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# Selective Hydro- and Deuterodechlorination of Trichloroacetamides under Controlled Electrochemical Conditions to Prepare Mono-, Di-, and Deuterochloroacetamides

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**Abstract.** Mono and dichloro acetamides were prepared via hydrodechlorination reaction of trichloroacetamides under controlled electrochemical conditions. The reactions were carried out in an undivided cell with constant current flow using *n*-$Bu_4NI$ as supporting electrolyte and methanol as solvent and proton source. Deuterodechlorination of trichloroacetamide was also successful using methanol-d4 as solvent under identical electrochemical conditions.

**Keywords:** Trichloroacetamide; Electrochemical hydrogenation; undivided cell; constant current; Overman reaction

Halogenated acetamides are an essential class of organic compounds with diverse applications in several areas of chemistry. For example, the α, α-dichloroacetamide structural sub-unit is commonly found in commercially available drugs such as chloramphenicol (antibiotic), florfenicol (antibiotic), quinfamide (antiamoebic), etofamide (antiprotozoal), etc. Recently, some novel dichloroacetamide analogs have been synthesized and investigated as anticancer and antiproliferative agents. [1] In addition, several dichloroacetamides such as benoxacor, furilazole, and AD-67 (Figure 1) are popularly used as safeners [2] to protect crops from herbicide toxicity. [3] On the other hand, α-chloroacetamide derivatives are versatile building blocks and are frequently used in organic synthesis. A wide range of valuable

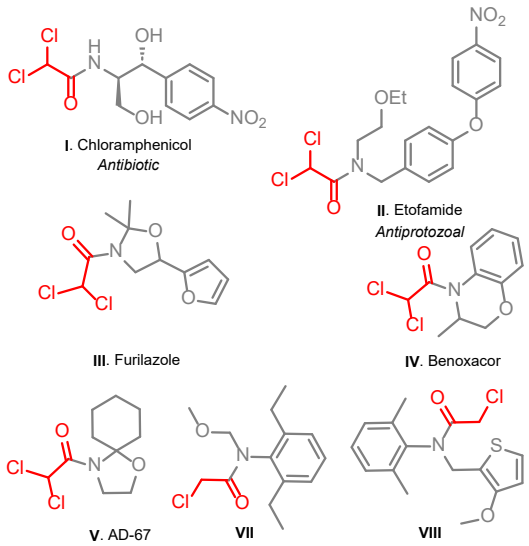
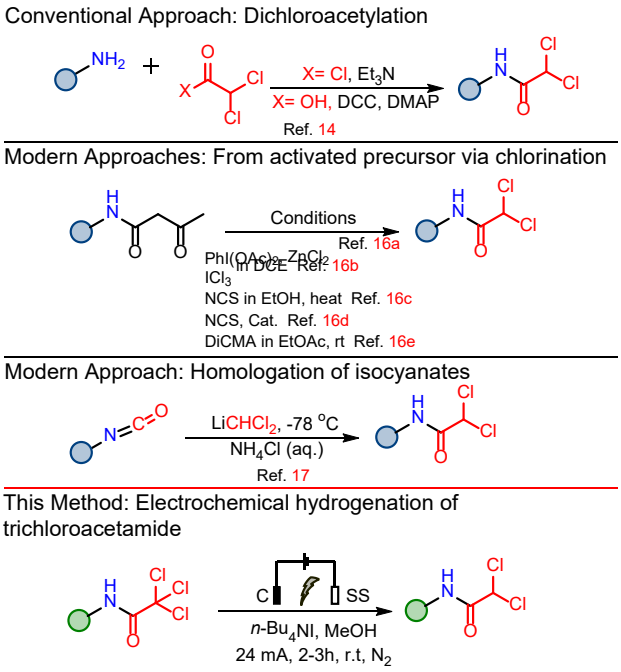



**Figure 1**. Halogenated acetamides in drugs, safeners, and pesticides

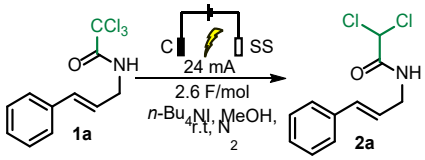
heterocyclic compounds have been prepared by using α-chloroacetamide as a suitable synthon. For example, differently substituted lactam, [4] aziridine, [5] piperazine, [6] imidazole, [7] pyrrole, [8] thiazolidine-4-one, [9] and thiophene [10] derivatives have been synthesized starting from α-chloroacetamides. In addition, a couple of α-chloroacetamides are well-known pesticides [11] (VII and VIII, Figure 1) and are also useful in macrocyclic ligand [12] and, solid phase synthesis. [13]




**Scheme 1**. An overview of the previous synthesis of dichloroacetamide

Owing to their wide-ranging application in diverse fields of chemistry, halogenated acetamides have attracted considerable attention from synthetic organic chemists. Consequently, several elegant synthetic routes have been developed over the past decades. Traditionally, α, α-dichloroacetamide derivatives have been prepared via dichloroacetylation of parent amine using dichloroacetic acid or dichloroacetyl chloride. [14] However, both reagents are health hazardous and are not environmentally friendly. Therefore, alternative approaches have focused on oxidative chlorination for accessing dichloroacetamides. Since direct dichlorination of acetamides suffers from over-halogenation [15] leading to the formation of trichloroacetamide, β-ketoamide was found to be a better alternative for direct dichlorination approaches. Various oxidative dichlorination agents such as $PhI(OAc)_2/ZnCl_2$, [16a] $ICl_3$, [16b] NCS (or NBS), [16c-d] and dichloromeldrum's acid (DiCMA) [16e] (Scheme 1) have been successfully employed in deacylative dichlorination approach to afford dichloroacetamide derivatives from β-ketoamides. In addition, the homologation of isocyanates by lithium carbenoid species is another noteworthy method for accessing dichloroacetamides.[17] Though the already reported methods are conceptually novel and synthetically useful, every technique has several drawbacks. Therefore, we envision developing a direct, room-temperature method to produce dichloroacetamides under environmentally benign, electrochemical hydrogenation conditions. The application of electrochemistry in organic synthesis has emerged as a prolific research area over the last two decades. [18]

**Table 1**. Optimization of the reaction conditions.



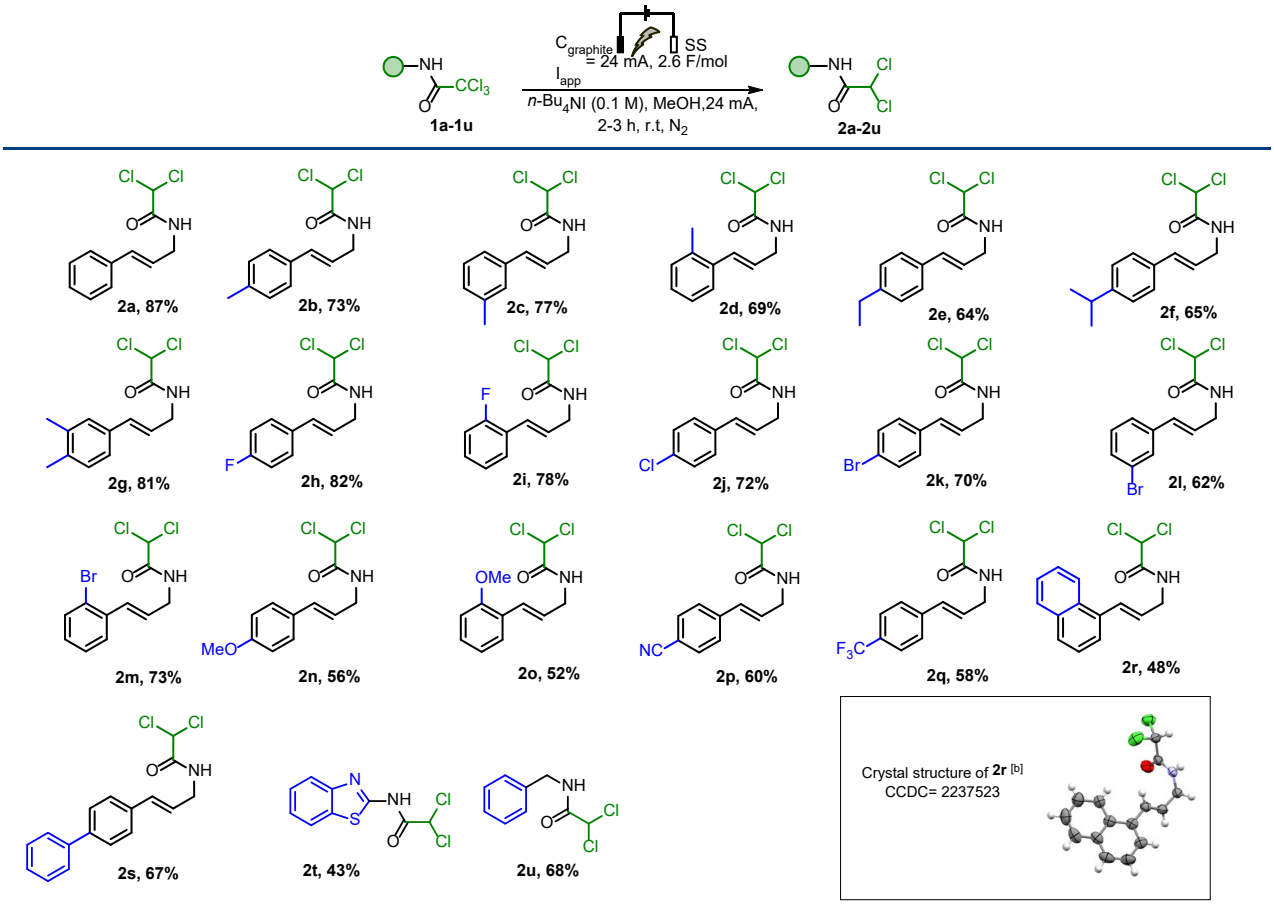

| Entry | Deviation from standard conditions | Yield[%][b] |
|---|---|---|
| 1 | None | 87 [a] |
| 2 | KI instead of *n*-$Bu_4NI$ | 74 |
| 3 | *n*-$Et_4NI$ instead of *n*-$Bu_4NI$ | 72 |
| 4 | *n*-$Bu_4NBr$ instead of *n*-$Bu_4NI$ | 29 |
| 5 | *n*-$Bu_4NPF_6$ instead of *n*-$Bu_4NI$ | N.R. |
| 6 | MeOH+$H_2O$ (1:1) as solvent | 85 |
| 7 | 30 mA rather than 24 mA | 64 |
| 8 | 20 mA current applied | 58 |
| 9 | Graphite, both as Anode and Cathode | 69 |
| 10 | Stainless steel, both as anode and cathode | Trace |
| 11 | Magnesium plate as cathode | 64 |
| 12 | Aluminium rod as cathode | 58 |
| 13 | Iron plate as cathode | 51 |
| 14 | Heated at 60 ˚C | decomposed |

[a] Optimized reaction conditions- C (graphite rod) as anode, stainless steel (SS) as cathode, constant current-24 mA (2.6 F/mol), undivided cell, *n*-$Bu_4NI$ (0.1 M) and **1a** (0.3 mmol) in MeOH (5 mL) stirred at r.t for 2 h. [b] Isolated yield

The significant advantages such as sustainability, minimal chemical waste, higher atom economy, and procedural simplicity made electrochemistry famous among synthetic organic chemists. Inspired by the enormous potential of organo-electrochemistry, we planned to develop a greener method for synthesizing dichloroacetamide derivatives via selective hydrogenation of trichloroacetamide under controlled electrochemical conditions. Though several direct hydrodechlorinations of trichloromethyl compounds under electrochemical conditions have already been reported [19], selective hydro and deuterodechlorination of trichloroacetamides under controlled electrochemical conditions remain unexplored. Herein, we report an electrochemical method for the selective hydro and deuterodechlorination of trichloroacetamides.

Initially, we selected trichloroacetamide **1a**, an Overman rearrangement [20] product, as our model substrate. The reaction was carried out in an undivided cell fitted with a pencil graphite cathode and stainless steel (SS) anode with a constant current flow at ambient temperature. After some initial experiments, we found that the reaction produced the best result when it was conducted under a steady

**Table 2**. Substrates scopes with trichloroacetamide derived from different cinnamyl alcohols and aryl/alkyl amines. [a]




[a] C (graphite rod) as anode, stainless steel (SS) as cathode, *n*-$Bu_4NI$ (0.1 M) as supporting electrolytes, Trichloroacetamides **1a-1u** in methanolic medium stirred at a constant current of 24 mA (2.6 F/mol). [b] ORTEP diagram of **2r** with 50% contour space probability level.

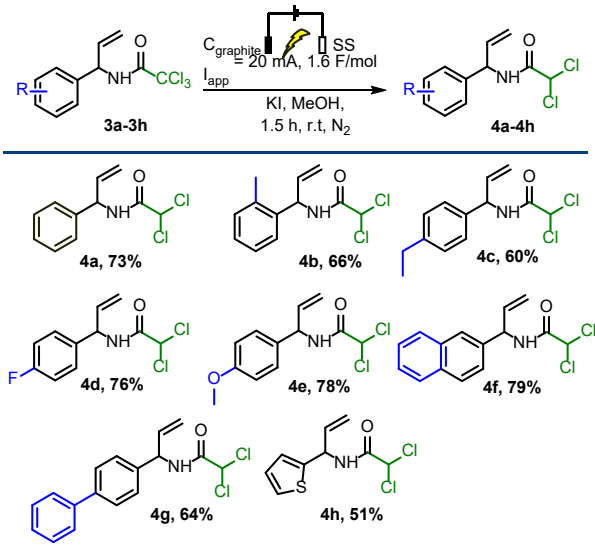
current flow of 24 mA for 2 h at room temperature in MeOH using *n*-$Bu_4NI$ (0.1 M) as a supporting electrolyte (Table 1, Entry 1). When the supporting electrolyte was replaced by KI, *n*-$Et_4NI$, and *n*-$Bu_4NBr$, the yields were lower than that of *n*-$Bu_4NI$ (Table 1, Entry 2-4). *n*-$Bu_4NPF_6$ was also investigated as a supporting electrolyte but the formation of the desired product was not observed (Table 1, Entry 5). Using water as a co-solvent (1:1) with methanol furnished the desired dichloroacetamide with a slightly lower yield (Table 1, Entry 6). The variation of the current flow during the electrochemical process did not produce any beneficial effect on the yield (Table 1, Entry 7-8). Graphite rods used both as anode and cathode were found to be less effective, whereas stainless steel, as the electrode material, was proved to be incompetent (Table 1, Entry 9-10). Other inexpensive and abundantly available metals, such as magnesium, aluminum, and iron, were also screened as cathodes, with no yield improvement (Table 1, Entry 11-13). Though the desired product **2a** was isolated with lower yields in each case, the massive corrosion of the cathode materials made the reaction slower and the extraction process tedious. The electrochemical reaction under heating condition (60 ºC) was proved unsuccessful, probably due to the product decomposition (Table 1, Entry 14).

With the optimized conditions in hand, we focused our attention on exploring the substrate scope of the reaction. A series of trichloroacetamide derivatives **1a-1u** were prepared [21] from allylic alcohols employing sequential Johnson-Claisen [22] *ortho*-ester and Overman rearrangement. [20] The trichloroacetamides **1a-1g** accessed from alkyl-substituted cinnamyl alcohols smoothly delivered the desired dichloroacetamide **2a-2g** with excellent yields under the optimized electrochemical conditions (Table 2, Entry 2a-2g).

Halogen (F, Cl, and Br) substituted (at different positions) trichloroacetamides **1h-1m** were found compatible under the electrochemical conditions to furnish expected dichloroacetamides **2h-2m** with good yields (Table 2, Entry 2h-2m). Two methoxy-substituted substrates **1n-1o** were subjected to the standard reaction conditions, and the corresponding dichloroacetamides **2n-2o** were isolated with good yields (Table 2, Entry 2n-2o). Trichloroacetamides bearing strong electron-withdrawing groups, such as

cyano and trifluoromethyl, **1p-1q**, respectively, were routinely transformed into their corresponding dichloroacetamide **2p** and **2q** under the optimized electrochemical conditions (Table 2, Entry 2p-2q). The survival of a reducible group such as cyano under reductive hydrogenation conditions may be considered an advantage of the protocol and increase the scope of synthetic application. Substrates with poly-aryl groups such as naphthyl and biphenyl **1r-1s** were smoothly converted to their respective dichloro analogs **2r-2s** with moderate yields (Table 2, Entry 2r-2s). Dichloroacetamide **2r** was crystalized from $CDCl_3$ as a pale-yellow block shape crystal, and the structural formula was further confirmed by X-ray crystallography. Two different trichloroacetamides **1t** and **1u**, prepared [21] from 2-aminobenzothiazole and benzylamine, respectively, furnished the desired dichloroacetamides **2t** and **2u** when applying the standard electrochemical conditions (Table 2, Entry 2t-2u). The successful formation of **2t** and **2u** broadens the substrate scope. Furthermore, it proves that the cinnamyl double bond plays no role in the reaction.

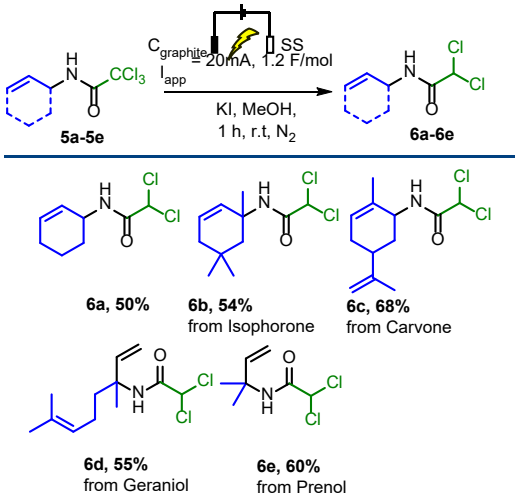
**Table 3**. Substrate Scope with trichloroacetamide derived from differently substituted cinnamyl alcohol [b]




[b] C (graphite rod) as anode, stainless steel (SS) as cathode, KI (0.1 M) as supporting electrolytes, Trichloroacetamides **3a-3h** in methanolic medium stirred at a constant current of 20 mA (1.6 F/mol).

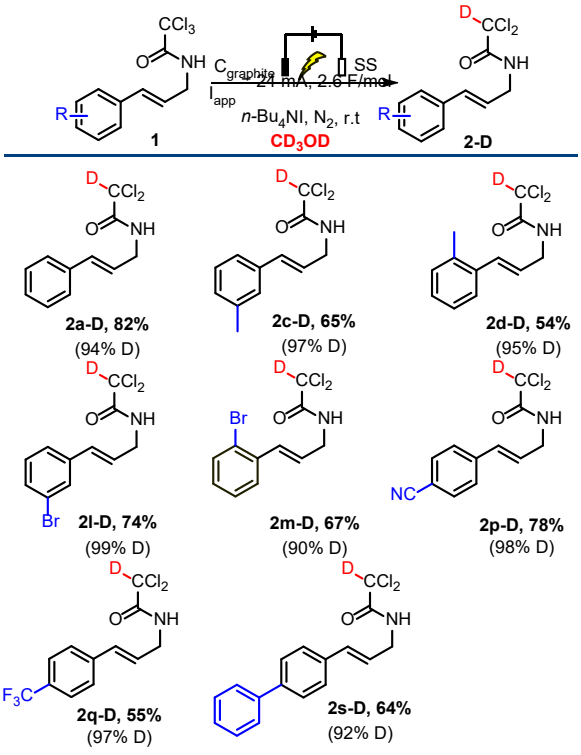
To enhance the scope and versatility of the described method, we extended the substrate scope using a new series of trichloroacetamides **3a-3h,** synthesized from differently substituted cinnamyl alcohol employing the Johnson-Claisen *ortho*-ester rearrangement and Overman reaction. The selective hydrogenation under a reductive electrochemical environment was gratifyingly successful for all substrates **3a-3h** with varying degrees of substitution pattern to afford the corresponding dichloroacetamide derivatives **4a-4h** (Table 3, Entry 4a-4h). All the substituents, including alkyl, halogen, methoxy, polyaryl, and thienyl, were proved compatible under the standard electrochemical conditions to furnish the desired products with good yields (Table 3).

**Table 4**. Substrate scope with alkyl trichloroacetamides [b]




[b] C (graphite rod) as anode, stainless steel (SS) as cathode, KI (0.1 M) as supporting electrolytes, Trichloroacetamides **5a-5e** in methanolic medium stirred at a constant current of 20 mA (1.2 F/mol).

**Table 5**. Electrochemical deuterodechlorination of trichloroacetamide [a]



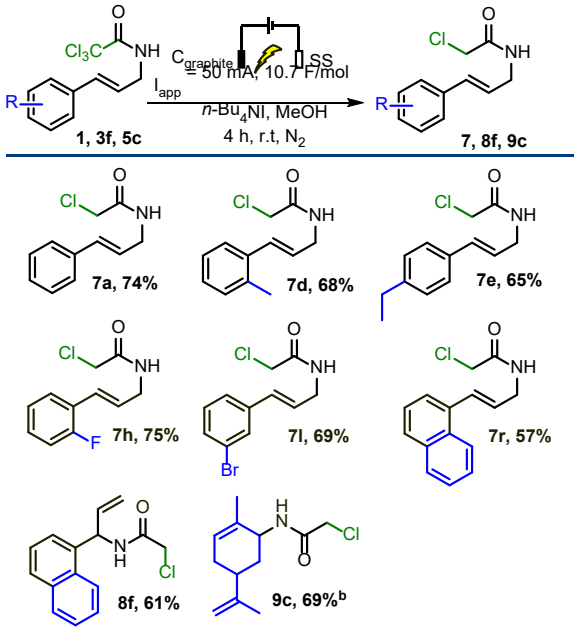

[a] C (graphite rod) as an anode, Stainless steel (SS) as a cathode, *n*-$Bu_4NI$ (0.1 M) as supporting electrolytes, Trichloroacetamides **1** in methanol-$d_4$ medium stirred at a constant current of 24 mA (2.6 F/mol)

Once again, the terminal double bond of the substrates remained unreacted under the studied electrochemical conditions. The survival of the vinylic moiety demonstrates the method's selectivity and enhances the scope of its synthetic application.

Five new trichloroacetamide derivatives **5a-5e** were prepared from various allylic alcohols and subjected to optimized electrochemical conditions to extend the substrate scope further to the aliphatic system. We were pleased to observe that all the aliphatic trichloroacetamides (both cyclic and acyclic) **5a-5e** were found compatible and furnished the desired dichloroacetamides **6a-6e** with moderate yields under the standard electrochemical conditions (Table 4, Entry 6a-6e). The protocol's success in aliphatic systems demonstrates the versatility and wide applicability of the electrochemical methodology.

Deuterium labeling experiments of small organic molecules are of immense importance for the elucidation of reaction mechanisms, [23] spectroscopic analysis, [24] drug discovery, [25] and materials modification. [26] Generally, replacing hydrogen with a deuterium atom helps to enhance the metabolic and pharmacokinetic properties of drug molecules without hampering the potency and stability of the therapeutic agent. [27] We envisioned that our newly developed electrochemical protocol might enable us to readily generate deuterated chloroacetamide if a suitable deuterium source is used in the reaction. Consequently, we carried out the electrochemical procedure on **1a** using $CD_3OD$ as solvent and deuterium source.

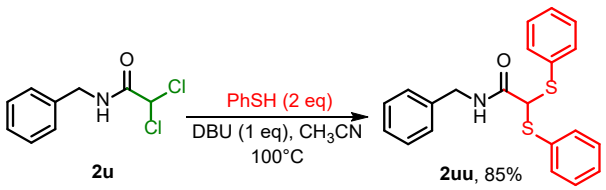
**Table 6**. Electrosynthesis of monochloroacetamides [c]



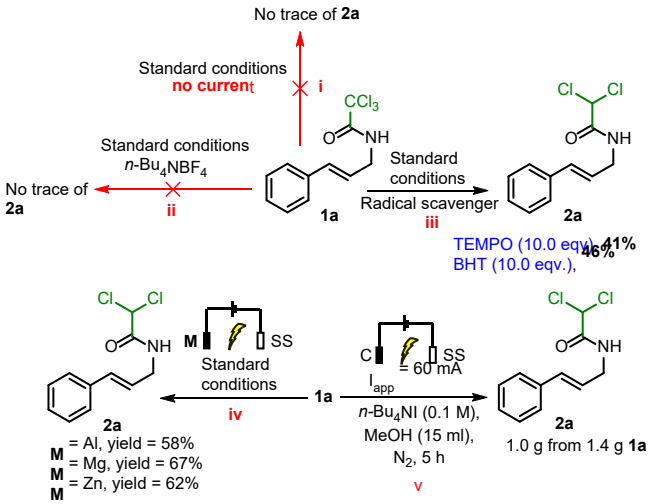

[c] C (graphite rod) as anode, stainless steel (SS) as cathode, *n*-$Bu_4NI$ (0.1 M) as supporting electrolytes, Trichloroacetamides **1**, **3f**, **5c** in methanolic medium stirred at a constant current of 50 mA (10.7 F/mol)

We found that the deutero-dechlorination was gratifyingly successful, and we obtained our desired product **2a-D** with excellent yield and a very high level of deuterium incorporation.

Similarly, we prepared several deuterated chloroacetamide derivatives to prove the generality of the method. As a result, several selected trichloroacetamides (**1c**, **1d**, **1l**, **1m**, **1p**, **1q**, and **1s**) were subjected to deutero-dechlorination reaction and desired deuterated products **2c-D**, **2d-D**, **2l-D**, **2m-D**, **2p-D**, **2q-D**, and **2s-D** were respectively obtained with good yield and excellent deuterium incorporation (Table 5). These deuterodechlorination reactions highlight an innovative method for deuterochloroacetamides and unequivocally prove that the $CD_3OD$ was the source of deuterium in the reaction mechanism.




**Scheme 2**. Derivatization of dichloroacetamide **2u**.




**Scheme 3**. Control experiments and gram scale synthesis.

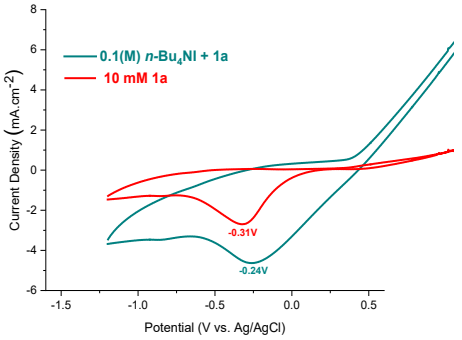
After successfully establishing the monohydrodechlorination and deuterodechlorination processes, we investigated dihydro-dechlorination under slightly modified electrochemical conditions. As mentioned above, chloroacetamide derivatives constitute a fundamental structural framework frequently used in organic synthesis and as some bioactive molecules.

After some experimentation, we found that the dihydrogenation products were exclusively obtained from trichloroacetamides if the reaction was carried out with a 50 mA current flow for 4h (Table 6), keeping other reaction parameters unchanged. To assess the applicability of the protocol, we investigated

the substrate scope for dihydrodechlorination reactions. Consequently, a series of selected trichloroacetamides **1a**, **1d**, **1e**, **1h**, **1l**, **1r**, **3f** and **5c** with different substituents such as alkyl (**1a**, **1d**, **1e**), halogen (**1h**, **1l**), poly aryl (**1r**, **3f**) and aliphatic appendage (**5c**) were subjected to modified electrochemical conditions and all of them afforded the expected chloroacetamide derivatives as an exclusive product with excellent yields (Table 6).

After successfully showcasing the broad substrate scope of the electrochemical hydrodechlorination reaction, we focused on demonstrating the synthetic utility of dichloroacetamide. Consequently, the dichloroacetamide **2u** was treated with thiophenol under basic condition, and bis (phenylthio) acetamide **2uu** was obtained with excellent yield (Scheme 2).

(a)




(b)

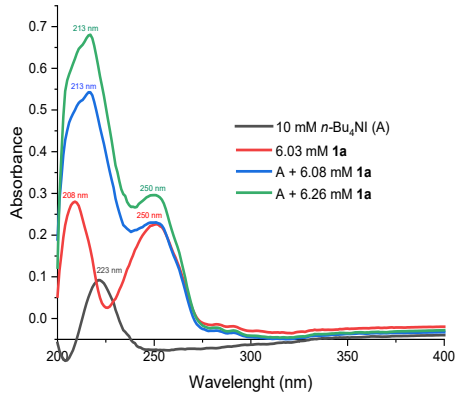



**Figure 2**. **(a)** I-V plot of *n*-$Bu_4NI$ + **1a** (dark cyan), and **1a** (red) at a scan of 0.1 $Vs^{-1}$ using cylindrical graphite rod (0.88 $cm^2$), Stainless steel plate, and Ag/AgCl as working, counter and reference electrodes respectively. **(b)** UV-Vis spectra of 10 mM of *n*-$Bu_4NI$, 6.03 mM of **1a**, 10 mM of *n*-$Bu_4NI$ with different concentration of **1a**.

To elucidate the plausible reaction mechanism, we carried out a series of control experiments (Scheme 3). No response was observed when the reaction was performed without passing electricity (Scheme 3, Reaction i). When using *n*-$Bu_4NBF_4$ as the supporting electrolyte, no desired product **2a** was formed (Scheme 3, Reaction ii). Therefore, we concluded that the selection of iodinated electrolyte such as *n*-$Bu_4NI$ was essential, and the role of iodine might be crucial. Again, we repeated the reaction in the presence of well-known radical scavengers such as TEMPO and BHT. With the 5.0 equivalent of either radical scavenger, the reaction took a more prolonged time, but the desired product was obtained with comparable yield. However, the reduced yield was obtained with 10.0 equivalent of radical quencher. (Scheme 3, Reaction iii). Since the product formation did not completely cease even after using the 10.0 equivalent of TEMPO/BHT, the possibility of a radical pathway was ruled out. On the contrary, three separate experiments were carried out using Al, Mg, and Zn metal as the anode (Sacrificial electrode) (Scheme 3, Reaction iv). The desired product was obtained in each case, though with a lower yield. So, the radical pathway is not possible; otherwise, the reaction would have been stopped as the iodine radical was expected to be quenched by sacrificial electrodes. As mentioned above, since we successfully prepared a series of deuterodechlorination products from trichloroacetamides (Table 5) using $CD_3OD$ as solvent, it was clear that the MeOH used as solvent was acting as a proton source.

To inspect the feasibility of the plausible mechanism, *n*-$Bu_4NI$ mediated selective hydrogenation of **1a**, UV-Vis spectroscopy, and cyclic voltammetry of model trichloroacetamide **1a** and *n*-$Bu_4NI$ were performed (Figure 2). As evident from the I-V characteristic plot, the reduction potential of trichloroacetamide **1a** alone comes at -0.31 V vs Ag/AgCl (Figure 2, entry a, red curve), which upon addition of electrolyte wholly disappeared with the formation of a new reduction hump at -0.24 V (Figure 2, entry b, cyan curve). This observation clearly suggests that $I^-$ coming from *n*-$Bu_4NI$ forms non-covalent interaction [28] with one of the three Cl atoms of trichloroacteamide, thus making the C-Cl bond vulnerable towards cathodic reduction.

This non-bonding interaction was further endorsed by analyzing the UV-Vis spectra of the solution of **1a**, *n*-$Bu_4NI$, and **1a** + *n*-$Bu_4NI$. The absorption of pure **1a** exhibits maxima at 208 nm (Figure 2, entry b, red curve). However, a substantial redshift of this peak happened to 213 nm after adding a fixed proportion of *n*-$Bu_4NI$ to the increasing amount of **1a**, implying the non-bonding interrelationship between them (Figure 2, entry b, blue and green curves).

Based on the results of the control experiments, CV and UV-Vis study, and existing literature reports, [29] a plausible reaction mechanism was depicted in Figure 3a. As a consequence of the crucial non-bonding XB donor-acceptor interaction between the Cl of **1a** and $I^-$, as supported by DFT calculations (Figure 3b). Then, the C–Cl bond of the activated trichloroacetamide **1a** underwent the cathodic reduction generating the $Cl^-$ with the resonance stabilized enolate **Int-2a**, as shown by atomic Hirshfeld charge analysis (Figure 3b).

Finally, protonation of the enolate **Int-2a** would generate the final hydrodichloroacetamide **2a**.

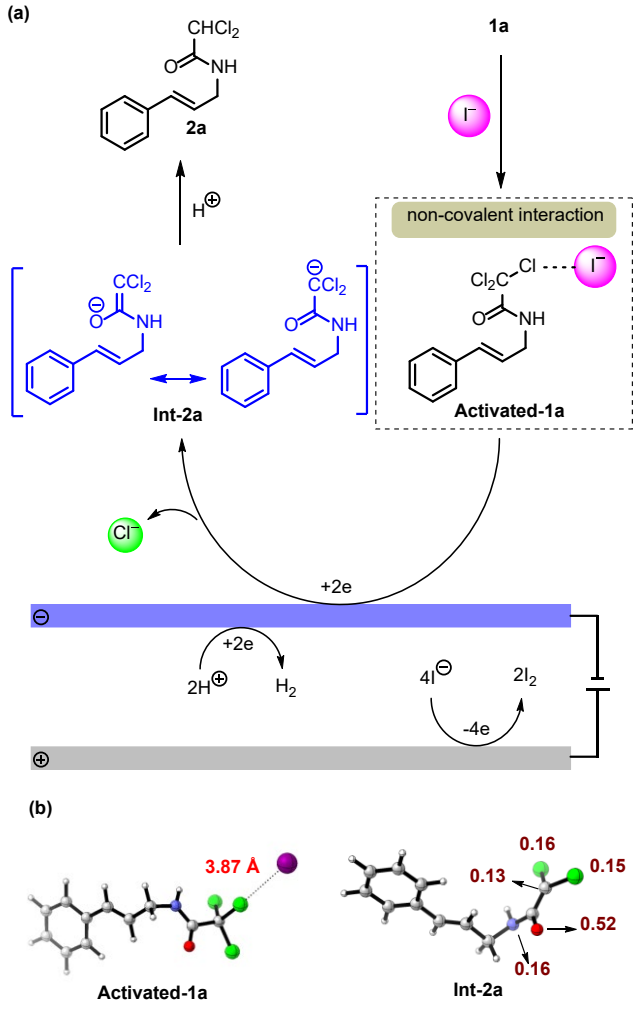



**Figure 3**. (a) Plausible reaction mechanism for the monodechlorination reaction of trichloroacetamide derivatives. (b) DFT optimized structures of **activated-1a** and enolate **Int-2a** at wB97xD/Def2TZVP level of theory. Atomic Hirshfeld charges are shown for **Int-2a**.[30,31]

## Conclusion

An electrochemical method for selective hydro and deuterodechlorination reaction of trichloroacetamide derivatives has been revealed. A large number of mono, di, and deuterochloroacetamides may be synthesized employing this electrochemical method from milligram to multi-gram scale. Inexpensive electrode materials and supporting electrolytes, shorter reaction time, consistent yield, reproducibility, and scalability are the major beneficial features of the reaction. The method's generality and synthetic versatility lie in its broad functional group compatibility, procedural simplicity, cost-effectiveness, and environmental benignity.

## Experimental Section

General information. All the electrochemical reactions were performed in three necked undivided peer-shaped containers (10 mL, 50 mL). Trichloroacetamides **1b-1s**, **3a-3h**, and **5a-5e** were synthesized as per the following synthetic procedure of **1a** and **3a**, respectively. *n*-$Bu_4NI$, KI, and other reagents were purchased from Sigma-Aldrich and used without further purification. The current was passed using **Orgel®** made by Eliteck Industries Private Ltd. This instrument can supply constant current or voltage through a switch while stirring with variable stirring speed (rpm). Isolated yields of the pure acetamide products were reported. Column chromatographic purifications were done using silica gel (100-200 mesh) manufactured by Spectrochem. IR spectra of all the chloroacetamides were recorded on the JASCO FT/IR-4600 instrument. High-resolution mass spectroscopies of acetamides were recorded on WATERS XEVO G2-XS QTof mass spectrometer. The single crystal XRD data of **2r** was recorded on a BRUKER D8 Quest diffractometer, and the structure was elucidated through Apex-IV software. $^1H$, $^{13}C\{^1H\}$ and $^{19}F$ NMR were recorded on BRUKER ASCEND 400 unit [$^1H$ NMR (400 MHz), $^{13}C\{^1H\}$ NMR (100 MHz), $^{19}F$ NMR (376 MHz)] taking TMS ($\delta$ = 0 ppm) as internal standard. Splitting patterns singlet, doublet, triplet, quartet, doublet of triplet, triplet of doublet, doublet of doublet of doublet, and multiplet were being abbreviated as s, d, t, q, dt, td, ddd, and m, respectively.

**General procedure for the electrosynthesis of dichloroacetamides 2a-2s.**

(*E*)-1,1,1-trichloro-6-phenylhex-5-en-2-one **1a** (0.43 mmol, 120 mg) was taken in a three-necked peer-shaped container (10 mL) with a magnetic stir bar. A graphite rod (0.2 cm, 2.5 cm, 3.6 $cm^2$) as anode and a stainless-steel plate (3.5 cm, 1.0 cm, 0.03 cm) as cathode were fitted. The cell was perfectly degassed and sealed after adding dry methanol (5 mL) and tetrabutylammonium iodide (0.1 M) while stirring. Finally, the cell was connected to an external constant current source (**Orgel®**) and electrolyzed for 2-2.5 h at a constant current of 24 mA. Upon completion, the solution was diluted with ethyl acetate and quenched with saturated sodium thiosulphate. The combined organic layer (2 × 10 mL) was concentrated and purified through flash chromatography to afford (E)-1,1-dichloro-6-phenylhex-5-en-2-one **2a** (87%, 91 mg) as a white solid.

*(E)-1,1-dichloro-6-phenylhex-5-en-2-one (2a).*

Eluent: ethyl acetate/ petroleum ether = 1:3, mp= 90-92°C, $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ = 4.14 (td, $J$ = 6.0, 1.5 Hz, 2H), 6.00 (s, 1H), 6.22 (dt, $J$ = 15.8, 6.3 Hz, 1H), 6.62 (dt, $J$ = 15.9, 1.6 Hz, 1H), 6.71 (s, 1H), 7.31-7.27 (m, 1H), 7.41-7.33 (m, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ = 42.4, 66.4, 123.7, 126.5, 128.1, 128.7, 133.4, 136.1, 164.1, IR (neat, $cm^{-1}$): 3278, 1668, HRMS (ESI) *m/z*: $(M + H)^+$ calcd for $C_{11}H_{11}Cl_2NO$: 244.0296; Found: 244.0285.

CCDC-2237523 (**2r**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

**Note**

The authors declare no competing financial interest.

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# Selective Hydro and Deuterodechlorination of Trichloroacetamide under Controlled Electrochemical Conditions: A Viable Approach towards Mono, Di, and Deuterochloroacetamides

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