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# A novel synthesis of tetrahydrofuran *via* alkoxy radical cyclisation

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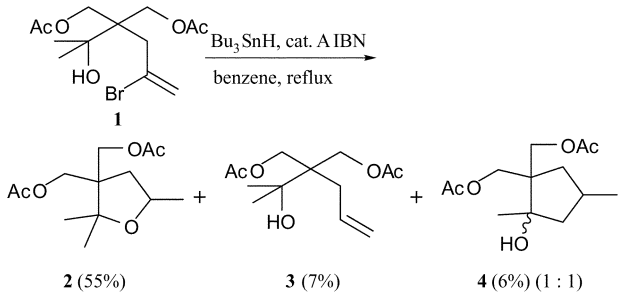
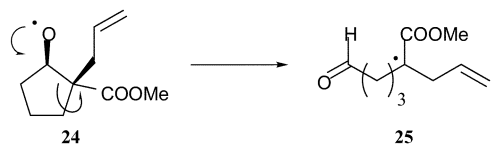
***Received (in Cambridge, UK) 21st November 2002, Accepted 20th December 2002***
***First published as an Advance Article on the web 14th January 2003***

**Tetrahydrofurans were synthesised *via* 5-*exo-trig* cyclisation of alkoxy radical generated by unprecedented 1,5-hydrogen shift from hydroxyl group to vinyl radical.**

Radical reactions are now widely used as a useful tool in organic synthesis. However, deeper insights are still required for its application to synthesis of the desired compound. It is generally accepted that the rate of homolysis would depend on bond dissociation energy, and the homolytic cleavage of oxygen–hydrogen bond demands a higher energy than that of the $sp^3$ carbon–hydrogen bond.[1] Therefore, to perform a radical cyclisation or reduction, it is not necessary to protect a hydroxy group and radical reactions are sometimes carried out in protic solvents.[2,3] Nevertheless, we observed an unusual furan formation during the course of our study on radical reaction of hydroxy vinyl bromide **1**. When vinyl bromide **1** was treated with $Bu_3SnH$ in the presence of catalytic amount of AIBN, tetrahydrofuran **2**[4] was formed by cyclisation of alkoxy radical **6**, generated from vinyl radical **5** in 55% yield together with dehalogenated compound **3** (7% yield) and cyclopentane **4** (6% yield) [Scheme 1 and eqn. (1)]† . It is surprising that the




**Scheme 1**



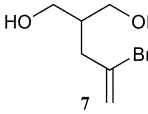
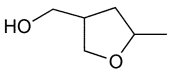
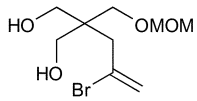
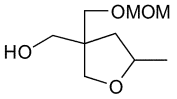
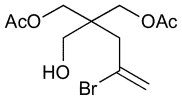
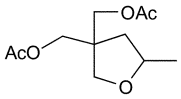
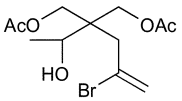
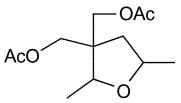
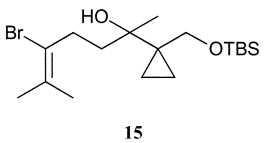
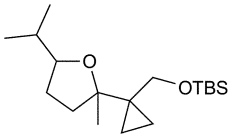
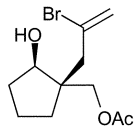
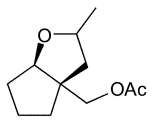
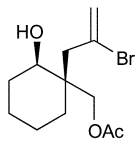
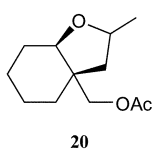

(1)

hydrogen atom of the hydroxy group is selectively abstracted in spite of the existence of two methyl groups. Here we disclose our interesting results and novel construction of highly functionalised tetrahydrofurans.

When simplified diol **7** was used as substrate, the yield of the furan **8** decreased (Table 1, entry 1). In contrast, a higher yield was obtained using more substituted diol **9** (entry 2). These results indicate that the presence of the quaternary carbon centre at the β position to hydroxy group controls the conformation of the carbon chain and accelerates the cyclisation according to the Thorpe-Ingold effect.[5] Similar consequences were observed when primary and secondary alcohols (**11** and **13**) were utilized as substrates (entries 3 and 4). Otherwise, the improvement of yield could be explained sterically by the presence of adjacent groups suppressing the termination of the alkoxy radical by $Bu_3SnH$. Furthermore, highly functionalised vinyl bromide **15** gave furan **16**[4] in 86% yield as a 1.5 : 1 mixture of two stereoisomers (entry 5).

To find the flexibility of the cyclisation, formations of bicyclic systems were examined. Both oxabicyclo[3.3.0]octane **18** and perhydrobenzofuran **20** were obtained in moderate yields, though they have two methylene hydrogens on their rings (entries 6 and 7). It is noteworthy that methylene hydrogen has a lower bond dissociation energy than methyl hydrogen by 2 kcal $mol^{-1}$. When the substrate **21**, having an electron withdrawing group at the β position to the hydroxy group, was

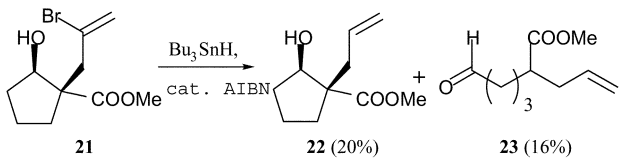
**Table 1** Syntheses of tetrahydrofurans *via* alkoxy radical cyclisation

| Entry | Substrate | Furan | Yield[a] (ratio of stereo-isomers)[b] |
|---|---|---|---|
| 1 |  **7** |  **8** | 21% (1 : 1) |
| 2 |  **9** |  **10** | 62% (1 : 1) |
| 3 |  **11** |  **12** | 36% |
| 4 |  **13** |  **14** | 64% (3.3 : 1) |
| 5 |  **15** |  **16** | 86% (15 : 1) |
| 6 |  **17** |  **18** | 39% (1 : 1) |
| 7 |  **19** |  **20** | 40% (33 : 1) |

[a] Yields of simple reduced products; entry 1: 64%, entry 2: 30%, entry 3: 64%, entry 4: 36%, entry 5: 0%, entry 6: 24%, entry 7: 22%. [b] The ratio of stereoisomers was determined by $^1H$ NMR.

DOI: 10.1039/b211568a

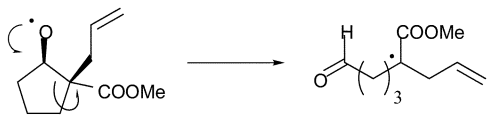
 




**21** **22** (20%) **23** (16%)

**Scheme 2**

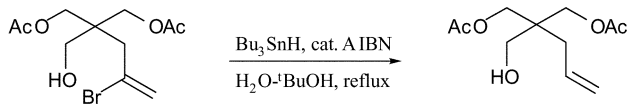
subjected to the radical reaction, no cyclisation took place, and aldehyde **23** was isolated in 16% yield (Scheme 2). The formation of aldehyde is a proof for 1,5-hydrogen shift *via* radical followed by β-cleavage which is characteristic of alkoxy radical **24**. No epimerised diastereomer in dehalogenated **22** implies that re-cyclisation of the stable radical **25** or intramolecular aldol reaction did not occur under the reaction conditions [eqn. (2)].




(2)

**24** **25**

As a further evidence of radical reaction, we expected that the yield of furan would decrease when the reaction was carried out in protic solvent. Actually, **11** was converted to **26** in 85% yield and no furan **12** was detected (Scheme 3).




**11** **26** (85%)

**Scheme 3**

In conclusion, we discovered an unprecedented 1,5-hydrogen shift from hydroxy group to vinyl radical leading to a novel way for the formation of tetrahydrofurans. It is considered that some other factors, such as a polar effect,[6] apart from bond dissociation energy could have important roles for the predominant rearrangement of the hydroxy hydrogen. In addition, it is notable that oxabicyclo[3.3.0]octane ring system and perhydrobenzofuran were prepared in moderate yields.

We thank the Research Fellowship of the Japan Society for the Promotion of Science for Young Scientists and Grant-in-Aid for Scientific Research on Priority Areas (A) "Exploitation of Multi Element Cyclic Molecules" from the Ministry of Education, Culture, Sports, Science and Technology, Japan for financial support of this research.

## Notes and references

† *Typical experimental procedure*: compound **2**: To a stirred solution of **1** in degassed benzene was slowly added a degassed benzene solution of $Bu_3SnH$ and AIBN over a period of 2 h under reflux. After 2 h of refluxing, the solvent was removed under reduced pressure. The residue was dissolved in $Et_2O$, and then KF in water was added. After being stirred vigorously for 2 days, the mixture was filtered through Celite. The filtrate was extracted with $Et_2O$. The residue upon workup was chromatographed on silica gel to give tetrahydrofuran **2**, dehalogenated **3** and **4**.

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4 All new compounds were fully characterized by spectroscopic techniques ($^1$H NMR, $^{13}$C NMR, IR, MS). Spectral data for representative compounds are as follows: **compound 2**; IR (neat) cm$^{-1}$: 1745 and 1238. $^1$H NMR (300 MHz) $\delta$: 4.06–4.28 (5H, m), 2.07 (6H, s), 1.99 (1H, dd, $J$ = 12.5, 7.5 Hz), 1.58 (1H, dd, $J$ = 12.5, 7.0 Hz), 1.26 (3H, d, $J$ = 5.0 Hz), 1.25 (3H, s), 1.21 (3H, s).$^{13}$C NMR (75 MHz) $\delta$: 171.09, 82.98, 71.01, 64.38, 63.62, 49.61, 38.70, 24.98, 23.42, 22.90, 20.82. MS (*m*/*z*): 258 ($M^+$) and 243 ($M^+ - CH_3$). HRMS (*m*/*z*) calcd for $C_{13}H_{22}O_5$: 258.1467. found: 258.1471. **major isomer of 16**; IR (neat C) cm$^{-1}$: 1257. $^1$H NMR (300 MHz) $\delta$: 3.66 (1H, d, $J$ = 10.0), 3.38 (1H, d, $J$ = 10.0), 3.35–3.43 (1H, m), 1.99 (1H, td, $J$ = 11.5, 7.0), 1.75–1.80 (2H, m), 1.49–1.64 (2H, m), 1.21 (3H, s), 0.89 (3H, d, $J$ = 6.0), 0.88 (9H, s), 0.82 (3H, d, $J$ = 6.0), 0.62–0.68 (1H, m), 0.47–0.53 (1H, m), 0.24–0.34 (2H, m), 0.01 (6H, s). $^{13}$C NMR (75 MHz) $\delta$: 85.80, 81.97, 67.09, 66.99, 37.26, 33.24, 29.84, 29.02, 26.53, 25.89, 19.57, 18.21, 18.12, 6.97, −5.51, −5.60. MS (*m*/*z*): 312 ($M^+$), 297 ($M^+ - CH_3$) and 255 ($M^+ - C_4H_9$). HRMS (*m*/*z*) calcd for $C_{18}H_{36}O_2Si$: 312.2485. found: 312.2513.

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