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# Chemistry of 3,4-Epoxy-2-methylene oxolanes: Highly Diastereoselective Electrophilic Additions.

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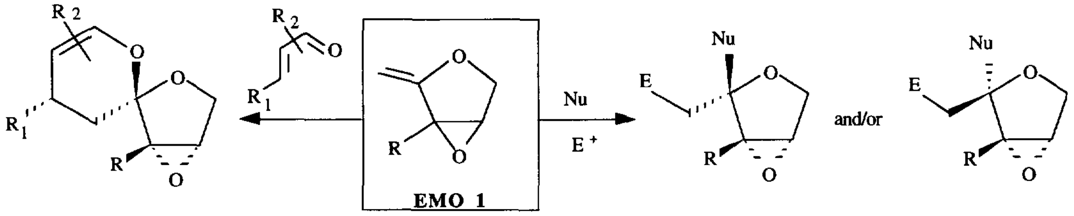
***Abstract:*** *electrophilic additions to the enol ether part of 3,4-epoxy-2-methylene oxolanes are described. The isomer resulting from an anti addition relative to the oxirane substituent was predominantly obtained. With phenylselenyl bromine as electrophile, a complete diastereoselectivity was achieved, again in favor of the trans isomer.*

Highly oxygenated heterocycles are widely distributed motifs among natural products. With such synthetic applications in mind, we recently reported on a mild and convenient access to oxygenated heterocycles via silver catalyzed cyclization of the appropriate acetylenic alcohols[3-4] or acids.[5, 6] Particulary interesting members of this family of sensitive heterocycles are the 3,4-epoxy-2-methylene oxolanes (EMO, Scheme 1, **1**). In these previously unknown compounds, the oxirane ring adjacent to the very reactive exocyclic enol ether function might offer a stereochemical bias during reaction at the enol ether part. We already demonstrated that during Diels-Alder type reactions the oxirane substituent behave as an effective inducer since a single diastereoisomer was obtained (Scheme 1, left side).[6-7] In this communication, we reported on an other aspect of the reactivity of 3,4-epoxy-2-methylene oxolanes, the selective electrophilic addition to the enol ether part of 3,4-epoxy-2-methylene oxolanes (Scheme 1, right side). Obviously, control of diastereoselectivity was our main objective since it is a prerequisite for any synthetic developments.



Scheme 1

Electrophilic addition to enol ethers is a well known reaction,[8] the most important and recent developments of which are in carbohydrate chemistry. In this field, this reaction is mainly used as a glycosylation method since it allows the introduction of nucleophilic alcohols to glycals.[9] We therefore started to investigate electrophilic additions to 3,4-epoxy-2-methylene oxolanes **1** using alcohols as nucleophiles. Since the diastereoselectivity of cycloadditions with 3,4-epoxy-2-methylene oxolanes **1** was unaffected by the presence of a substituent adjacent to the exocyclic double bond[6-7] (Scheme 1, left side, R = H, Me), 3,4-epoxy-3-methyl-2-methylene oxolane **1b**

(R = Me), one of the most conveniently available member of the serie, was first studied. In order to determine suitable conditions with which electrophilic additions could occur without extensive degradation of the sensitive starting material, **1b** was summitted in solvents of different polarities to various alcohols in the presence of NIS (Table 1). Allyl alcohol was selected as nucleophile for convenience in the structure determination of the adducts, the double bond acting as a marker in the NMR spectra.

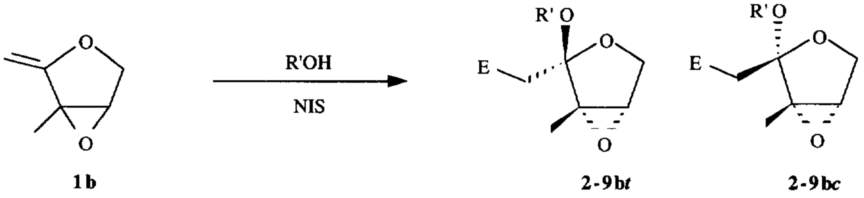


Table 1: Electrophilic additions of various alcohols to 3,4-epoxy-2-methylene oxolane **1b**

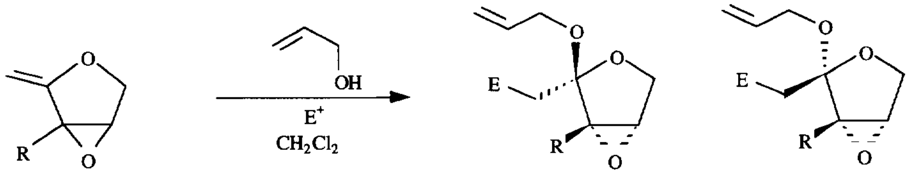
| Entry | Nucleophile | Solvent | Time | Yield[a] | Product diastereoselectivity[b] | | |
|---|---|---|---|---|---|---|---|
| 1 | allyl alcohol | PhH | 1h | 76% | **2bc** [c] | 90-10 | **2b*t*** [c] |
| 2 | allyl alcohol | THF | 7h | 48% | **2bc** | 90-10 | **2b*t*** |
| 3 | allyl alcohol | MeCN | 7h | 38% | **2bc** | 90-10 | **2b*t*** |
| 4 | allyl alcohol | $CH_2Cl_2$ | 5mn | 79% | **2bc** | 90-10 | **2b*t*** |
| 5 | methyl alcohol | $CH_2Cl_2$ | 5mn | 71% | **3*c*** | 90-10 | **3*t*** |
| 6 | propargyl alcohol | $CH_2Cl_2$ | 5mn | 78% | **4*c*** | 90-10 | **4*t*** |
| 7 | homoallyl alcohol | $CH_2Cl_2$ | 5mn | 86% | **5*c*** | 90-10 | **5*t*** |
| 8 | homopropargyl alcohol | $CH_2Cl_2$ | 5mn | 86% | **6*c*** | 91-9 | **6*t*** |
| 9 | pentenyl alcohol | $CH_2Cl_2$ | 5mn | 76% | **7*c*** | 90-10 | **7*t*** |
| 10 | isopropyl alcohol | $CH_2Cl_2$ | 35mn | 89% | **8*c*** | 87-13 | **8*t*** |
| 11 | terbutyl alcohol | $CH_2Cl_2$ | 55mn | 67% | **9*c*** | 81-19 | **9*t*** |

a) yields of isolated products; b) ratio determined by $^1H$ NMR on the crude mixture ; c) the subscripts *t* or *c* refer to the relative stereochemistry of the oxygenated substituents in the product (*trans* or *cis* respectively).

In non-polar solvent such as benzene, the electrophilic addition occured readily and gave the expected diastereoisomeric adducts **2b*t*** and **2bc** in good yield (Table 1, entry 1). Each diastereoisomer was readily separable by chromatography, and NMR studies[10] revealed that the major diastereoisomer resulted from an alcohol addition *anti* relative to the oxirane group. Polar solvents dramatically slowed down the reaction (Table 1, entries 2-3 vs 1) and lowered the yield. Nevertheless, the diastereoisomeric ratio was unchanged. Methylene chloride proved to be a perfect solvent in which electrophiles reacted cleanly and rapidly with 2-methylene oxolane (Table 1, entry 4 vs 1-3).

The diastereoselectivity was almost insensitive to the nature of the nucleophilic alcohol (Table 1, entries 4-10). Only a slight decrease of selectivity was observed when going from primary alcohols (Table 1, entries 4-9) to secondary (entry 10) and tertiary alcohol (entry 11). Even with the hindered *tert*-butanol, the *trans* adduct was still the predominant isomer (entry 11).

Since neither the nucleophile nor the reaction conditions could improve the diastereoselectivity of this electrophilic addition, the influence of the nature of both the electrophilic reagent and the epoxide substituent of 2-methylene oxolanes was then investigated (Table 2). The lack of substituent (R = H vs R = Me) in the vicinity of the enol ether function significantly decreased the relative amount of the *trans* diastereoisomer (entries 1 vs 6, 2 vs 7 and 3 vs 8). In contrast, the presence of a bulky group (R = $SiMe_3$) increase the ratio in favor of the *trans* isomer (entries 6 vs 9 and 7 vs 10). More interestingly, the diastereoselectivity proved also to be highly dependent on the nature of the electrophile. With **1b** as substrate, N-halogenosuccinimide reagents (NCS, NBS, NIS) gave basically the same diastereoisomeric ratio with the *trans* diastereoisomer as the major product (entries 4-6). The use of more complex electrophiles clearly improved this ratio, again in favor of the *trans* isomer (entries 2-3 vs



**1a-c** **2a-ct** **10-12a-ct** **2a-cc** **10-12a-cc**

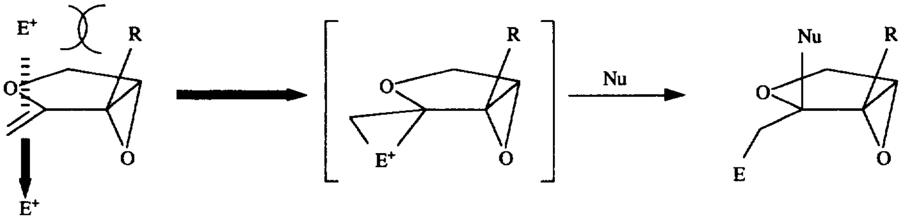
Table 2: Electrophilic additions of allylic alcohol to 3,4-epoxy-2-methylene oxolanes in the presence of various electrophiles

| Entry | Substrate | | Electrophile | Yield[a] | Product diastereoselectivity[b] | | |
|---|---|---|---|---|---|---|---|
| 1 | **1a** | R = H | NIS | 79% | **2a*t***[c] | 66-34 | **2a*c***[c] |
| 2 | | " | $I(coll)_2ClO_4$ | 76% | **2a*t*** | 88-12 | **2a*c*** |
| 3 | | " | PhSeBr | 74% | **10a*t*** | 94-6 | **10a*c*** |
| 4 | **1b** | R = Me | NCS | 50% | **11*t*** | 88-12 | **11*c*** |
| 5 | | " | NBS | 50% | **12*t*** | 88-12 | **12*c*** |
| 6 | | " | NIS | 79% | **2b*t*** | 90-10 | **2b*c*** |
| 7 | | " | $I(coll)_2ClO_4$ | 74% | **2b*t*** | 97-3 | **2b*c*** |
| 8 | | " | PhSeBr | 94% | **10b*t*** | 100-0 | **10b*c*** |
| 9 | **1c** | R = $SiMe_3$ | NIS | 79% | **2c*t*** | 95-5 | **2c*c*** |
| 10 | | " | $I(coll)_2ClO_4$ | 74% | **2c*t*** | 100-0 | **2c*c*** |

a) yields of isolated products; b) ratio determined by $^1H$ NMR on the crude mixture; c) the subscripts a, b or c refer to the nature of the R group (Me, H or TMS respectively) and the subscripts *t* or *c* to the relative stereochemistry of the oxygenated substituents in the product (*trans* or *cis* respectively).

1, 7-8 vs 6 and 10 vs 9). With phenylselenyl bromine as reagent, a complete diastereofacial differentiation was achieved since a single diastereoisomer could be detected (entry 8, 10).

The role on the diastereoface differentiation played by the nature of the R group and of the electrophilic reagent might reflect the importance of some steric hindrance around the reactive site.[11] Indeed, the fact that larger electrophilic reagents (I(coll)$_2$ClO$_4$, PhSeCl) increased the diastereoselection might account for steric interactions in the transition state. As a result, the reagent would predominantly approach the π-system from the less crowded face (*anti* to the R group, *syn* to the oxirane substituent) and therefore nucleophilic attack on the so-formed transient species[12] would occur on the opposite face giving rise to the *trans* isomer (Scheme 2). However electronic effects can not be ruled out.[13]



Scheme 2

Although a complete diastereoface differentiation has been achieved using phenylselenyl bromine as electrophile, further works are now in progress in order to get a better understanding of the factors involved in the asymmetric induction described here.

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## References and notes:

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