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A Facile One-Pot Synthesis of 2,2,2-Trichloroacetates Through Acid-Catalyzed Deimination and Its Applications

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A novel one-pot approach for the synthesis of trichloroacetates is described. Use of inexpensive, commercially available trichloroacetonitrile as a trichloroacyl source has made this protocol have more industrial applications. This one-pot approach is applicable to a wide range of alcohols as demonstrated by 28 examples with good to excellent yields in the order of 93%. Trichloroacetates were characterized by infrared, NMR spectra and further the structure of 2-(1,3-dioxoisoindolin-2-yl)ethyl-2,2,2-trichloroacetate was confirmed by single-crystal X-ray diffraction. Moreover, benzyl trichloroacetates synthesized were converted into corresponding benzyl iodides in good yields (51-70%). In addition, bypassing harsh reagents, use of cheaper, commercially available sodium iodide as nucleophile and mild reaction conditions are some of practical features of this methodology.

Introduction

The halogens are ubiquitous and are found in many natural products and biologically active compounds as an integral part of them.[1] Among these halogenated compounds so formed, substitution with chlorine especially the one involving fully chlorinated trichloromethyl group (CCl_3) has piqued the interest among chemists all-over due to its abundant presence in naturally occurring compounds as well as it being in the repertoire of pharmaceuticals and agrochemicals.[2] Also, trichloromethyl group (CCl_3) plays a pivotal role in the biological activity of many molecules, such as larvicidal activity, to treat anxiety disorders and anti-Alzheimer's Salubrinal (Figure 1).[3–5]

Further, the trichloroacetate synthon is having ample importance with its applications in the synthetic organic chemistry.[6] It has considerably taken advantage in the carbohydrate chemistry as leaving group,[7] Cai and co-workers extensively used in glycosylation employing Lewis acid.[8] Furthermore, the trichloroacetate has also been used as carbenes[9] source and as precursors in the Mannich-type of reactions,[10] Corey and Link developed a novel synthetic approach 'Jocic reaction' for preparation of chiral-amino acids, *via* trichloromethylcarbinol as an intermediate.[11] Also, the trichloroacetate core is used as solvents, buffers, and found in many biologically relevant molecules including.[12] Consequently, the development of methods towards the synthesis of trichloroacetate compounds is of continued interest.

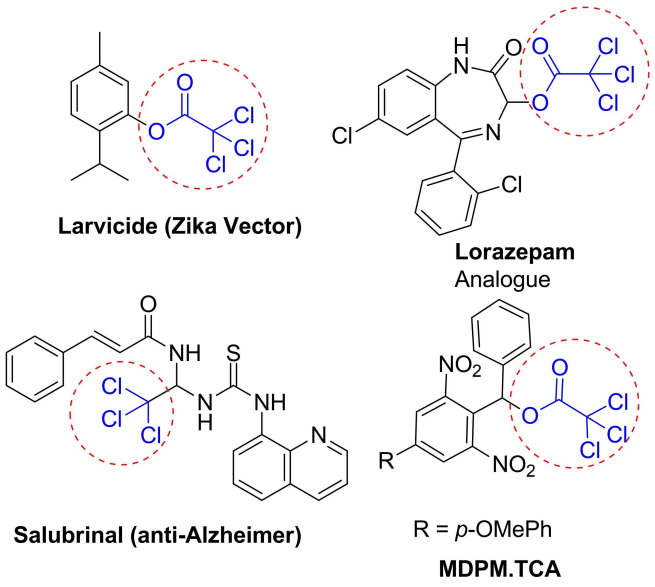

Figure 1. Some of the important trichloromethyl and trichloroacetates.

On the other hand, the classical approach for the synthesis of substituted trichloroacetates is the reaction of trichloroacetic acid with corresponding alcohols in presence of Ce $(NH_4)_2(NO_3)_6$,[13] benzoquinone/Ph_2POR,[14] Tetrachloroethylene/photoirradiation,[15] trichloroacetyl chloride/base,[16] or hexachloroacetone with alcohols using organic bases or thionyl chlorides.[17] Of these esterification methods, the presence of a stoichiometric amount or more of a base resulting in the formation of a considerable amount of undesired chemical waste. Moreover, due to the high reactivity of these acylating agents, selectivity among the different types of alcohols are generally not satisfactory. Also, the harsh reagents and/or the

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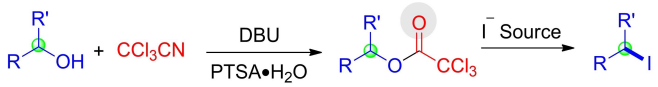
conditions at elevated temperature are the disadvantages of the protocol.

According to green chemistry principles,[18] it would be useful to develop a metal-free, less toxic, inexpensive, and environmentally benign synthesis of trichloro esters from readily available alcohols and trichloroacetonitrile under mild conditions.

In order to simplify the synthesis, herein we report an efficient one-pot synthesis of trichloroacetates from trichloroacetonitrile with various alcohols in mild reaction conditions *via* trichloroacetamidate intermediate (Scheme 1).



Scheme 1. Schematic representation of one-pot esterification and its application.

Although, the *in situ* generated trichloroacetamidate rearranges to trichloroacetamide in presence of Lewis acid, which was first reported by Cramer and co-workers.[19] Later a number of reports have been documented thereafter.[20] Our efforts towards the synthesis of substituted trichloroacetates are successful *via* circumventing the rearrangement of imidate to amide.

Results and Discussion

In order to test our hypothesis, a reaction was conducted between benzyl alcohol **1a** as a model substrate and trichloroacetonitrile **2** in presence $BF_3{\cdot}OEt_2$ as an activator in CH_2Cl_2 to transform into the corresponding trichloroacetates. To our delight the formation of **3a** was observed in 5% in CH_2Cl_2 at 0 °C (Table1, entry 1). These results provoked us to optimize the reaction conditions to improve the product yield. Then $FeCl_3$ gave the trichloroester **3a** in 65%, whereas $AlCl_3$ was inefficient for the transformation (Table 1, entry 2–3). Further, the acids, SiO_2, TFA, (±) CSA and $PTSA{\cdot}H_2O$ were screened and found that the $PTSA{\cdot}H_2O$ was the best catalyst for the transformation (Table 1, entry 4–7).

It was observed that of all the solvents examined, CH_2Cl_2 was the most efficient (Table 1, entries 7–12). A control experiment was also carried out in absence of catalyst, showed inferior results (Table 1, entry 13).

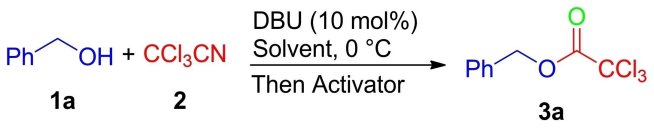
With optimized reaction conditions (Table 1, entry 7), then we have validated the scope of the substrates with our one-pot operation. Firstly, various benzyl alcohols were treated with DBU in CH_2Cl_2 followed by the hydrolysis of trichloroacetamidate to the trichloroester in presence of PTSA. We have further investigated the effect of substituents on benzyl alcohols and found that a little effect on the product yields (Table 2). Methyl, halogen (at *ortho*, *meta* and *para* positions) substituted benzyl alcohols also reacted smoothly to give the corresponding 2,2,2-trichloroacetates (Table 2, **3b-h**). Electron withdrawing groups such as -CN, $-NO_2$ did not hamper the product yields (Table 2, **3i-k**).

Furthermore, we have extended our protocol to the aromatic alcohols. It is worth mentioning that, aromatic alcohols gave corresponding trichloroacetate comparatively low yields than benzyl alcohols.

Later, we applied our one-pot procedure to other aliphatic alcohols and observed good yields. Apart from the traditional FTIR, ^1H and ^{13}CNMR spectral analysis, the formation of trichloroester was also confirmed by single crystal X-ray diffraction of compound **3ab** (Figure 2).

Next, we put our forward effort to check the compatibility of our method with complex molecules such as cholesterol.

Table 1. Optimization of the Reaction Conditions.[a]

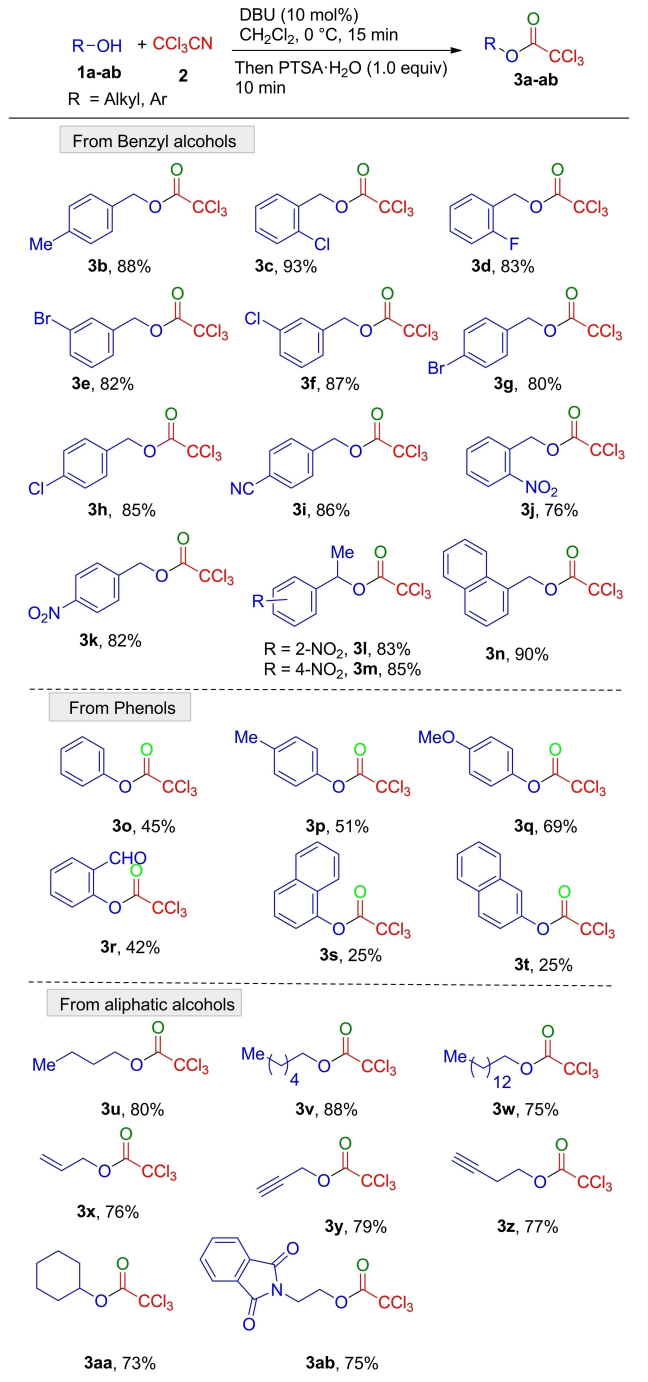


1a **2** **3a**

Entry	Activator(equiv)	Solvent	Time (h)	Yield (%)[b]
1	$BF_3{\cdot}OEt_2$	CH_2Cl_2	24	5
2	$FeCl_3$	CH_2Cl_2	3	65
3	$AlCl_3$	CH_2Cl_2	0.5	0
4	TFA	CH_2Cl_2	1.5	80
5	SiO_2	CH_2Cl_2	24	10
6	(±) CSA	CH_2Cl_2	1	73
7	**$PTSA{\cdot}H_2O$**	**CH_2Cl_2**	**10 min**	**93**
8	$PTSA{\cdot}H_2O$	CH_2Cl_2	4	86[c]
9	$PTSA{\cdot}H_2O$	CH_2Cl_2	6	72[d]
10	$PTSA{\cdot}H_2O$	$MeNO_2$	0.5	82
11	$PTSA{\cdot}H_2O$	Toluene	1	80
12	$PTSA{\cdot}H_2O$	DMF	1.5	85
13	-	CH_2Cl_2	24	0

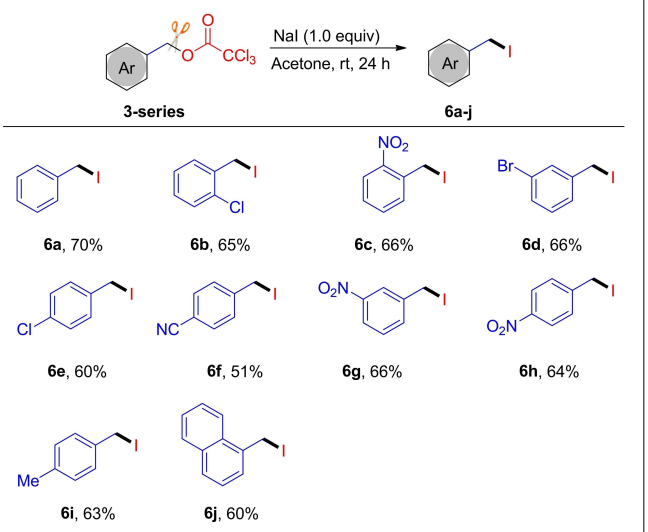
[a] Reaction Conditions: Benzyl alcohol **1a** (1.0 mmol), CCl_3CN **2** (1.5 mmol), DBU (10 mol%), activator (1.0 mmol), CH_2Cl_2 (1.0 mL) at 0 °C. [b] Yields are of isolated pure products. [c] $PTSA{\cdot}H_2O$ (0.5 mmol). [d] $PTSA{\cdot}H_2O$ (0.2 mmol).

Table 2. Synthesis of Trichloroacetate Derivatives.[a,b]



[a] Reaction Conditions: Alcohol **1 a-ab** (1.0 mmol), CCl_3CN (1.5 mmol), DBU (10 mol%), PTSA·H_2O (1.0 mmol), CH_2Cl_2 (1.0 mL) at 0 °C. [b] Yields are of isolated pure products.

Table 3. Synthesis of Functionalized Benzyl Iodides.[a,b]



[a] Reaction Conditions: Trichloroester (1.0 mmol), NaI (1.0 mmol), acetone (1.0 mL) at room temperature.

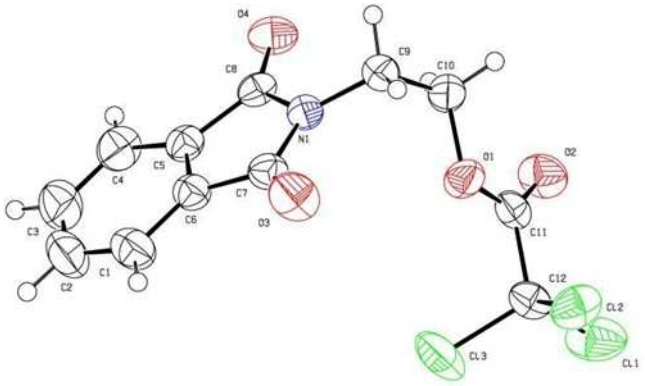
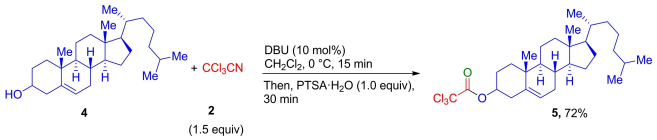


Figure 2. ORTEP representation of 2-(1,3-dioxoisoindolin-2-yl)ethyl-2,2,2-trichloroacetate **3 ab.**



Scheme 2. Trichloromethyl esterification of cholesterol.

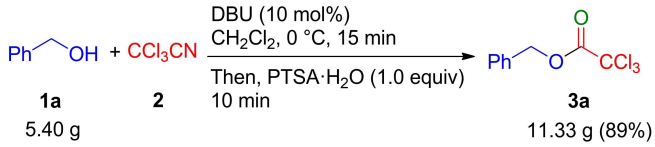
Notably, cholesterol **4** afforded corresponding tricholoroester **5** product in good in 72% yield (Scheme 2).

Next, we are interested to study the nucleophilic displacement reactions on benzyl trichloroacetates because it contains both reactive benzylic position and good leaving nature of trichloroacetate. Surprisingly, Iodide displaced the trichloroacetate to produce benzyl iodides in good yields under mild condition (Table 3).

We have then synthesized the library of benzyl iodides and listed in the table 3. The iodine replacement has been occurred employing 1.0 mmol of sodium iodide in acetone at room temperature (Table 3). All primary benzyl substituted trichloromethyl esters smoothly gave corresponding benzyl iodides in moderate to good yields (Table 3, **6 a-j**). Aliphatic and secondary benzylic-trichloroacetates did not undergo the

nucleophilic displacement reaction with iodine at optimized reaction conditions.

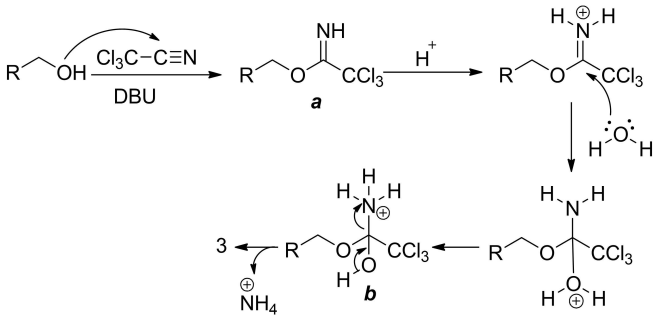
In addition, the reaction was investigated in gram-scale using benzyl alcohol **1a** as a model substrate (Scheme 3) and



Scheme 3. Gram-Scale synthesis of benzyl trichloroacetate.

found to produce the corresponding benzyl 2,2,2-trichloroacetate **3a** in 89%. The reaction suggest that the protocol is scalable.

The plausible reaction mechanism pathway is proposed for the reaction in scheme 4. The alcohols react with trichloroacetonitrile in presence of DBU to form trichloroacetamidate intermediate **a**. Then the intermediate **a** gets protonation with acid followed by addition of water and elimination of ammonia occurs sequentially to yield the corresponding trichloroester.



Scheme 4. Plausible reaction mechanism.

Conclusions

In conclusion, we described here a novel one-pot approach for the synthesis of 2,2,2-trichloroacetates from commercially available trichloroacetonitrile and wide variety of substituted alcohols. In addition, the synthesis of functionalized benzyl iodides has been studied towards the sustainable approach. Further, bypassing harsh reagents, use of commercially available trichloroacetonitrile as an acylating agent, inexpensive sodium iodide as nucleophile and mild reaction conditions are some of the practical features of this methodology.

Supporting Information Summary

Detailed experimental procedure, characterization data (^{1}H, ^{13}C NMR spectra) for all synthesized products **3a-3ab, 5** and **6a-j** and X-ray crystallography data of **3ab** are given in the Supporting Information.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Benzyl Iodides · Deimination · Esterification · One-Pot Reaction · Trichloroacetates

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