Note on Carbonyl Derivatives with a Chiral Phosphorylhydrazine

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(2S,4S,5R)-3,4-Dimethyl-2-hydrazido-5-phenyl-1,3,2-oxazaphospholidin-2-oxide, Chiral Ketones, HPLC, ^{31}P NMR Spectra

Hydrazones of chiral and achiral ketones with enantiomerically pure phosphorylhydrazine **4** are prepared and analysed by ^{31}P NMR spectroscopy and HPLC for their diastereoisomeric purity.

Optically pure substituted chlorophosphoridates have been used to estimate enantiomeric excesses (e.e.) of alcohols and amines by ^{31}P NMR spectroscopy [1, 2]. We were interested to find out whether the cyclic phosphorylhydrazine **4** could serve in a similar way for the e.e. determination of sensitive chiral ketones after formation of the hydrazone **5.**

A ketone with $R^1 \neq R^2$ and a chiral R group can form two pairs of *syn*/*anti* diastereomeric hydrazones **5.** It remained to be seen whether these would exhibit ^{31}P signals sufficiently apart from each other or whether these compounds could be separated by chromatographic techniques.

Starting with (−)-ephedrin (**1**), the preparation of the epimeric 2-chloro-3,4-dimethyl-1,3,2-oxazaphospholidin-2-oxides is straightforward, the (2R,4S,5R) compound **2** being formed in 71% yield [3]. The transformation from **1** *via* **2** into **4** with aqueous hydrazine (51% yield) is performed best as a one-pot process because **2** is very sensitive towards hydrolysis. Aldehydes and acetophenone react quantitatively with a small excess of hydrazine **4** at room temperature or after short refluxing in ethanol. Other ketones are converted best by refluxing in dichloromethane in the presence of molecular sieves as water scavenger. Under these conditions, sterically demanding ketones cannot be transformed totally into hydrazones unfortunately. The same applies to some α,β-unsaturated ketones, *e.g.* carvone. Reactions with these compounds can be performed in ethanol in the presence of acids but some by-products are formed inevitably.

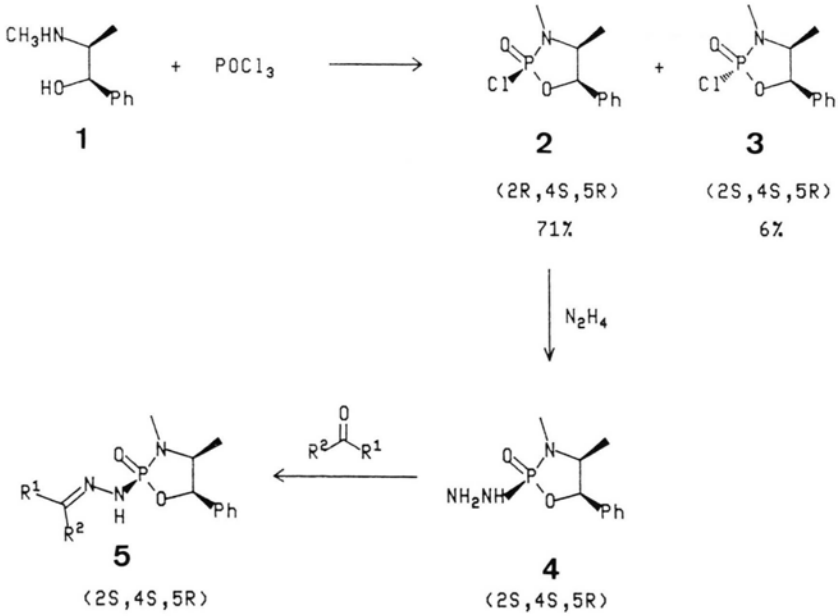

Table I gives a survey of the carbonyl compounds converted into phosphorylhydrazones **5.** If not indicated otherwise racemates were used. ^{1}H NMR spectra showed that the raw hydrazones were essentially free from by-products (except for starting

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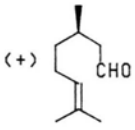
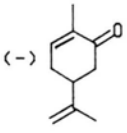
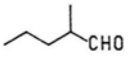
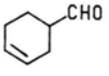
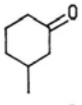
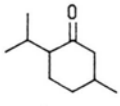
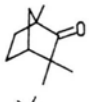
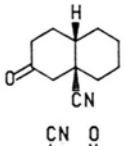
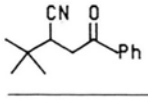
Table I. Preparation of carbonyl derivatives of (2S,4S,5R)-3,4-dimethyl-2-hydrazido-5-phenyl-1,3,2-oxazaphospholidin-2-oxide (**4**) and determination of isomeric ratios by ^{31}P NMR spectroscopy and HPLC.

Carbonyl Compound	Method of[a] preparation	^{31}P NMR signals[b] (ratio)	HPLC-peaks[c] (ratio)
	A, 4 h	18.99/18.51 94:6	5.2/8.2 5:95
	B, 2 h	–	11.2
	A, 3 h	–	4.1/8.9 45:55
	A, 3 h	19.49/19.26 10:90	3.4/4.9 30:70
	B, Reaction incomplete	19.78/19.72 50:50	–
	A, 3 h	–	5.1/7.1 97:3
	A, 3 h	–	6.9/7.2/8.1 28:53:19
	A, 2 h	18.93	4.8/5.9/6.2 10:43:47
	B, 20 h	19.79/19.73 50:50	5.6/6.2/6.7/7.7 5:10:40:45
	B, 20 h	20.19/20.13/20.11 50:25:25	6.2/6.9/8.3/9.6 20:32:21:27
	B, 72 h	19.63	5.9
	B, Reaction incomplete	–	–
	B, Reaction incomplete	–	–
	B, 24 h	19.59/19.43 6:94	5.9/7.0/7.2/8.3 3:12:42:43
	B, 3 h	20.30/20.24/20.20/19.75 41:20:8:31	4.4/6.7[d] 32:68
	B, 340 h	19.29/19.25 75:25	3.2/4.5/5.1 57:41:2

[a] Method A: Refluxing in ethanol; method B: Refluxing in CH_2Cl_2 with molecular sieves; [b] ^{31}P NMR: 300 MHz in chloroform, δ values; [c] HPLC: Si60, ethylacetate 3.5 ml/min, retention times in min; [d] second signal with shoulder.

materials when the reactions were incomplete). There was no indication of diastereomeric mixtures in the ^1H NMR spectra. ^{31}P NMR spectroscopy and HPLC analysis gave matching results in the analysis of acetophenone hydrazones. Severe difficulties, however, were observed with the more complex compounds: Where 4 diastereomers were expected the ^{31}P NMR exhibited between one and four peaks which were spaced very closely and overlapped sometimes. Similarly, HPLC gave only occasionally the expected total resolution of 4 isomers. Only in some cases virtually identical results were obtained by both methods due to tailing and difficulties in exact integration. Thus, 2- and 3-methylcyclohexanone derivatives gave 4 peaks each in HPLC analysis, but only 2 or 3 by ^{31}P spectroscopy, whereas *trans*-9-cyano-2-decalone exhibited 4 signals in the ^{31}P spectrum and 2 ones in HPLC.

In conclusion then, preparation of the hydrazones **5** and analysis by combined application of ^{31}P NMR spectroscopy and HPLC permits the analysis for enantiomeric purity of the starting ketones only in some cases.

Experimental

NMR-spectra were measured in $CDCl_3$ with an AM 300 (Bruker). HPLC-separations were performed with a Milton Roy apparatus utilizing an UV-detector, with column material Si60, and ethyl acetate as eluent.

(2S,4S,5R)-3,4-Dimethyl-2-hydrazido-5-phenyl-1,3,2-oxazaphospholidin-2-oxide (**4**)

A solution of 16.5 g (100 mmol) (−)-ephedrin (containing *ca.* 5% H_2O) in 250 ml benzene is stirred for 1 h with molecular sieves (4 Å). The molecular sieves are filtered off and washed with 250 ml benzene. 70 ml (500 mmol) triethylamine are added to the combined benzene solutions, and 9.6 ml (100 mmol) $POCl_3$ are slowly dropped in. The precipitate of $N(C_2H_5)_3HCl$ is filtered off after 1/2 h, and the filtrate is slowly added to a solution of 6.5 g (200 mmol) absol. N_2H_4 in 110 ml methanol at 7−10 °C within 1 h. The precipitate is filtered off, and the solvent is removed *in vacuo*. Thereafter the residue is crystallized from ethanol. 12.2 g (51%) yield. The diastereomeric hydrazide (from **3**) is lost with the mother liquor. M.p. 176−178 °C. $[\alpha]_{436}^{25}$ −190°, $[\alpha]_{546}^{25}$ −108°, $[\alpha]_{578}^{25}$ −95°, $[\alpha]_{589}^{25}$ −88°. ^{31}P NMR: δ 25.54. ^1H NMR: δ 7.3−7.4 (m, 5H), 5.71 (d, J = 6.5 Hz, 1H), 4.61 (br d, NH), 3.70 (dq, J = 19.5+6.6, 1H), 3.42 (br s, NH_2), 2.75 (d, J = 9.3, NCH_3), 0.84 (d, J = 6.6, 3H).

$C_{10}H_{16}N_3O_2P$ (241.2)

Calcd	C 49.79	H 6.69	N 17.42,
Found	C 49.95	H 6.93	N 17.53.

Formation of hydrazones (**5**)

Method A: 1.2 g (5 mmol) **4** and 5 mmol of the carbonyl compound are heated in 10 ml of ethanol (see Table I). The solvent is removed *in vacuo*, and the residue is dissolved in ether, washed with water, dried (Na_2SO_4), and evaporated to dryness.

Method B: 530 mg (2.2 mmol) **4,** 2 mmol of the carbonyl compound and 1 g molecular sieves are refluxed in 10 ml dry CH_2Cl_2 (see Table I). The solution is filtered, washed with water, dried (Na_2SO_4), and evaporated to dryness.

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