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ARTICLE TYPE

Synthesis of *n*-alkyl terminal halohydrin esters from acid halides and cyclic ethers or thioethers under solvent- and catalyst-free conditions

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An efficient and eco-friendly protocol has been developed for the preparation of *n*-alkyl terminal halohydrin esters under solvent- and catalyst-free conditions. Ring opening of cyclic ethers by organic acid halides affords the 1,4- and 1,5-halohydrins, OH-protected by different acyl groups. The green reaction conditions, simple work-up procedures, high yields and broad substrate scope of the reaction highlight the positive features of this method.

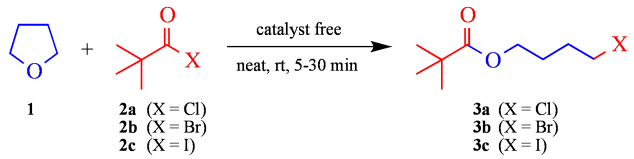
The concept of sustainability is a hot topic in contemporary chemical research as a means to access new therapeutic agents and novel materials.[1] The interest in methodology development is not only limited to improving yields of products, but also seeks to avoid the use of hazardous organic solvents and the production of chemical waste.[2] Eco-friendly chemical reactions and solvent-free procedures are gaining in importance, and thus, a number of new chemical processes have been designed to proceed under green reaction conditions.[3]

Halohydrins and their derivatives represent a large class of compounds, which have been used frequently in the synthesis of biologically active molecules.[4,5] Among these building blocks, 1,4- and 1,5-halohydrins and their derivatives are valuable structural motifs.[6] The most straightforward approach for the synthesis of OH-protected 1,4- and 1,5-halohydrins has been the ring-opening of cyclic ethers with organic acid halides in the presence of strong Lewis acid catalysts at high temperatures.[7] Additonally, multi-step conversions of 4- and 5-halocarboxylates and monohalogenation of 1,4- and 1,5-diols followed by OH protection,[5] have also proven to be important strategies for this purpose. In the litureture, uncatalized ring-opening reactions of cyclic ethers have also been reported with acetyl iodide and iodoglyoxalates.

Although these procedures have their advantages, they also suffer from limitations such as tedious reaction procedures, pH conditions that degrade other functional groups, contamination by side products, low yields, the hygroscopic nature of catalysts and the use of chlorinated organic solvents. These requirements render them commercially as well as ecologically untenable, and consequently, restrict them from extensive industrial applications. To overcome these problems, the development of more general and convenient processes using readily accessible and inexpensive substrates is a continuing goal. In this connection, we wish to advance a simple and efficient protocol for the preparation of OH-protected terminal halohydrins under green reaction conditions.

In recent decades, the adoption of green chemistry methods has increased dramatically. The use of chemical transformations under solvent- and catalyst-free conditions are significantly safer as well as less toxic and more cost effective. Meanwhile, the ring opening of cyclic ethers is attracting increased attention in synthetic organic and material chemistry.[6] These factors have led us to focus on the synthesis of terminal halohydrins and their derivatives under more eco-friendly reaction conditions.

In an extension of our previous work on pivaloylation of alcohols,[9] protective opening of epoxide (POE) with pivaloyl halides,[10] and synthesis of chloroesters,[11] we report herein our recent progress on an efficient method for the preparation of 4-halobutyl and 5-halopentyl esters. Direct treatment of five- and six-membered cyclic ethers (Scheme 1) with organic acid halides under neat and catalyst-free conditions at room temperature furnishes these targets in excellent yields.



1 **2a** (X = Cl) **2b** (X = Br) **2c** (X = I) **3a** (X = Cl) **3b** (X = Br) **3c** (X = I)

Scheme 1. Opening of tetrahydrofuran (**1**) with pivaloyl halides (**2a-2c**) under green reaction conditions.

The reaction of tetrahydrofuran (THF, **1**) with Piv-Cl (**2a**) afforded 4-chlorobutyl pivalate (**3a**, 99% yield) under neat and catalyst free conditions at rt within 30 min (Scheme 1). The same reaction proceeded smoothly with Piv-Br (**2b**) and Piv-I (**2c**) to afford 4-bromobutyl pivalate (**3b**, 99% yield, 10 min) and 4-iodobutyl pivalate (**3c**, 100% yields, < 5 min), respectively, under similar conditions. It is noteworthy that, in these three transformations, the rate of reaction gradually increased from

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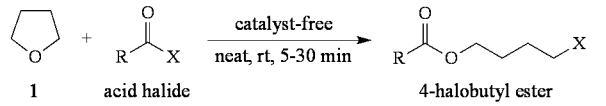
Piv-Cl to Piv-Br to Piv-I in accord with the relative leaving group–nucleophile character of the anions Cl^- to Br^- to I^- (Table 1).

Table 1. Opening of THF ring with organic acid halides under solvent- and catalyst-free conditions.[a]



1 acid halide 4-halobutyl ester

entry	acid halide	product	time (min)	Yield (%)
1	**2a**	**3a**	30	99
2	**2b**	**3b**	10	99
3	**2c**	**3c**	< 5	100
4	**4**	**11**	10	95
5	**5**	**12**	5	99
6	**6**	**13**	< 5	99
7	**7**	**14**	5	100
8	**8**	**15**	10	95
9	**9**	**16**	10	100
10	**10**	**17**	20	99

[a]Reaction conditions: THF (1.0 eq), R-CO-X (1.1 eq). Yields given are isolated yields.

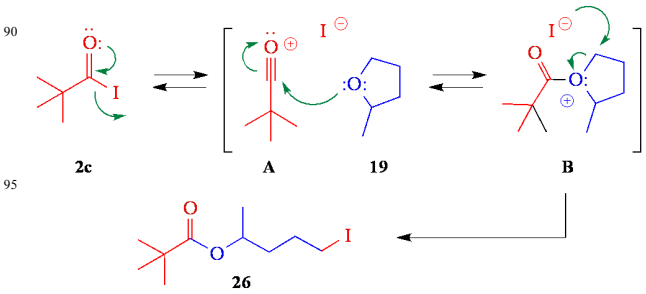
To assess the advantages of solvent-free conditions, we treated THF (**1**) with Piv-Cl (**2a**) in different aprotic and protic solvent systems (CH_2Cl_2, CH_3CN, Ether and MeOH), including aqueous media (H_2O), as done in our previous report on the POE reaction with pivaloyl halides.[10] In the present screening studies, we observed that the neat reaction afforded far better yields of 4-chlorobutyl pivalate (**3a**) than under any of the aprotic media examined. Furthermore, in all cases using protic solvents including water, the same procedure afforded neither **3a** nor the predicted 4-chlorobutanol product in contrast to the POE method.[10]

As part of our effort to elevate the synthetic value of our new protocol, we have screened a selection of different organic acid halides[12] (Table 1) under the same reaction conditions. In this investigation, we obtained some unanticipated results. With the exception of THF, the other ether substrates failed to afford the expected ring-opened products with pivaloyl chloride or bromide. With acyl iodides, however, all of the cyclic ethers reacted smoothly under the standard protocol and the corresponding 4-iodobutanol esters **11-17** were formed in high yields (>95%) within 5-10 min at rt (Table 1).

Following optimization of the reaction conditions, we turned our attention to evaluating the substrate scope and limitations of the current procedure. For this purpose, we used several five- and six-membered cyclic ethers, as well as tetrahydrothiophene, in combination with a series of acid iodides (Table 2). In all attempts, the cyclic ethers reacted rapidly and cleanly with the acid iodides to afford the corresponding ring opened products under neat and catalyst-free conditions at rt.

Under the optimized conditions, 2,5-dihydrofuran (**18**) reacted with different acyl iodides to give the corresponding OH-protected (*Z*)-4-iodobut-2-en-1-ols **22-25** (Table 2). Products incorporating a double bond would allow for further synthetic elaboration, and thus, could prove more useful in applications aimed toward the assembly of complex bioactive molecules.[5] No *cis* to *trans* isomerization was detected in any of the reactions.

The reaction of 2-methyltetrahydrofuran (**19**) with acyl iodides under neat and catalyst-free conditions afforded regioselective ring-opened products **26-30**. In contrast to many previously reported methods, this new protocol afforded the product resulting from regioselective ring opening from the less sterically hindered side.[7] A proposed mechanism for the reaction is illustrated in Scheme 2. Initial generation of the acylium ion **A**

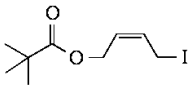
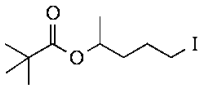
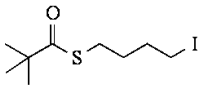
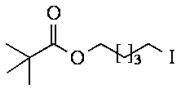
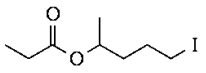
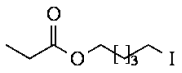
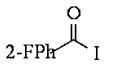
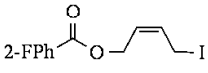
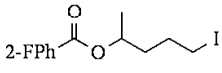
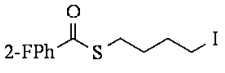
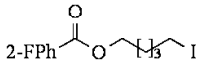
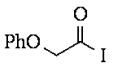
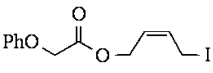
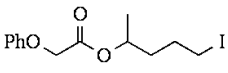
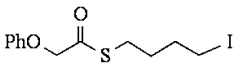
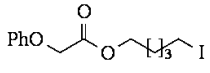
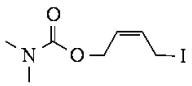
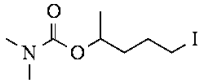
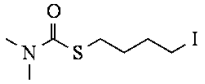
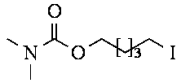


Scheme 2. Proposed reaction mechanism for product formation from 2-methyltetrahydrofuran (**19**) and pivaloyl iodide (**2c**).

by loss of iodide would be followed by addition of the ether oxygen to the acylium carbon to give the cyclic oxonium intermediate **B**. Attack by I^- at the α-carbon of this oxonium species would then open the ring to give product **26**. As expected, this S_N2 ring-opening process preferentially occurs at the less hindered C5 of the heterocycle. The observation that THF (**1**) does not react with pure NaI under these reaction conditions confirms that addition of the ether oxygen to the acyl cation takes place prior to nucleophilic attack by the halide ion (Scheme 2).

The generality of the ring opening reaction of cyclic ethers was further extended to tetrahydrothiophene (**20**). Despite the greater nucleophilicity of the sulfur in this substrate, only the acyl iodides reacted to produce *S*-4-iodobutylthioesters **31-34**. To the best of our knowledge, this is the first report describing the ring

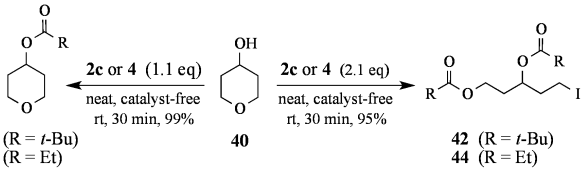
Table 2. Opening of cyclic ethers/thioethers with organic acid iodides under solvent- and catalyst-free conditions at rt.[a]

entry	Acid Iodide	**18**	**19**	**20**	**21**
1	 **2c**	 **22** (100%)	 **26** (98%)	 **31** (100%)	 **35** (100%)
2	 **4**	——	 **27** (95%)	——	 **36** (99%)
3	 **8**	 **23** (95%)	 **28** (95%)	 **32** (97%)	 **37** (94%)
4	 **9**	 **24** (99%)	 **29** (97%)	 **33** (100%)	 **38** (99%)
5	 **10**	 **25** (98%)	 **30** (95%)	 **34** (98%)	 **39** (98%)

[a]Reaction conditions: Cyclic ether (1.0 eq), R-CO-I (1.1 eq). Yields given are isolated yields.

opening of a cyclic thioether by an organic acid halide under a solvent- and catalyst-free regime. Access to thioesters of this type could facilitate future efforts to synthesize sulfur containing bioactive natural products.[13] The mechanism for ring opening of tetrahydrothiophene should parallel that shown in Scheme 2.

Reaction of tetrahydro-2*H*-pyran (**21**) with different acyl iodides afforded OH-protected 5-iodopentanols **35-39** (Table 2). Once again, acid chlorides and bromides proved unreactive toward **21** under the optimized conditions. To further demonstrate the the utility of the current transformation, we investigated the use of 4-hydroxytetrahydro-2*H*-pyran (**40**) as a substrate (Scheme 3). Standard treatment of **40** with 1.1 eq of Piv-I (**2c**) afforded the OH-protected tetrahydro-2*H*-pyran-4-yl pivalate (**41**). Treatment of **40** with 2.1 eq of **2c**, however, proceeded smoothly to afford



Scheme 3. The ring opening reaction of 4-hydroxytetrahydro-2*H*-pyran (**40**) with **2c** (R = *t*-Bu) and **4** (R = Et). Yields given are isolated yields.

the ring-opened product, 5-iodopentane-1,3-dipivalate (**42**), in high yield (95%) within 30 min. Similar results were achieved when substrate **40** was reacted with 1.1 eq and 2.1 eq of propionyl iodide (**4**) to give the OH-protected 4-hydroxytetrahydro-2*H*-pyran (**43**) and 5-iodopentane-1,3-dipropionate (**44**), respectively.

In conclusion, we have developed an improved procedure for the preparation of 4-iodobutanol and 5-iodopentanol esters under solvent- and catalyst-free conditions. This protocol has considerable potential in the area of synthetic organic chemistry and significantly enhances our ability to deliver important organic molecules in a more efficient and eco-friendly manner. Indeed, this new protocol offers numerous advantages including high yields, straightforward reaction conditions and broad scope, while eliminating the need to use hazardous solvents and/or expensive catalysts. The present methodology could find wide application in the synthesis of biologically active natural products and new therapeutic agents.

General Experimental Procedure

The reaction was carried out by simple addition of the organic acid halide (1.1 mmol) to the cyclic ether (1.0 mmol) in a 10 mL round-bottomed flask under solvent- and catalyst-free conditions at rt. The reaction mixture was stirred at room temperature and monitored by TLC. Upon completion, the crude mixture was diluted with EtOAc (5 mL) and washed with saturated aqueous $NaHCO_3$ (5 mL). The resulting solution was extracted again with EtOAc (10 mL) and the combined organic layers were dried over Na_2SO_4. The mixture was then concentrated *in vacuo* to yield the corresponding product. Column chromatography was performed, if necessary, but generally the products required no further purification.

Procedure for the preparaion of Acid Iodide/ Acid Bromides.

The required acid iodides/acid bromides were prepared by simple addition of 1.2 Eq. NaI/LiBr to the corresponding acid chlorides (1 Eq.) in a 5 mL pear shaped flask and stirred for 10 min under closed vessel conditions at rt.[11] When the acid chlorides completely converted into acid iodides/acid bromides, the colourless reaction mixtures (for acid iodides) were turned to dark blackish yellow (for acid iodides)/ reddish yellow (for acid bromides). We have used these prepared acid halides directly for the ring cleavage reactions with out purification.

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Synthesis of *n*-alkyl terminal halohydrin esters from acid halides and cyclic ethers or thioethers under solvent- and catalyst-free conditions

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Abstract:

An efficient and eco-friendly protocol has been developed for the preparation of *n*-alkyl terminal halohydrin esters under solvent- and catalyst-free conditions. Ring opening of cyclic ethers by organic acid halides affords the 1,4- and 1,5- halohydrins, OH-protected by different acyl groups. The green reaction conditions, simple work-up procedures, high yields and broad substrate scope of the reaction highlight the positive features of this method.

Graphical Abstract: