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Original Article

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N- and *O*-Trideuteromethylation of Drugs and Intermediates with Trimethyloxosulphonium Iodide-d_9 Enabled by a Mechanochemical Synthesis

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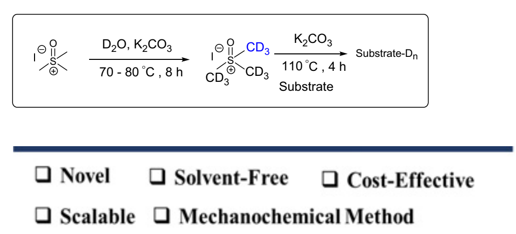
SIGNIFICANCE

- The study introduces a sustainable, solvent-free method for introducing the trideuteromethyl group in drug structures using trimethyloxosulphonium iodide-d_9 (TDMSOI) with the aim of enhancing the in vivo half-life of drugs, simultaneously reducing the hazardous and toxic reagents traditionally used in drug synthesis.
- The presented approach promotes scalable, cost-effective, safer, and eco-friendly drug/intermediate synthesis.
- The present method is an environment-friendly and more sustainable strategic approach based on mechanochemistry for achieving sustainable development goal(s).



Keywords

Deuterated drugs, Solvent-free synthesis, Mechanochemistry, Green synthesis, Trideuteromethylation

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ABSTRACT

Solvent-free, sustainable organic synthetic approaches based on the use of microwaves, ultrasound, or mechanochemistry are needed from a green chemistry perspective. Mechanochemical synthesis involves the coupling of mechanical and chemical processes at the molecular level. In the present study, we have applied mechanochemistry for the deuteration of drugs and intermediates, particularly *N*- and *O*-trideuteromethylation. Conventionally, MeI-d_3, a carcinogenic and relatively expensive reagent, is used for introducing a trideuteromethyl (–OCD_3) group in drugs/intermediates. Here, the utility of trimethyloxosulphonium iodide-d_9 (TDMSOI) was investigated as the –OCD_3 source, for developing and optimizing a novel, one-pot, solvent-free, mechanochemical method for *N*- and *O*-trideuteromethylation of several drugs/intermediates with appreciable degree of deuteration (~90% D), particularly those containing phenol, acid, and amine functional groups. The investigated method is scalable and is of potential interest to the Medicinal Chemistry and Drug Discovery community, given the perceived importance of deuteration as a viable strategy for affecting the in vivo half-life of drugs.

1. Introduction

Mechanochemistry involves chemical reactions carried out using mechanical energy, usually at ambient temperature. It offers several advantages such as solvent-free reactions, reduced waste generation, higher reaction speed and yields, and moderate reaction conditions (low energy consumption) [1]. The standard instrument for mechanochemical grinding, the “mortar-and-pestle,” was first employed in 1820 by Faraday during the reduction of AgCl by other metals [2]. Ling and Baker were the first to document the mechanochemical organic synthesis back in 1893 [3]. Mechanochemical grinding or milling has been employed for carrying out various solvent-free organic reactions in recent years, making it a valuable and popular approach in various scientific endeavors [4–7]. Milling, grinding, and other forms of mechanical action have been developed as viable alternatives to solution chemistry. Mechanochemistry opens the door to a new reaction environment where synthetic techniques, reactions, and compounds hitherto unavailable in solution can be realized [8, 9].

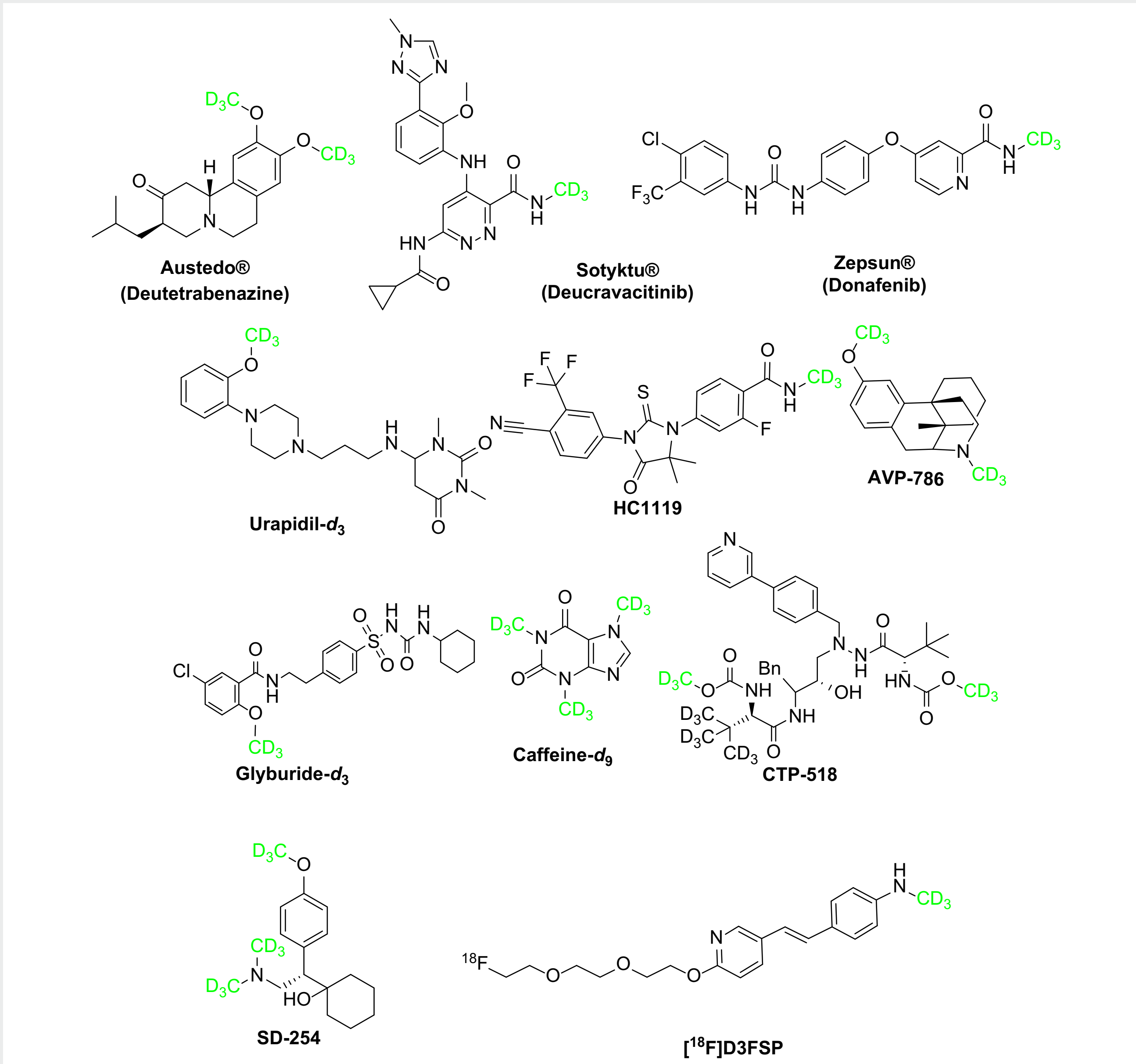
The significance of H-isotopes (deuterium (^2H) and tritium (^3H)) in mechanistic, spectrometric, and tracer studies has long been recognized [10]. Furthermore, well-known applications of H-isotopes may be found in practically every field of biological sciences, nuclear research, and beyond. The capacity to precisely detect isotope ratios now allows for a dynamic perspective of the biosynthetic pathways, protein turnover, and systems and systems-wide metabolic networks, paving the way for a number of scientific advancements in biomedical research. In medicinal chemistry, replacing ^1H with ^2H has lately attracted a lot of interest as a strategy for modifying drug candidates' overall disposition, mainly the in vivo metabolism. Deuterium's safety profile, the capacity to affect the in vivo half-life, and bioavailability of small molecules promote its use in a wide range of applications. However, deuterium's use in biological research and medicine development is hampered by a paucity of deuterated compounds [11–14]. Recent literature summarizes the progress in the development of synthetic methodology for the deuteration of organic molecules [15]. ▶**Figure 1** shows the molecular structures of a few approved deuterated drugs and developmental candidates, containing the –OCD_3 group(s).

Strategically located ‘Methyl’ group and the ensuing ‘magic methyl’ effect in bioactive molecules hold an unmatched place in medicinal chemistry [16–18]. On similar lines, XCH_3 (X = O, N, S, and so on) is another well-known, easy-to-metabolize group. To increase the metabolic stability of these Me-containing drugs, researchers have worked on developing –XCD_3 analogues [19–21]. In 2017, the USFDA-authorized Austedo® (deutetrabenazine) (▶**Figure 1**) as the first deuterated medication for the treatment of chorea associated with Huntington's disease [22, 23]. Other drug examples include deucravatinib and donafenib. Examples of clinical candidates include SD-254, [^{18}F]D3FSP, CTP-518, HC1119, AVP-786, glyburide-d_3, urapidil-d_3, and caffeine-d_9 [24–31].

Despite its increased utility in medicinal chemistry and drug discovery, the practical techniques and reagents for inserting the –CD_3 group into target molecules of interest remain relatively difficult [32–51] (Scheme 1). The –CD_3 source reagents, e.g., CD_3I and dimethyl sulfate-d_6 ($(CD_3)_2SO_4$), are commonly utilized. However, they are carcinogenic, toxic, relatively less abundant, and expensive. Other relatively expensive reagents, such as CD_3OD and DMSO-d_6, are attractive alternatives due to their lower toxicity. Nonetheless, a scarcity of synthetic approaches limits their further use. The synthesis of $ArOCD_3$ was made possible by employing the well-known palladium-catalyzed coupling of alcohols (e.g., CD_3OD) with aryl halides (Routes A and C, Scheme 1) [52, 53]. Vanderheiden and colleagues have discovered an exciting, metal-free, CF_3CO_2H-mediated radical reaction with aryl triazenes (Route B, Scheme 1) [54].

Shen and Zhang proposed the unique idea of trideuteromethylation in a ‘one-pot’ operation for the efficient synthesis of a new reagent, TDMSOI (Route D, Scheme 1) [32]. A novel sulfoxonium metathesis reaction involving TMSOI and DMSO-d_6 has been devised. The ability of the new versatile reagent, coupled with the optimized ‘one-pot’ protocol to install the CD_3 moiety into broad functionalities such as phenols, thiophenols, acidic amines, and enolizable methylene units in high yield and at a sound level of deuteration, was successfully demonstrated. The strategy used expensive DMSO-d_6 as a solvent and ^2H source; the reaction involved higher temperatures and long heating hours (120 °C, 2 h; 65 °C, 18 h). Caporaso et al. achieved radical trideuteromethylation with DMSO-d_6 for the synthesis of heterocycles and labelled building blocks [55].

A broadly applicable strategy for trideuteromethylation involving alkylation of diverse, polar functional groups such as –OH, –NH_2, –COOH, and so on would greatly aid in the medicinal chemistry investigations and the ensuing drug development. In the present investigation, we devised a novel, one-pot, solvent-free, scalable, trideuteromethylation method involving mechanochemistry based on TDMSOI as a –CD_3

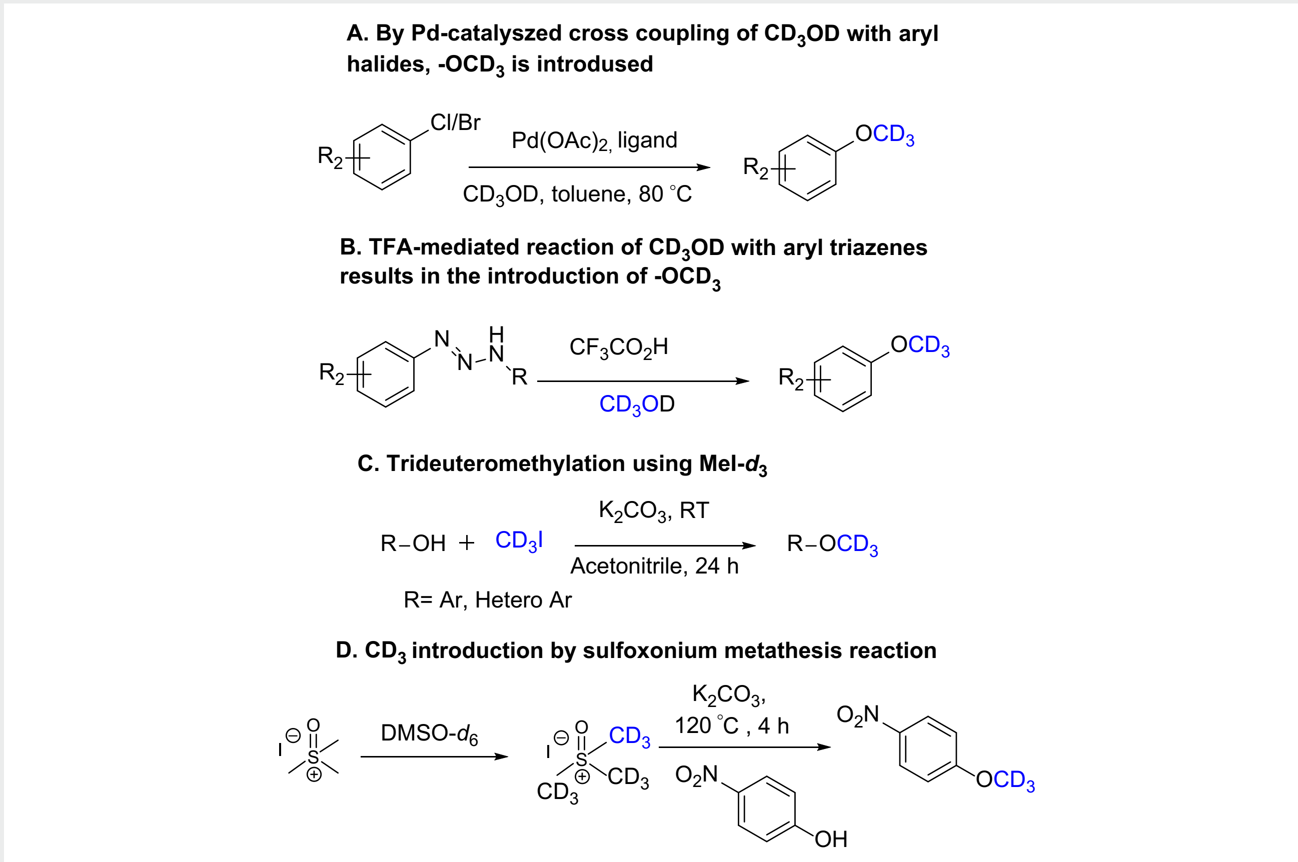


▸ **Figure 1** Approved drugs and clinical candidates containing $-CD_3$ group(s).

source, with improved yield and degree of deuteration. The presented method avoids the use of previously reported trideuteromethylating reagents such as CD_3I and $(CD_3)_2SO_4$ [56, 57]. The applications of the presented method were explored for expanding its scope with reference to the nature of the substrate and the reaction conditions.

2. Results and Discussion

According to the previous work of Cotton et al., the synthesis of MeI-d_3 from TMSOI-d_9 was carried out directly by simple pyrolysis [57]. Here, we have applied the same idea for the one-pot trideuteromethylation of suitable substrates by simple trituration in a mortar and pestle under a moisture-free atmosphere. Here, we could hypothesize that due to mechanical force and heating, MeI-d_3 was obtained in situ from TMSOI-d_9, which acted as a $-CD_3$ source. Consequently, the RX^- (X = OH, NH_2, COOH, etc.) ion was generated due to the presence of a base (e.g., K_2CO_3, Na_2CO_3, NaH, t-BuOK, and KOH), ultimately forming RX-CD_3 (▸ **Figure 2**). Further details of the proposed methodology are discussed at length in the succeeding subsections. Every attempt is made to outline the synthetic details precisely. The choice of substrates was governed by the targeted functional groups, such as phenolic –OH, aromatic $-NH_2$, and ketones containing α-Hs. Depending on the outcomes, additional experiments were planned to investigate the deuteration trend for a particular set of substrates.



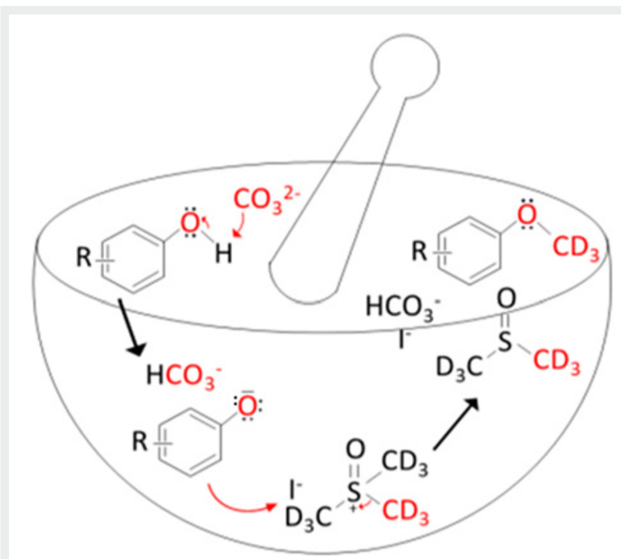
Scheme 1 Generic summary of the $-CD_3$ group introduction methods.

2.1. Synthesis of TMSOI-d_9

The reagent TMSOI-d_9 was prepared using the technique reported by Cotton et al. Recent literature revealed a few interesting synthetic strategies for trideuteromethylation of varied substrates [58]. First, TMSOI salt was synthesized by refluxing MeI (0.3 mol, 2.34 equiv) and DMSO (0.128 mol) in an RBF under N_2 atmosphere for 72 h at 50 °C. Then, the salt crystals were recovered and washed with Et_2O or $CHCl_3$ to yield the product in reasonable yield (60%). The resulting salt was then readily deuterated by recrystallizing it with an excess of D_2O [58, 59]. The deuterated salt was further recrystallized with an excess of D_2O (6.95 mol, 54.3 equiv) in the presence of a catalytic amount of K_2CO_3 for 8 h at 70 °C, which was the optimized condition for deuteration (▶**Table 1**, Entry 6); after cooling, it resulted in pure TMSOI-d_9 (80% yield).

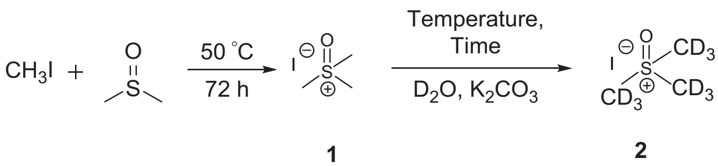
2.2. One-pot trideuteromethylation of model substrate, *p*-nitrophenol

A model reaction with 4-nitrophenol **3a** (▶**Table 2**) was probed for process optimization of the proposed method (▶**Figure 3**). In the initial attempt, synthesis of **4a** was carried out using 1 equiv of TMSOI-d_9 and 1 equiv of K_2CO_3 wherein the reaction mixture was triturated in mortar-pestle at RT for 4 h, under N_2 atmosphere, ensuring exclusion of moisture (▶**Table 2**, Entry 1), but the reaction was far from initiating. We reasoned that the energy generated from trituration alone was insufficient to generate CD_3I from TMSOI-d_9 in situ. According to Le Chatelier's principle, greater temperatures and longer heating



▶**Figure 2** Plausible mechanism of trideuteromethylation using the proposed methodology.

▸**Table 1** Optimization of TMSOI-d_9 synthesis.



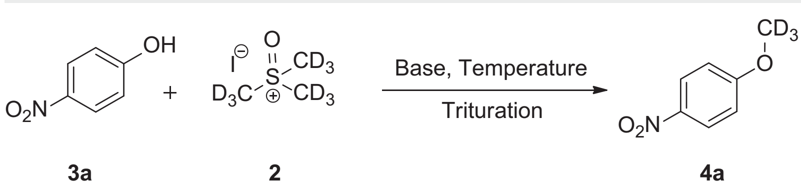
Entry	Time (h)	Temp. (°C)	Yield (%)	Deuterium exchange
1	1	110	85	Incomplete
2	24	110	20	Complete
3	24	90	35	Complete
4	12	90	55	Complete
5	8	90	65	Complete
6	8	70	80	Complete

times propel the reaction forward, favoring the creation of the desired product [58]. Further optimization on these lines did, in fact, significantly enhance the yield (Entries 2–4).

The reaction conditions used for entry 4 (110 °C, 2 h) were the best choice for further screening. When the loading of K_2CO_3 was increased to 1.5 equiv, ^2H incorporations were slightly reduced while the yield increased slightly. Eventually, various bases were examined, including Na_2CO_3, NaH, t-BuOK, and KOH, which resulted in lower ^2H incorporations compared to K_2CO_3 (Entries 7–9 vs. 4), with the exception of Na_2CO_3, which had somewhat better ^2H incorporations but lower yield. In contrast, KOH did not yield any results. Nonetheless, it was discovered that the electronic nature of the substrate had a significant impact on the base choice. As a result, several bases were utilized to investigate the process's substrate breadth.

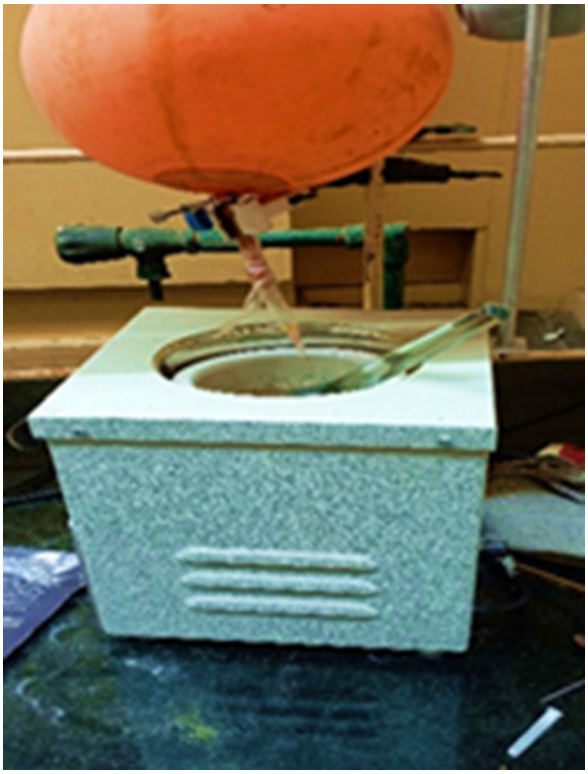
Following optimization of the reaction conditions, with the best response conditions in hand, a range of reactions was investigated using a variety of phenolic substrates (Scheme 2).

▸**Table 2** Process optimization of the proposed reaction.[a–c]



Entry	Temp. (°C)	Time (h)	Equiv	Base	Yield (%)	%D
1	RT	4	1	K_2CO_3	–	–
2	60	4	1	K_2CO_3	–	–
3	80	4	1	K_2CO_3	5	–
4	110	2	1	K_2CO_3	95	94
5	110	2	1.5	K_2CO_3	90	91
6	110	2	1	Na_2CO_3	70	97
7	110	1	1	NaH	62	57
8	110	1	1	t-BuOK	68	82
9	110	4	1	KOH	–	–
10[c]	50	12	1	K_2CO_3	90	91

[a] *Reaction conditions*: For experimental details and the isolated yield, see the *Supporting Information*.
[b] ^1H NMR was used to determine the degree of ^2H incorporation.
[c] MeI-d_3 was used instead of TMSOI-d_9.



▶ **Figure 3** Reaction setup.

The findings revealed that the regimen was effective and functioned as a basic technique for producing structurally varied aryl trideuteromethyl ethers. A wide range of phenols with electron-withdrawing or electron-donating substituents might effectively engage in the process, deliver outstanding to exceptional yields, and ^{2}H incorporation in product **4**. The reaction was also applied to a bisphenol (emodin, **3i**) for trideuteromethylation, but only one phenolic group was trideuteromethylated due to differences in their respective acidities.

2.3. One-pot trideuteromethylation of varied phenolic substrates

In the case of phenolic substrates containing a carbonyl group, such as ketones (**3b–d**) and amides (**3h**), $-CD_3$ exchange was observed at the α-Me group (**4b–d** and **4h**), but the degree of ^{2}H incorporation was unsatisfactory. For comparison, here we attempted $-CD_3$ incorporation of paracetamol (**3h**) conventionally by using MeI-d_3, which resulted in the formation of trideuteromethyl ether (**4j**), and no ^{2}H exchange on the α-carbon of the amide group was seen. Interestingly, in our method, ^{2}H exchange was observed at the α-carbon of the amide group (**4h**), although the degree of ^{2}H exchange was lower. Also, the deuteration was slightly better by our method, but the yield was lower. The broad application of this technology, in particular, made it possible to obtain the $-CD_3$ versions of important pharmacological and natural product targets (**4h–4j**) from their phenol precursors.

2.4. One-pot trideuteromethylation of additional substrates

We moved on to other substrates after successfully incorporating the $-CD_3$ group onto phenols (Scheme 2). Surprisingly, when the improved technique was applied to aryl/alkanoic carboxylic acids, smooth conversion into the appropriate $-CD_3$ esters, e.g., **6c** with high ^{2}H incorporation (93%), was seen. The corresponding $-CD_3$ insertion onto N-containing moieties is an extremely valuable procedure. It was shown that 1*H*-benzotriazole and other amine substrates could be converted into their $-CD_3$ versions with a high degree of ^{2}H incorporation (**6a–b**) by our method (Scheme 3). For the amino group-containing substrate (**6a**), the yield was low if K_2CO_3 was used as a base in comparison to Na_2CO_3, where the degree of deuteration was appreciable. Multiple $-CD_3$-containing primary amino group was also possible with a good degree of ^{2}H incorporation, but the yield was a bit less (data not shown). Overall, our extensive investigations were fruitful in grafting $-CD_3$ group onto phenols, carboxylic acids, and amines.

3. Experimental

3.1. Materials

The solvents (including dry solvents) and reagents were purchased from commercial suppliers, e.g., SD Fine Chemicals, Mumbai, India, and others, were used as such, unless otherwise discussed. All reactions were performed under an inert atmosphere (N_2) unless otherwise noted. Analytical silica gel 60 F_{254}-coated TLC plates were purchased from Merck Millipore (Billerica, MA) and were visualized under short- and long-UV light.

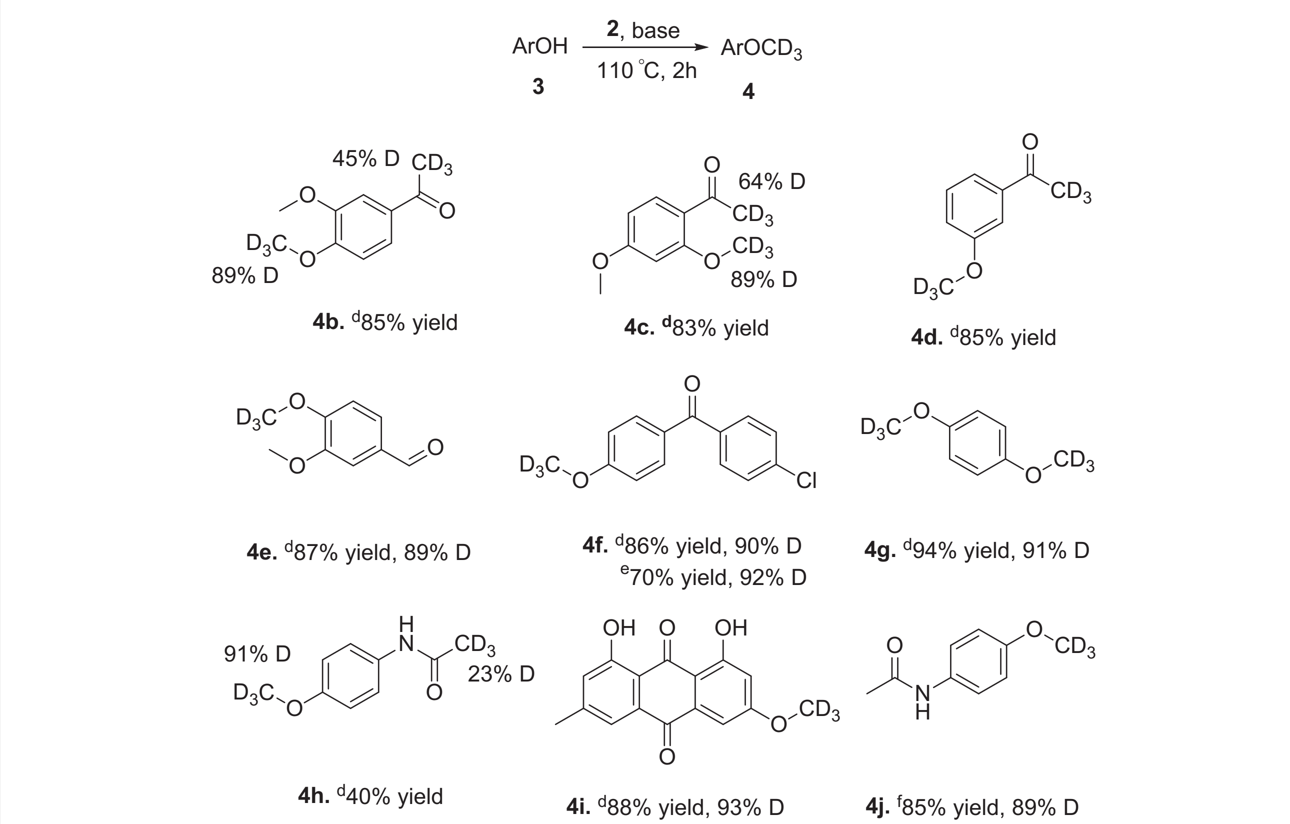
3.2. Instrumental

Melting points were recorded using Veego Instruments, VMP-DS model, capillary melting point apparatus (Mumbai, Maharashtra, India), and are uncorrected. FTIR spectra were obtained with the help of a Jasco FT-IR spectrometer using the ATR sampling technique. The samples were scanned in the region of 4000–600 cm^{-1}. ^{1}H NMR spectra were routinely recorded on Agilent 400 MHz NMR spectrometer, with tetramethylsilane (TMS) as an internal standard and the recorded spectra was processed using evaluation version of MestReNova software (note: $CDCl_3$ referenced at 7.26 ppm in ^{1}H NMR; DMSO-d_6 referenced at 2.50 ppm in ^{1}H; D_2O referenced at 4.63 ppm in ^{1}H).

3.3. General procedure for synthesis of TDMSOI

TDMSOI was synthesized in two parts. In Part 1, trimethylsulfoxonium iodide (TMSOI) salt was synthesized by heating MeI (2.34 equiv) and DMSO (1 equiv) for 72 h at 50 °C. After 72 h, the salt crystals were recovered by filtration, washed with Et_2O or $CHCl_3$, and dried in vacuum oven at 40 °C overnight.

In Part 2, the resulting TMSOI salt was recrystallized with an excess of D_2O (54.3 equiv) in the presence of the catalytic amount of anhydrous K_2CO_3 for a specific time and temperature (▶ **Table 1**). The precursor (TMSOI) and the product



Scheme 2 Scope of trideuteromethylation for various phenolic substrates.[a,b]
[a]*Reaction conditions*: For experimental details and the isolated yield, see the Supporting Information.
[b]^{1}H NMR was used to determine ^{2}H incorporation.
[c]K_2CO_3 as a base.
[d]Na_2CO_3 as a base.
[e]MeI-d_3 was used instead of TMSOI-d_9.

(TDMSOI) structures were confirmed by ^{1}H NMR and FT-IR spectra.

IR (FT-IR) (cm^{-1}): 2960.2, 2359.5, 2341.2, 1553.2, 1219.8, 1035.6, 949.8, 768.5, 684.5, 673.6, 418.5; ^{1}H NMR (400 MHz, D_2O) δ ppm, No signal.

3.4. General procedure for trideuteromethylation of a suitable substrate

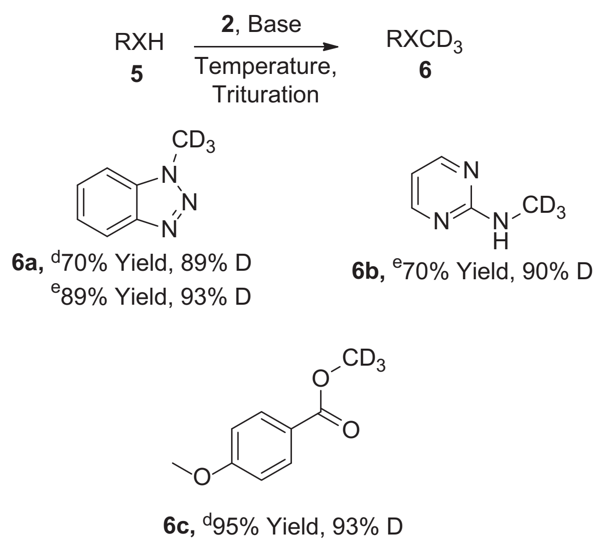
In a mortar, substrate (phenol, acid, or amine) and TDMSOI were taken along with the base. The reaction mass was triturated with a pestle for the necessary amount of time at the indicated temperature over a silica bath. The reaction was monitored with TLC with the indicated solvent system. After completion of the reaction, the cooled reaction mass was quenched with brine solution, and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, and the solvent was evaporated in vacuo to obtain the crude product. The pure product was obtained following column chromatography with the stated solvent system. ^{1}H NMR spectroscopy was used to determine the degree of ^{2}H incorporation in the substrate (Eq. (1)). The integrals were checked against a peak that corresponded to a certain point.

$$\%\text{deuteration} = 100 - [(\text{residual integral})/(\text{number of labeling sites}) \times 100] \tag{1}$$

1-(Methoxy-d$_3$)-4-nitrobenzene (4a) Pale-yellow solid; Yield: 189.2 mg (95%). Deuterium incorporation (confirmed using ^{1}H NMR spectra): 90.66% D. IR (FT-IR) (cm^{-1}): 3116, 2927, 2360, 1890, 1585, 1492, 1323, 1254, 1099, 1018, 845, 748, 687, 606, 528, 494; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.20–8.17 (d, 2H, J = 12 Hz), 6.95–6.92 (d, 2H, J = 12 Hz), 3.87–3.83 (dd, 0.28 H).

4. Conclusions

Our extensive investigations led to the development of a novel, one-pot, adaptable, solvent-free, mechanochemical method for $-CD_3$ incorporation into drugs, intermediates, reference standards, and other substrates containing varied functional groups in high yields and with a desirable amount of deuteration. This innovative approach can be used instead of the commonly used, costly, and hazardous reagents such as CD_3I and $(CD_3)_2SO_4$ for the same purpose. The adaptability of the trideuteromethylation reagent, TMSOI-d_9, as well as the protocol's



Scheme 3 Scope of carboxylic acid and amine as substrates[a,b]
[a]*Reaction conditions*: For experimental details and the isolated yield, see Supporting Information.
[b]^{1}H NMR was used to determine ^{2}H incorporation.
[c]K_2CO_3 as a base.
[d]Na_2CO_3 as a base.

simplicity and effectiveness, are predicted to make it helpful in techniques for the practical manufacture of highly valued –CD_3-incorporated molecules, a new tool in modern drug development. There is a scope for extending the method to additional substrates with complex functional groups.

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Contributors' Statement

Data collection: PMD, SJD and OCH; Study design: PSK, PMD; Synthesis: PMD, SJD and OCH; Data analysis and interpretation: All authors; Manuscript writing: All authors.

Conflict of Interest

The authors declare that they have no conflict of interest.

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