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SYNTHESIS OF ENANTIOPURE SUBSTITUTED 1,4-DIOXANES BY MICHAEL INITIATED RING CLOSURE REACTIONS

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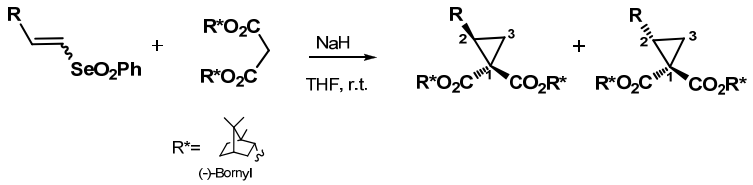
Abstract

Enantiomerically pure substituted 1,4-dioxanes have been prepared from vinyl phenyl selenones and the commercially available enantiopure 1,2-diols in the presence of sodium hydride. This simple and novel one step procedure is an example of the *Michael initiated ring closure reactions* (MIRC) and involves a conjugate addition of the alkoxide anions derived from the 1,2-diols to the vinyl phenyl selenones. The carbanions thus generated then suffer a proton transfer to give the alkoxide ions which effect the intramolecular displacement of the $PhSeO_2$ group affording the substituted 1,4-dioxanes as the result of a ring closure reaction.

Introduction

The great leaving ability of selenone group both in intermolecular[1] and in intramolecular[2] nucleophilic substitutions is well documented. On the contrary lower attention has been devoted to the use of vinyl selenones[3] in which the $PhSeO_2$ group activates the carbon-carbon double bond towards the addition of several nucleophilic reagents at β-carbon and at same time it can act as a good leaving group in the following cyclization reaction.

While a variety of sulfonium ylides were widely employed in the asymmetric MIRC[4] reactions the corresponding vinyl selenonium salt[5] or the vinyl selenones[6] were scarcely investigated. Some years ago it has been reported that oxetane derivatives can be prepared from 3-hydroxyvinyl selenones through the Michael addition of methanol and subsequent anion transfer to induce the intramolecular substitution of the $ArSeO_2$ group by the oxygen atom.[6a,b] Kuwajima[6c,d] et al and our group[6e] reported that the treatment of vinyl selenones with activated methylenic compounds in basic media leads to the formation of cyclopropanes via an addition-substitution reaction. Using this procedure we have recently effected the synthesis of cyclopropane derivatives employing the enolate ions of di-(-)-bornyl malonate as nucleophiles. (Scheme 1). A mixture of two diastereomeric cyclopropane derivatives was obtained but these could be easily separated by chromatography and the removal of the bornyl group gave highly enantiomerically enriched cyclopropanes.[7]



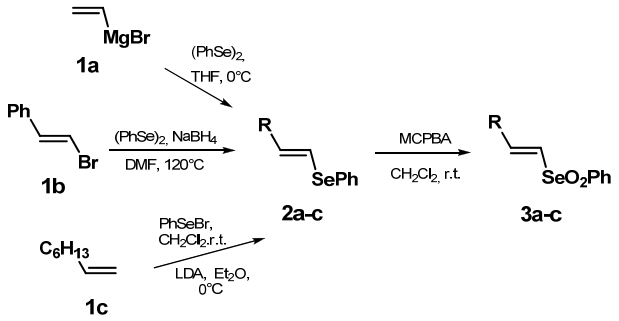
Scheme 1.

We now report an analogous *Michael initiated ring closure* reaction employing vinyl phenyl selenones and commercial enantiopure diols as chiral sources to prepare several isomeric 1,4-dioxanes in enantiomerically pure form. The synthesis of these compounds in an efficient and straightforward manner is not trivial. Very few methods are reported in the literature for the synthesis of these enantiomerically enriched heterocycles.[8] Aggarwald has recently reported an innovative and efficient method for the concise synthesis of six–membered rings like morpholine, thiomorpholine and piperazine from β-heteroatom amino compounds and vinyl sulfonium salt as Michael acceptors.[9] To the best of our knowledge no use of vinyl selenones as Michael acceptors for the synthesis of these important heterocycles has been reported to date.

Results and discussion

The vinyl phenyl selenones (**3a-c**) necessary for the present investigation were synthesized starting from the corresponding vinyl phenyl selenides (**2a-d**) using *m*-chloroperbenzoic acid (MCPBA) as oxidant in dichloromethane at room temperature. (Scheme 2, Table1). The vinyl phenyl selenide **2a** was synthesized starting from vinyl magnesium bromide **1a** and diphenyl diselenide according to the procedure described in the literature.[10] The phenyl vinyl phenyl

selenide **2b** was obtained according to the previously described vinylic substitution starting from the corresponding commercially available bromide **1b**.[11] The alkyl vinyl selenide **2c** was synthesized by the one pot Markovnikov addition of phenylselenyl bromide to the corresponding alkene **1c** followed by dehydrobromination with LDA.[12] (Scheme 2, Table 1).

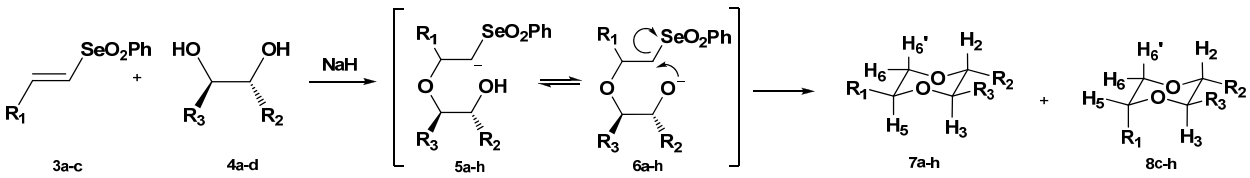


Scheme 2.

Entry	R	Selenide, 2	Yield (%)	Selenone, 3	Yield (%)
1a	H	**2a**	92	**3a**	86
1b	Ph	**2b**	94	**3b**	90
1c	C_6H_{13}	**2c**	78	**3c**	77

Table 1.

As indicated in Scheme 3, the MIRC reaction of the selenones **3a-c** with the commercially available enantiopure 1,2-diols **4a-d,** in the presence of sodium hydride is suggested to initially give the carbanions **5a-h** which then suffer a proton transfer to **6a-h**. The intramolecular displacement of the $PhSeO_2$ group by the oxygen anions affords the 1,4-dioxanes **7a-h**, **8c-h** (Scheme 3). The reaction conditions and the reaction yields are reported in Table **2**.

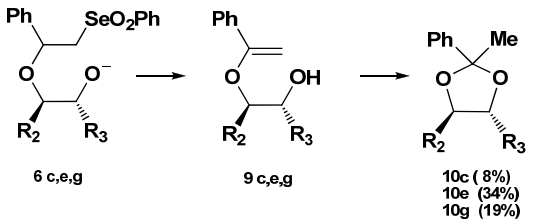


Scheme 3.

Entries	Selenones (*E*) 3a-c		Diols (*R*,*R*) 4a-d				1,4-Dioxanes 7a-h, 8c-8h			
		R_1		R_2	R_3	Reaction Conditions				
1	**3a**	H	**4a**	Ph	H	THF, 0°C, 1 day	**7a** (2*R*)	72		
2	**3a**	H	**4b**	Ph	Ph	THF, r.t., 5h	**7b** (2*R*,3*R*)	63		
3	**3b**	Ph	**4b**	Ph	Ph	THF, 0°C, 4 days	**7c** (2*R*,3*R*,5*S*)	26	**8c** (2*R*,3*R*,5*R*)	16
4	**3c**	C_6H_{13}	**4b**	Ph	Ph	THF, 0°C, 3 days	**7d** (2*R*,3*R*,5*S*)	17	**8d** (2*R*,3*R*,5*R*)	56
5	**3b**	Ph	**4c**	Me	Me	THF, 0°C, 5 days	**7e** (2*R*,3*R*,5*S*)	31	**8e** (2*R*,3*R*,5*R*)	17
6	**3c**	C_6H_{13}	**4c**	Me	Me	THF, 0°C, 6 days	**7f** (2*R*,3*R*,5*S*)	13	**8f** (2*R*,3*R*,5*R*)	34
7	**3b**	Ph	**4d**	$-(CH_2)_4-$		Toluene, r.t., 36h	**7g** (2*S*,4a*R*,8a*R*)	26	**8g** (2*R*,4a*R*,8a*R*)	47
8	**3c**	C_6H_{13}	**4d**	$-(CH_2)_4-$		THF, r.t., 5 days	**7h** (2*S*,4a*R*,8a*R*)	15	**8h** (2*R*,4a*R*,8a*R*)	40

Table 2

The configurations of the carbon atoms in the 2- and 3- positions were obviously unchanged in respect to those of the starting 1,2-diols **4a-d**. With the exception of compound **7b**, which presents a complex A_2B_2 nmr spectrum,[13] all the other 1,4-dioxanes **7a**, **7c-h** and **8c-h** presented proton nmr spectra which could be easily interpreted. The values of the vicinal coupling costants of the protons H_2 with the protons H_3, $J_{2,3}$, varies between 8.4 and 10.2 Hz, indicating that the R_2 and R_3 groups occupy an equatorial positions in the chair conformations as indicated in Scheme 3.
Starting from selenone **3a** (entries 1-2) compounds **7a** and **7b** were obtained in good yields and in enantiomerically pure form. Starting from selenones **3b** and **3c** a mixture of two diastereisomeric 1,4-dioxanes **7c-h, 8c-h** (entries 3-8) are formed. These compounds **7c-h, 8c-h** were obtained in good yields and in enantiomerically pure form after column chromatography. The absolute configurations of the newly generated stereogenic centers (at carbons C_5) were determined on the basis of the values of the vicinal coupling constants between the proton H_5 with the two protons in position 6. All the protons of compounds **7c-h, 8c-h** could be unambiguously assigned from the result of 2D spectra (H,H-Cosy and HSQC or HMQC spectra). In compounds **7c-h** the values of the vicinal coupling constants $J_{5,6'}$ and $J_{5,6}$ ranged from 10.3 and 11.2 Hz, and from 2.3and 2.5 Hz, respectively. These coupling costants clearly suggest that the R_1 groups occupy an equatorial positions assuming a chair conformation for the six-membered ring (Scheme 3). In compounds **8c-h** the values of the vicinal coupling constants $J_{5,6'}$ and $J_{5,6}$ varied from 0 and 1.2 Hz and from 3.2 and 3.7 Hz. The absence of large axial axial costants suggests that R_1 group occupies an axial position (Scheme 3).
In addition to the 1,4 dioxanes **7c,e,g** and **8c,e,g** in the cases of selenones **3b** (R_1= Ph, entries 3,5,7), the alkoxide ions **6c,e,g** also behave as bases [14] and give the alkenes **9c,e,g** which, on attempted purification by column chromatography on silica gel, were partially converted into the acetals **10c,e,g.**



Scheme 4

The enantiomeric purities of the 1,4-dioxanes **7a-e, 7g, 8c-d, 8g** were confirmed by HPLC analysis using the chiral column Chiralpak AD-H. In the case of compound **8e** the enantiomeric purity was instead determined by ^{1}H-NMR using (S)-(+)-2,2,2-trifluoro-1-(9-antryl)ethanol.

Conclusion

We have described a novel synthetic route to enantiomerically pure substituted 1,4-dioxanes starting from the commercially available enantiopure 1,2-diols and appropriately substituted vinyl phenyl selenones. This simple, one step procedure is very interesting also because it can find applications in the preparation of more complex dioxanes as chiral building blocks.[15] We are presently investigating possible modifications of this methodology in order to test its potential applications for the preparation of other biologically active molecules.

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