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First syntheses of 2-hydrogeno-2-oxo-1,4,2-oxazaphosphinanes via intramolecular esterification

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Abstract—Synthesis of 2-hydrogeno-2-oxo-1,4,2-oxazaphosphinanes via either intramolecular transesterification, using potassium *tert*-butylate as catalytic agent, or phosphinic acid esterification, is described for the first time.

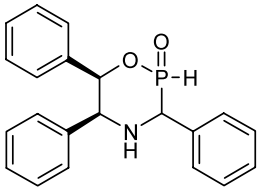
In a previous work,[1] we described a general one-pot synthesis of phosphino-dipeptides analogs of pseudo-dipeptides. As a part of our ongoing efforts for the preparation of biologically active phosphinic acids and asymmetric syntheses of phosphino-dipeptides analogs, we decided to explore the synthesis of a new class of 1,4,2-oxazaphosphinanes. Although compounds as 2-alkyl-2-oxo-1,4,2-oxazaphosphinanes[2] and 2-alkoxy-2-oxo-1,4,2-oxazaphosphinanes[3] were synthesized, surprisingly 2-hydrogeno-2-oxo-1,4,2-oxazaphosphinanes **1**, with a P–H bond, are not described in the literature.

Therefore, among various methods used for the synthesis of oxazaphosphinanes, we chose intramolecular transesterification of aminoalkylphosphinates **2** or direct esterification of the corresponding phosphinic acid **3** to obtain the 2-hydrogeno-2-oxo-1,4,2-oxazaphosphinanes **1** (Fig. 1).

Precursor of compounds **2** or **3**, the *N*-benzylidene-2-amino-1,2-diphenylethanol **5** is obtained as described in Scheme 1.

trans-Stilbene is converted to epoxide using dimethyldioxirane generated in situ by an Oxone/$NaHCO_3$/acetonitrile system.[4] Aminolysis with ammonia in methanol affords a racemic mixture of β-hydroxylamines **4**,[5] which are condensed with benzaldehyde in dichloromethane to give the racemic imine **5**[6] in 85% isolated yield after recrystallization in ethanol.

Methyl hypophosphite **6** is obtained by treatment of hypophosphorous acid with trimethyl-orthoformate in a THF/toluene (1/1) solution as described previously.[1] After dilution of the reaction mixture with THF, addition of imines **5** affords phosphinates **2** in 75% yield, determined by ^{31}P NMR. Cyclization occurs under potassium *tert*-butylate catalysis to give a mixture of



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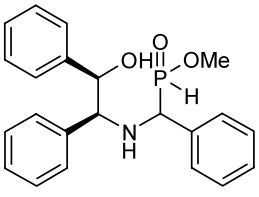

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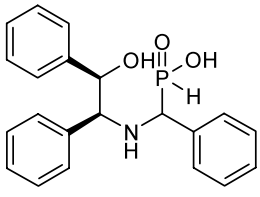

3 (+/-)

Figure 1. 2-Hydrogeno-2-oxo-1,4,2-oxazaphosphinane **1** and its precursors **2** and **3**.

Keywords: aminophosphinic acid; phosphorus heterocycles; intramolecular cyclization; oxazaphosphinane.
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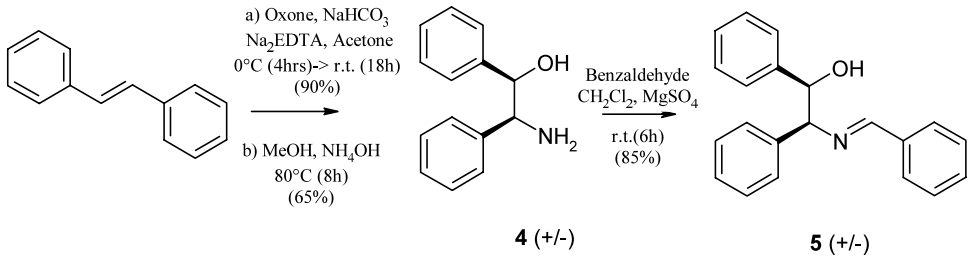


Scheme 1. Synthesis of *N*-benzylidene-2-amino-1,2-diphenylethanol **5**.

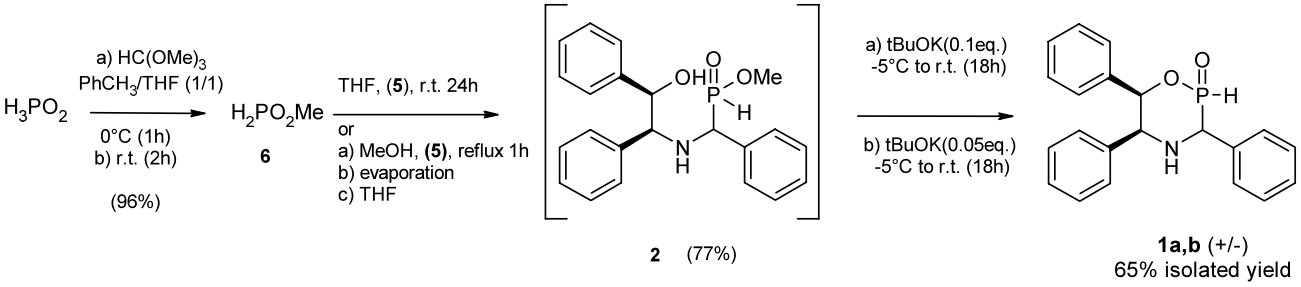
two diastereoisomers **1a**,**b** in 65% isolated yield and in a 3:1 ratio[7a] (Scheme 2). Analog synthesis can be done using methanol as solvent, in the second step, and gives a mixture of diastereoisomers **1a**,**b** in 56% isolated yield and in a 1:4 ratio.[7b]

An alternative route for the synthesis of 3,5,6-triphenyl-2-hydrogeno-2-oxo-1,4,2-oxazaphosphinane **1** is an intramolecular esterification of phosphinic acid **3**. Among various possibilities for esterification of phosphinic acids (DCC/DMAP,[8] heteroazeotropic or thermic deshydratation,[9] and more recently orthosilicates reagents[10]), we chose the DCC/DMAP way (Scheme 3). Phosphinic acid **3** is easily obtained in 69% isolated yield by filtration of a methanolic solution of hypophosphorous acid with imine **5** refluxed for 4 h.[11] Intramolecular esterification of phosphinic acid with DCC/DMAP, instead of methanol in dichloromethane, also gives the same two diastereoisomers **1a** and **1b**, in a 3:2 ratio and in a 60% yield (determined by ^{31}P NMR).[12] Cyclization by azeotropic elimination of water was also tried in toluene with a Dean–Stark trap, but only little amount of cycles **1a**,**b** were detected after several days reflux.

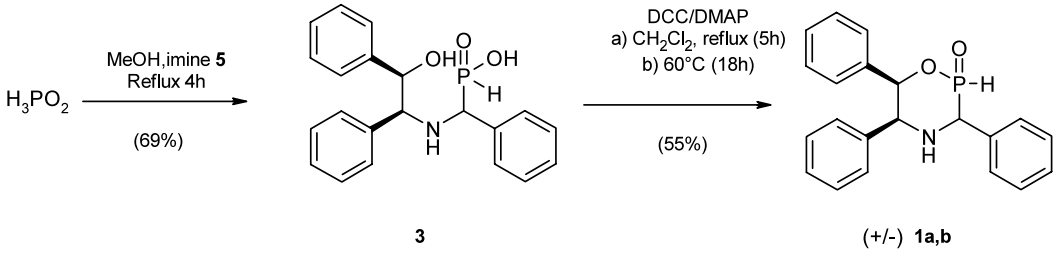
Figure 2 presents the solid-state structure determined by X-ray diffraction analysis of suitable crystals of **1a**. ^1H NMR coupling constants are given just beside. It appears that the boat-like conformation is preferred bearing the three phenyl groups on a *cis* position to the cycle, the P=O bond being consequently *trans*.

In conclusion, we have synthesized, for the first time, the 3,5,6-triphenyl-2-hydrogeno-2-oxo-1,4,2-oxazaphosphinane via intramolecular transesterification of methyl phosphinate under potassium *tert*-butylate catalysis or intramolecular direct transesterification of the corresponding phosphinic acid and determined by X-ray diffraction the structure of one diastereoisomer **1a**. Future developments include preparation of various substituted phosphorylated heterocycles and asymmetric synthesis of phosphino-dipeptides analogs using enantiopure 1,2-diphenylethanol.[13] Results will be reported in due course.

Data for:
(2S,3R*,5R*,6S*)-(±)-3,5,6-Triphenyl-2-hydrogeno-2-oxo-1,4,2-oxazaphosphinane* ***(1a)***



Scheme 2. Intramolecular transesterification of methyl phosphinate.



Scheme 3. Intramolecular esterification of phosphinic acid.

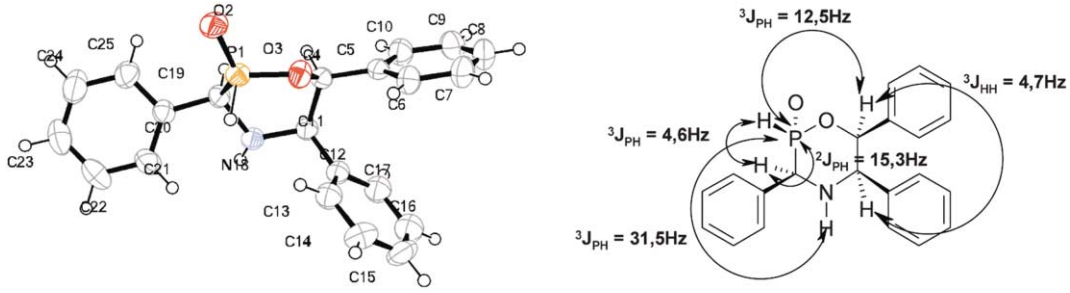


Figure 2. X-Ray structure of **1a** and ^{1}H NMR analysis.

^{31}P NMR (81.0 MHz, $CDCl_3$): δ 28.53; ^{1}H NMR (200.13 MHz, $CDCl_3$): δ 2.20 (d, 1H, $^3J_{PH}$ = 31.5 Hz, N*H*), 4.60 (dd, 1H, $^2J_{PH}$ = 15.3 Hz, $^3J_{HH}$ = 4.7 Hz, PC*H*N), 4.86 (d, 1H, $^3J_{HH}$ = 4.5 Hz, NC*H*Ph), 5.62 (dd, 1H, $^3J_{PH}$ = 12.5 Hz, $^3J_{HH}$ = 4.5 Hz, OC*H*Ph), 7.12–7.66 (m, 15H, C*H*ar), 7.18 (dd, 1H, $^1J_{PH}$ = 578.3 Hz, $^3J_{HH}$ = 4.9 Hz, P*H*); ^{13}C NMR (50.32 MHz, $CDCl_3$): δ 64.38 (d, $^1J_{PC}$ = 92.7 Hz, N*C*HPh), 64.75 (d, $^3J_{PC}$ = 2.6 Hz, N*C*HPh), 85.92 (d, $^2J_{PC}$ = 7.8 Hz, O*C*HPh), 127.42–129.27 (m, *C*Har), 134.07 (d, $^2J_{PC}$ = 5.6 Hz, *C*ar), 135.52 (d, $^3J_{PC}$ = 2.6 Hz, *C*ar), 137.27 (s, *C*ar); IR (KBr): 3260, 3090, 3060, 3020, 2865, 2400, 1455, 1235, 1195, 1020, 1000, 940, 810, 700; HRMS FAB$^+$ (NBA): calcd for $C_{21}H_{21}O_2NP$: 350.1310. Found: 350.1326; 350.1 [M+H]$^+$ (19%), 284.2 (100%), 180.1 (60%), 106.1 (20%).

(5R,6S*)-(±)-3,5,6-Triphenyl-2-hydrogeno-2-oxo-1,4,2-oxazaphosphinane* ***(1b)***

^{31}P NMR (81.0 MHz, $CDCl_3$): δ 35.88; ^{1}H NMR (200.13 MHz, $CDCl_3$): δ 2.25 (d, 1H, $^3J_{PH}$ = 26.0 Hz, N*H*), 4.30 (dd, 1H, $^2J_{PH}$ = 14.3 Hz, $^3J_{HH}$ = 5.5 Hz, PC*H*N), 4.59 (d, 1H, $^3J_{HH}$ = 2.7 Hz, NC*H*Ph), 6.14 (dd, 1H, $^3J_{PH}$ = 4.4 Hz, $^3J_{HH}$ = 3.5 Hz, OC*H*Ph), 7.10–7.50 (m, 15H, C*H*ar), 6.96 (dd, 1H, $^1J_{PH}$ = 554.6 Hz, $^3J_{HH}$ = 5.3 Hz, P*H*); ^{13}C NMR (50.32 MHz, $CDCl_3$): δ 55.40 (d, $^1J_{PC}$ = 96.0 Hz, P*C*HN), 61.33 (s, N*C*HPh), 83.45 (d, $^2J_{PC}$ = 7.8 Hz, O*C*HPh), 125.27–128.82 (m, *C*Har), 133.27 (d, $^2J_{PC}$ = 6.0 Hz, *C*ar), 136.14 (d, $^4J_{PC}$ = 1.1 Hz, *C*ar), 136.60 (d, $^3J_{PC}$ = 7.8 Hz, *C*ar); IR (KBr): 3340, 3290, 3060, 2910, 2360, 1490, 1450, 1105, 1235, 1150, 1040, 950, 800; HRMS FAB$^+$ (NBA): calcd for $C_{21}H_{21}O_2NP$: 350.1310. Found: 350.1330; 350.1 [M+H]$^+$ (15%), 284.2 (58%), 180.1 (62%), 106.1 (40%).

[(1R,2S*)-(±)-(2-Hydroxy-1,2-diphenyl-ethylamino)-phenyl-methyl]-phosphinic acid* ***(3a,b)***

3a: ^{31}P NMR (81.0 MHz, D_2O/NaOD): δ 27.71; ^{1}H NMR (250.13 MHz, D_2O/NaOD): δ 3.23 (d, 1H, $^2J_{PH}$ = 15.5 Hz, PC*H*N), 3.53 (d, 1H, $^3J_{HH}$ = 8.1 Hz, NC*H*Ph), 4.72 (d, 1H, $^3J_{HH}$ = 8.0 Hz, OC*H*Ph), 6.60 (d, 1H, $^1J_{PH}$ = 521.9 Hz, P*H*), 6.7–7.3 (m, 15H, C*H*ar); ^{13}C NMR (50.32 MHz, D_2O/NaOD): δ 68.29 (d, $^1J_{PC}$ = 49.1 Hz, P*C*HN), 78.55 (s, N*C*HPh), 79.92 (s, O*C*HPh), 129.82–131.83 (m, *C*Har), 137.70 (d, $^2J_{PC}$ = 4.1 Hz, *C*ar), 141.36 (s, *C*ar), 143.53 (s, *C*ar); IR (KBr): 3300, 3060, 3040, 2960, 2940, 2660, 2340, 2320, 1610, 1220, 1195, 1070, 1050, 960, 775, 750, 700, 510, 460; HRMS FAB$^+$ (NBA): calcd for $C_{21}H_{23}NO_3P$: 368.1443. Found: 368.1416; 368.1 [M+H]$^+$ (10%), 106.1 (90%).

3b: ^{31}P NMR (81.0 MHz, D_2O/NaOD): δ 28.66; ^{1}H NMR (250.13 MHz, D_2O/NaOD): δ 3.24 (d, 1H, $^2J_{PH}$ = 15.9 Hz, PC*H*N), 3.77 (d, 1H, $^3J_{HH}$ = 6.8 Hz, NC*H*Ph), 4.88 (d, 1H, $^3J_{HH}$ = 6.8 Hz, OC*H*Ph), 6.61 (d, 1H, $^1J_{PH}$ = 519.3 Hz, P*H*), 6.7–7.3 (m, 15H, C*H*ar); ^{13}C NMR (50.32 MHz, D_2O/NaOD): δ 68.55 (d, $^1J_{PC}$ = 45.8 Hz, P*C*HN), 78.55 (s, N*C*HPh), 79.92 (s, O*C*HPh), 129.82–131.83 (m, *C*Har), 138.75 (d, $^2J_{PC}$ = 3.4 Hz, *C*ar), 142.54 (s, *C*ar), 143.99 (s, *C*ar); IR (KBr): 3300, 3060, 3040, 2960, 2940, 2660, 2340, 2320, 1610, 1220, 1195, 1070, 1050, 960, 775, 750, 700, 510, 460; HRMS FAB$^+$ (NBA): calcd for $C_{21}H_{23}NO_3P$: 368.1443. Found: 368.1416; 368.1 [M+H]$^+$ (10%), 106.1 (90%).

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7. (a) **Experimental procedure for (5*R**,6*S**)-(±)-3,5,6-triphenyl-2-hydrogeno-2-oxo-1,4,2-oxazaphosphinane (1a,b) via methyl phosphinate (2)**: In a 50 ml flask containing the reaction mixture of methyl hypophosphite (19.8

mmol) under N_2 is added dry THF (11 ml) and *N*-benzylidene-2-amino-1,2-diphenylethanol (5.97 g, 19.8 mmol). After stirring for 24 h at room temperature, 0.1 equiv. of a solution of sublimed *t*-BuOK in dry THF is added dropwise at −5°C. The reaction mixture is then stirred for 2 h in an ice bath and precipitation occurs at room temperature overnight. The precipitate is filtered off (**1a**, 1.35 g). Filtrate is cooled to −5°C before a second addition of base (0.05 equiv.), after stirring 2 h in an ice bath and 18 h at room temperature, the second precipitate is filtered off (**1a** and **1b**, 63:37 ratio , 3.01 g). (**1a** and **1b**, 3:1 ratio, 65% isolated yield); (b) **Experimental procedure for (5*R**,6*S**)-(±)-3,5,6-triphenyl-2-hydrogeno-2-oxo-1,4,2-oxazaphosphinane (1a,b) via methylphosphinate (2)**: In a 50 ml flask containing the reaction mixture of methyl hypophosphite (19.8 mmol) under N_2, is added dry MeOH (38 ml) and *N*-benzylidene-2-amino-1,2-diphenylethanol (5.97 g, 19.8 mmol). After stirring for 1 h under reflux, the reaction mixture is evaporated and THF (22 ml) is added. Addition of *t*-BuOK and obtention of the desired heterocycles follows the same procedure as described in Ref. 7a. (**1a** and **1b**, 1:4 ratio, 56% isolated yield).

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12. **Experimental procedure for (5*R**,6*S**)-(±)-3,5,6-triphenyl-2-hydrogeno-2-oxo-1,4,2-oxazaphosphinane (1a,b) via esterification of phosphinic acid (3)**: In a 10 ml flask, phosphinic acid (**3**) (0.7 g, 1.91 mmol) under N_2 and DMAP (0.13 g, 1.06 mmol) dissolved in CH_2Cl_2 (3.5 ml). A solution of DCC (0.43 g, 2.08 mmol) in CH_2Cl_2 (1.2 ml) is then added under stirring at room temperature, and the reaction mixture is refluxed 6 h. Evaporation of CH_2Cl_2 and heating overnight at 70°C give heterocycles (**1a**,**b**) (2:3 ratio, 60% yield determined by ^{31}P NMR).
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