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Synthesis of *S,S,O*-Orthoesters and 1,1-Difluoroalkyl Ethers via Reaction of Peroxides with Lithiated 1,3-Dithianes

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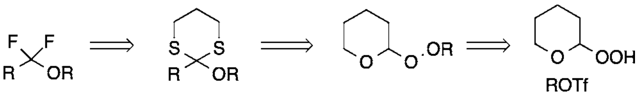
Supporting Information

ABSTRACT: Alkyl tetrahydropyranyl peroxides (ROOTHP) transfer alkoxide (OR) to lithiated 1,3-dithianes. The derived *S,S,O*-orthoesters undergo fluorodesulfurization with HF/pyridine and *N*-bromosuccinamide (NBS) to furnish difluoromethyl ethers. The overall protocol can be applied to synthesis of both terminal ($ROCF_2H$) and internal ($ROCF_2R'$) ethers. Application of the same set of reactions to a lithiated tris(alkylthio)alkane is shown to generate a trifluoromethyl ether.

Although many synthetic methods are available for the introduction of difluoromethyl groups adjacent to carbon, nitrogen, and sulfur,[1,2] there are fewer routes for the synthesis of difluoromethyl ethers and fewer yet that can be applied to both terminal ($ROCF_2H$) or internal ($ROCF_2R$) ethers.[2] We now demonstrate that the reaction of lithiated 1,3-dithianes and alkyl tetrahydropyranyl peroxides provides an efficient entry to both internal and terminal *S,S,O*-orthoesters, which are in turn readily converted to the corresponding difluoroalkyl ethers (Scheme 1).

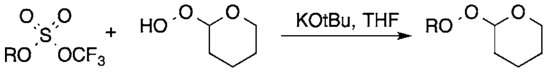
Scheme 1. Retrosynthesis



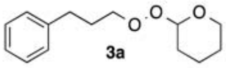
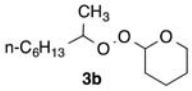
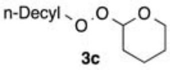
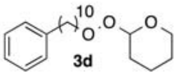
S,S,O-Orthoesters have been previously prepared by trapping of 1,3-dithiolane-2-ylium salts with alcohols,[3a,b] by thioacetalization of orthoformates,[3c] and by exchange of alkoxide.[3d] They have been observed as intermediates during the cross-dehydrogenative coupling of dithianes and alcohols.[3e] Our proposed route, involving intermolecular reaction of dialkyl peroxides with lithiated dithianes, had little precedent. Alkyl peroxides, endoperoxides, hydroperoxides, and bistrimethysilyl peroxide have been long known to react as electrophiles toward simple (unstabilized) organometallic reagents.[4] Recent work in our laboratory demonstrated successful *intramolecular* but not *intermolecular* reactions of alkyl peroxides with ketone enolates.[5] We could find no example of an intermolecular reaction between a dialkyl peroxide and a stabilized carbanion; the closest example is the hydroxylation of a lithiated sulfone by bistrimethylsilyl peroxide.[6]

Monoperoxyacetal electrophiles were prepared by alkylation of 2-tetrahydropyranyl hydroperoxide (**1**) with alkyl triflates in the presence of KOtBu (Table 1).[7,8] This methodology, originally developed for bisalkylation of 1,1-dihydroperoxides,[9] proved remarkably efficient for preparation of dialkyl peroxides; the yield for displacement at a secondary center exceeds any previous report.[10]

Table 1. Synthesis of Peroxide Electrophiles



1

R (triflate)	peroxide	yield (%)
$Ph(CH_2)_3$ **2a**	 **3a**	82
2-octyl **2b**	 **3b**	70
n-decyl **2c**	 **3c**	79
$Ph(CH_2)_{10}$ **2d**	 **3d**	75

Peroxides **3a**−**d** were next investigated for reactivity toward lithiated 1,3-dithianes, a class of nucleophiles known to react with carbonyl groups, epoxides, and alkyl halides.[11] As shown in Table 2, reaction of lithiated dithianes **4a**−**c** with **3a**−**d** at room temperature furnished moderate to good yields of the *S,S,O*-orthoesters (**5a**−**h**);[12] only minor differences were observed when reactions were conducted at −78 °C or in refluxing THF (not shown). The orthoesters are stable to routine isolation and chromatography but undergo rapid decomposition in the presence of even trace amounts of strong acid, presumably reflecting hydrolysis and/or elimination of the alkoxide.[3d,13] Orthoesters **5a** and **5c** were obtained in pure form following flash chromatography. However, **5b**, **5d**, and **5e** were accompanied by recovered starting materials which could only be completely

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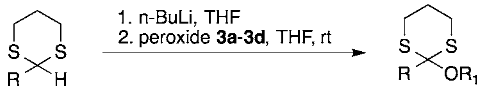
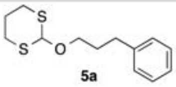
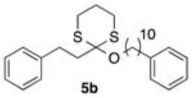
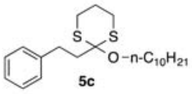
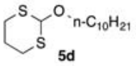
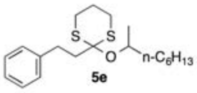
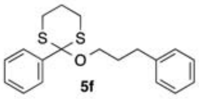
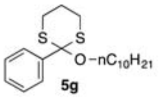
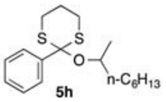
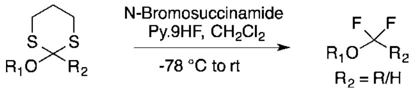
Table 2. Synthesis of *S,S,O*-Orthoesters



peroxide	dithiane R	*S,S,O*-orthoester	yield[a] (%) A	B	C
3a	H **4a**	 **5a**	63	67	58
3d	Ph(CH$_2$)$_2$ **4b**	 **5b**	57	72	73
3c	Ph(CH$_2$)$_2$ **4b**	 **5c**	70	71	55
3c	H **4a**	 **5d**	33	64	60
3b	Ph(CH$_2$)$_2$ **4b**	 **5e**	25	--	45
3a	Ph **4c**	 **5f**	--	71	--
3c	Ph **4c**	 **5g**	--	77	--
3b	Ph **4c**	 **5h**	--	65	--

[a] Conditions: (A) 1 equiv of *n*-BuLi; (B) 1.5 equiv of *n*-BuLi; (C) 5 mmol scale using 1.5 equiv of *n*-BuLi. See ref 12 for details.

Table 3. Synthesis of Difluoroethers from Orthoesters



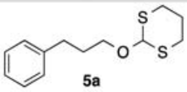
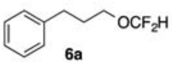
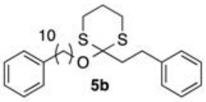
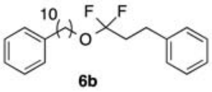
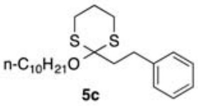
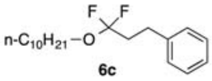
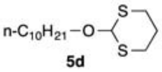
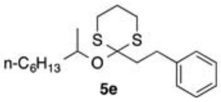
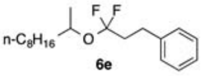
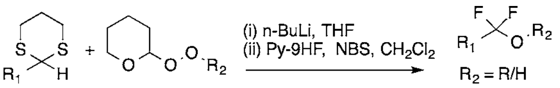
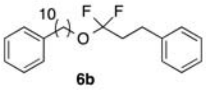
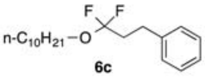
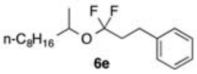
S,S,O-orthoester	difluoroether	yield (%)
 **5a**	 **6a**	62
 **5b**	 **6b**	70
 **5c**	 **6c**	69
 **5d**	$n\text{-}C_{10}H_{21}{-}OCF_2H$ **6d**	73
 **5e**	 **6e**	40

Table 4. Direct Synthesis of 1,1-Difluoroethers



peroxide	dithiane	difluoroether	yield[a] (%)
3d	**4b**	 **6b**	51
3c	**4b**	 **6c**	43
3c	**4a**	$n\text{-}C_{10}H_{21}{-}OCF_2H$ **6d**	26
3b	**4b**	 **6e**	39

[a] Yield over two steps.

removed using HPLC. Fortunately, the recovered dithiane did not interfere with subsequent fluorodesulfurization (see below).

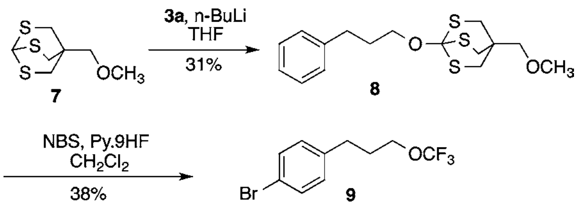
We next investigated fluorodesulfurization of the *S,S,O*-orthoesters, a reaction reported for only a handful of substrates.[14] Building upon methodology described for conversion of 1,3-dithianes into 1,1-difluoroalkanes,[15] we reacted the orthoesters **5a−e** with a combination of *N*-bromosuccinimide (NBS) and pyridine·9HF and obtained difluoroethers **6a−e** in good yields (Table 3).[16]

The *S,S,O*-orthoesters **5b−d** could also be directly subjected to oxidative fluorodesulfurization following filtration of the crude reaction mixtures through alumina.[16] This protocol delivers moderate yields of terminal and internal difluoroalkylethers in a rapid two-step protocol from the corresponding peroxide (Table 4).

The successful synthesis of *S,S,O*-orthoesters and difluoroalkyl ethers led us to investigate an extension of our strategy to synthesis of *S,S,S,O*-orthocarbonates and derived trifluoromethyl ethers.[17,18] Our initial results were not auspicious; reaction of peroxide **3a** with lithiated tris(methylthiomethane) resulted in the formation of multiple decomposition products (not shown). Assuming the problem reflected facile α elimination of lithium thioalkoxide from the lithiated trithiane,[19] we turned to [2.2.2]trithiaoctane **7**, which was prepared using a known procedure.[20] Deprotonation of trithiane **7** with *n*-BuLi, followed by addition of **3a**, resulted in a slow reaction that generated a modest yield of the *S,S,S,O* orthocarbonate **8** accompanied by recovered peroxide. Fluorination of **8** under the same conditions employed earlier provided brominated trifluoroether **9** in modest yield (Scheme 2).[21]

In conclusion, we have demonstrated the first example of intermolecular reaction of dialkyl peroxides with stabilized carbanions. The methodology allows preparation of internal and terminal *S,S,O*-orthoesters and difluoroalkyl ethers, and can be

Scheme 2. Synthesis of a Trifluoromethyl Ether



extended to the synthesis of *S,S,S,O*-orthocarbonates and trifluoromethyl ethers.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, references for peroxide safety, ^{1}H and ^{13}C NMR spectra of new compounds, and ^{19}F spectra for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.
Safety note: Although no safety issues were encountered in the course of this work, any preparative work with peroxides should be conducted with an awareness of the potential for spontaneous and exothermic decomposition reactions. See the Supporting Information for information related to peroxide safety.

■ ACKNOWLEDGMENTS

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(8) General procedure for synthesis of alkyl tetrahydropyranyl peroxides **3a**−**d**: An alcohol (10 mmol) was dissolved in dry CH_2Cl_2 (30 mL). The solution was cooled to 0 °C, and triflic anhydride (14 mmol) and 2,6-lutidine (14.5 mmol) were sequentially added via syringe. The reaction was stirred for 15 min at 0 °C and then diluted with ice-cold hexane (60 mL). The resulting solution was washed with ice-cold 0.1 M aq $KHSO_4$ (40 mL), and the separated aqueous layer was extracted with another portion of cold hexane (40 mL). The combined organic layers were dried over Na_2SO_4 and concentrated on a rotary evaporator (bath temperature 10 °C). The residue was placed under high vacuum (≤0.5 mmHg) to generate nearly pure triflate, which was immediately placed in a −20 °C freezer and used for the next hour. 2-Tetrahydropyranyl peroxide (**1**) (10 mmol) was added under nitrogen to a 0 °C solution of KOtBu (10 mmol) in dry THF (50 mL). The mixture was stirred for 3 min, whereupon was added the preformed alkyl triflate (10 mmol). The reaction was stirred at 0 °C for 10 min, then quenched with water, and extracted with 10% ethyl acetate/hexanes. The organic layer was dried over Na_2SO_4, and the residue obtained upon concentration was chromatographed using 1% ethyl acetate/hexanes.

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(12) General procedure for synthesis of *S,S,O*-orthoesters: *n*-BuLi (0.75 mmol) was added to a solution of the dithiane (0.5 mmol) in dry THF (4 mL) at room temperature. The reaction was stirred for 10 min, and then the peroxide (0.5 mmol) was added dropwise as a solution in THF (1 mL/mmol scale) via syringe. The reaction was stirred for 40 min and then quenched by addition of acetone (0.5 mL/mmol substrate). The resulting solution was filtered through a 2-in. pad of neutral alumina (50−200 μm) and flushed with 25 mL of ethyl acetate. The residue obtained upon concentration of the filtrate was purified by silica gel chromatography. For reactions using only 1 equiv of *n*-BuLi, compounds **5b**, **5,d** and **5e** were additionally purified by preparative HPLC using 5% ethyl acetate/hexanes. For reactions on a 5 mmol scale, the crude reaction mixture was diluted with 120 mL of hexanes and washed with water (2 × 20 mL). The separated organic layer was dried over sodium sulfate and the concentrated residue purified by chromatography (1% ethyl acetate/hexanes).

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(16) General procedure for synthesis of difluoroethers: Pyridine·9HF (3 mmol) was added (plastic syringe, Teflon needle) to a −78 °C solution of *N*-bromosuccinamide (2.5 mmol) in dry CH_2Cl_2 (8 mL). The solution was stirred for 5 min. A solution of *S,S,O* orthoester (1 mmol) in dry CH_2Cl_2 (2 mL) was added dropwise. The cold bath was removed after 20 min, and the reaction was allowed to room temperature while stirring (∼10 min). The reaction mixture was placed under a blanket of nitrogen and diluted with hexanes (10 mL); the liquid portion was passed through a 2-in. plug of neutral alumina (50−200 μm) in a plastic syringe barrel fitted with a cotton plug leaving the solid residue in the reaction flask. The product was eluted with 30 mL hexanes and the residue obtained upon concentration of the combined organic layers was purified through silica gel using 1% ether/pentane. Note that the yields reported in Table 4 reflect conversion of peroxide to difluoroether (two steps). This method also implemented on a 0.5 mmol scale from pure orthoesters (Table 3).

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(21) The trifluoromethyl ether was synthesized from purified orthocarbonate by the procedure described in ref 16 except that 5 equiv of NBS and 2 equiv of Py·9HF were employed.