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Synthesis of chiral 4-nitrophenyl alkyl methylphosphonothioates: $BF_3{\cdot}Et_2O$-catalyzed alcoholysis of phosphonamidothioates

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Abstract—Facile and highly enantioselective synthesis of 4-nitrophenyl alkyl methylphosphonothioates **5a**–**f** was achieved in high yields via $BF_3{\cdot}Et_2O$-catalyzed alcoholysis of resolved phosphonamidothioates **4a** and **4b**.

The stereoselective synthesis of chiral phosphonates has attracted considerable interest in recent years.[1] Chiral phosphonates demonstrate potential differential inhibition of cholinesterases, since these enzymes are highly stereospecific for asymmetric organophosphorus inhibitors.[2–4] They are widely used for the elucidation of enzymatic reaction mechanisms.[3,4] Chiral phosphonate ester inhibitors mimic in both their charge distribution and geometry the second transition state occurring during enzymic carboxyester hydrolysis.[3a,b,5,6] Moreover, they are particularly good active-site probes of serine hydrolase enzymes by providing one more ligand for interacting with active-site residues than carboxyl esters.[3,7] Covalent modification of the active sites is not readily reversible in general. This problem is compounded in phosphates and phosphonates with an alkyl side chain that can be dealkylated in an S_N1 or S_N2 mechanism commonly known as aging.[8] Dealkylation leads to irreversible inhibition of enzymes and high toxicity.

Phosphonate esters with 4-nitrophenoxy substitution are efficient inhibitors of enzymes because the 4-nitrophenoxy moiety departs readily, while a covalent bond forms between the nucleophilic Oγ of the active serine of the enzyme and the phosphorus atom.[3c,9,10] The development of different chiral inhibitors of serine hydrolases for mechanistic studies as well as for application prompted us to focus our attention on synthetic methods towards optically pure 4-nitrophenyl alkyl methylphosphonothioates.

The standard method for the preparation of optically active phosphonothioates is conversion of resolved phosphonothioic acids with chiral amines into their chlorides and subsequent reaction with alcohols or phenols.[11] This method is tedious and affords poor yields. However, optically active insecticides were synthesized[12] recently in moderate yields by adopting stereoselective P–O and P–N bond cleavage via H_2SO_4-catalyzed alcoholysis.[13] Herein we wish to report an efficient stereospecific cleavage of the P–N bond via the $BF_3{\cdot}Et_2O$-catalyzed alcoholysis, and a facile and highly enantioselective synthetic method for the preparation of chiral 4-nitrophenyl alkyl methylphosphonothioates in high yields using (*S*)-(−)-α-methylbenzylamine (**3**) as chiral resolving agent.

Table 1. Physical properties of 4-nitrophenyl *N*-(α-methylbenzyl) methylphosphoramidothioates **4a**–**b**[a]

Product no.	Yield (%)	Mp (°C)	$[\alpha]_D^{25}$ ($c=2$, $CHCl_3$)	Molecular formula	^{31}P NMR, δ ($CDCl_3$)
4a[17]	34	121–122	−122.0	$C_{15}H_{17}N_2O_3PS$	81.55
4b[18]	28	80–81	+60.5	(336.35)	80.83

[a] Diastereomeric purity is 100%.

Keywords: asymmetric synthesis; phosphonamidothioates; $BF_3{\cdot}Et_2O$-catalyzed alcoholysis; (*S*)-(−)-α-methylbenzylamine.

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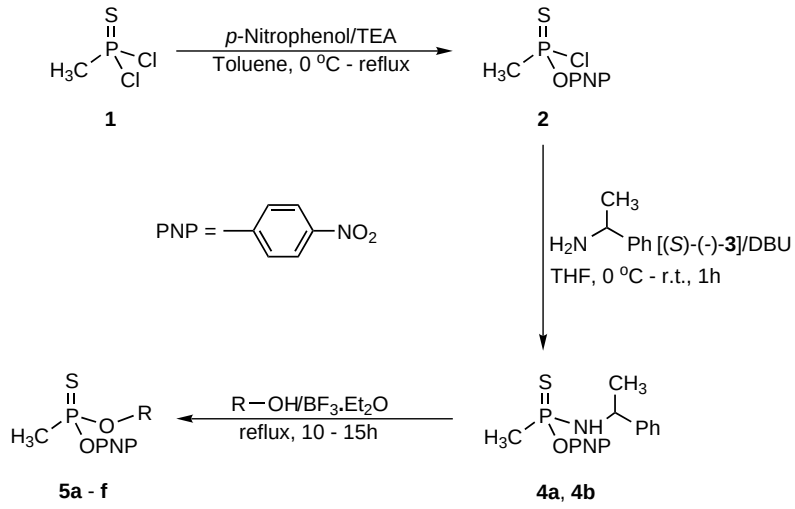

Scheme 1.

Table 2. Physical properties of optically active 4-nitrophenyl alkyl methylphosphonothioates **5a**–**f**

Precursor	Product no.	R	Yield (%)	$[\alpha]_D^{25}$ ($c=2$, $CHCl_3$)	Molecular formula	^{31}P NMR, δ ($CDCl_3$)
4a	**5a**[20]	CH_3	76	(*S*): −12.5	$C_8H_{10}NO_4PS$	97.22
4b			79	(*R*): +11.8	(247.21)	
4a	**5b**[21]	C_2H_5	74	(*S*): −9.5	$C_9H_{12}NO_4PS$	94.96
4b			72	(*R*): +9.2	(261.24)	
4a	**5c**[22]	$CH(CH_3)_2$	69	(*S*): −8.4	$C_{10}H_{14}NO_4PS$	93.31
4b			70	(*R*): +8.6	(275.26)	
4a	**5d**[23]	$(CH_2)_2CH_3$	72	(*S*): −7.8	$C_{10}H_{14}NO_4PS$	95.20
4b			70	(*R*): +7.2	(275.26)	
4a	**5e**[24]	$CH(CH_3)C_2H_5$	62	–	$C_{11}H_{16}NO_4PS$	82.91[a]
4b	**5f**[25]	(*R*)(−)	59	–	(289.29)	83.41[a]

[a] Diastereomeric purity is 99%.

4-Nitrophenyl methylphosphonothiochloridate (**2**) was conveniently synthesized in fairly good yield from equimolar quantities of methylphosphonothioic dichloride (**1**) and 4-nitrophenol in the presence of triethylamine (TEA).[14] The crucial intermediate, a diastereomeric mixture of phosphonamidothioate, **4**, was prepared in almost quantitative yield by reacting phosphonothiochloridate **2** with **3** in the presence of diazabicycloundecane (DBU) in tetrahydrofuran (THF) under a N_2 atmosphere.[15] The diastereomers of **4** were easily separated by fractional crystallization from a benzene–hexane mixture.[16] The less soluble diastereomer **4a**[17] was first recrystallized from a 1:5 mixture of benzene–hexane and then the more soluble diastereomer **4b**[18] was recrystallized from a 1:7 mixture of benzene–hexane. Determination of ^1H and ^{31}P NMR chemical shifts using a Jeol 270 MHz spectrometer revealed 100% purity of both diastereomers P(*R*+)C(*S*−) and P(*S*)C(*S*). The optical rotations of the compounds were also determined and are shown in Table 1.

Finally, the $BF_3{\cdot}Et_2O$-catalyzed alcoholysis[19] of phosphonamidothioates **4a** and **4b**, through the stereospecific P–N bond cleavage (Scheme 1), at reflux temperatures for 10–15 h resulted in the corresponding phosphonothioates **5a**–**f**[20–25] in good yields. (Table 2). The success of the asymmetric synthesis is prominently illustrated by the separate ^{31}P NMR signals for the diastereomers (**4a**, **4b**, **5e** and **5f**) with above 99% diastereomeric purity and by the optical rotations for the enantiomers (**5a**–**d**).

In conclusion, facile and highly enantioselective preparation of 4-nitrophenyl methyl alkylphosphonothioates **5a**–**f** was achieved in high yields via $BF_3{\cdot}Et_2O$-catalyzed alcoholysis of resolved phosphonamidothioates **4**.

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14. 4-Nitrophenol (4.67 g, 33.6 mmol) and TEA (3.40 g, 33.6 mmol) in 50 mL of dry toluene was added dropwise over a period of 15 min to methylphosphonothiodichloridate (**1**, 5 g, 33.6 mmol) in 50 mL of dry toluene at 0°C. After stirring for an additional 30 min at 0°C, the temperature of the reaction mixture was slowly raised and refluxed for 8 h. The precipitated TEA·HCl was filtered off and the solvent was removed under vacuum. The crude product was vacuum distilled at 134–138°C/0.05 mmHg to obtain pure monochloride **2**; yield 5.40 g (63%). The distilled product was solidified at rt and recrystallized from $CHCl_3$/hexane to obtain crystalline product, mp 71–72°C. ^{1}H NMR (270 MHz, $CDCl_3$): δ (ppm) 2.56 (d, *J* 15 Hz, 3H), 7.43 (dd, *J* 9, 2 Hz, 2H), 8.29 (d, *J* 9 Hz, 2H); ^{31}P NMR (270 MHz, $CDCl_3$): δ (ppm, phosphoric acid standard) 93.06.
15. *Synthesis of 4-nitrophenyl N-(α-methylbenzyl) methylphosphonamidothioate (**4**)*: (*S*)-(−)-α-Methylbenzylamine (**3**; 0.24 mL, 1.9 mmol) and DBU (0.28 mL, 1.9 mmol) in 10 mL of dry THF was added dropwise to the stirred solution of phosphonothiochloridate **2** (475 mg, 1.9 mmol) in 10 mL of dry THF under a N_2 atmosphere at 0°C. After 15 min the solution was slowly raised to rt and stirring was continued for an additional hour. The precipitate was filtered off, the solvent was removed under reduced pressure and the crude product **4** was purified by short path silica gel column chromatography using 3:1 hexane–ethyl acetate as eluent.
16. The diastereomeric mixture of phosphoramidothioate **4** (0.5 g) was dissolved in 5 mL of a boiling solution of a 1:5 mixture of benzene–hexane, was allowed to cool and left at rt for overnight. The crystals were filtered, washed with the same solvent mixture and the same recrystallization process repeated three times to afford an optically pure, higher melting diastereomer **4a**,[17] mp 121–122°C; yield 34%. The first mother liquor was concentrated under reduced pressure to obtain a solid, which was recrystallized three times from 5 mL of a boiling 1:7 mixture of benzene–hexane to obtain optically pure, lower melting diastereomer **4b**,[18] mp 80–81°C; yield 28%.
17. **4a**: Mp 121–122°C; ^{1}H NMR (270 MHz, $CDCl_3$): δ (ppm) 1.44 (d, 3H, *J* 7 Hz), 1.74 (d, 3H, *J* 16 Hz), 3.56 (bs, 1H), 4.49–4.57 (m, 1H), 7.23–7.34 (m, 7H), 8.19 (d, 2H, *J* 9 Hz); ^{31}P NMR (270 MHz, $CDCl_3$): δ (ppm, phosphoric acid standard) 81.55.
18. **4b**: Mp 80–81°C; ^{1}H NMR (270 MHz, $CDCl_3$): δ (ppm) 1.50 (d, 3H, *J* 7 Hz), 2.05 (d, 3H, *J* 16 Hz), 3.53 (bs, 1H), 4.45–4.59 (m, 1H), 7.05 (d, 2H, *J* 9 Hz), 7.21–7.41 (m, 5H), 8.03 (d, 2H, *J* 9 Hz); ^{31}P NMR (270 MHz, $CDCl_3$): δ (ppm, phosphoric acid standard) 80.83.
19. *Synthesis of phosphonothioates (**5**)*: Phosphonamidothioate **4** (1 mmol) was dissolved in 3 mL anhydrous alcohol, the solution was cooled to 0°C under a N_2 atmosphere and $BF_3{\cdot}Et_2O$ (5 mmol) was added dropwise from a syringe. After 1 h, the solution was allowed to slowly reach rt and after stirring for an additional hour, the reaction mixture was slowly heated to reflux temperature and allowed to continue for 10–15 h. The reaction mixture was concentrated, the residue was dissolved in 10 mL of $CHCl_3$ and washed successively with 5 mL of 1% K_2CO_3, saturated NH_4Cl, brine and finally with water. The $CHCl_3$ layer was dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. The resulting product was purified on a short path silica gel column using a 3:1 mixture of hexane–ethyl acetate as eluent to afford pure compound **5**.
20. **5a**: ^{1}H NMR (270 MHz, $CDCl_3$): δ (ppm) 2.03 (d, 3H, *J* 16 Hz), 3.80 (d, 2H, *J* 14 Hz), 7.29 (dd, 2H, *J* 11 Hz), 8.24 (d, 2H, *J* 9 Hz); ^{31}P NMR (270 MHz, $CDCl_3$): δ (ppm, phosphoric acid standard) 97.22.
21. **5b**: ^{1}H NMR (270 MHz, $CDCl_3$): δ (ppm) 1.32 (t, 3H, *J* 7 Hz), 2.02 (d, 3H, *J* 16 Hz), 4.08–4.31 (m, 2H), 7.30 (d, 2H, *J* 9 Hz), 8.24 (d, 2H, *J* 9 Hz); ^{31}P NMR (270 MHz, $CDCl_3$): δ (ppm, phosphoric acid standard) 94.96.
22. **5c**: ^{1}H NMR (270 MHz, $CDCl_3$): δ (ppm) 1.30 (d, 6H, *J* 6 Hz), 2.01 (d, 3H, *J* 16 Hz), 4.91 (m, 1H), 7.32 (dd, 2H,

J 9, 2 Hz), 8.23 (d, 2H, *J* 9 Hz); ^{31}P NMR (270 MHz, $CDCl_3$): δ (ppm, phosphoric acid standard) 93.31.

23. **5d**: ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.95 (t, 3H, *J* 8 Hz), 1.69 (m, 2H), 2.03 (d, 3H, *J* 15 Hz), 4.01 (m, 2H), 7.29 (dd, 2H, *J* 9, 2 Hz), 8.23 (d, 2H, *J* 9 Hz); ^{31}P NMR (270 MHz, $CDCl_3$): δ (ppm, phosphoric acid standard) 95.20.
24. **5e**: ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.91 (t, 3H, *J* 7 Hz), 1.16 (d, 3H, *J* 6 Hz), 1.60 (m, 2H), 1.99 (d, 3H, *J* 16 Hz), 4.29 (m, 1H), 7.02 (dd, 2H, *J* 9, 2 Hz), 8.01 (d, 2H, *J* 9 Hz); ^{31}P NMR (270 MHz, $CDCl_3$): δ (ppm, phosphoric acid standard) 82.98.
25. **5f**: ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.90 (t, 3H, *J* 7 Hz), 1.13 (d, 3H, *J* 7 Hz), 1.56 (m, 2H), 1.88 (d, 3H, *J* 15 Hz), 4.28 (m, 2H), 7.18 (dd, 2H, *J* 9, 2 Hz), 8.14 (d, 2H, *J* 9 Hz); ^{31}P NMR (270 MHz, $CDCl_3$): δ (ppm, phosphoric acid standard) 83.41.