyl-CoA reductase.

Acknowledgements

We are grateful to the 'Centre National de la Recherche Scientifique' (CNRS) and the 'Ministère de l'Education Nationale de la Recherche et des Technologies' (MENRT) for financial support. C.L. thanks the MENRT for research grant.

References

1. (a) Adler, E. *Wood Sci. Technol.* **1977**, *11*, 169–218; (b) Freudenberg, K.; Neish, A. *Constitution and Biosynthesis of Lignin*; Springer Verlag: Berlin, 1968; p. 78; (c) Monties, B. *Methods in Plant Biochemistry*; Academic Press, 1989; Vol. 1, pp. 113–157.
2. *Plant Cell Wall Polymers, Biogenesis and Biodegradation*, Lewis, N. G.; Paice, M. G. ACS Symposium Series, Washington, 1989, 399.

3. Grisebach, H. *The Biochemistry of Plants*; Academic Press, 1981; Vol. 7, pp. 457–478.
4. Duran, E.; Duran, H.; Cazaux, L.; Gorrichon, L.; Tisnes, P.; Sarni, F. *Bull. Soc. Chim. Fr.* **1987**, *1*, 143–148.
5. Kennedy, K.; Baltas, M.; Douglas, K. T.; Duran, H.; Embrey, K. J.; Giraudon, J. G.; McKie, J. H.; Grima-Pettenati, J.; Gorrichon, L. *J. Enzym. Inhib.* **1998**, *14*, 217–237.
6. Witter, D. J.; Vederas, J. C. *J. Org. Chem.* **1996**, *61*, 2613–2623.
7. Hirschmann, R.; Yager, K. M.; Taylor, C. M.; Witherington, J.; Sprengeler, P. A.; Phillips, B. W.; Moore, W.; Smith, A. B. *J. Am. Chem. Soc.* **1997**, *119*, 8177–8190.
8. Morise, X.; Savignac, P.; Guillemin, J. C.; Denis, J. M. *Synth. Commun.* **1991**, *21*, 793–798.
9. Malachowski, W. P.; Coward, J. K. *J. Org. Chem.* **1994**, *59*, 7616–7624.
10. Hoye, R. C.; Baigorria, A. S.; Danielson, M. E.; Pragman, A. A.; Rajapakse, H. A. *J. Org. Chem.* **1999**, *64*, 2450–2453.
11. (a) Ingrassia, L. Thesis, University Paul Sabatier Toulouse III, 2000; (b) *General procedure for the transesterification as shown in* Scheme 3. *Synthesis of silylated phosphonothioester* **4a**–**d**. To a solution of silylated phosphonodiester (1.8 mmol) in anhydrous dichloromethane (10 mL) under a nitrogen atmosphere, was added oxalyl chloride (8.6 mmol) and the mixture was stirred at room temperature for 20 h. The excess of oxalyl chloride and dichloromethane were removed under vacuum to give quantitatively phosphonochloridate. To a solution of *N*-acetylcysteamine (3.9 mmol) in dichloromethane (2 mL) was added a mixture of previous phosphonochloridate (1.8 mmol) and triethylamine (3.8 mmol) in dichloromethane (1 mL). The reaction mixture was stirred at room temperature for 16 h. Dichloromethane was evaporated under vacuum. The crude material obtained was dissolved in ethyl acetate and filtered. The filtrate was washed with a saturated solution of sodium bicarbonate, then water. The organic layer was dried over sodium sulfate and concentrated. The crude mixture was purified by column chromatography on silica gel (eluent: EtOAc) to provide desired product **4a** (0.72 g, 67% yield), **4b** (0.60 g, 49% yield), **4c** (0.70 g, 62% yield), **4d** (0.20 g, 37% yield).
Selected data for **4a**: R_f=0.62 (EtOAc:MeOH, 9:1), ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.10 (s, 9H), 1.37 (t, J=7.0 Hz, 3H), 1.98 (s, 3H), 2.93 (m, 2H), 3.51 (m, 2H), 3.61 (s, 3H), 4.20 (m, 2H), 6.16 (dd, J=17.2 Hz, J=23.4 Hz, 1H), 6.67 (d, J=8.2 Hz, 1H), 6.83 (dd, J=8.2 Hz, J=2.0 Hz, 1H), 6.92 (d, J=2.0 Hz, 1H), 7.17 (s, 1H), 7.38 (m, 7H), 7.69 (dd, J=7.4 Hz, J=1.2 Hz, 4H); ^{13}C NMR (50 MHz, $CDCl_3$), δ 16.38 (d, J=6.9 Hz), 19.80 (s), 23.08 (s), 26.57 (s), 29.13 (s), 40.88 (s), 55.39 (s), 62.46 (d, J=6.7 Hz), 110.92 (s), 115.04 (d, J=155.2 Hz), 120.36 (s), 122.00 (s), 127.64 (s), 128.04 (s), 129.82 (s), 133.01 (s), 135.28 (s), 147.84 (s), 148.44 (d, J=6.3 Hz), 150.88 (s), 170.70 (s); ^{31}P NMR (81 MHz, $CDCl_3$), δ 46.24 (s).
Selected data for **4b**: R_f=0.25 (EtOAc), ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.09 (s, 9H), 1.36 (t, J=7.0 Hz, 3H), 1.98 (s, 3H), 2.94 (m, 2H), 3.48 (m, 2H), 4.18 (m, 2H), 6.16 (dd, J=17.1 Hz, J=23.5 Hz, 1H), 6.76 (d, J=8.5 Hz, 2H), 7.14 (s, 1H), 7.27 (d, J=8.5 Hz, 2H), 7.39 (m, 7H), 7.69 (d, J=7.6 Hz, 4H); ^{13}C NMR (50 MHz, $CDCl_3$), δ 16.40 (d, J=6.5 Hz), 19.46 (s), 23.06 (s), 26.46 (s), 29.24 (s), 40.65 (s), 62.26 (d, J=6.7 Hz), 115.23 (d, J=154.0 Hz), 120.27 (s), 127.40 (d, J=23.2 Hz), 127.97 (s), 129.55 (s), 130.19 (s), 132.22 (s), 135.40 (s), 147.84 (d, J=31.4 Hz), 158.01 (s), 170.79 (s); ^{31}P NMR (81 MHz, $CDCl_3$), δ 46.24 (s).
Selected data for **4c**: R_f=0.25 (EtOAc), ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.08 (s, 9H), 1.37 (t, J=7.0 Hz, 3H), 1.98 (s, 3H), 2.96 (m, 2H), 3.45 (s, 6H), 3.52 (m, 2H), 4.19 (m, 2H), 6.18 (dd, J=17.1 Hz, J=23.2 Hz, 1H), 6.58 (s, 2H), 7.16 (s, 1H), 7.33 (m, 7H), 7.68 (d, J=7.6 Hz, 4H); ^{13}C NMR (50 MHz, $CDCl_3$), δ 16.39 (d, J=6.9 Hz), 20.17 (s), 23.11 (s), 26.70 (s), 29.16 (s), 40.88 (s), 55.25 (s), 62.46 (d, J=7.0 Hz,), 105.06 (s), 115.20 (d, J=155.4 Hz), 126.64 (s), 127.13 (s), 129.26 (s), 134.11 (s), 135.05 (s), 148.76 (d, J=6.4 Hz), 151.12 (s), 170.70 (s); ^{31}P NMR (81 MHz, $CDCl_3$), δ 45.96 (s).
Selected data for **4d**: R_f=0.35 (EtOAc), ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.34 (t, J=7.0 Hz, 3H), 1.94 (s, 3H), 2.91 (m, 2H), 3.47 (m, 2H), 3.91 (s, 6H), 4.17 (m, 2H), 6.23 (dd, J=17.2 Hz, J=23.2 Hz, 1H), 6.82 (d, J=8.2 Hz, 1H), 7.00 (s, 1H), 7.04 (d, J=8.2 Hz, 1H), 7.23 (s, 1H) 7.38 (dd, J=17.2 Hz, J=23.6 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$), δ 16.36 (d, J=6.8 Hz), 23.06 (s), 29.18 (s), 40.74 (s), 55.91 (s), 62.37 (d, J=6.9 Hz), 109.39 (s), 110.94 (s), 115.19 (d, J=155.2 Hz), 122.73 (s), 127.21 (d, J=23.6 Hz), 148.11 (d, J=6.4 Hz), 149.21 (s), 151.37 (s), 170.66 (s); ^{31}P NMR (81 MHz, $CDCl_3$), δ 45.99 (s).
12. (a) Picq, D.; Anker, D. *Carbohydr. Res.* **1987**, *166*, 309–313; (b) McClinton, M. A. *Aldrichim. Acta* **1995**, *28*, 31–35.