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Radical chain reactions using THP as a solvent

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Abstract—THP (tetrahydropyran) has been found to show an excellent stability towards autooxidation, compared with THF. Tributyltin hydride mediated radical cyclization, when conducted in THF as a solvent, suffers from competition of hydrogen abstraction from the solvent, whereas the use of THP resulted in the course to negligible degree. Tributyltin hydride, TTMSS, and hexanethiol mediated radical reactions were carried out successfully using THP as a solvent.

Tin, silicon, thiyl radicals are frequently utilized in radical chain reactions.[1] Generally, benzene is preferred as a solvent in terms of its strong C–H bond, however, it is sometimes experienced that the key radical species react with benzene to form undesirable aromatic byproducts. Some other drawbacks of benzene include its toxicity and the narrow temperatures inherent to relatively high freezing point of 5.5 °C also limit the use of benzene, and in this context, toluene is often used as a substitute of benzene. If the substrate exposed to radical reaction conditions has low solubility to benzene, polar solvents have to be chosen. THF (tetrahydrofuran) which can dissolve a wide range of organic molecules is sometimes used in radical reactions; however, rather weak C–H bond adjacent to oxygen is always risk-exposing for valuable substrates. In this Letter, we report that THP (tetrahydropyran), whose boiling point is 88 °C, can be used for radical chain reactions, such as tributyltin hydride mediated reduction and cyclization, TTMSS (tris(trimethylsilyl)silane) and thiol mediated hydrosilylation and hydothiolation of alkenes and alkynes.[2]

At the outset, we checked the formation of peroxide by autooxidation of THF and THP to compare the relative ease. As shown in Figure 1, THP showed very strong reluctance towards autooxidation even for 30 days exposure to air, whereas 500 ppm of the peroxide was formed for the case of THF. The quality of THP can last 60 days when 250 ppm of BHT (dibutylhydroxytoluene) was added as an anti-oxidant.

Having affirmative data on the stability to autooxidation with THP in hand, we then tested THP for radical reduction and cyclization of organic halides using tributyltin hydride and AIBN. Reduction of organic bromides **1a**, **1b**, and **1c** was successfully carried out (Scheme 1). For example, a solution of 3β-bromo-5-cholestene (**1b**, 1 mmol), AIBN (0.1 mmol), and Bu_3SnH (1.5 mmol) in tetrahydropyran (5 mL) was stirred for 2 h at reflux.[3] The reaction mixture was treated with

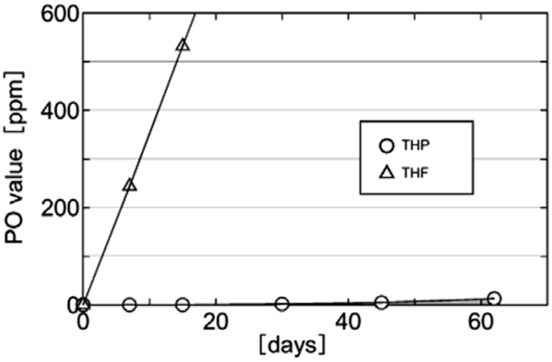

Figure 1. Stability of THF and THP towards autooxidation.

Keywords: Radical reaction; THP; Tin radical; Silicon radical; Thiyl radical.

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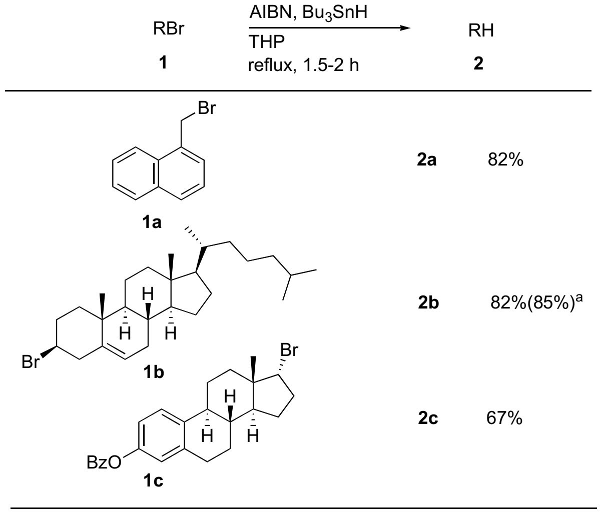
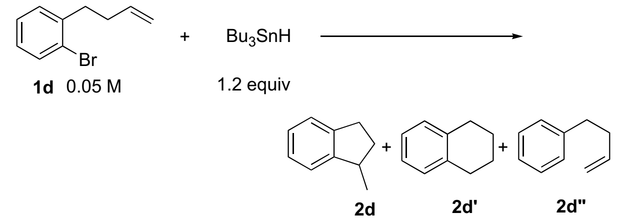


[a]Recycled THP was used.

Scheme 1. Radical reduction of **1a**–**c** in THP.

Table 1. Tin-mediated radical reaction of **1d** in THP and other solvents

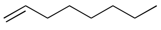
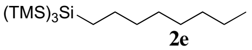
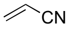
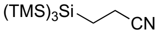
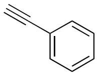
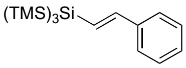
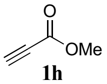
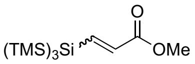
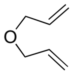
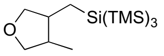
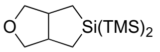
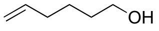
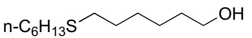
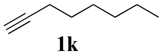
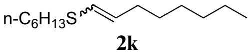
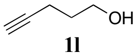
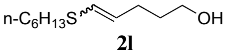
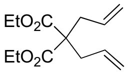
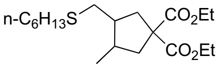
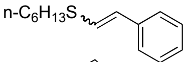
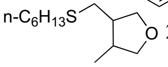


Entry	Solvent	Initiator	Conditions	Product ratio[a]		
1	THF	AIBN	66 °C, 2 h	79	4	17
2	C_6H_6	AIBN	80 °C, 2 h	91	5	4
3	Toluene	AIBN	80 °C, 2 h	89	5	6
4	THP	AIBN	80 °C, 2 h	86	4	10
5	C_6H_6	BEt_3[b]	15 °C, 4.5 h	93	3	4
6	THP	BEt_3[b]	15 °C, 4 h	88	3	9

[a] Estimated by GC. Yields are 70–95%.

[b] Hexane solution was used.

Table 2. Radical addition reaction of TTMSS[a] and *n*-HexSH[b] in THP

Entry	Substrate	Product	Yield[c] (%)
1	 **1a**	 **2e**	85
2	 **1f**	 **2f**	86
3	 **1g**	 **2g**	76
4	 **1h**	 **2h**	85 ($E/Z = 10/90$)
5	 **1i**	 **2i**	40 (cis/trans = 23/77)
		 **2i′**	45
6	 **1j**	 **2j**	81
7	 **1k**	 **2k**	66 ($E/Z = 50/50$)
8	 **1l**	 **2l**	64 ($E/Z = 52/48$)
9	 **1m**	 **2m**	67 (49/51)
10	**1g**	 **2n**	72 ($E/Z = 92/8$)
11	**1i**	 **2o**	78 (65/35)

[a] Conditions: substrate (1 mmol), $(TMS)_3SiH$ (1.1–1.2 mmol), V-65 (2,2′-azobis(2,4-dimethyl valeronitrile)) (20 mol %), THP (2 mL), 70 °C, 4 h.

[b] Conditions: substrate (1 mmol), *n*-HexSH (1.2–1.5 equiv), THP (2 or 10 mL (entries 7, 10, and 11)), AIBN (2,2′-azobis(isobutyronitrile)) (20 mol %), 80 °C, 2–3 h.

[c] Isolated yield after silica gel chromatography.

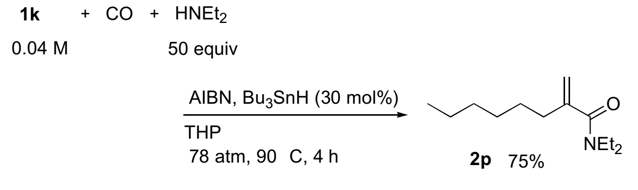
saturated KF solution. The resulting suspension involving Bu_3SnF was filtered and the filtrate was separated and dried over anhydrous $MgSO_4$. Purification by flash column chromatography (silica gel, hexane) gave 5-cholestene (**2b**) (82%). Similarly, reduction of 17α-bromo-estradiol 3-benzoate (**1c**) gave 17-hydro-estradiol 3-benzoate (**2c**) in 67% yield after chromatographic purification. It should be stated that, unlike water-miscible THF, THP made two layers when mixed with water, which facilitated the biphasic aqueous/organic workup procedure in the above case. If required, the recovery of THP is inherently easy to carry out unlike the case of water soluble ether solvents.[4,5]

Then, we checked the cyclization of 2-(4-butenyl)phenyl radical using tributyltin hydride and AIBN with different solvents (Table 1).[6] Under the employed conditions the radical cyclization courses leading to **2d** and **2d′** are principal, whereas the direct hydrogen abstraction path by aryl radicals from tributyltin hydride and solvent leading to **2d″** competes to some extent. In the case of THF, the 83/17 ratio of cyclization/uncyclization was observed (entry 1), whereas the ratios 90/10, 94/6, and 96/4 were observed for THP, toluene, and benzene, respectively (entries 2–4). These results suggest that the direct hydrogen abstraction path of aryl radicals from solvent competes most seriously with THF, whereas such a path is rather modest for THP and toluene, compared with THF.[7,8]

We then turned our attention to TTMSS (tris(trimethylsilyl)silane) mediated hydrosilylation of alkenes and alkynes[9] using THP as a solvent (Table 2). All worked well and gave the corresponding hydrosilylated products in good to high yields. Silylation-radical-cyclization sequence of bisallyl ether **1i** was also successful, which gave a mixture of **2i** and **2i′** (entry 5). We also confirmed that radical addition reactions of hexanethiol to alkenes and alkynes worked well using THP as a solvent (entries 6–11).

Finally, we carried out tributyltin hydride mediated radical carbonylation[10] to give acrylic amide. As shown in Scheme 2, the desired amide was obtained in comparable yield with the case when we used benzene for the same reaction.[11] Thus, a series of chain propagation steps: tin radical addition to carbon–carbon triple bond, carbonyaltion of the resulting vinyl radical, ionic trapping of the ketenyl radicals, hydrogen-migration, β-fission to leave tin radical out, were consistent with the use of THP.

In summary, we have demonstrated that the tributyltin hydride mediated radical reduction, cyclization, and radical addition of TTMSS and hexanethiol to alkenes and alkynes can be successfully carried out using THP as the solvent. Thus, for these reactions, THP serves as a good substitute for toxic benzene, less polar toluene, and air-unstable, water-miscible THF for these types of radical reactions.



Scheme 2. Radical aminocarbonylation of **1k** to **2p** in THP.

Acknowledgments

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References and notes

1. *Radical in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vols. 1 and 2.
2. For the use of THP in SmI_2 reaction, see: Kagan, H. B. *Tetrahedron* **2003**, *59*, 10351.
3. A solution of 3β-bromo-5-cholestene (**1b**, 444 mg, 0.99 mmol), AIBN (16.2 mg, 0.099 mmol) and Bu_3SnH (393 μL, 1.5 mmol) in tetrahydropyran (5 mL) was refluxed for 2 h. The reaction mixture was cooled to room temperature, quenched with saturated KF solution (2 mL) and stirred for 24 h at room temperature. The resulting suspension was filtered through a pad of Celite, washed with THP, and the ethereal layer of the filtrate was separated. Drying with anhydrous $MgSO_4$, concentration and purification by flash column chromatography (silica gel, hexane) gave 5-cholestene (**2b**, 302 mg, 0.82 mmol, 82%). $[\alpha]_D^{28}$ −51.7 (*c* 1.28, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.68 (s, 3H), 0.86 (d, 3H, $J = 2.0$ Hz), 0.87 (d, 3 H, $J = 1.6$ Hz), 0.92 (d, 3H, $J = 6.8$ Hz), 0.92–1.62 (m, 23H), 1.00 (s, 3H), 1.69–1.76 (m, 1H), 1.78–1.87 (m, 2H), 1.91–2.03 (m, 3H), 2.18–2.29 (m, 1H), 5.27 (br dt, 1H, $J = 5.2$, 1.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.0, 18.9, 19.6, 20.9, 22.7, 23.0, 24.0, 24.4, 28.17, 28.23, 28.4, 31.99, 32.04, 33.1, 36.0, 36.4, 37.7, 39.7, 40.0, 42.5, 50.7, 56.3, 57.0, 119.1, 143.9; FT-IR (film) ν 3033, 2932, 2866, 1671, 1465, 1445, 1376, 1334, 1254, 1168, 1145, 1049, 1026 cm^{-1}; MS (EI, 70 eV) *m*/*z* (%): 370 (M^+, 100), 355 (91), 301 (29), 275 (36), 257 (46), 215 (74), 161 (37), 147 (43), 145 (45), 135 (37), 109 (53); HRMS (EI, 70 eV) calcd for $C_{27}H_{46}$ (M^+) 370.3600, found 370.3573.
4. For measured mutual solubility: THP to water: 8.57 wt%; water to THP 2.5 wt%.
5. One referee suggested the use of dioxane and DME as a substitute for THF. However, dioxane is highly toxic and prone to cause peroxide formation by air. Since these ether solvents are miscible with water, the recovery/reuse is not easy to carry out, when aqueous workup is employed as in the case of tin hydride/RX reactions.
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8. We also tested THP as a solvent for allyltributyltin mediated radical reactions of iodooctane, however, the slow S_H2' addition reaction to give 1-dodecene allowed for the competition of the direct abstraction of α-hydrogen from THP to give octane. For rate constants of primary alkyl radical addition to allyltin, see: (a) Curran, D. P.; van Elburg, E. J.; Giese, B.; Gilges, S. *Tetrahedron Lett.*

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11. Uenoyama, Y.; Fukuyama, T.; Nobuta, O.; Matsubara, H.; Ryu, I. *Angew. Chem., Int. Ed.* **2005**, *44*, 1075.