Horner–Wadsworth–Emmons Reactions in THF: Effect of Hydroperoxide Species

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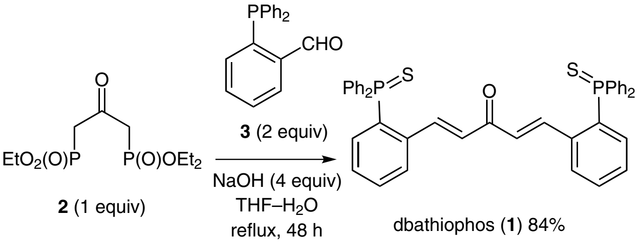
Abstract: Horner–Wadsworth–Emmons (HWE) reactions routinely employ tetrahydrofuran (THF) as the reaction solvent. In this paper we show that THF adducts (derived from THF–hydroperoxide species) of HWE phosphonate ester compounds are formed under microwave irradiation (i.e., under pressure), or in the presence of a reductant [e.g., $P(OEt)_3$] in a conventionally heated reaction.

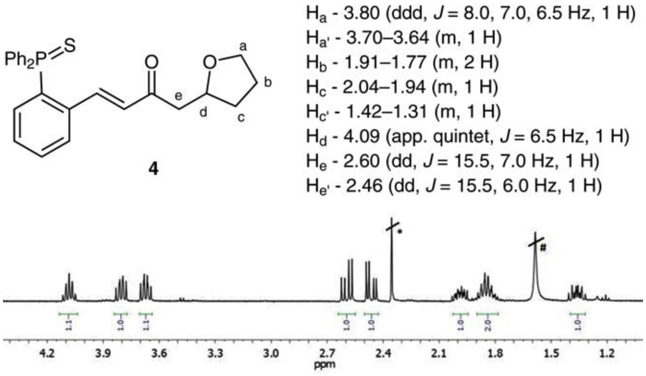
Key words: alkenes, phosphorus, peroxides, furan, reduction

The Horner–Wadsworth–Emmons (HWE) reaction (also known as Horner–Wittig) of stabilized phosphonate anions with aldehydes or ketones in the presence of a suitable base is widely employed in synthetic chemistry, with many variants appearing in natural product syntheses.[1] The reaction has been optimised over the years, allowing either *Z*- or *E*-alkenes to be obtained with high stereoselectivity. We recently identified[2] dbathiophos ligand **1** as a flexible multidentate ligand for Cu^I. Further optimisation studies concerning the synthesis of **1** have revealed a competing reaction path when conducted with microwave assistance and using THF as the solvent, the findings of which are detailed herein.

Compound **1** is readily accessed by conventional heating methods (reaction of **2** and **3** in the presence of NaOH in THF–H_2O) in a closed system (Schlenk tube) in 84% yield after 48 hours at reflux (Scheme 1).[2a] On conducting the same reaction in a microwave reactor[3] it was discovered that the reaction time could be shortened to ca. one hour, which gave **1** in 67% yield. Increasing the equivalents of **2** from 1.0 to 1.2 resulted in a higher yield (80%). It was during this optimisation that in one reaction[4] the yield of **1** was lowered dramatically (to 25%), and a second unknown product was formed, also in 25% yield. The ^{1}H NMR spectrum of the unknown product is shown in Figure 1. ESI-MS showed a mass ion of $m/z = 433.1380$, which corresponds to $C_{26}H_{26}O_2PS$ $[MH]^+$. This suggests the presence of an oxygen-containing cyclic ring (either tetrahydrofuran or tetrahydropyran – presumably derived from the THF solvent vide infra). The ^{1}H NMR spectrum of the side product showed that one C=C bond had formed (not shown), but relatively complex aliphatic signals were observed between δ = 1.2–4.1 ppm. Comparison of related literature compounds[5] indicated that the side product contained a tetrahydrofuran ring, indicating **4** as a plausible structure.



Scheme 1 HWE reaction of **2** and **3** to give dbathiophos **1**



H_a - 3.80 (ddd, J = 8.0, 7.0, 6.5 Hz, 1 H)
$H_{a'}$ - 3.70–3.64 (m, 1 H)
H_b - 1.91–1.77 (m, 2 H)
H_c - 2.04–1.94 (m, 1 H)
$H_{c'}$ - 1.42–1.31 (m, 1 H)
H_d - 4.09 (app. quintet, J = 6.5 Hz, 1 H)
H_e - 2.60 (dd, J = 15.5, 7.0 Hz, 1 H)
$H_{e'}$ - 2.46 (dd, J = 15.5, 6.0 Hz, 1 H)

Figure 1 ^{1}H NMR spectrum (expanded) of the unexpected side product **4** in the HWE reaction of **2** and **3** to give **1** (* = toluene; # = H_2O)

The chemical structure of the side product was unambiguously confirmed by single-crystal X-ray diffraction (Figure 2). Interestingly, the crystal packing forces **4** to adopt a conformation (in the solid state) where the enone moiety is s-*trans*. A 2D NOESY spectrum of **4** in $CDCl_3$ shows a strong NOE between the α-olefin proton and the *ortho* proton on the aromatic ring, showing that this conformation is also adopted in solution.

To fully understand how **4** had formed, a series of reactions were carried out in the absence of aldehyde (Scheme 2). Compound **2** was converted in low yield into bis(tetrahydrofuran)acetone (**5**) in 8% yield. Benzylidene acetone phosphonate ester (**6**),[6] subjected to same reaction conditions, gave compound **7** in 19% yield. Altering the base from NaOH to NaOMe did not appreciably alter the yield of **7** (21%). In the absence of water, however, this latter reaction did not give **7**. Phosphonate ester hydrolysis was

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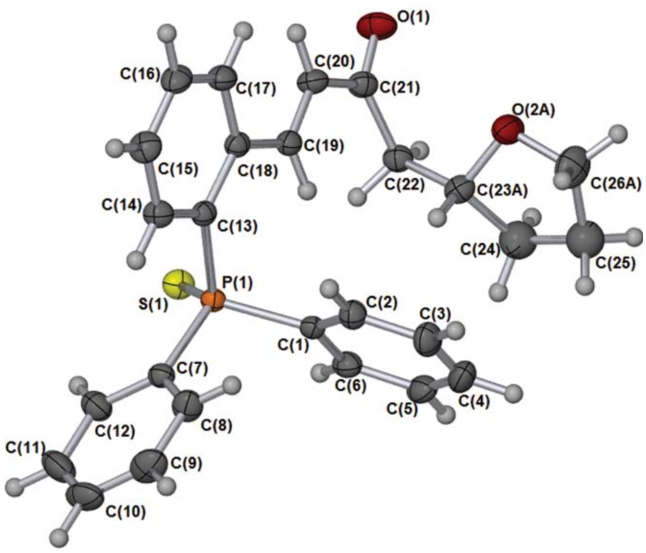
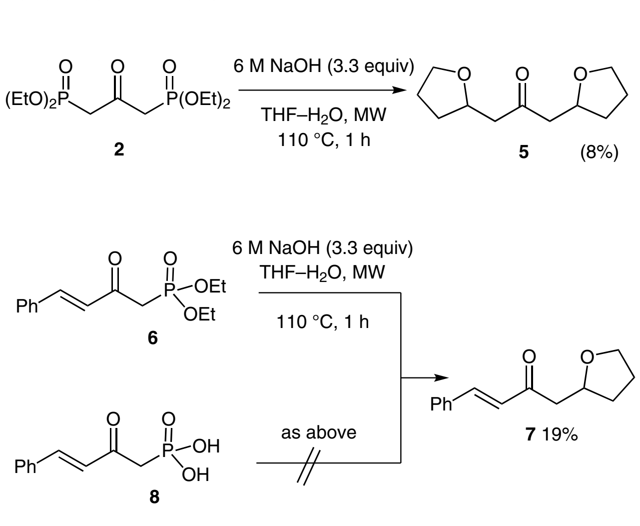


Figure 2 X-ray structure of compound **4**. Thermal ellipsoids shown at 50% probability; disorder is observed around the THF moiety. Selected bond angles (°): O(1)–C(21)–C(20): 119.69(13), C(18)–C(13)–P(1): 120.25(10)



Scheme 2 Reactions in the absence of aldehyde

considered as a possibility. However, benzylidene acetone phosphonic acid (**8**)[7] did not give **7**, ruling it out as an intermediate.

The unexpected introduction of a THF motif has previously been observed for other reaction types [8] and their formation attributed to either carbene or radical mechanisms. Davies and Pérez both described transition-metal-catalysed carbene reactions,[9] whereas Zhang and co-workers functionalised a variety of ring-containing ethers using a radical methodology.[10] In the reaction described here, it is not immediately obvious by which mechanism side product **4** is being formed, as no intentionally added transition metals or radical initiators are present. However, the reaction conditions can be considered 'forcing', even for a microwave reaction (1 h at 110 °C). Crucially, compounds such as **4** were not found in the conventionally heated reaction above trace levels (>1%). We suspect that the microwave-heated reaction generates higher pressures than the conventionally heated reaction.

An intermediate acylcarbene (formed by α-elimination),[11] followed by a C–H insertion reaction with THF, could potentially explain the formation of the THF adducts. However, on the addition of carbene traps, for example, cyclohexene, norbornene, and 1,2-tetramethylethene, to either **2** or **6** no cyclopropanation formation was observed by NMR spectroscopic or MS analysis. Changing the solvent to 1,4-dioxane gave the same outcome.

Tetrahydrofuran-2-hydroperoxide (THF-OOH) was identified as an alternative intermediate, formed by the reaction of THF with O_2 (air) in the presence of light.[12] THF-OOH could either generate a THF radical species, or be reduced under the forcing microwave conditions to 2-hydroxytetrahydrofuran (THF-OH). Whilst no precautions were taken to distil THF or use degassed water in either the HWE or control reactions (vide supra), regular testing of the laboratory-grade THF using peroxidase test strips[13] showed low but variable quantities of peroxide (typically ca. 1–5 ppm), which quantitatively could not fully account for amounts of THF adducts observed in the above reactions. A more quantifiable test for THF-OOH was clearly required (special precaution: if THF is suspected of containing THF-OOH it should not be distilled!).

Triethyl phosphite [$P(OEt)_3$] reacts[14] smoothly and efficiently with hydroperoxides to yield the triethyl phosphate [$PO(OEt)_3$] and the corresponding alcohol, THF-OH. It was recognised that this would provide a useful tool for quantification of the total amount of THF-OOH in solution (monitoring reactions by ^{31}P NMR spectroscopy). Upon addition of $P(OEt)_3$ to the HWE reaction of **2** and **3**, the formation of $PO(OEt)_3$ (after 1 h) was observed and quantified by ^{31}P NMR spectroscopy (Table 1).

Table 1 Addition of $P(OEt)_3$ to the Reaction **2** + **3** → **1** + **4**[a]

$P(OEt)_3$ (equiv)	$P(OEt)_3/PO(OEt)_3$ ratio	$PO(OEt)_3$ (equiv formed)	Peroxide concn (mM)[b]	Yield (%) of **4** (**1**)
1	1:0.2	0.17	25	19 (33)
0.5	1:0.5	0.17	25	17 (22)

[a] Monitored by ^{31}P NMR spectroscopy.

[b] The concentration of peroxide was obtained from relating the ratio of $P(OEt)_3/PO(OEt)_3$ by ^{31}P NMR spectroscopic analysis to the equivalents, and thus mmol of $PO(OEt)_3$ formed, which was considered equal to the amount of THF-OOH in the solvent. Finally, this value was converted into mM.

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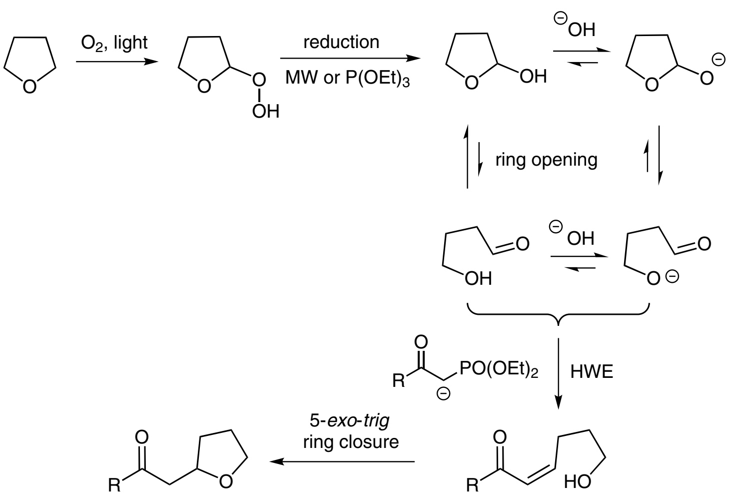

Scheme 3 Formation and reduction of THF-OOH in HWE reactions

Regardless of the amount of $P(OEt)_3$ added (0.5 or 1 equiv) the same amount of $PO(OEt)_3$ (0.17 equiv) was recorded, which closely matches the observed yields of **4**.[15] From the amount of $PO(OEt)_3$ formed, the concentration of THF-OOH was calculated as 25 mM.[16] Finally, reactions of **2** and **3** conducted under a rigorous inert atmosphere, using distilled and degassed THF and degassed water (kept in the dark), no side product **4** was observed.

Using conventional heating, compound **4** was not previously observed, yet under microwave irradiation it was. It was therefore hypothesised that the MW irradiation promoted THF-OOH reduction to THF-OH. Therefore, $P(OEt)_3$ was added to the conventionally heated reaction, which led to the formation of **4**.

Finally, an independent reaction of THF-OH with compound **2** in the presence of NaOH in THF–H_2O gave bis-THF product **5** in 56% yield. A competition experiment (see the Supporting Information) showed that the THF-OH, which is a masked aldehyde, is more reactive than aldehyde **3**.

The involvement of THF-OOH in HWE reactions is shown in a tentative mechanism given in Scheme 3. Once THF-OOH is formed, a reduction step is required to give THF-OH. This compound is in equilibrium with the ring-opened aldehyde (given the basic conditions of the reaction, we suspect that hydroxide deprotonates THF-OH, with the equilibrium lying to the side of the ring-opened aldehyde–alkoxide intermediate).

An alternative possibility is that γ-butyrolactone is formed during the decomposition of THF-OOH.[17,18] However, an alkene reduction step would then be necessary to explain the formation of compounds such as **4**.

In conclusion, the reduction of THF-OOH to give THF-OH (a masked aldehyde) occurs under microwave-assisted HWE reaction conditions. THF-OH effectively competes with the intentionally added aldehyde (carbonyl) reactant. HWE reactions routinely employ THF as the reaction solvent. To circumvent this problem one should degas the THF solvent at the very least (and any co-solvent, e.g., water) and test rigorously for the presence of peroxides in laboratory-grade THF. For the HWE reactions detailed herein, the conventionally heated reactions showed no side products containing a THF moiety. However, the employment of a suitable reductant, for example, $P(OEt)_3$, led to formation of the same side products. Thus, a substrate containing a suitable functionality may play the same role.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

References and Notes

(1) Kelly, S. E. In *Comprehensive Organic Synthesis*; Vol. 1; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, **1991**, 729.

(2) (a) Jarvis, A. G.; Whitwood, A. C.; Fairlamb, I. J. S. *Dalton Trans.* **2011**, *40*, 3695. (b) For a review on the use of dba-Z ligands in palladium catalysis, see: Fairlamb, I. J. S. *Org. Biomol. Chem.* **2008**, *6*, 3645.

(3) For other reported MW-assisted HWE reactions, see: (a) Dakdouki, S. C.; Villemin, D.; Bar, N. *Eur. J. Org. Chem.* **2010**, 333. (b) Rossi, D.; Carnevale, Baraglia. A.; Serra, M.; Azzolina, O.; Collina, S. *Molecules* **2010**, *15*, 5928. Microwave-assisted Wittig reactions (ref. 2c. in THF) have been described, see: (c) Frattini, S.; Quai, M.; Cereda, E. *Tetrahedron Lett.* **2001**, *42*, 6827. (d) Wu, J.; Wu, H.; Weia, S.; Dai, W.-M. *Tetrahedron Lett.* **2004**, *45*, 4401.

(4) 1,3-Bis(phosphonato)acetone (**2**, 215 mg, 1.2 equiv, 0.65 mmol) was added to a stirring solution of compound **3** (350 mg, 2 equiv, 1.09 mmol) in THF (3 mL). To this NaOH (87 mg, 4 equiv, 2.17 mmol) dissolved in H_2O (0.35 mL) was added dropwise. The mixture was heated in a microwave for ca. 1.5 h at 110 °C. After cooling, the solution was washed with sat. NH_4Cl (aq, 5 mL) and extracted with EtOAc (5 × 5

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mL). The organic phases were combined and then dried over Na_2SO_3 and filtered. After removing the solvent in vacuo the product was purified by column chromatography on silica gel eluting with EtOAc–toluene (5:95, v/v) to afford **1** (88 mg, 25%) and compound **4** as an off-white solid (71 mg, 25%). In a repeat reaction, **4** was isolated in 21% yield (after 1 h heating in the microwave).

Compound **4**: mp 152–154 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.36 (d, *J* = 16.5 Hz, 1 H, Hh), 7.87–7.78 (m, 4 H, Ar), 7.73–7.68 (m, 1 H, Hj), 7.57–7.43 (m, 7 H, Hk, *p*-H and Ar), 7.29 (app. tdd, *J* = 7.5, 2.5, 1.5 Hz, 1 H, Hl), 7.03 (ddd, *J* = 14.5, 8.0, 1.5 Hz, 1 H, Hm), 6.34 (d, *J* = 16.5 Hz, 1 H, Hg), 4.09 (app. quin, *J* = 6.5 Hz, 1 H, Hd), 3.80 (ddd, *J* = 8.0, 7.0, 6.5 Hz, 1 H, Ha), 3.70–3.64 (m, 1 H, Ha), 2.60 (dd, *J* = 15.5, 7.0 Hz, 1 H, He), 2.46 (dd, *J* = 15.5, 6.0 Hz, 1 H, He), 2.04–1.94 (m, 1 H, Hc), 1.91–1.77 (m, 2 H, Hb), 1.42–1.31 (m, 1 H, Hc). ^{31}P NMR (162 MHz, $CDCl_3$): δ = 42.23 (s). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.5 (Cf), 143.3 (d, *J* = 8 Hz, Hh), 138.5 (d, *J* = 8 Hz, Ci), 133.6 (d, *J* = 83 Hz, *ipso*-C), 133.1 (d, *J* = 11 Hz, Cm), 132.60 (d, *J* = 11 Hz, Ar), 132.56 (d, *J* = 11 Hz, Ar), 132.2 (d, *J* = 3 Hz, Ck), 132.2 (d, *J* = 84 Hz, *ipso*-C), 132.1 (d, *J* = 85 Hz, *ipso*-C), 132.1 (d, *J* = 3 Hz, *p*-Ar), 132.0 (d, *J* = 3 Hz, *p*-Ar), 131. 7 (d, *J* = 10 Hz, Ci), 129.6 (Cg), 129.4 (d, *J* = 12 Hz), 128.9 (d, *J* = 13 Hz, Ar), 128.8 (d, *J* = 13 Hz, Ar), 128.6 (d, *J* = 9 Hz, Cj), 75.3 (Cd), 67.9 (Ca), 44.4 (Ce), 31.6 (Cb), 25.7 (Cc). ESI-HRMS: *m/z* calcd for $C_{26}H_{26}OPS$: 433.1386; found: 433.1380 $[MH]^+$. ESI-LRMS: *m/z* (rel. %): 455 (80) $[MNa]^+$, 433 (100) $[MH]^+$, 401 (4), 301 (4), 236 (7). IR (ATR): ν = 2966 (w), 2861 (w), 1658 (br, m), 1583 (w), 1478 (w), 1457 (w), 1435 (m), 1387 (w), 1311 (w), 1260 (w), 1184 (w), 1162 (m), 1120 (w), 1097 (m), 1059 (m), 1027 (m), 998 (m), 970 (m), 798 (br, m), 755 (m), 709 (s), 690 (s) cm^{-1}. Crystals suitable for study by X-ray diffraction were grown by slow evaporation from 1,4-dioxane.

(5) (a) Jung, H. H.; Floreancig, P. E. *Org. Lett.* **2006**, *8*, 1949. (b) Gauthier, R.; Axiotis, G. P.; Chastrette, M. *J. Organomet. Chem.* **1977**, *140*, 245.

(6) Kim, D. Y.; Kong, M. S.; Lee, K. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1361.

(7) (a) Kumar, G. D. K.; Saenz, D.; Lokesh, G. L.; Natarajan, A. *Tetrahedron Lett.* **2006**, *47*, 6281. (b) Xu, Y.; Qian, L.; Prestwich, G. D. *Org. Lett.* **2003**, *5*, 2267. (c) Hawkins, M. J.; Powell, E. T.; Leo, G. C.; Gauthier, D. A.; Greco, M. N.; Maryanoff, B. *Org. Lett.* **2006**, *8*, 3429.

(8) (a) Mahlokozera, T.; Goods, J. B.; Childs, A. M.; Thamattoor, D. M. *Org. Lett.* **2009**, *11*, 5095. (b) For a related reference on unexpected reactions of THF, see: Wang, X.-S.; Zhou, J.; Yang, K.; Li, Y.-L. *Tetrahedron Lett.* **2011**, *52*, 612.

(9) (a) Davies, H. M. L.; Hansen, T.; Churchill, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 3063. (b) Diaz-Requejo, M. M.; Belderraín, T. R.; Nicasio, C. M.; Trofimenko, S.; Pérez, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 896.

(10) Cheng, K.; Huang, L.; Zhang, Y. *Org. Lett.* **2009**, *11*, 2908.

(11) (a) Moody, C. J.; Whitham, G. H. *Reactive Intermediates*; Oxford University Press: Oxford, **2006**. (b) Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry*, Chap. 1; University Science Books: Sausalito, **2006**. (c) Doyle, M. P.; Duffy, R.; Ratnikov, M.; Zhou, L. *Chem. Rev.* **2010**, *110*, 704.

(12) (a) Hill, D. J. T.; Shao, L. Y.; Pomery, P. J.; Whittaker, A. K. *Polymer* **2001**, *42*, 4791. (b) Parsons, A. F. *An Introduction to Free Radical Chemistry*; Blackwell Science: Oxford, **2000**. (c) Troisi, L.; Granito, C.; Ronzini, L.; Rosato, F.; Videtta, V. *Tetrahedron Lett.* **2010**, *51*, 5980.

(13) (a) Armarego, W. L. F.; Li, L. C. *Purification of Laboratory Chemicals*, 6th ed.; Elsevier: Oxford, **2009**, 73. (b) Hill, R. H.; Finster, D. *Laboratory Safety for Chemistry Students*; Wiley: Hoboken, **2010**, 5–56.

(14) Tsuji, S.; Kondo, M.; Ishiguro, K.; Sawaki, Y. *J. Org. Chem.* **1993**, *58*, 5055.

(15) A control reaction of $P(OEt)_3$ and 6 M NaOH in dioxane showed no evidence of oxidation of $P(OEt)_3$ under the reaction conditions by ^{31}P NMR spectroscopic analysis.

(16) The concentration of THF-OOH was determined in ‘Suzuki–Miyaura’ reaction mixtures employing aq THF (10:1) as $\geq$8.0 mM, see: Butters, M.; Harvey, J. N.; Jover, J.; Lennox, A. J. J.; Lloyd-Jones, G. C.; Murray, P. M. *Angew. Chem. Int. Ed.* **2010**, *49*, 5156.

(17) Robertson, A. *Nature (London)* **1948**, *162*, 153.

(18) Due to health and safety restrictions we have been unable to run direct control reactions with THF-OOH. The isolation and purification of THF-OOH has been previously attempted, see: (a) Nikishin, G. I.; Glukhovtsev, V. G.; Peikova, M. A.; Ignatenko, A. V. *Izv. Akad. Nauk SSSR Ser. Khim.* **1971**, *10*, 2323. (b) We do not recommend purification of THF-OOH by distillation – this could be extremely hazardous and dangerous!

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