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On the Stereoselectivity of Alkenoxyl Radical 6-*exo-trig* Cyclizations

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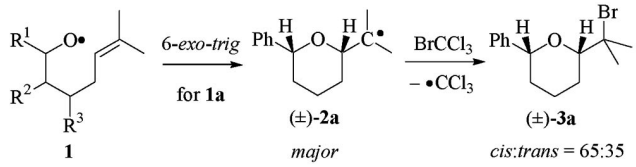
The investigated set of 6-exo-*trig* cyclizations occurs irreversibly and justifies the use of tetrahydropyran-derived transition structures for rationalizing 2,6-*cis*, 2,5-*trans*, and 2,4-*cis* stereoselectivity in ring-closure reactions of 1-, 2-, and 3-phenyl-6-methyl-5-hepten-1-oxyl radicals.

Introduction

Substituents that increase π-nucleophilicity of olefinic double bonds facilitate 6-*exo-trig* cyclizations of 5-hexen-1-oxyl radicals (e.g. **1a**→**2a**, Scheme 1) at the expense of an otherwise significantly interfering 1,5-H-atom transfer.[1–5] Among the discoveries that followed this perception, diastereoselectivity in the 6-methyl-1-phenylhept-5-en-1-oxyl radical cyclization **1a**→**2a** probably was most important (Scheme 1).[1] From data available in 2004, the origin of the 2,6-*cis* selectivity, however, remained unclear. From a book chapter summarizing state of the art heptenyl and related radical cyclizations it became obvious that selectivity in carbon radical 6-*exo-trig* cyclizations still is explained on a phenomenological basis using adapted stereochemical conventions.[6] The applied models, however, are neither based on physical organic investigations nor on computational analysis. In view of this unsatisfactory theoretical background and the necessity to obtain clear cut information on principles that guide diastereoselection in the synthesis of 2,5- and 2,4-disubstituted tetrahydropyrans via 6-*exo-trig* alkenoxyl radical reactions in an ongoing project, an independent investigation on this subject was devised. The major results from this study clarify that the explored type of 6-*exo-trig* reaction occurs irreversibly. This finding suggests that 2,6-*cis*, 2,5-*trans*, and 2,4-*cis* selectivity in cyclizations of 1-, 2-, and 3-phenyl-6-methyl-5-hepten-1-oxyl radicals orginates from kinetically controlled reactions, justifying the use of transition structures for rationalizing stereoselectivity in this chemistry.



R^1	R^2	R^3	1
Ph	H	H	**1a**
H	Ph	H	**1b**
H	H	Ph	**1c**

Scheme 1. Structural formulae and indexing of phenyl-substituted 6-methylhept-5-en-1-oxyl radicals **1a**–**c**, and stereoselective synthesis of tetrahydropyran **3a** via alkenoxyl radical 6-*exo-trig* cyclization **1a** → **2a** in the presence of $BrCCl_3$ (T = 80 °C).[1]

Results and Discussion

Generation of alkenoxyl radicals for the pursuit of stereoselectivity in alkenoxyl radical 6-*exo-trig* cyclizations was achieved under pH neutral non oxidative conditions in thermally induced transformations starting from *N*-alkoxy-4-methyl-5-(*p*-methoxyphenyl)thiazole-2(3*H*)-thiones **4b**–**c** (Scheme 2).[7] $BrCCl_3$ preferentially served as mediator, as the site of bromination corresponds to the position of carbon radical intermediates formed in the alkenoxyl radical reaction of interest.[8] Required radical precursors **4b**–**c** were prepared from *N*-hydroxy-4-methyl-5-(*p*-methoxyphenyl)thiazole-2(3*H*)-thione tetraethylammonium salt[9,10] (not shown) and appropriate alkenyl tosylates in 61% (for **4b**) and 78% (for **4c**) yield, by adapting established procedures (see the Supporting Information). Compounds **4b**–**c** were obtained as yellowish crystalline solids that were stored in amber-colored flasks.

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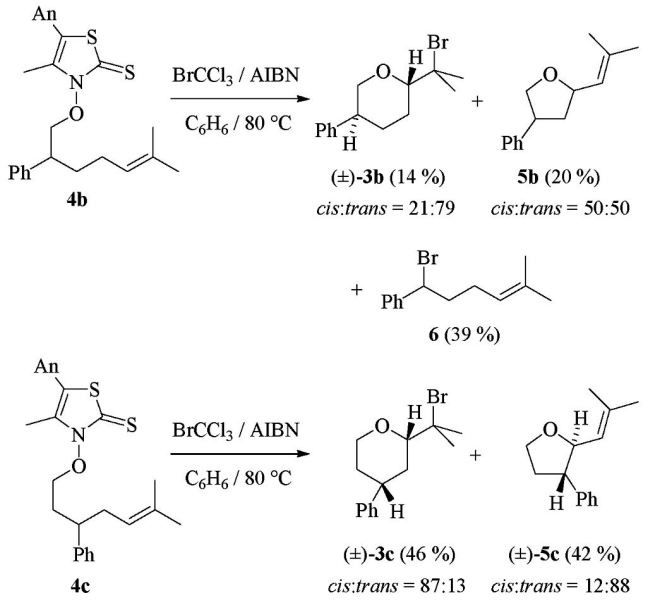
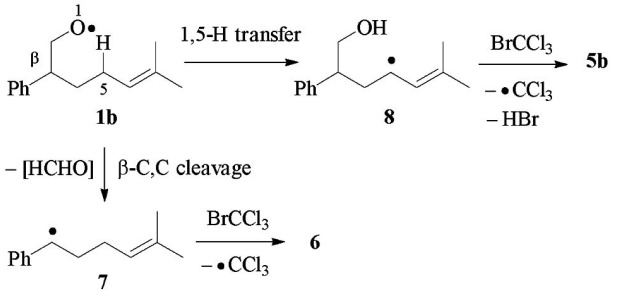


Scheme 2. Thermally induced transformation of *N*-(6-methylhept-5-en-1-oxy)thiazolethiones **4b**–**c** in the presence of $BrCCl_3$ and AIBN (An = *p*-$MeOC_6H_4$).

Treatment of *N*-(6-methyl-2-phenylhept-5-en-1-oxy)thiazolethione **4b** (c_0 = 0.08 M) in a solution of $BrCCl_3$ (c_0 = 0.8 M) and C_6H_6 with small portions of AIBN until complete consumption of the starting material had occurred (ca. 2–3 h), furnished after chromatographic work up of the reaction mixture 5-phenyl-2-(2-bromoprop-2-yl)tetrahydropyran (**3b**) (14%, *cis*/*trans* = 21:79), 2-(2-methylprop-1-enyl)-4-phenyltetrahydrofuran (**5b**) (20%, *cis*/*trans* = 50:50), and 6-bromo-2-methyl-6-phenylhex-2-ene (**6**) (39%) (Scheme 2). This material accounted for a mass balance of 73%. Stereochemical analysis of tetrahydropyran **3b** was performed on the basis of one- and two-dimensional NMR-techniques (^1H NMR, ^{13}C NMR, NOESY, HMQC). The low yield of 6-*exo*-*trig* cyclization product **3b** was explicable by including bromoalkene **6** into mechanistic interpretation (Scheme 3). Formation of the latter compound in notable yield points to efficient β-C,C-bond cleavage in the 6-methyl-2-phenylhept-5-en-1-oxyl radical (**1b**) and liberation of stabilized secondary benzylic radical **7**. Trapping of carbon radical **7** with $BrCCl_3$ would explain the formation of bromoolefin **6** from thiazolethione **4b** on the basis of a well established oxygen radical reaction.[11,12] Formation of tetrahydrofuran **5b** is explicable in a multistep sequence starting with 1,5-H-atom transfer **1b**→**8**, Br atom trapping of allylic radical **8** and intramolecular cycloetherification via HBr elimination (Scheme 3).

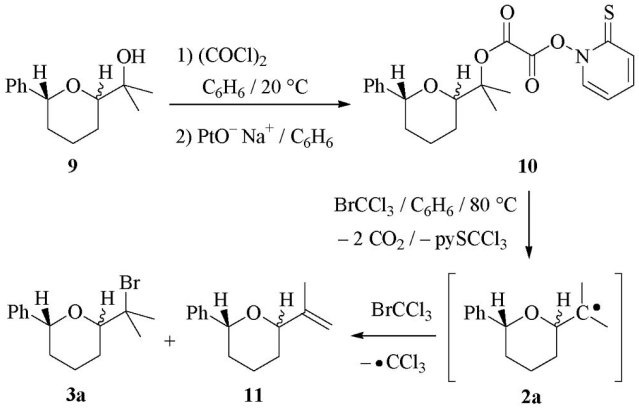
Conversion of *N*-(6-methyl-3-phenyl-5-heptenoxy)thiazolethione **4c** (c_0 = 0.08 M) in benzene solution containing 0.8 M $BrCCl_3$ at 80 °C furnished 46% of 4-phenyl-2-(2-bromoprop-2-yl)tetrahydropyran (**3c**) (*cis*/*trans* = 87:13) and 42% of 2-(2-methylprop-1-enyl)-3-phenyltetrahydrofuran (**5c**) (*cis*/*trans* = 12:88) (^1H NMR, reaction in C_6D_6, anisole as internal standard; 88% mass balance). Purification of the reaction mixture via column chromatography was paralleled by a minor loss of products thus providing 39% of analytically pure **3c** (*cis*/*trans* = 79:21) and 25% of **5c** (*cis*/*trans* < 5:95, ^1H NMR). Stereochemical analysis of tetrahydropyran **3c** was performed in extension to the strategy outlined for isomer **3b**.



Scheme 3. Mechanistic interpretation of 6-methyl-2-phenylhept-5-en-1-oxyl radical reactions other than 6-*exo*-*trig* ring closure (formation of formaldehyde was not verified).

The origin of diastereoselectivity in alkenoxyl radical 6-*exo*-*trig* reactions was clarified in a stereochemical analysis. A reversible ring closure would imply that a notable fraction of cyclized radical **2a** would undergo β-cleavage to yield alkenoxyl radical **1a**. As a result, the isomeric ratio of independently generated stereochemically homogeneous intermediates *cis*-**2a** and *trans*-**2a** should change (thermodynamic control). If configuration of intermediates *cis*-**2a** and *trans*-**2a** were retained over a time span that exceeded their life-times in comparison to that from synthesis of **3a** by 1–2 orders of magnitude, cyclization **1a**→**2a** had to be classified as irreversible process under such conditions.

The question posed above was experimentally addressed as follows. Diastereomerically pure tertiary alcohols *cis*-**9** (*cis*/*trans* > 99:1) and *trans*-**9** (*cis*/*trans* < 1:99)[13] (GC) were prepared and treated with an excess of oxalyl chloride. This step furnished alkyl chlorosemioxalates (not shown), which were converted with *N*-(hydroxy)pyridine-2(1*H*)-thione sodium salt ($PtO^- Na^+$) into mixed oxalates *cis*-**10** and *trans*-**10**, respectively (Scheme 4). Thermally-induced



Scheme 4. Generation of (tetrahydropyran-2-yl)prop-2-yl radicals **2a** from tertiary alcohols *cis*/*trans*-**9** [for stereochemical analysis see text and Table 1; py = pyridin-2-yl; $PtO^- Na^+$ = *N*-hydroxypyridine-2(1*H*)-thione sodium salt].

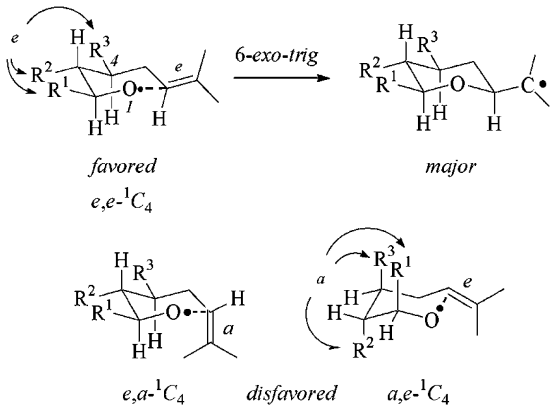
Table 1. Formation of tetrahydropyrans **3a** and **11** from (tetrahydropyran-2-yl)-2-propanols **9**.

Entry	(±)-**9**/M	$BrCCl_3$/M	Conversion[a]	(±)-**3a**/% (*cis*/*trans* ratio)[b]	(±)-**11**/% (*cis*/*trans* ratio)[b]
1	*cis*-**9**/8.3×10^{-3}	8.3×10^{-2}	87 %	58 (> 99:1)	7 (> 99:1)
2	*cis*-**9**/8.3×10^{-4}	8.3×10^{-3}	49 %	34 (> 99:1)	8 (> 99:1)
3	*trans*-**9**/8.3×10^{-3}	8.3×10^{-2}	77 %	27 (< 1:99)	12 (< 1:99)
4	*trans*-**9**/8.3×10^{-4}	8.3×10^{-3}	75 %	13 (< 1:99)	8 (< 1:99)

[a] Referenced vs. unreacted alcohol **9**. [b] Stereochemical analysis was performed via GC of crude reaction mixtures using authentic samples as reference, ^{1}H NMR, and NOESY investigations of purified products.

decomposition of mixed oxalates **10** ($c_0 = 8\times10^{-3}$ to 8×10^{-4} M) afforded derived tertiary carbon radicals,[14,15] i.e. *cis*-**2a** (from *cis*-**10**) and *trans*-**2a** (from *trans*-**10**). Radicals *cis*-**2a** and *trans*-**2a**, respectively, were trapped with an at least 10-fold excess of $BrCCl_3$ ($c_0 = 8\times10^{-2}$ to 8×10^{-3} M). The former reaction afforded *cis*-**3a** (*cis*/*trans* > 99:1), olefin *cis*-**11**, and minor amounts of unreacted alcohol *cis*-**9**, starting from *cis*-**9** (Table 1, entries 1–2). In a similar manner *trans*-**3a** (*cis*/*trans* < 1:99), olefin *trans*-**11**, and unspent substrate *trans*-**9** were obtained, if *trans*-**9** served as starting material (Table 1, entries 3–4). 6-Methyl-1-phenylhept-5-en-1-ol and/or 6-methyl-1-phenylhept-5-en-1-one were detected (GC) in neither of the runs.

According to results from stereochemical analysis, ring opening reactions *cis*-**2a**→**1a** and *trans*-**2a**→**1a** were not relevant under selected conditions. This argumentation is based on the stereochemical integrity within both tetrahydropyran series (*cis* and *trans* isomers). Observed diastereoselectivities of product **3a**, and presumably also of derivatives **3b**–**c**, thus originated from kinetically controlled reactions. Since 5-hexen-1-oxyl radicals are neutral intermediates, their chains are expected to fold upon an approach of reacting entities in a chair-like manner, for minimizing strain and steric repulsion. The underlying transition structure that is formed in this scenario is expected to resemble a distorted $^1C_4$-conformation of tetrahydropyran having one



Scheme 5. Transition structure-based stereochemical model for predicting major product formation in 6-*exo*-*trig* cyclizations of substituted 5-hexen-1-oxyl radicals **1a**–**c** [$^1C_4$ denotes the chair conformation of distorted tetrahydropyran, with atoms 1 (O) and 4 (C) offset in opposite direction from the tetrahydropyran plane; letters printed in italics refer to positioning of substituent R^1–R^3 = H or Ph (first descriptor) and isopropylidene substituent (second descriptor)].

notably stretched (ca. 2.1 Å)[16] C,O-bond, similar to the scenario outlined in the heuristic chair-E model[6] for carbon radical 6-*exo*-*trig* cyclizations. Sterically demanding phenyl groups are considered to preferentially adopt sites that are similar to equatorial positions in tetrahydropyran. In extension to results from a theoretical treatment of the 4-penten-1-oxyl radical ring closure[16] it is furthermore expected that the isopropylidene entity resides in a location, where it experiences least severe synclinal interactions, i.e. equatorial-like, in order to adhere with the tetrahydropyran notation (Scheme 5). A gradual decrease in stereodirecting effect as the distance between reacting entities increases (**1a** > **1b** > **1c**), and estimated $\Delta\Delta G^{\ddagger}$ values of 1.8–5.6 kJ mol^{-1} (ca. 80 °C) for stereodifferentiating processes are in accord with this interpretation.[16]

Concluding Remarks

The use of transition structures as mnemonic device for interpreting and predicting stereoselecitivity in the investigated type of alkenoxyl radical 6-*exo*-*trig* cyclization is expected to serve as impetus for application of the method in stereoselective synthesis, possibly by increasing efficiency of tetrahydropyran synthesis using polar substituents other than CH_3 attached to the terminal position of the vinyl entity. From what is known in 4-penten-1-oxyl radical chemistry it is expected that substitution at this site will change rates but not facial selectivity of intramolecular alkoxyl radical additions.[17,18] The motivation for pursuing this chemistry originates from unique selectivity of 5-hexen-1-oxyl radicals. Ionic bromocyclizations of ω,ω-dimethyl-substituted hex-5-en-1-ols (not shown), for example, will not prefer the 6-*exo*-mode of ring closure.[19,20]

Supporting Information (see also the footnote on the first page of this article): Experimental procedures, characterization data of compounds **3**–**6**.

Acknowledgments

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