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COMMUNICATION

Protective opening of epoxide using pivaloyl halides under catalyst-free conditions†

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An efficient and environmentally benign protocol for protective opening of epoxide (POE) with pivaloyl halides in solvent-free conditions and in aqueous media under catalyst-free conditions has been developed. The green reaction conditions, simple work-up procedures, high yields and broad scope of the reaction illustrate the good synthetic utility of this method. The key advantages of the reaction are regioselectivity and reconvertability of products into their prior epoxides in the presence of mild reaction conditions.

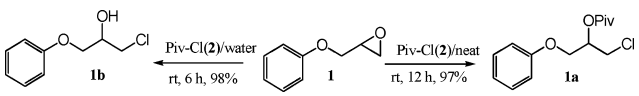
Vicinal halohydrins and their derivatives are versatile building blocks for the synthesis of biologically active compounds, and especially of halogenated marine natural products.[1,2] Opening of suitably appended epoxides is an important procedure for these vicinal halohydrins and their derivatives. Therefore, there is great current interest in epoxide ring-opening chemistry. Over the past decades, many protocols have been established for the epoxide ring opening.[3,4] Despite having rich literature on epoxide ring-opening chemistry, still no method exists with pivaloyl halides.

Preparation of *vic*-halohydrins by epoxide opening are well known with elemental halogens, hydrogen halides, metal halides *etc*.[5] Although these protocols have their own advantages, they endure one or more limitations such as tedious reaction procedures, extreme pH levels affecting other functional groups, unwanted byproducts, low yields, hygroscopic nature of catalyst and use of hazardous solvents, which makes them commercially as well as environmentally unfavourable, and consequently restricting them for large-scale applications.

Another aspect is maintenance and protection of the oxirane ring in the case of total synthesis of natural products with epoxide functionality.[6] The difficulty associated with epoxides is their instability due to the highly strained three-membered ring. This makes epoxides react with a wide variety of reagents such as electrophiles, nucleophiles, acids, bases, some reducing agents and oxidizing agents.[7,8] To circumvent these problems, there is a substantial need for protective opening of the oxirane ring into its derivatives from which it can be easily reconstructed with consistent regio- and stereoselectivity. In view of these typical limitations, there is a requirement for widely applicable alternative approaches, preferably using aqueous or solvent-free conditions.

Green chemical reactions have become a preeminent issue in recent decades. Reactions in solvent-free or aqueous media under catalyst-free conditions are considerably more safe, non-toxic, environmentally friendly and inexpensive. The context of protective opening of epoxide (POE) is gaining increased interest in synthetic organic chemistry, and thus this tenet gave us attention to focus on preparation of *vic*-halopivaloylates and *vic*-halohydrins under green reaction conditions.

In continuation of our previous work on pivaloylation of alcohols,[9] herein we report our recent progress on an inexpensive and highly efficient protocol for POE with pivaloyl halides under catalyst-free conditions at room temperature. Pivaloylation of oxiranes in solvent-free conditions afforded *vic*-halopivaloylates and the same in water afforded simple *vic*-halohydrins (Scheme 1). These two products, *vic*-halopivaloylates and *vic*-halohydrins can be easily reconvertable into their prior epoxide in protic solvents under mild reaction conditions,[10] like K_2CO_3 in MeOH *etc*. To the best of our knowledge, this is the first report of regioselective ring opening of epoxide with pivaloyl halides in solvent-free and aqueous media under catalyst-free conditions at rt.



Scheme 1 Opening of epoxide with Piv-Cl under catalyst-free conditions.

In a model POE reaction, the 2-phenoxymethyl-oxirane (**1**) is reacted with pivaloyl chloride (**2**) under neat and catalyst-free conditions at room temperature for 12 h, afforded 2,2-dimethyl-propionic acid 1-chloromethyl-2-phenoxy-ethyl ester (**1a**) in 97% yields (Scheme 1) with high regioselectivity. When the same reaction was carried out in aqueous and catalyst-free conditions at room temperature for 6 h afforded 1-chloro-3-phenoxy-propan-2-ol (**1b**) in 98% yield and 2, 2-dimethyl-propionic acid. The latter was removed during workup. In fact, in both conditions, the halide ion (Cl^-) reacted on the less sterically

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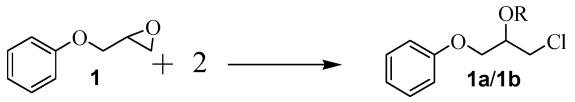
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c1gc15506g

Table 1 Solvent effect on epoxide ring opening with Piv-Cl[a]



Entry	Solvent	Time (h)	Product	Yields[b] (%)
1	Neat	12	**1a**	97
2	CH_2Cl_2	12	**1a**	95
3	CH_3CN	12	**1a**	86
4	Ether	12	**1a**	93
5	MeOH	6	**1b**	93[c]
6	Isopropanol	6	**1b**	89[c]
7	*tert*-Butanol	6	**1b**	84[c]
8	Water	6	**1b**	98[c]

[a] Reaction conditions: epoxide (1.0 eq.), Piv-Cl (1.1 eq.), catalyst-free, at rt. [b] Isolated yields (R = Piv, H[c]).

hindered side of the terminal epoxide to give predominantly a single product with high regioselectivity.

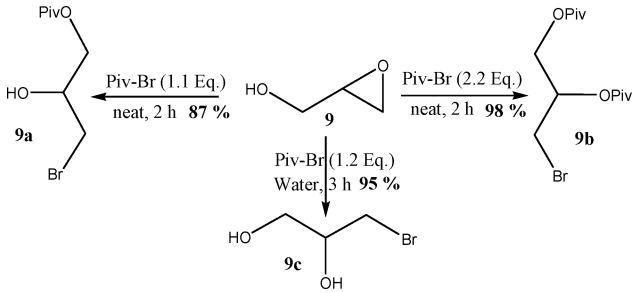
To investigate the advantageous role of the neat and aqueous conditions, we carried out the above reaction in different solvents such as CH_2Cl_2, MeCN, Et_2O, MeOH, isopropanol and *tert*-butanol. In these screening studies, we observed that in aprotic solvents, the reaction afforded 2, 2-dimethyl-propionic acid 1-chloromethyl-2-phenoxy-ethyl ester (**1a**) (Table 1, entries 1–4), whereas the same reaction in protic solvents afforded 1-chloro-3-phenoxy-propan-2-ol (**1b**) (Table 1, entries 5–8). It is also worth noting that the reaction time with protic solvents has reduced to half as compared to aprotic solvents.

It is noteworthy that when the POE reaction is carried out by using Piv-Br and Piv-I[11] instead of Piv-Cl in neat and aqueous media under catalyst-free conditions we have come across interesting results, such as the rate of reaction increased gradually from Cl to Br to I as the electronegativity decreases from chlorine to iodine (Table 2). In the course of our quest to increase the synthetic utility of our new method, we used Piv-CN, Piv-N_3, Piv-NO_3, and Piv-NO_2, *etc.*, for POE in solvent-free as well as aqueous media under catalyst-free conditions, without success.

After screening the reaction conditions, we turned our attention to examine the substrate scope and limitations of this simple procedure (POE) under neat reaction conditions, by using some structurally diverse epoxides (Table 2) and pivaloyl halides. In all attempts, the reactions proceeded smoothly, the epoxide ring opening appeared to be regiospecific and the nucleophilic attack of halide ions occurred at the less hindered side of epoxide. The corresponding *vic*-halopivaloylates were obtained in excellent yields in all cases; the results are summarized in Table 2.

The generality of the method (POE) was also extended to aqueous media to examine the substrate scope and limitations. In each case, the reactions proceeded smoothly under aqueous and catalyst-free conditions to afford the corresponding *vic*-halohydrins in excellent yields (Table 2).

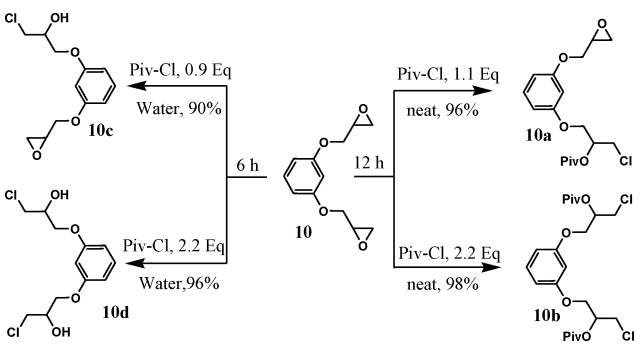
We further investigated the viability and worth of this POE in the aspect of natural products synthesis. In this connection, a well-known starting material glycidol (**9**) (Scheme 2) is used as a substrate and reacted with Piv-Br in different conditions. When the glycidol reacted with one equivalent of Piv-Br under neat and closed vessel conditions, without using any catalyst, the reaction afforded primary pivaloylated ring opening product (**9a**) in 87%



Scheme 2 Opening of glycidol with Piv-Br under catalyst-free conditions in both aqueous and neat conditions at rt.

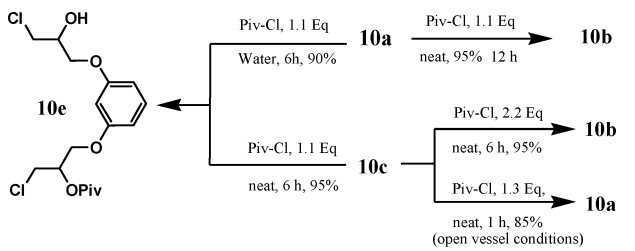
yields. The formation of **9a** is explained from our earlier work,[9] initially the primary alcohol in glycidol was pivaloylated, and thus released HBr opened the epoxide ring to yield product **9a**. When the same reaction is performed in aqueous and catalyst-free conditions afforded 1,2-dihydroxy compound **9c** in high yields (95%). In this exercise, when two equivalents of Piv-Br is reacted with glycidol under neat and closed vessel conditions, 1,2-dipivaloyl ester (**9b**) was obtained in excellent yields (98%). The compounds obtained in Scheme 2 have vital usage in synthetic organic chemistry.[10]

To further investigate the generality of the present method POE, we turned our attention to compound **10** containing two epoxide rings (Scheme 3). When the **10** reacted with one equivalent of Piv-Cl, predominantly one epoxide ring was opened to afford **10a** (12 h, 96%) in excellent yields, while the same reaction conducted by using adequate amounts of Piv-Cl (2.2 eq.), the reaction yielded **10b** (98%) in 12 h. Nevertheless, in aqueous media under catalyst-free conditions, the reaction of compound **10** with 0.9 eq. of Piv-Cl afforded **10c** (90%) and with 2.2 eq. of Piv-Cl yielded **10d** (96%) at rt in 6 h (Scheme 3).



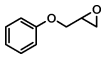
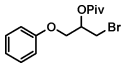
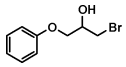
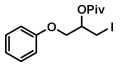
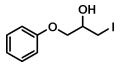
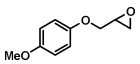
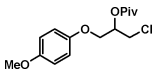
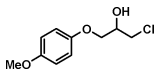
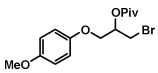
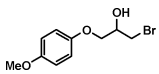
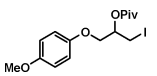
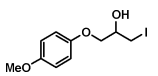
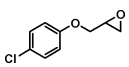
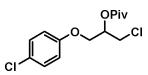
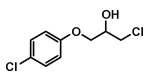
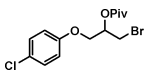
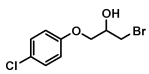
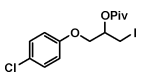
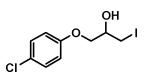
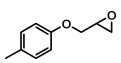
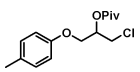
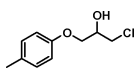
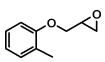
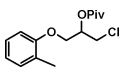
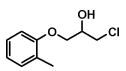
Scheme 3

The mono epoxide compounds (**10a** & **10c**) from Scheme 3, were used as substrates in POE method (Scheme 4). When



Scheme 4

Table 2 Opening of epoxide with Piv-X, both in solvent-free and aqueous media under catalyst-free conditions[a]

Entry		Product in neat(a)	Product in water (b)	Yields[b] (%)	Yields[c] (%)
1				99	95
				99	97
2				100	98
				98	98
				100	98
3				99	98
				100	98
				100	97
4				100	97
5				97	96
6				96	96
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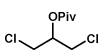
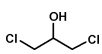
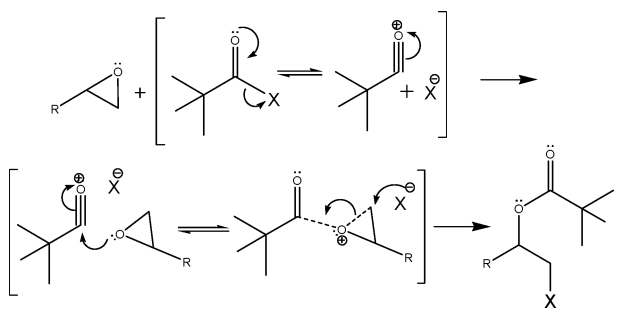
8				96	96

[a] Reaction conditions: epoxide (1.0 eq.), Piv-X (1.1 eq.), catalyst-free, at rt. [b] Isolated yields in neat conditions. [c] Isolated yields in aqueous conditions.

the compound **10a** reacted with Piv-Cl (1.1 eq) under neat and aqueous conditions, products **10c** (95%) and **10e** (90%) were obtained in good yields respectively. When **10c** reacted with 1.1 eq. of Piv-Cl under neat conditions, the reaction afforded **10e** (95%) in high yields, while the same reaction performed using 2.2 eq. of Piv-Cl afforded **10b** in 95% yields. The reaction of **10c** with Piv-Cl (1.3 eq) under neat and open vessel conditions afforded **10a** in considerable yields (85%).

A tentative mechanism has been suggested for POE reaction in Scheme 5. Initially the acyl cation facilitates the electrophilic attack on the oxygen atom of the epoxide ring followed by nucleophilic attack of halide ion on the less sterically hindered side of epoxide to give the desired products. In aqueous conditions, first the pivaloyl halides will get hydrolyzed to afford pivalic acid and HCl. The formed HCl react with epoxide to afford *vic*-halohydrins.



Scheme 5 Proposed mechanism for the formation *vic*-halo pivaloylates.

We have used benzoyl and acetyl chlorides in the same reaction (POE) conditions. The reaction with benzoyl chloride is found to be unsuccessful, whereas with acetyl chloride the reaction follows the same order as pivaloyl chloride.

In summary, we have developed a simple and efficient protocol for protective opening of epoxide (POE) without using any catalyst under solvent-free conditions and also the preparation of *vic*-halohydrins in aqueous media under catalyst-free conditions by using Piv-X. The POE is well warranted in synthetic organic chemistry because this method eliminates the use of hazardous, volatile organic solvents and expensive catalysts. Furthermore, this new protocol offers several advantages including improved yields, and simple experimental procedure. The present methodology is environmentally benign and also useful in synthesis of biologically active natural products and carbohydrate chemistry.

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Notes and references

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