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Simple Enantiomeric Excess Determination of Alcohols Using Chiral Selones and ^{77}Se NMR Spectroscopy.[1]

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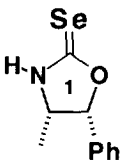
Abstract: Coupling of a chiral selone derivatizing agent to chiral and racemic alcohols mediated with triphosgene gives adducts in yields ranging from 78-100%. ^{77}Se NMR spectroscopy conveniently allows the determination of the enantiomeric excesses of the parent chiral alcohol.

The development of new nuclear magnetic resonance (NMR) spectroscopic methods and reagents for the convenient determination of enantiomeric excesses (ee's) and absolute configurations of chiral compounds has been of growing interest for some time.[2] We have been exploiting the extreme chemical shift sensitivity of the ^{77}Se nucleus for the detection and quantitation of chirality at remotely disposed chiral centers in carboxylic acids and acid chlorides.[3] In addition, these selenium-based chiral derivatizing agents (CDA's) have proven to be useful for the assignment of absolute configuration in several derivatized amino acids.[4]

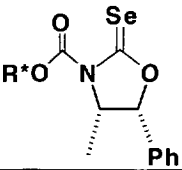
In an effort to increase the utility of these selone CDA's we have developed a one-pot triphosgene-mediated coupling of both chiral and racemic alcohols to selone CDA **1**.[5] Evaluation of the resulting adducts by ^{77}Se NMR spectroscopy has demonstrated that the outstanding chemical shift sensitivity of the selenium nucleus has been preserved in these systems (Table 1). Coupling the alcohol of choice to **1** is accomplished using a carbonyl bridge which is derived from triphosgene. We have reacted a series of alcohols with our CDA and have found that both 1° and 2° alcohols undergo the coupling reaction in high yield (Table 1). However, tertiary alcohols either do not react under the conditions studied or do so in low yield.



The ^{77}Se NMR analysis of these alcohol-based adducts indicates that the chemical shift sensitivity of the selenium nucleus found in our studies of carboxylic acids and acid chlorides has now been extended to these systems. Remarkably, for entry 1 (Table 1) the chiral center is 7 bonds removed from the observing selenium nucleus and the $\Delta\delta$ = 0.3 ppm! Other CDA's have been unable to detect this chiral center.[2] Moreover, acid sensitive functional groups tolerate the reaction conditions (Table 1; entries 7, 9). In general, these adducts gave a greater $\Delta\delta$ for the same bond distances when compared to the $\Delta\delta$ in carboxylic acid adducts.[3]

In summary, we have outlined a simple triphosgene mediated procedure for the formation of an adduct between 1° and 2° alcohols and **1**. From ^{77}Se NMR analysis of the adducts we, and others,[3g] are confident that oxazolidin-2-selones are a new class of sensitive CDA's. These new CDA's are likely to enjoy widespread use for detection and quantitation of remotely disposed chiral centers. We are currently investigating the use of **1**

Table 1. Coupling Data and ^{77}Se Chemical Shifts of (+,-) Alcohols with (4S,5R)-4-Methyl-5-Phenyl-Oxazolidin-2-Selone.



Entry	R*	δ ^{77}Se (ppm)[1]	# of Bonds[2]	Yields %
1	(R,S)-$CH_3(Ph)CHCH_2CH_2$-	497.5, 497.2	7	78
2	(R,S)-$CH_3(Ph)CHCH_2$-	496.3, 495.9	6	90
3	(R,S)-$CH_3CH_2(CH_3)CHCH_2$-	492.9, 492.8[3]	6	96
4	(S)-$CH_3CH_2(CH_3)CHCH_2$-	492.8	6	99
5	(R,S)-Menthol	492.8, 491.1	5	100
6	(S)-Menthol	492.8	5	98
7	(R,S)-Solketal[4]	504.3, 504.0	6	95
8	(R)-Solketal	504.3	6	95
9	(R,S)-$CH_2CH(CH_3)CH$-	494.6, 494.4	5	80

1) Selenium chemical shifts have been shown to be solvent, concentration, and temperature dependent.[3f] 2) Number of bonds from the observing selenium nucleus to the chiral center. 3) The selenium NMR exibited base line resolution. 4) Trade name for 2,2-dimethyl-1,3-dioxolane-4-methanol.

for detection and quantitation of chirality in amines and alkyl halides.

References and Notes

1. R & D 100 Award winner for 1993; Patent Nos. 5,122,472 and 5,344,936. We gratefully acknowledge partial financial support from the National Stable Isotopes Resource, NIH Division of Research Resources (RR 02231).

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5. A representative procedure is as follows. To a solution of triphosgene (0.034 g, 0.225 mmol) in CH_2Cl_2 (3.0 mL) was added pyridine (0.027 mL, 0.337 mmol) dropwise at 0°C. After 5 min, menthol (0.035 g, 0.225 mmol) was then added in one portion at 0°C. The mixture was warmed to room temperature and stirred for 2-3 h. To a solution of Selone **1** (0.081 g, 0.337 mmol) and triethylamine (0.093 mL, 0.674 mmol) was added dropwise the chloroformate solution at -78°C, and the resulting bright yellow solution was warmed to room temperature. The mixture was filtered through silica gel and concentrated. The residue was purified by flash chromatography (silica gel, CH_2Cl_2) to provide 0.095 g (100%) of the adduct. All compounds have been completely characterized by ^1H, ^{13}C, ^{77}Se, IR, and HRMS. Under the conditions studied, we have not observed kinetic resolution in the formation of the (R,S) alcohol adducts.

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