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# On the synthesis of β-bromohydrine ethers via intermolecular alkoxyl radical addition to bicyclo[2.2.1]heptene

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**Abstract**—Primary, secondary, and tertiary alkoxyl radicals add *exo*-selectively to the olefinic π-bond in bicyclo[2.2.1]heptene to afford *exo*-2-alkoxybicyclo[2.2.1]hept-3-yl radicals, which are trapped with $BrCCl_3$ preferentially from the *endo* face to furnish β-bromohydrine ethers in 23–67% yield.


The affinity to add to an olefinic π-bond decreases with the steric size of an alkoxyl radical.[1] Additions that occur at the lower end of the reactivity scale, however, face severe competition from alternative processes such as alkoxyl radical β-fragmentation (formation of carbonyl compounds and alkyl radicals)[2] or homolytic substitutions. The most significant homolytic substitution involving alkoxyl radicals in organic media is the H-atom transfer[3] from a hydrocarbon subunit of a reactant and/or a solvent molecule, thus lowering the yield of an *O*-radical addition product in a very effective manner.[4]

According to a recent interpretation of selectivity data in intramolecular reactions, alkoxyl radicals add under kinetic control to alkyl-substituted π-bonds.[5] If the same guideline applied for the intermolecular version, yields of addition products should be predictable by considering rate constants and reactant concentrations associated with the major competing elementary reactions, that is, the addition and the H-atom abstraction, since the latter proceeds irreversibly as well.[4] The *tert*-butoxyl radical thus is expected to add to bicyclo[2.2.1]heptene (**1**) [$k^{add} = 1.09 \times 10^6\ M^{-1}\ s^{-1}$ (300 K)][6] in synthetically useful yields, in a ~3 M solution of the olefin in a poorly H-atom delivering solvent, for instance, benzene or α,α,α-trifluorotoluene (TFT).[7] Neither H-atom transfer nor *tert*-butoxyl radical β-fragmentation are expected to significantly interfere with C,O bond formation under such conditions.[4] To the best of our knowledge, this concept has hitherto not been applied to prepare functionalized ethers on a synthetic scale. In view of this background, it was the aim of the present study to explore the scope of intermolecular alkoxyl radical additions to olefins using $BrCCl_3$ as the terminal trapping reagent. In view of the propensity, particularly, of the *tert*-butoxyl radical to abstract allylic H-atoms,[1,4] we restricted ourselves to the use of bicyclo[2.2.1]heptene (**1**) as substrate. The major finding of the present study states that the synthesis of norbornene-derived β-bromohydrine ethers under such conditions is feasible, even in a stereoselective manner. The yield of addition product gradually increases along the series of alkoxyl radical substituents $C(CH_3)_3 < ClC_6H_4(CH_3)_2C \sim C_6H_5(CH_3)_2C < CH(CH_3)_2 < CH_3$.

*N*-(Alkoxy)-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thiones **2a**–**c** (Fig. 1), precursors for the generation of the corresponding alkoxyl radicals (not shown) in photochemically or thermally induced transformations, were prepared as reported previously.[8] Pale yellow crystalline *N*-(cumyloxy)thiazolethione **2d** (15%) and *N*-(*p*-chlorophenyl) derivative **2e** (13%) were synthesized by adapting published procedures.[8,9] †

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† Satisfactory analytical data were obtained for all new compounds prepared in this study.

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| 2 | R |
|---|---|
| **a** | $CH_3$ |
| **b** | $CH(CH_3)_2$ |
| **c** | $C(CH)_3$ |
| **d** | $C(CH_3)_2C_6H_5$ |
| **e** | $C(CH_3)_2(p\text{-}ClC_6H_4)$ |

**Figure 1.** Indexing of major reactants of the present study. An = *p*-$(H_3CO)C_6H_4$.

Thermal activation (80 °C) of *N*-(methoxy)thiazolethione **2a** ($c_0 = 2.7 \times 10^{-2}$ M) in the presence of bicyclo[2.2.1]heptene (**1**) ($c_0 = 2.7$ M), $BrCCl_3$ ($c_0 = 2.7 \times 10^{-1}$ M), and AIBN in $C_6H_6$ afforded 67% of 2-*exo*-3-bromobicyclo[2.2.1]hept-2-yl methyl ether (**3a**). Ratio and concentration of reactants, as well as further reaction parameters, were established in an independent study (not shown), which in turn was based on the theoretical considerations outlined above. Quantification of volatile compound **3a** was attainable by GC (3-*exo*: 3-*endo* = 28:72; Table 1, entry 1).[‡] Its structure was verified after purification (column chromatography) by one- and two-dimensional $^1H$ and $^{13}C$ NMR methods, including NOESY measurements. Adapting conditions outlined above to transformations starting from secondary and tertiary *N*-alkoxythiazolethiones **2b–e** provided the derived target compounds **3b–e**. The hitherto best yields of β-bromohydrine ethers **3b–e** gradually increased along the series of substituents R = $C(CH_3)_3$ (23%) via $ClC_6H_4(CH_3)_2C$ (44%), $C_6H_5(CH_3)_2C$ (46%), to $CH(CH_3)_2$ (51%) (Table 1, entries 4, 7, 11, and 13).

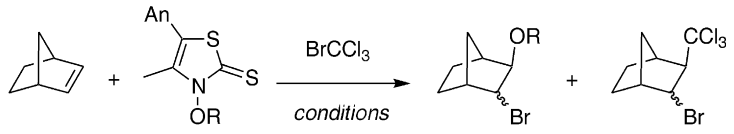
The data obtained in the present study (Table 1) point to an increased efficiency of β-bromohydrine ether synthesis from thiazolethiones **2a–c** using conventional thermal conditions (conductive heating) instead of the activation of these radical precursors in a monomode microwave instrument[¶] or a Rayonet® chamber photoreactor equipped with 350 nm light bulbs (Table 1, entries 1–9). In photochemically-induced transformations, solutions of **2b** and **2c** in $BrCCl_3$, TFT, and olefin **1** gradually darkened. This observation was related to extended reaction times and less chemoselective transformations observed for those reactions. For *N*-cumyloxy derivatives **2d** (Table 1, entry 11) and **2e** (Table 1, entry 13), photoexcitation in turn was the most efficient means of alkoxyl radical generation. This finding was correlated with the restricted thermal stability of compounds **2d–e** at elevated temperatures. If heated, for example, in a solution of $BrCCl_3$ and TFT under microwave conditions (150 °C), *N*-(cumyloxy)thiazolethione **2d** decomposes to furnish bromomethane (**5**),[10] acetophenone (**6**) (30%), 2-phenylpropan-2-ol (**7**) (20%), α-methylstyrene (**8**) (31%), 2-trichloromethylsulfanylthiazole **9** (23%), and 1,1′-bis[5-(*p*-methoxyphenyl)-4-methylthiaz-2-yl]disulfane (**10**) (19%). Formation of olefin **8** is expected to occur in a Tschugaeff-type elimination, which has hitherto not been reported for tertiary *N*-(alkoxy)thiazolethiones.[8] The origin of the remaining products (Scheme 1) is explicable on the basis of a well established chain mechanism using the selected type of alkoxyl radical precursor (Scheme 2).[4,11]

Alkoxyl radical addition occurred in all instances exclusively ($^1H$ NMR) from the *exo* face of olefin **1**. This selectivity is explicable by considering steric effects and stereoelectronic requirements associated with the C,O-bond formation.[12] An approximate orthogonal approach of the radical onto to the HOMO of olefin **1** (not shown) is considered to be sterically less demanding for the *exo* than for the *endo* mode of addition. The selectivity of the bromination step probably originates from 1,2-induction due to steric repulsion between the *exo*-oriented alkoxy substituent in, for example, adduct **11** (Scheme 2) and $BrCCl_3$, thus favoring heteroatom transfer from the sterically least encroached side.

[‡] A solution of **1** (51.0 mmol), *N*-(cumyloxy)thiazolethione **2d** (510 μmol), and $BrCCl_3$ (5.10 mmol) in α,α,α-trifluorotoluene (18.5 ml) was photolyzed for 40 min at room temperature in a Rayonet® photoreactor ($\lambda = 350$ nm). The reaction mixture was concentrated under reduced pressure and purified by column chromatography ($SiO_2$). For a mixture of 2-isomers of 2-bromo-3*exo*-(2-phenylprop-2-yloxy)bicyclo[2.2.1]heptane (**3d**): MS (70 eV, EI): *m*/*z* (%) = 229 (7) $[C_{16}H_{21}O]^+$, 175 (3) $[C_7H_{10}{}^{81}Br]^+$, 173 (3) $[C_7H_{10}{}^{79}Br]^+$, 120 (45) $[C_8H_8O]^+$, 119 (100) $[C_9H_{11}]^+$, 103 (10) $[C_8H_8]^+$, 91 (64) $[C_7H_7]^+$. 2-*endo*-Bromo-3-*exo*-(2-phenylprop-2-yloxy)bicyclo[2.2.1]-heptane 2-*exo*-3-*endo*-(**3d**): $R_f = 0.47$ [pentane/$Et_2O$ = 20:1 (v/v)]; $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta = 0.93$–0.99 (m, 1H, 5-H), 1.31–1.34 (m, 1H, 7-H), 1.36–1.49 (m, 2H, 5-H and 6-H), 1.54 (s, 3H, $CH_3$), 1.59 (s, 3H, $CH_3$), 1.73–1.83 (m, 2H, 6-H and 7-H), 2.06 ($m_c$, 1H, 4-H), 2.39 ($m_c$, 1H, 1-H), 3.22 (t, $J = 1.9$ Hz, 1H, 3-H), 4.01 ($m_c$, 1H, 2-H), 7.23–7.27 (m, 1H, , Ar–H), 7.32–7.36 (m, 2H, Ar–H), 7.45–7.46 (m, 2H, Ar–H); $^{13}C$ NMR (150 MHz, $CDCl_3$): $\delta = 24.0$, 24.6, 29.1, 29.6, 34.5, 42.8, 44.2, 63.1, 77.3, 84.4, 126.1, 126.9, 128.1, 146.6. 2-*exo*-Bomo-3-*exo*-(2-phenylprop-2-yloxy)-bicyclo[2.2.1]heptane 2-*exo*-3-*exo*-(**3d**): $R_f = 0.46$ [pentane/$Et_2O$ = 20:1 (v/v)]; $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta = 0.85$–0.92 (m, 1H, 5-H), 0.99–1.06 (m, 1H, 6-H), 1.12–1.15 ($m_c$, 1H, 7-H), 1.32–1.41 ($m_c$, 1H, 5-H), 1.47–1.53 (m, 1H, 6-H), 1.58 (s, 3H, $CH_3$), 1.59 (s, 3H, $CH_3$), 2.06 ($m_c$, 1H, 7-H), 2.14 ($m_c$, 1H, 1-H), 2.48 ($m_c$, 1H, 4-H), 3.11 ($m_c$, 1H, 3-H), 3.93 (dd, 1H, $^3J = 6.4$, 1.9 Hz, 2-H), 7.23–7.26 (m, 1H, , Ar–H), 7.32–7.36 (m, 2H, Ar–H), 7.52–7.55 (m, 2H, Ar–H); $^{13}C$ NMR (150 MHz, $CDCl_3$): $\delta = 25.5$, 27.0, 28.7 (2 × C), 33.6, 44.2, 46.5, 61.6, 76.5, 78.6, 126.4, 126.8, 128.0, 147.0.

[¶] Discover instrument (CEM) [300 W, 80 ml quartz glass vessel equipped with a 20 bar excess pressure valve, stirring device, cooling fan, temperature measurement via IR sensor; mode: power time; $p_{max} = 10$ bar]. It is for safety reasons highly recommended to adhere to the precautions outlined in Ref. 8.

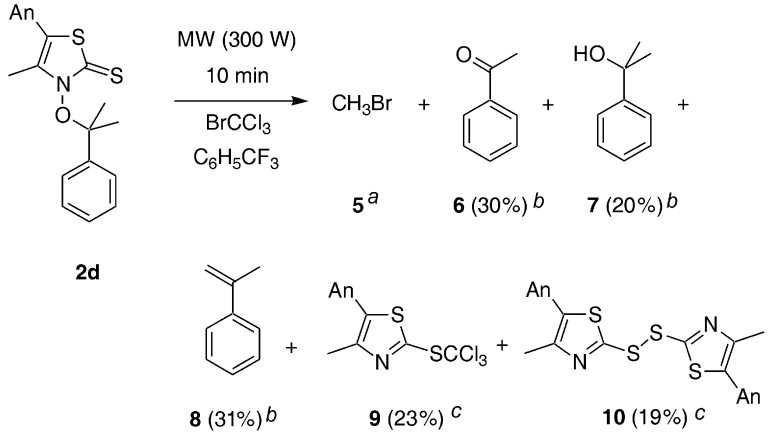
**Table 1.** Formation of β-bromohydrine ethers **3** from *N*-(alkoxy)thiazolethiones **2**, $BrCCl_3$ and bicyclo[2.2.1]heptene (**1**)




**1** **2** **3** **4**

| Entry | 2 | Conditions | Solvent | 3 [% from 2] | 3 3-*exo*:3-*endo* | 4 [% from $BrCCl_3$] | 4 3-*exo*:3-*endo* |
|---|---|---|---|---|---|---|---|
| 1 | **2a** | Δ*T* (80 °C)/AIBN | $C_6H_6$ | 67 | 28:72[a] | 67 | 7:93 |
| 2 | **2a** | MW (150 °C) | $C_6H_5CF_3$ | 50 | 26:74 | 77 | 9:91 |
| 3 | **2a** | *hv* (20 °C) | $C_6H_5CF_3$ | 17 | 27:73 | 92 | 12:88 |
| 4 | **2b** | Δ*T* (80 °C)/AIBN | $C_6H_6$ | 51 | 24:76[b] | 66 | 7:93 |
| 5 | **2b** | MW (150 °C) | $C_6H_5CF_3$ | 33 | 25:75 | 80 | 9:91 |
| 6 | **2b** | *hv* (20 °C) | $C_6H_5CF_3$ | 26 | 23:77 | 93 | 11:89 |
| 7 | **2c** | Δ*T* (80 °C)/AIBN | $C_6H_6$ | 23 | 14:86[c] | 76 | 7:93 |
| 8 | **2c** | MW (150 °C) | $C_6H_5CF_3$ | 11 | 28:72 | 88 | 9:91 |
| 9 | **2c** | *hv* (20 °C) | $C_6H_5CF_3$ | 20 | 20:80 | 90 | 7:93 |
| 10 | **2d** | MW (150 °C) | $C_6H_5CF_3$ | 3[d] | 26:74 | 84 | 20:80 |
| 11 | **2d** | *hv* (20 °C) | $C_6H_5CF_3$ | 46 | 24:76 | 92 | 7:93 |
| 12 | **2e** | MW (150 °C) | $C_6H_5CF_3$ | 3[e] | 26:74 | 85 | 20:80 |
| 13 | **2e** | *hv* (20 °C) | $C_6H_5CF_3$ | 44 | 22:78 | 93 | 7:93 |

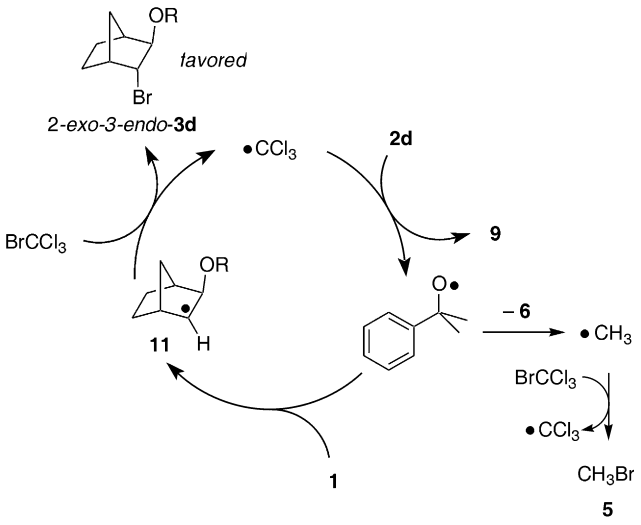
MW: monomode microwave instrument; *hv*: Rayonet® chamber photoreactor equipped with 350 nm light bulbs. Speciation of products not mentioned in Table 1: 2-methyl-2-(2-*exo*-3-*endo*-3-bromobicyclo[2.2.1]hept-2-yl)propannitrile (3%[a], 2%[b,c]), acetophenone (**6**) (55%),[d] 1-methyl-1-phenylethan-1-ol (**7**) (22%),[d] α-methylstyrene (**8**) (3%),[d] α-methyl-(*p*-chlorophenyl)styrene (28%),[e] 2-(*p*-chlorophenyl)propan-2-ol (35%),[e] methyl-(*p*-chlorophenyl)ketone (30%)[e].




**Scheme 1.** Products formed from thermal decomposition of *N*-(cumyloxy)thiazolethione **2d** in the presence of $BrCCl_3$ in a monomode microwave instrument (300 W, 150 °C). [a]GC–MS, [b]quantitative GC analysis, [c]purification via column chromatography.

The synthesis of β-bromohydrine ethers **3** in the present investigation was consistently paralleled by formation of the $BrCCl_3$-addition product **4**.[13] This result shows that the thiocarbonyl group in thione **2** is one but probably not the most effective functionality for trapping chain carrying $^{\cdot}CCl_3$ radicals.[13] Support for this argumentation comes from an experiment that was conducted by heating (80 °C) olefin **1**, $BrCCl_3$, and AIBN in a solution of $C_6H_6$ in the absence of **2**. The reaction provides 38% of 3-bromo-2-*exo*-(trichloromethyl)bicyclo[2.2.1]heptane **4** in a 3-*exo*:3-*endo* ratio of 7:93.

In conclusion, the feasibility of β-bromohydrine ether synthesis via intermolecular alkoxyl radical addition to bicyclo[2.2.1]heptene (**1**) has been successfully demonstrated. Although some of the yields remained at the moderate level, we wish to point out that the synthesis of derivatives of **3**, which have attracted the attention as, for example, pesticides[14] and pharmacological active compounds,[15] is in several instances difficult to achieve using ionic transformations.[16,17] We are well aware of the beneficial reactivity of bicyclo[2.2.1]heptene (**1**) for the present investigation, in particular due to its reluctance to undergo allylic H-atom abstraction. The aim to broaden the scope of the alkoxyl radical method by varying the type of olefin used as a radical acceptor is being extensively pursued in this laboratory at the moment.




**Scheme 2.** Formation of β-bromohydrine ether 2-*exo*-3-*endo*-**3d** as major product from *N*-(cumyloxy)thiazolethione **2d**, norbornene **1** and $BrCCl_3$ in a radical chain reaction (R = 2-phenylprop-2-yl).

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