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Tetrahedron Letters 45 (2004) 5619–5621
Tetrahedron Letters

On the 6-*exo-trig* ring closure of substituted 5-hexen-1-oxyl radicals

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Received 26 March 2004; revised 21 May 2004; accepted 26 May 2004
Available online 15 June 2004

Abstract—Substituted 5-hexen-1-oxyl radicals have been generated from *N*-(5-hexen-1-oxy)-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thiones under tin-free conditions and have been successfully applied as reactive intermediates in a mechanistic study on the formation of bromomethyl-substituted tetrahydropyrans via 6-*exo-trig* selective cyclizations.

The synthesis of tetrahydropyrans via cyclization of 5-hexen-1-oxyl radicals is a challenge because the 6-*exo-trig* mode of ring closure can, in most instances, not compete with other alkoxyl radical consuming processes, such as the homolytic substitution (e.g., δ-hydrogen atom transfer) or the β-fragmentation.[1,2] Reports in the literature on 6-*exo-trig* cyclizations of oxygen-centered radicals therefore are restricted to transformations of intermediates that lack in abstractable δ-hydrogen atoms,[3] or favor the intramolecular addition on the basis of conformational effects.[4] On the other hand, the pursuit of alkoxyl radical-based diastereoselective 5-*exo-trig* cyclizations continues to receive attention, for example, in the field of natural product synthesis.[5] This method provides, for example, regioselectivities that are not attainable using traditional electrophile-induced ring closure reactions of the corresponding alkenols.[6–8] In view of this mechanistic and synthetic background it was the aim of the present study to investigate 6-*exo-trig* cyclizations of 5-hexen-1-oxyl radicals by improving the efficiency of the *O*-radical addition step using the rate enhancing effect of a C_6H_5 group or two CH_3 substituents located at the terminal position of an olefinic π-bond.[9]

Pale yellow crystalline alkoxyl radical precursors **1** were prepared in extension to a literature procedure, starting from *N*-(hydroxy)-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione tetraethylammonium salt and the corresponding 5-hexen-1-yl tosylates in 63% (**1a**), 78% (**1b**), 69% yield (**1c**), or from a derived alkenyl chloride in 74% yield (**1d**).[10,†]

The reaction between *N*-(5-hexen-1-oxy)thiazolethione **1a** and $BrCCl_3$ in the presence of AIBN at 80 °C afforded 6-bromo-4-hexen-1-ol (**2**) [57%, (*E*):(*Z*) = 74:26], 4-bromo-5-hexen-1-ol (**3**) (8%), 2-(vinyl)tetrahydrofuran (**4a**) (8%), and 2-(bromomethyl)tetrahydropyran (**5a**) (7%, Scheme 1). The latter product was unambiguously identified by GC–MS using an authentic sample as reference. The sequence outlined in Scheme 1 thus provides the first experimental evidence for the fact that formation of 6-*exo-trig*-cyclized intermediate **7a** starting from 5-hexenoxyl radical **6a** is feasible under such conditions. The relative yields of products **2**, **3** and **4a**, **5a**, however, indicate that the δ-hydrogen atom transfer **6a** → **8a** constitutes the major reaction channel for intermediate **6a**.[11] The latter reaction furnishes allylic radical **8a**, which is trapped by $BrCCl_3$ for thermochemical reasons preferentially from the terminal position to furnish internal olefin **2** as major product [65%, (*E*):(*Z*) = 74:26].[12] The synthesis of 2-(vinyl)tetrahydrofuran (**4a**)—a product that is already present in the crude reaction mixture (^{1}H NMR)—may be associated with HBr elimination from allylic bromide **3**, which in turn formed as minor product from the bromine atom trapping of allylic radical **8a**. It should, however, be noted that an alternative route for the formation of

Keywords: Alkoxyl radical; Cyclization; Bromine atom transfer; Tetrahydropyran; Thiazolethione.
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† Satisfactory analytical data were obtained for all new compounds prepared in this study.

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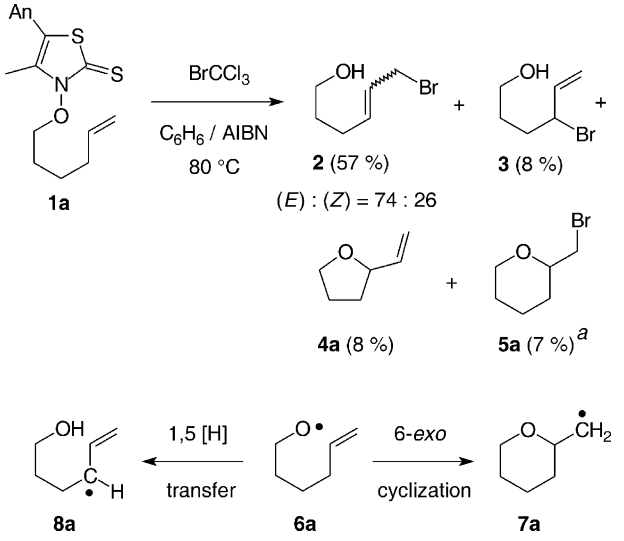
doi:10.1016/j.tetlet.2004.05.131

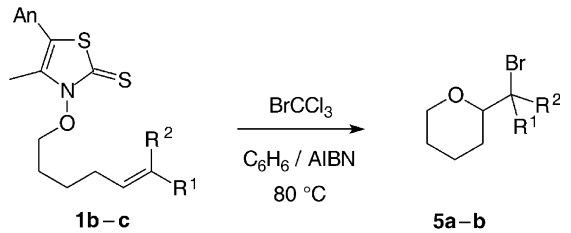


Scheme 1. Product formation from *N*-(5-hexen-1-oxy)thiazolethione **1a** and $BrCCl_3$ (top) and an illustration of underlying alkoxyl radical reaction mechanisms (bottom). An = *p*-$H_3COC_6H_4$. [a]GC–MS analysis.

2-substituted oxolane **4a**, that is a S_N2'-type transformation of 1,6-bromohydrin **2**, cannot not be excluded at the moment.

Treatment of *N*-(6-phenyl-5-hexen-1-oxy)thiazolethione **1b** with $BrCCl_3$ and AIBN in hot C_6H_6 (80 °C, Table 1, entry 1) afforded, after purification of the crude material by chromatography, 31% of 2-(1-bromo-1-benzyl)tetrahydropyran (**5b**) and a number of labile products that could not be purified to homogeneity and therefore remained unidentified. The reaction between *N*-(6-methyl-5-hepten-1-oxy)thiazolethione **1c** and $BrCCl_3$ was conducted under conditions that were established for derivative **1b**, to afford 39% of 2-(1-bromo-1-methylethyl)tetrahydropyran (**5c**) as only detectable alkoxyl radical product (Table 1, entry 2). On the basis of the assumption that the rate constant of δ-hydrogen atom transfer in all 5-hexenoxyl radicals **6** that have been applied in the present study is similar, an improved efficiency for tetrahydropyran formation from thiones **1b** and **1c** may be correlated with an increased rate constant for the intramolecular addition of the electrophilic *O*-radical.[13] This interpretation agrees with results from a kinetic study, which indicated that the relative rate constants of 5-*exo-trig* cyclizations of terminally unsubstituted 4-penten-1-oxyl radicals are by a factor of 10–15 smaller than those of the corresponding ω,ω-dimethyl-substituted derivatives.[9]

Table 1. Synthesis of β-brominated tetrahydropyrans from *N*-(5-hexen-1-oxy)thiazolethiones **1b** and **1c** and $BrCCl_3$ (An = *p*-$H_3COC_6H_4$)

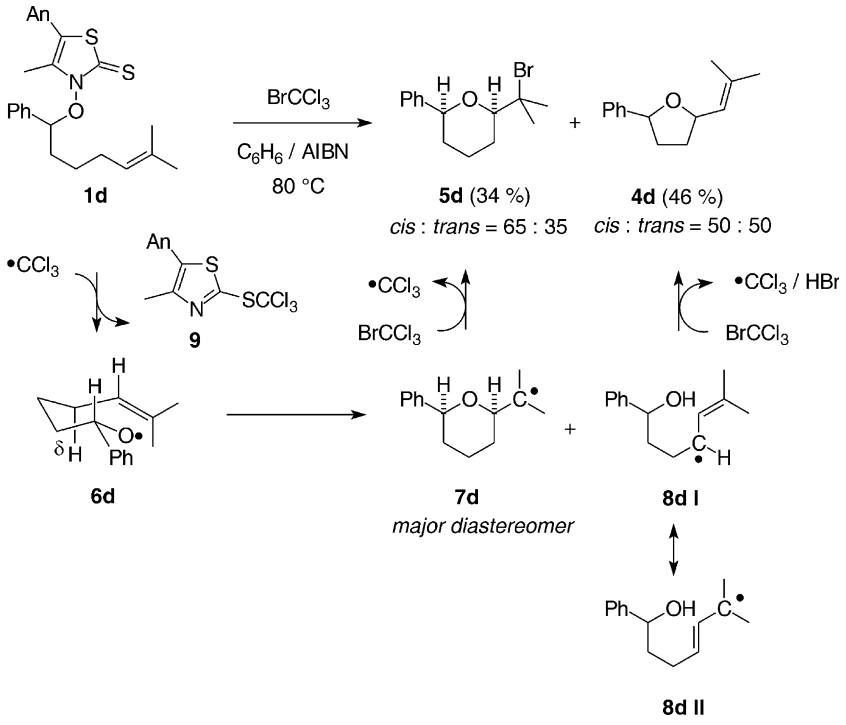


Entry	**1**	R^1	R^2	**5**	Yield [%]
1	**1b**	C_6H_5	H	**5b**	31
2	**1c**	CH_3	CH_3	**5c**	39

In a fourth experiment, *N*-(1-phenyl-6-methyl-5-hepten-1-oxy)thiazolethione **1d** and $BrCCl_3$ were treated with AIBN (C_6H_6, 80 °C) to provide 34% of 2-(1-bromo-1-methylethyl)-6-phenyl tetrahydropyran (**5d**) (*cis*:*trans* = 65:35)[‡] and 46% of 2-phenyl-5-(dimethylvinyl)tetrahydrofuran (**4d**) (*cis*:*trans* = 50:50) on a preparative scale. The relative configuration of 2,6-substituted tetrahydropyrans *cis*-**5d** and *trans*-**5d**, which originated from the 6-*exo-trig* cyclization of 5-hexen-1-oxyl radical **6d** and subsequent bromine atom trapping of intermediate **7d**, has been derived from results of NOESY experiments. According to a proposed model for an explanation of the observed diastereoselectivity, the 6-*exo-trig* cyclization **6d** → **7d** proceeds via an energetically favored transition state similar to the arrangement that has been outlined for alkenoxyl radical **6d** in Scheme 2.[14] This interpretation is based on a kinetic control of the 6-*exo-trig* cyclization under these conditions, comparable to the tetrahydrofuran formation via 5-*exo-trig* ring closure reactions of likewise substituted 4-penten-1-oxyl radicals.[5] The observation that the synthesis of 2,5-disubstituted tetrahydrofuran **4d** occurs without stereochemical preference is indicative of an δ-hydrogen atom transfer **6d** → **8d** as initial step, which is followed by bromine atom trapping of intermediate **8d**—starting either from resonance formula **8dI** or from **8dII**—and subsequent HBr elimination. Trichloromethylsulfanyl-substituted thiazole **9** has been identified by ^1H NMR and by TLC in comparison to reference data from the literature.[10]

In summary, we have shown that 6-*exo-trig* cyclizations of 6-substituted 5-hexen-1-oxyl radicals effectively compete with δ-hydrogen atom transfer reactions thus leading, after bromine atom trapping, to bromomethyl-substituted tetrahydropyrans. It is worth mentioning that the formation of 6-*exo-trig*-bromocyclized products **5b–d** using polar, for example, NBS-mediated, bromo-

[‡] 6-(1-Bromo-1-methylethyl)-2-(phenyl)tetrahydropyran (**5d** (*cis*:*trans* = 65:35): MS (70 eV, EI): *m*/*z* (%) = 282.1/284.1 (2) [M^+], 259.0 (6) [$C_{12}H_{20}BrO^+$], 245.0 (7) [$C_{11}H_{18}BrO^+$], 161.2 (100) [$C_{11}H_{13}O^+$], 77.1 (49) [$C_6H_5^+$], 59.1 (72) [$C_3H_7O^+$]; HRMS [$M^+-C_3H_6Br$]: calcd 161.0966 found 161.0965(1). *cis*-**5d**: $R_f = 0.84$ [petroleum ether/*tert*-butyl methyl ether = 10:1 (v/v)]; ^1H NMR ($CDCl_3$, 600 MHz): δ = 1.43–1.53 (m, 2H, 3-H and 5-H), 1.68–1.73 (m, 1H, 4-H), 1.80 (s, 3H, 2-CH_3), 1.81 (s, 3H, 2-CH_3), 1.87–1.89 (m, 1H, 5-H), 2.00–2.07 (m, 2H, 3-H and 4-H), 3.45 (dd, 1H, ^3J = 11.1, 1.8 Hz, 2-H), 4.45 (dd, 1H, ^3J = 11.4, 2.2 Hz, 6-H), 7.25–7.43 (m, 5H, Ph–H); ^{13}C NMR ($CDCl_3$, 151 MHz): δ = 23.8, 26.4, 29.7, 31.3, 33.7, 68.1, 79.7, 84.9, 125.4, 127.2, 128.4, 143.4. *trans*-**5d**: $R_f = 0.76$ [petroleum ether/*tert*-butyl methyl ether = 10:1]; ^1H NMR ($CDCl_3$, 600 MHz): δ = 1.77 (s, 3H, 2-CH_3), 1.80 (s, 3H, 2-CH_3), 1.56–1.67 (m, 2H, 3-H and 4-H), 1.76–1.83 (m, 2H, 3-H and 4-H), 2.03–2.07 (m, 1H, 5-H), 2.28–2.32 (m, 1H, 5-H), 3.21 (dd, 1H, ^3J = 10.8, 2.1 Hz, 2-H), 5.22 (d, 1H, ^3J = 5.3 Hz, 6-H), 7.25–7.43 (m, 5H, Ph–H); ^{13}C NMR ($CDCl_3$, 151 MHz): δ = 18.7, 25.5, 27.1, 31.0, 31.2, 69.1, 73.8, 77.0, 126.3, 127.1, 128.8, 140.3.



Scheme 2. Competing reaction channels for alkenoxyl radical **6d**: diastereoselective 6-*exo*-*trig*-cyclization and δ-hydrogen atom transfer. An = *p*-$H_3COC_6H_4$.

cyclizations of the corresponding alkenols is considered to be disfavored on the basis of polar effects.[6] The diastereoselective formation of 2-(1-bromo-1-methylethyl)-6-(phenyl)tetrahydropyran *cis*-(**5d**) is noteworthy. It poses the question, whether or not 6-*exo*-*trig*-cyclizations follow stereochemical guidelines, similar to those which have been established for 4-penten-1-oxyl radical cyclizations.[15]

Acknowledgements

Generous financial support was provided by the Deutsche Forschungsgemeinschaft (Grant, Ha 1705/5-2).

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