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ARTICLE

High-yielding Aqueous Synthesis of Chloroacetophenones and Aroyl Chlorohydrins

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The use of large amounts of volatile organic solvents in industrial chemical processes contributes to widespread environment pollution. To help solve this problem, water and a phase transfer catalyst were used to replace organic solvents in the transformations of bromoacetophenones into chloroacetophenones and aroyl epoxides into aroyl chlorohydrins. The reactions were promoted by sulfonyl chlorides and gave quantitative or close to quantitative yields. Notably, chromatographic purification, which is laborious and consumes large amounts of organic solvents, was not needed. These two processes have opened a green and cost-effective channel to prepare chemical intermediates chloroacetophenones and aroyl chlorohydrins. The reaction mechanisms are discussed based on control experiments.

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INTRODUCTION

One of the problems plaguing chemical industries is the use of volatile organic solvents as reaction media and as eluents for chromatographic purification. The resulting solvents and labor costs as well as the pollution caused by these solvents are all serious problems. Therefore, various methods have been developed to reduce the amount of volatile organic solvents such as solvent-free mechanical chemical conversions,[1-7] deep eutectic solvent-mediated reactions,[8] ionic liquid-mediated reactions[9-13] and aqueous reactions.[14-22] Our group has developed several types of aqueous reactions,[23-26] some of which perform even better than the conventional organic solvent-mediated reactions. For example, when organic solvents were replaced with water in aqueous Darzens reactions between haloketones and aldehydes, a quantitative yield of the pure product was obtained after a simple filtration workup (i.e. no chromatography).[26] These types of reactions not only reduce labor costs and solvent consumption but they also reduce pollution which are all goals of our research.

Chloroacetophenones and aroylchlorohydrins are two important intermediates in organic synthesis[27-30] and the latter are bioactive compounds.[31-33] Chloroacetophenones are accessible *via* the oxidation of acetophenones using chloride sources such as N-chlorosuccinimide,[13, 34] HCl,[35, 36] Cl_2[37] or NaCl[38, 39] and oxidants such as O_2,[35] H_2O_2[40] or $K_2S_2O_8$,[39] or *via* halogen-exchange reactions starting with bromoacetophenones using LiCl,[41] NaCl,[38, 42] HCl,[43] $TiCl_3$[44] or $S_4N_5SbCl_5$[45] as chlorination agents. Aroylchlorohydrins are accessible by reacting aroyl epoxides with reagents such as HCl,[46] $TiCl_4$,[47, 48] F_3CCO_2H/LiCl,[49] AcOH/LiCl[50] or $CeCl_3$.[48]

Most of the above reactions are mediated by volatile organic solvents and the yields are less than quantitative. Further, for some aroylchlorohydrins, the stereoselectivities are not satisfactory.[47, 48] Green solvents such as aqueous CH_3CN and ionic liquids have both been applied to these reactions, but generally the yields are poor.[13, 38]

Herein, the preparations of chloroacetophenones using bromoacetophenones and of aroylchlorohydrins using aroyl epoxides are reported. Both reactions were promoted by sulfonyl chlorides mediated by water and most of the reaction yields were quantitative or close to quantitative. Chromatography was not needed to purify the products in these reactions.

RESULTS AND DISCUSSION

First, a mixture of bromoacetophenone (300 mg), hexadecyltrimethyl ammonium bromide (CTMAB, 0.1 equiv), Li_2CO_3 (1.2 equiv), $PhSO_2Cl$ (6.0 equiv) and water (5.0 mL) was stirred at room temperature. The reaction produced chloroacetophenone (**2a**) in 83% yield in 1.8 h (Table 1, entry 1). Without water, the yield was 91% (Table 1, entry 2) and without CTMAB, the reaction did not occur (Table 1, entry 3). When Li_2CO_3 was eliminated, the yield became quantitative but the reaction took 4 h (Table 1, entry 4). Next a serious of phase transfer catalysts (PTCs) were screened (Table 1, entries 4-10). All the PTCs gave quantitative yields but the reaction rate was the fastest (3 h) for benzyl triethyl ammonium chloride (TEBAC) (Table 1, entry 10).The effect of changing the amount of $PhSO_2Cl$ from 0.1-20.0 equiv was then studied (Table 1, entries 10-17). When the amount of $PhSO_2Cl$ was 8.0 equiv or higher, the reaction times decreased to 2.8 h and the yields increased from 9.5% to quantitative. The amount of

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Electronic Supplementary Information (ESI) available: Pictures of the synthesis of **2a**, general experimental information, general procedure for all products, analytic data of all products, references and NMR spectra for all compounds.. See DOI: 10.1039/x0xx00000x

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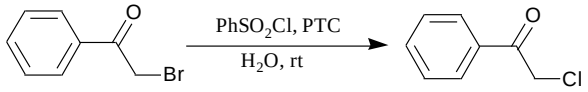
TEBAC was then varied from 0.01-2.0 equiv (Table 1, entries 15 and 18-24) and the fastest rate (1.5 h) was achieved with 0.5 equiv of TEBAC (Table 1, entry 23). Finally the effect of the amount of water (2.0-10.0 mL) was tested (Table 1, entries 23 and 25-27) and the best result was obtained with 5 and 2 mL of H_2O (Table 1, entries 23 and 25). From these results, the optimized conditions were determined to be bromoacetophenone (**1a**, 1.0 equiv), benzenesulfonyl chloride (8.0 equiv), TEBAC (0.5 equiv), H_2O (5 mL) at rt, which produced a quantitative yield in 1.5 h (Table 1, entry 23).

Table 1 Optimization of the aqueous reaction between bromoacetophenone and benzenesulfonyl chloride[a]



1a **2a**

Entry	**1a** (equiv)	$PhSO_2Cl$ (equiv)	PTC (equiv)[d]	H_2O (mL)	Li_2CO_3 (equiv)	t (h)	**2a** Yield(%)[b]
1	1.0	6.0	CTMAB (0.1)	5.0	1.2	1.8	83
2	1.0	6.0	CTMAB (0.1)	-	1.2	2.3	91
3	1.0	6.0	-	5.0	1.2	24	NR[c]
4	1.0	6.0	CTMAB (0.1)	5.0	-	4.0	>99
5	1.0	6.0	TBAB (0.1)	5.0	-	3.5	>99
6	1.0	6.0	Aliquat 336 (0.1)	5.0	-	3.5	>99
7	1.0	6.0	TBAF (0.1)	5.0	-	4.0	>99
8	1.0	6.0	SDS (0.1)	5.0	-	6.7	>99
9	1.0	6.0	DTAC (0.1)	5.0	-	3.6	>99
10	1.0	6.0	TEBAC (0.1)	5.0	-	3.0	>99
11	1.0	0.1	TEBAC (0.1)	5.0	-	24	9.5
12	1.0	0.5	TEBAC (0.1)	5.0	-	24	19
13	1.0	1.0	TEBAC (0.1)	5.0	-	24	52
14	1.0	4.0	TEBAC (0.1)	5.0	-	7.0	>99
15	1.0	8.0	TEBAC (0.1)	5.0	-	2.8	>99
16	1.0	10.0	TEBAC (0.1)	5.0	-	2.8	>99
17	1.0	20.0	TEBAC (0.1)	5.0	-	2.8	>99
18	1.0	8.0	TEBAC (0.01)	5.0	-	24	21
19	1.0	8.0	TEBAC (0.03)	5.0	-	24	65
20	1.0	8.0	TEBAC (0.05)	5.0	-	6.0	91
21	1.0	8.0	TEBAC (0.08)	5.0	-	3.7	>99
22	1.0	8.0	TEBAC (0.3)	5.0	-	2.1	>99
23	1.0	8.0	TEBAC (0.5)	5.0	-	1.5	>99
24	1.0	8.0	TEBAC (2.0)	5.0	-	1.5	>99
25	1.0	8.0	TEBAC (0.5)	2.0	-	1.5	>99
26	1.0	8.0	TEBAC (0.5)	8.0	-	2.0	>99
27	1.0	8.0	TEBAC (0.5)	10.0	-	2.0	>99

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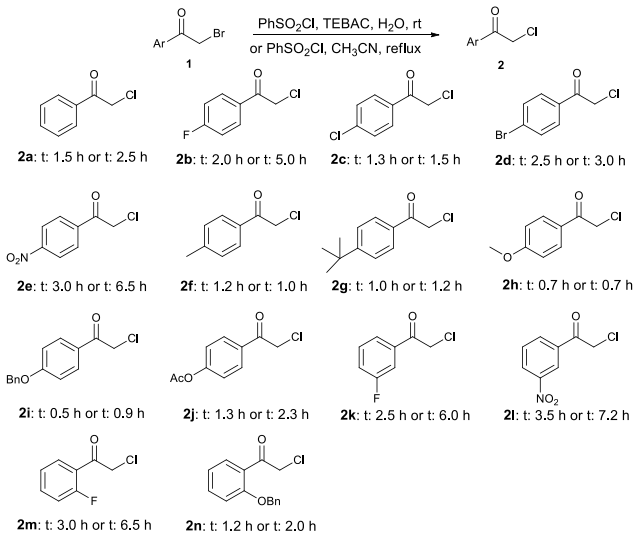
[a]Reaction conditions: bromoacetophenone (300 mg), benzenesulfonyl chloride, base, phase transfer catalyst (PTC), H_2O at rt. [b]All yields were isolated yields. [c]NR: No reaction. [d]TBAB=tetrabutyl ammonium bromide; Aliquat 336=tricapryl methyl ammonium chloride; TBAF=tetrabutyl ammonium fluoride; SDS=sodium dodecyl sulfonate; DTAC=dodecyl trimethyl ammonium chloride.

Under the optimized conditions, fourteen bromoacetophenones were successfully transformed into chloroacetophenones (Scheme 1, **2a**-**2n**). All the yields were quantitative and the reaction rates fast (0.5-3.5 h). At the end of the reactions, the excess $PhSO_2Cl$ was hydrolyzed using Na_2CO_3 and then the products were extracted. Then simple concentrations resulted in pure products. The reactions could be scaled up to 10 g with the same results. All the reaction mixtures became milky liquids under agitation in both 0.3 g and 10 g scales, which probably indicates that they are micelle-mediated reactions (SI, S2, Pictures 1 and 2).[51, 52]

The yields for the synthesis of these products reported in the literature are in the range of 36-100% and all the procedures utilize volatile organic solvents and require aqueous workups and chromatography to purify the products.[13, 34-40, 42-45, 53] In this study, external heating, organic solvents as reaction media and as elutes for chromatography were saved.

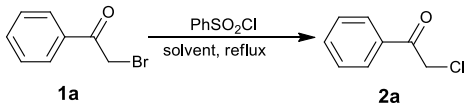
As shown in Scheme 1, the reaction rates for the substrates bearing electron-donating groups such as alkyl or alkoxyl groups were faster than those for the substrates bearing electron-withdrawing groups such as halo and nitro groups (**2f**-**2j** *vs* **2b**-**2e**). The rates for *meta*-substituted groups were similar to those for *para*-substituted groups (**2k** *vs* **2b**, **2l** *vs* **2e**). However, *ortho*-substituted groups had substantially slower reaction rates (**2b** *vs* **2m**, **2i** *vs* **2n**), which is probably due to steric effects.



Scheme 1 Quantitative synthesis of choroacetophenones from bromoacetophenones and benzenesulfonyl chloride. [a]Reaction conditions: bromoacetophenones (300 mg), benzenesulfonyl chloride, TEBAC (0.5 equiv) and H_2O (5 mL) at rt or CH_3CN (4 mL) at 85 °C. All yields were isolated yields.

For comparison, nine common organic solvents were used as the reaction media instead of water and PTC (Table 2, entries 1-9). For eight of the solvents, no reactions occurred (Table 2, entries 2-9). Only the reaction mediated by acetonitrile gave the desired product quantitatively (Table 2, entry 1). The amount of $PhSO_2Cl$ was then varied between 0.1 and 10.0 equiv (Table 2, entries 1 and 10-19) and the acetonitrile volume was adjusted from 2.0 to 30.0 mL (Table 2, entries 1 and 20-25). The optimized conditions were $PhSO_2Cl$ (6.0 equiv) and CH_3CN (4.0 mL), which produced the product in quantitative yields in 2.5 h (Table 2, entry 21).

Table 2 Optimization of the reaction between bromoacetophenone and benzenesulfonyl chloride in organic solvents[a]



Entry	**1a** (equiv)	$PhSO_2Cl$ (equiv)	Solvent (mL)[d]	T (h)	**2a** Yield (%)[b]
1	1.0	6.0	CH_3CN (10.0)	3.0	>99
2	1.0	6.0	CH_3OH (10.0)	24	NR[c]
3	1.0	6.0	CH_2Cl_2 (10.0)	24	NR
4	1.0	6.0	$CHCl_3$ (10.0)	24	NR
5	1.0	6.0	THF (10.0)	24	NR
6	1.0	6.0	EA (10.0)	24	NR
7	1.0	6.0	toluene (10.0)	24	NR
8	1.0	6.0	cyclohexane (10.0)	24	NR
9	1.0	6.0	1,4-dioxane (10.0)	24	NR
10	1.0	0.1	CH_3CN (10.0)	24	trace
11	1.0	0.5	CH_3CN (10.0)	24	10
12	1.0	1.0	CH_3CN (10.0)	24	65
13	1.0	1.2	CH_3CN (10.0)	17	84
14	1.0	1.5	CH_3CN (10.0)	9.0	94
15	1.0	2.0	CH_3CN (10.0)	5.0	96
16	1.0	3.0	CH_3CN (10.0)	5.0	96
17	1.0	4.0	CH_3CN (10.0)	4.0	>99
18	1.0	8.0	CH_3CN (10.0)	3.5	>99
19	1.0	10.0	CH_3CN (10.0)	3.5	>99
20	1.0	6.0	CH_3CN (2.0)	5.5	>99
21	1.0	6.0	CH_3CN (4.0)	2.5	>99
22	1.0	6.0	CH_3CN (6.0)	2.5	>99
23	1.0	6.0	CH_3CN (8.0)	3.0	>99
24	1.0	6.0	CH_3CN (20.0)	7.0	>99
25	1.0	6.0	CH_3CN (30.0)	12	>99

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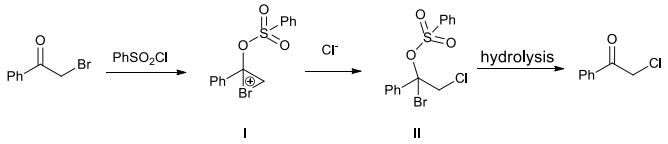
[a]Reaction conditions: bromoacetophenone (300 mg), benzenesulfonyl chloride, CH_3CN at 85 °C. [b]All yields were isolated yields. [c]NR: No reaction. [d]THF=tetrahydrofuran; EA=ethyl acetate.

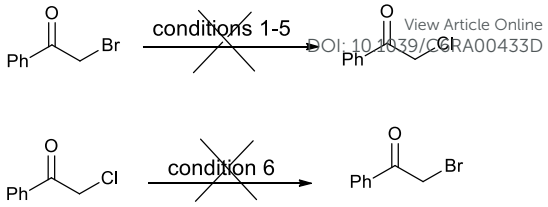
These optimized conditions were then applied to the substrates **2a**-**2n** in Scheme 1 again. As in the water-mediated reactions, all the reactions gave quantitative yields of products, and a similar electronic effect on the reaction rates was observed. However, in most cases, the acetonitrile-mediated reactions had substantial slower reaction rates. The fact that halogen exchange reactions do not occur in most of the organic solvents and occur in water indicates that the hydrophobic core effect[51, 52] for the possible micelle-mediated reactions enables the reactions.

A plausible mechanism for the reaction between bromoacetophenone and benzenesulfonyl chloride is shown in Scheme 2. First, benzenesulfonate **I** is formed *via* a reaction between bromoacetophenone and benzenesulfonyl chloride. The opening of the bromonium ring by chloride then leads to the formation of **II**. This type of compounds (**II**) is not known in the literature, supposed to be very reactive with water because of the two geminal good leaving groups on the benzylic position. The hydrolysis of **II** results the final product.

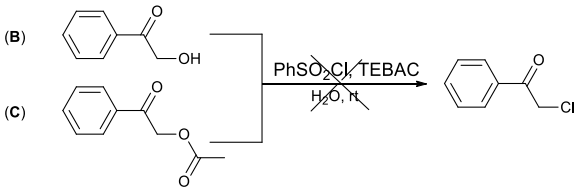


Scheme 2 A possible mechanism for the reaction between bromoacetophenone and benzenesulfonyl chloride

Next, a series of experiments were performed to verify the mechanism and to better understand the role of sulfonyl chloride (Scheme 3). Treating bromoacetophenone with MsOH/LiCl, HCl, or $PhSO_3H$/LiCl in water (Scheme 3, (**A**), conditions 1, 2 and 3) resulted in no reaction. This excludes that proton acids catalyzed the reaction since proton acids can be generated from the hydrolysis of sulfonyl chlorides. No reaction took place in the presence of LiCl or NaCl (Scheme 3, (**A**), conditions 4 and 5) when no sulfonyl chloride was present. This points to the indispensible role of sulfonyl chloride. Moreover, chloroacetophenone could not be transformed into bromoacetophenone in the presence of $PhSO_2Cl$ and KBr in micellar media (Scheme 3, (**A**), condition 6). The possible reason is that the three-membered bromonium (Scheme 2, **I**) is present in substantial amounts which facilitates the reaction while the three-membered chloronium is only present in trace amounts according to previous reports.[53, 54] For this reason, acetoxyacetophenone and α-hydroxyacetophenone could not be transformed into chloroacetophenones in the presence of $PhSO_2Cl$ in water (Scheme 3, (**B**) and (**C**)). Since the electron-donating group helps stabilize the positive charge of **I** to facilitate the reaction, the reaction rates for the substrates bearing electron-donating groups such as alkyl or alkoxyl groups were faster than those for the substrates bearing electron-withdrawing groups such as halo and nitro groups (Scheme 1, **2f**-**2j** *vs* **2b**-**2e**).

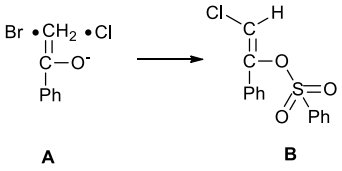


Condition 1: bromoacetophenone (100 mg), methylsulfonic acid (8.0 equiv), LiCl (8.0 equiv), TEBAC (0.5 equiv), H_2O (0.7 mL), rt, NR. Condition 2: bromoacetophenone (100 mg), HCl (aq) (8.0 equiv), TEBAC (0.5 equiv), H_2O (0.7 mL), rt, NR. Condition 3: bromoacetophenone (100 mg), benzenesulfonic acid (8.0 equiv), LiCl (8.0 equiv), TEBAC (0.5 equiv), H_2O (0.7 mL), rt, NR. Condition 4: bromoacetophenone (100 mg), LiCl (8.0 equiv), TEBAC (0.5 equiv), H_2O (0.7 mL), rt, NR. Condition 5: bromoacetophenone (100 mg), NaCl (8.0 equiv), TEBAC (0.5 equiv), H_2O (0.7 mL), rt, NR. Condition 6: chloroacetophenone (100 mg), benzenesulfonyl chloride (8.0 equiv), KBr (8.0 equiv), benzyltriethylammonium bromide (BTEAB) (0.5 equiv), H_2O (0.7 mL), rt, NR.



Scheme 3 Reactions to verify the mechanism and confirm the role of sulfonyl chloride

It is known that bromoacetophenones are more reactive than ordinary alkyl bromides. A number of mechanisms have been proposed to explain this.[55-60] Lewis *et al*. reported that an enolate structure contributes to the transition state (Scheme 4, **A**).[55] If this mechanism were operating in our case, an enol benzenesulfonate (Scheme 4, **B**) from **A** and benzenesulfonyl chloride would be the final product, which is known to be a type of stable compounds.[61, 62] However it was not found in our crude products. Although our mechanism is different, it is in agreement with all the experimental data. The following experiments on the synthesis of chlorohydrins were performed in order to provide further support for our mechanism.



Scheme 4 A would-be product for the mechanism proposed by Lewis *et al.*

Similar aqueous reaction conditions were used to transform benzoyl epoxide **3a** to benzoyl chlorohydrin **4a** (Table 3). Neither the yields nor reaction rates were satisfactory with 1.5 or 6.0 equiv of $PhSO_2Cl$ (Table 3, entries 1 and 2). With 1.5 equiv of MsCl, the reaction yield was 69% and when the amount of MsCl was increased to 3.0, 4.5, 6.0 or 7.5 equiv, the yields were improved up to 97% (Table 3, entries 3-7). Using 6.0 or 7.5 equiv of MsCl gave the same reaction rate, so the optimized reaction conditions use 6.0 equiv of MsCl (Table 3, entry 6).

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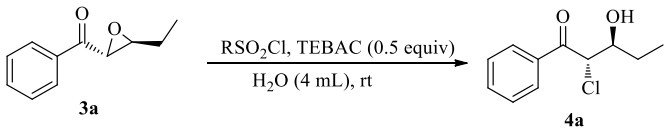
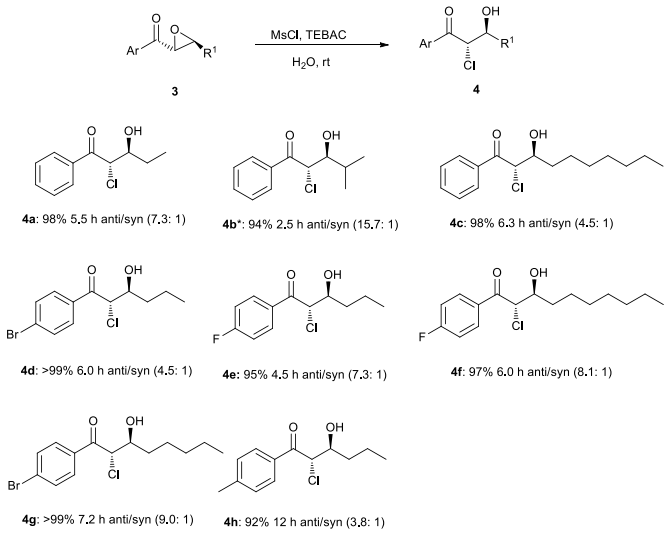
Table 3 Optimization of the ring-opening reaction of benzoyl epoxide **3a** in water[a]



Entry	**3a** (equiv)	RSO_2Cl (equiv)	t(h)	**4a** Yield (%)[b]
1	1.0	$PhSO_2Cl$ (1.5)	24	57
2	1.0	$PhSO_2Cl$ (6.0)	16	93
3	1.0	MsCl (1.5)	24	69
4	1.0	MsCl (3.0)	13	96
5	1.0	MsCl (4.5)	8.5	97
6	1.0	MsCl (6.0)	5.5	97
7	1.0	MsCl (7.5)	5.5	97

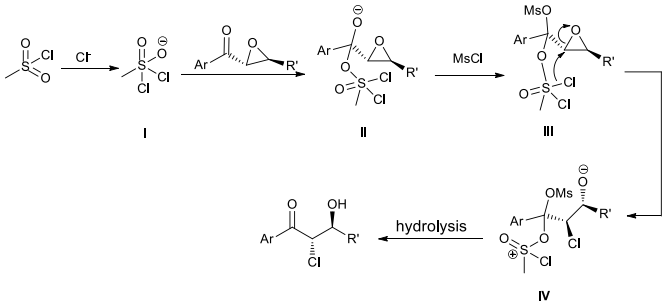
[a]Reaction conditions: **3a** (500 mg), RSO_2Cl, TEBAC (0.5 equiv), H_2O (4 mL) at rt. [b]All yields were isolated yields.

Altogether 8 aroyl epoxides were subjected to the optimized conditions (Scheme 5, **4a**-**4h**) and chlorohydrins were obtained in close to quantitative yields. The reactions were stereoselective, leading to *anti*-stereoisomers as the major products (*anti*/*syn*=15.7:1 to 3.8:1). All the reactions except the one for **4b** were conducted at rt and were complete in 4.5-12 h. The reactions were worked up by washing the extracted ethyl acetate layer with water to get rid of excess MsCl. Simple concentrations yielded pure products.



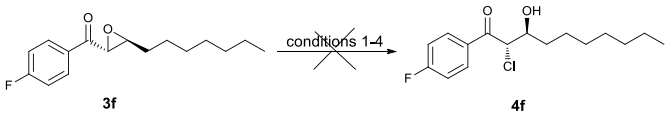
Scheme 5 Ring-opening reactions of aroyl epoxides in water. [a]Reaction conditions: aroyl epoxides (500 mg), MsCl (6.0 equiv),TEBAC (0.5 equiv) and H_2O (4 mL) at rt. All yields were isolated yields. [b]Reaction temperature: 60°C.

The syntheses of open chain chlorohydrins reported in the literature require organic solvent-mediated reactions and chromatography for purification.[46-50] Those reaction yields range from 40-95%[47-50] and in some cases, the stereoselectivities of the products were poor.[47, 48] Therefore, our procedure compares favorably to current procedures in terms of yield, product purification, stereoselectivity and greenness of reaction media. In addition, the reaction scale can easily be increased to 10 g with the same results. Based on these results, the following mechanism is plausible (Scheme 6). The addition of Cl^- to the S=O bond of MsCl leads to **I,** which then adds to the C=O bond of aroyl epoxide to form **II**. Mesylation of **II** by MsCl forms **III**. The intramolecular opening of the epoxy ring by chloride then gives **IV**. After hydrolysis, the chlorohydrin is produced.



Scheme 6 A possible mechanism for the reaction between aroyl epoxide and MsCl

To verify the mechanism, additional investigations were performed with aroyl epoxide **3f** (Scheme 7). The ring-opening reaction did not occur with MsOH/LiCl, HCl, LiCl or NaCl in water, indicating that this reaction is not catalyzed by proton acids and that MsCl is indispensable for promoting the reaction. The enolate mechanism put forward by Lewis *et al*.[56] cannot explain the higher reaction rates for substrates bearing electron-deficient phenyl rings compared to those for substrates bearing electron-rich phenyl rings (Scheme 5, **4d**-**4g** *vs* **4h**). However, this fact is in agreement with our mechanism. The hydrophobic core effect [51, 52] is assumed to be crucial for the formation of intermediates **I** and **II** (Scheme 6).



Scheme 7 Reactions to verify the mechanism in Scheme 6. Condition 1: aroyl epoxide **3f** (100 mg), methylsulfonic acid (8.0 equiv), LiCl (8.0 equiv), TEBAC (0.5 equiv), H_2O (0.7 mL), rt, NR. Condition 2: aroyl epoxide **3f** (100 mg), HCl (aq) (8.0 equiv), TEBAC (0.5 equiv), H_2O (0.7 mL), rt, NR. Condition 3: aroyl epoxide **3f** (100 mg), LiCl (8.0 equiv), TEBAC (0.5 equiv), H_2O (0.7 mL), rt, NR. Condition 4: aroyl epoxide **3f** (100 mg), NaCl (8.0 equiv), TEBAC (0.5 equiv), H_2O (0.7 mL), rt, NR.

EXPERIMENTAL SECTION

General Experimental Information

All of the chemicals were obtained from commercial sources or prepared according to standard methods. NMR spectra were recorded with a 400 MHz spectrometer for ^1H NMR, and a 100 MHz spectrometer for ^{13}C NMR. TMS was used as an internal standard. Chemical shifts (δ) are reported relative to TMS (^1H) or $CDCl_3$ (^{13}C). Multiplicities are reported as follows: singlet(s), doublet (d), triplet (t), quartet (q), multiplet (m), dd (doublet of

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doublets) and dt (doublet of triplets). Coupling constants are reported in Hertz (Hz). Melting points were recorded with a micro melting point apparatus. Infrared analyses (KBr pellet) were performed on a FTIR spectrometer. High resolution mass spectra (HRMS) were recorded on a QTOF mass analyzer with electro spray ionization (ESI).

Procedure I: Typical 300 mg-scale synthesis of chloroacetophenone (2a) using water as solvent

Bromoacetophenone (300 mg), $PhSO_2Cl$ (8.0 equiv), TEBAC (0.5 equiv) and water (5.0 mL) were added to a 50-mL round-bottom flask. After the mixture was stirred at rt for 1.5 h and TLC indicated completion of the reaction, the reaction was stopped and cooled in an ice-bath. Then saturated Na_2CO_3 aq. (10 mL) was added to the reaction mixture with stirring until $PhSO_2Cl$ disappeared. The mixture was then extracted with ethyl acetate (3 x 10 mL), dried over Na_2SO_4 and evaporated to give a white product **2a** (235 mg, >99%).

Synthesis of 2a in 10 g scale

The synthesis of **2a** starting from 10 g of bromoacetophenone was performed in a 250-mL round-bottom flask using the same procedure as above to yield **2a** (7.8 g, >99%, t: 1.5 h).

Procedure II: Typical 300 mg-scale synthesis of 2a using acetonitrile as solvent

Bromoacetophenone (300 mg), $PhSO_2Cl$ (6.0 equiv) and acetonitrile (4.0 mL) were added to a 50-mL round-bottom flask. After the mixture was stirred at 85 ^oC for 2.5 h and TLC indicated completion of the reaction, the reaction mixture was concentrated under vacuum. Then saturated Na_2CO_3 aq. (10 mL) was added to the concentrate in an ice bath, which was stirred until $PhSO_2Cl$ disappeared. The mixture was then extracted with ethyl acetate (3 x 10 mL), dried over Na_2SO_4 and evaporated to give a white product **2a** (231 mg, >99%).

Typical 500 mg-scale synthesis procedure using the synthesis of 2-chloro-3-hydroxy-1-phenyl-1-pentanone (4a) as an example

In a 50-mL round-bottom flask, a mixture of *trans*-3-ethyl-2-oxiranyl-1-phenylmethanone (**3a)** (500 mg), MsCl (6.0 equiv), TEBAC (0.5 equiv) and water (4.0 mL) was stirred at rt for 5.5 h until TLC indicated completion of the reaction. Then the mixture was washed with ice water until MsCl disappeared. The product was then extracted with ethyl acetate (3 x 10 mL), and dried over Na_2SO_4. The ethyl acetate was evaporated to give **4a** (585 mg, 97% yield, *anti*/*syn*=7.3:1).

Synthesis of 1-(4-bromophenyl)-2-chloro-3-hydroxy-1-hexanone (4d) in 10 g scale

The synthesis of **4d** starting from 10 g of *trans*-1-(4-bromophenyl)-3-propyl-2-oxiranylmethanone (**3d**) was performed in a 250-mL round-bottom flask using the same procedure as above to yield **4d** (11.3 g, >99%, t: 6.5 h).

Conclusions

In conclusion, water-mediated reactions promoted by sulfonyl chlorides for transforming bromoacetophenones to chloroacetophenones and aroyl epoxides to aroylchlorohydrins have been realized. Most probably due to the micellar hydrophobic core effect, these reactions have resulted in pure and quantitative products under mild conditions. Therefore, the costs for both volatile organic solvents and labours were reduced substantially. As it was easy to increase the two reaction scales, they would be beneficial in reducing environmental pollution in industrial chemical processes.

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High-yielding Aqueous Synthesis of Chloroacetophenones and Aroyl Chlorohydrins

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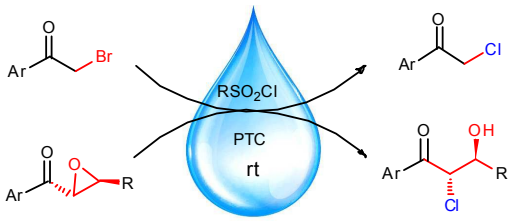

22 examples, stereoselective, high-yielding, scalable, chromatography-free

Two new reactions for preparing chloroacetophenones and aroyl chlorohydrins promoted by sulfonyl chloride and mediated by water are reported.

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