Tetrahedron Letters, Vol.27, No.8, pp 997-1000, 1986 0040-4039/86 $3.00 + .00
Printed in Great Britain

ALKYLPHOSPHONIC DICHLORIDES, NEW REAGENTS FOR THE ENANTIOMERIC EXCESS DETERMINATION OF CHIRAL ALCOHOLS AND THIOLS BY ^{31}P NMR

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Abstract. The enantiomeric excess of chiral alcohols and thiols (1) is obtained by ^{31}P NMR measurement of the ratios of diastereoisomeric (thio)phosphonates from 1 and methylphosphonic dichloride.

Recently we described a method for the enantiomeric excess (e.e.) determination of chiral alcohols without use of any chiral auxiliary compounds.[1] This new and facile method is based on the principle of formation of diastereoisomeric phosphonates 3 of (partly-)racemic alcohols 1 by a phosphorus containing coupling reagent (eq. 1). High resolution of ^{31}P NMR signals and consequently accurate integration is obtained. The method is applicable to chiral alcohols with large variations in structures.

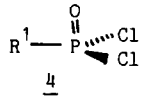
We describe here an extrapolation of this principle to alternative reagents for the e.e.-determination of chiral alcohols and their application for the e.e.-determination of chiral thiols.

eq. 1. $PCl_3 + 3RXH \longrightarrow P(XR)_3 \xrightarrow{HCl} HP(=X)(XR)_2 + RCl \qquad (X=O,S)$

1 2 3

For this latter goal we had to modify the coupling reagent because phosphothianates (3, X=S) are not obtained from thiols (1, X=S) analogously to eq. 1. Instead, alkyl-trithiophosphites (2, X=S) are formed. Furthermore (thio)phosphites (2, X=O,S) did not give well resolved ^{31}P NMR absorptions for the diastereoisomers.

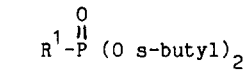
The modified reagents are alkylphosphonic dichlorides of general structure 4.[2]



4

To select the coupling reagent 4 (R^1=alkyl) that gives the best resolved ^{31}P NMR spectra we compared ^{31}P NMR data of the diastereoisomeric phosphonates (5) with different R^1-groups formed from 4 and racemic 2-butanol. The results are given in Table 1.

Table 1: ^{31}P NMR data for alkyl-O,O-di(s-butyl)phosphonates (5)[4]

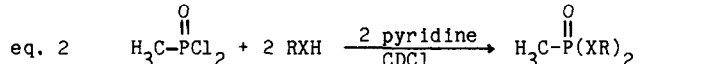


5

R^1	δ(meso)Hz	δ(meso)Hz	δ(d,l)Hz
H	389	455	427
CH_3	2285	2335	2311
C_2H_5	2527	2564	2546
C_3H_7	2422	2458	2440
C_4H_9	2457	2492	2475
$C_6H_5CH_2$	1969	2000	1985

Except for R=H, the largest shift differences are obtained with the smallest alkylgroup present in 5 (eq. R^1=CH_3). Therefore CH_3POCl_2 (6)[3] was tested as the reagent for the enantiomeric excess determination of several chiral alcohols and thiols (eq. 2). Reaction of 6 with 2 equiv. of alcohol or thiol in the presence of pyridine gave nearly quantitative yields of three diastereoisomeric phosphonates 7.

eq. 2



6 1 7 (X=O,S)

The ^{31}P NMR spectra of 7 show three well separated singlets in a ratio that is directly related to the enantiomeric excess of the alcohol or thiol RXH (1)[1] (see figure 1). The results of this technique with racemic alcohols and thiols[5] are summarized in Table 2.

As is clear from the results of entries 1-8 in Table 2, the meso:d,l ratios are in accord with those expected for racemic compounds. Entry 9 pertains to very nearly optically pure thioisovaleric acid. Experiments were also carried out with partially enriched thiols. The thiols shown in entries 6 and 8 (88 and 60% enantiomerically pure, respectively, as determined by optical rotation) were determined by the present method to have enantiomeric purities of 90 and 61% respectively. This is the first successful application of our technique for the e.e.-determination of chiral thiols.

Fig. 1: ^{31}P NMR spectrum of phosphonate 7 of racemic diethylthiomalate ($CDCl_3$)[4]

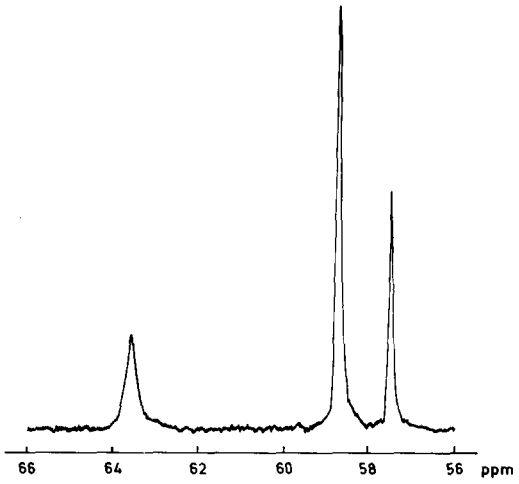
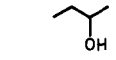
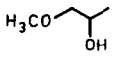
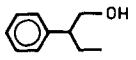
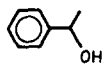
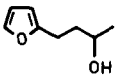
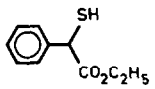
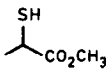
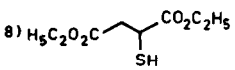
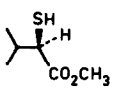


Table 2: ^{31}P NMR data for phosphonates 7 of racemic alcohols and thiols[4]

$H_3C-\overset{\overset{O}{\|}}{P}(XR)_2$

7

	RXH	δ(meso)Hz	δ(meso)Hz	δ(d,l)Hz	ratio meso; d,l[6]
1)		2285	2335	2311	49 : 51
2)		2335	2508	2425	52 : 48
3)		2442	2486	2465	49 : 51
4)		2320	2398	2355	49 : 51
5)		2284	2338	2316	51 : 49
6)		4641	4808	4736	49 : 51
7)		4660	4987	4725	49 : 51
8)		4660	5166	4760	49.5 : 50.5
9)		—	—	4728	⩽ 2 : 98[a]

a. obtained from enantiomerically pure S-2-bromo-isovaleric acid[5]

As is illustrated by the examples in Table 2 $MePOCl_2$ is a reasonable alternative to PCl_3 for e.e.-determinations of chiral alcohols. Both methods are complementary for alcohols with slightly larger shift differences when PCl_3 is used. $MePOCl_2$ is a solid and therefore more easily handled than PCl_3. Furthermore the coupling reaction is performed under basic conditions which might be an advantage with some acid sensitive alcohols. This reagent requires also only two equivalents of alcohol. A drawback of this reagent is the longer reaction time required for the phosphonate synthesis (eq. 2 vs. eq. 1) and the formation of byproducts. For these reasons we recommend $MePOCl_2$ as the reagent of choice for e.e.-determinations of chiral thiols and as an alternative to the prefered reagent PCl_3 for e.e.-determinations of chiral alcohols.

A typical experiment follows:
To a stirred solution of thiol (1 mmol) and pyridine (1 mmol)[8] in 1 ml $CDCl_3$ was added 0.5 mmol of 6 dissolved in 1 ml of $CDCl_3$. After stirring for 10 minutes the reaction mixture was transferred into a 10 mm NMR tube and the ^{31}P NMR spectrum recorded. For alcohols a similar procedure was followed with a reaction temperature of 0° and 16 hrs reaction time.

References

1. B.L. Feringa, A.A. Smaardijk and H. Wynberg, J. Am. Chem. Soc. (1985) **107**, 4798.
2. A.M. Kinnear and E.A. Perren, J. Chem. Soc. (1952), 3437.
3. K.L. Agarwal and F. Riftina, Nucl. Acid. Res. (1979) 6, 3009.
4. All spectra were recorded in $CDCl_3$ at 80.988 MHz on a Nicolet 200 NT spectrometer; chemical shift values are in Hz with 85% H_3PO_3 (δ 0.0 Hz) as an external standard.
5. Racemic thiols were prepared from the commercially available α-mercapto acids (entries 7, 8).
   Racemic ethyl-thiomandelate (entry 6) and (partially) enriched thiols (entries 6, 8, 9) were prepared from the corresponding alcohols or bromides by S_N2-reaction with cesium-thioacetate or cesium-thiobenzoate in DMF and subsequent hydrolysis: B. Strijtveen and R.M. Kellogg, manuscript in preparation.
6. For most of the examples studied the ratio of the two meso-compounds deviates from the statistically one to one ratio.
7. When chiral recognition (a deviation of the meso/d,l-ratio of 50:50) occurs in the phosphonate synthesis as was observed for racemic menthol, the described principles might be applicable under certain conditions.[1,9,10]
8. Excess of pyridine does not influence the e.e.-determination except for compounds sensitive to racemization under basic conditions. This was observed with the phosphonate derived from diethyl-thiomalate of e.e. = 60%.
9. J.P. Vigneron, M. Dhaenens and A. Horeau, Tetrahedron (1973) **29**, 1055.
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(Received in UK 20 December 1985)