



Cite this: *RSC Adv.*, 2025, 15, 34746

Dimethyl(alkyl) sulfates as Lewis acid type catalysts for acetalization and related reactions of carbonyl compounds

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The catalytic activity of dimethyl sulfate (DMS) and its higher homologs in converting carbonyl compounds to *O,O*-dimethylacetal/ketals is demonstrated. Our mechanistic investigations proved that previously reported Schmitz and Langvad claims stating DMS as an alkylating agent and a source of sulfuric acid in the acetalization of aldehydes were erroneous. Carbonyl compounds were converted to methyl, ethyl acetals/ketals, 1,3-dioxalanes and 1,3-dioxanes, and cyclohexane-1,3-diones into vinylogous esters. Selective aldehyde protection and ketone reduction were preferentially achieved in a single step. This study represents the first instance of using alkylating agents, such as dimethyl, diethyl, diisopropyl, and di-*n*-butyl sulfates, as catalysts in organic transformations. The catalysis proceeds even in the presence of base, demonstrating that dialkyl sulfates act like Lewis acid-type catalysts. Noncovalent interactions arising from the polar covalent bonds of the alkyl group in dialkyl sulfate are responsible for catalytic activation. Acetalization was found to be instantaneous in the presence of DMS in methanol; this was attributed to the contribution from traces of hidden protons in the presence of base.

Received 3rd September 2025
Accepted 11th September 2025

DOI: 10.1039/d5ra06610g

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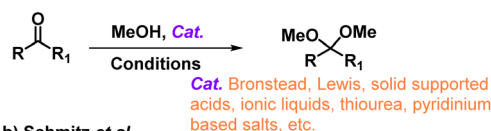
1 Introduction

Catalysis has experienced a tremendous transition from metal catalysts to organic small-molecule catalysts in accordance with sustainability. Organic small molecule catalysis is becoming more prevalent and encompassing a greater range of chemical transformations. In addition to the standard Lewis and Brønsted acid catalysts, a large variety of small molecules have been explored as catalysts.^{1–3} We present here neutral alkyl electrophiles such as dimethyl sulfate and its higher homologs as mild Lewis acid-type catalysts. For the first time, we showed that these dialkyl sulfates catalyse acetalization and related reactions of carbonyl compounds.

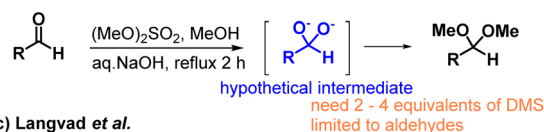
Acetals are prominent functional groups; their formation and cleavage are the fundamental reactions in organic chemistry.^{4–8} They play an important role as protecting groups in multistep synthesis. Acetalization stands as one of the extensively studied fundamental reactions of organic synthesis. Acetals can be prepared using a straightforward method from a carbonyl molecule condensing with alcohols or diols (Scheme 1a). The reaction is generally promoted by strong Brønsted and Lewis acids while removing a byproduct water molecule.^{9–11} In addition, transition metal catalysts,¹² lanthanide complexes,¹³ pyridinium-based salts,¹⁴ ionic liquids,¹⁵ NHC-based catalysts,¹⁶ solid-supported metal-salts,¹⁷ and urea-based catalysts¹⁸ have been utilized. The corrosive, strong acids in a protic

environment have a significant disadvantage; they are worsened when acid-sensitive functional groups are present. Also, certain methods have their own drawbacks, such as the use of expensive and rare-metals and need for expensive and multi-step synthesis for catalyst preparation. Moreover, typical reaction

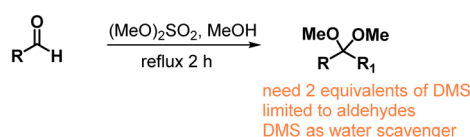
a) Reported acetalization



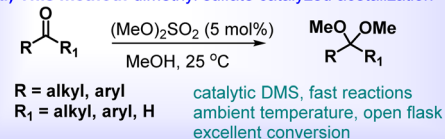
b) Schmitz *et al.*



c) Langvad *et al.*



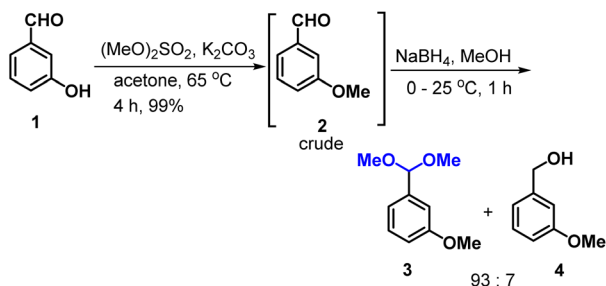
d) This method: dimethyl sulfate catalyzed acetalization



Scheme 1 Carbonyl compounds to *O,O*-dimethyl acetals/ketals.

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Scheme 2 Initial studies for the preparation of 3-methoxybenzaldehyde dimethyl acetal.

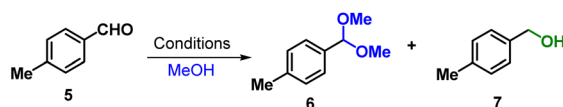
conditions require anhydrous solvents, azeotropic techniques, or use of dehydrating agents and have a narrow substrate scope.

In this manuscript, we demonstrated that, unlike traditional acid-catalyzed acetalizations, our protocol proceeds under neutral/basic conditions, avoids strong acids and expensive metal catalysts, and tolerates acid-sensitive functional groups. The acetalization of aldehydes is operationally simple, works at ambient conditions in open air on multigram scale in short reaction times, and it does not require dehydrating agents or azeotropic techniques. Use of NaBH_4 to quench the DMS reduce the unreacted carbonyl compound makes it convenient to easy separation of acetals from unreacted carbonyl compounds (mostly, acetals have closure R_f values, and sensitive to silica

column). Additionally, this method allows selective aldehyde protection with simultaneous ketone reduction in a single step. This would be best alternative to Luche's reduction^{19,20} that avoid Lanthanide metal salts. Moreover, it provides selective aldehyde protection and ketone reduction in the presence of other reactive functional groups (Scheme 6). We propose the features of our protocol position it as a complementary and practical alternative to established methods, while also uncovering the overlooked catalytic role of dialkyl sulfates. The objective of this manuscript is to highlight this disregarded catalytic function of dimethyl(alkyl) sulfates, which traditionally regarded solely as alkylating reagents, demonstrated now as potential catalysts.

Finding the abnormal chemical behaviour of bench-top reagents opens up new avenues within chemical space. Organosulfates or sulfate esters play an important role in life, as they are linked with proteins, lipids, carbohydrates, and steroids.^{21–23} Alkyl sulfate-esters are widely used as xenobiotics in the form of surfactants in household and industry.²⁴ Dialkyl sulfates are best alternatives to haloalkanes; they are excellent alkylating agents, easily accessible on the commercial market. They possess many useful applications as reagents in both academia and industry. Moreover, dimethyl sulfate is preferred by the industry because of its low cost and high reactivity.^{25,26} Despite extensive applications as alkylating agents, DMS and its higher analogs have never been regarded as catalysts for any chemical

Table 1 Optimization for acetalization^a



Entry	Conditions	Yield ^b [5 : 6 : 7]
1	$(\text{MeO})_2\text{SO}_2$ (0.1 eq.), 30 min	8 : 92 : 0
2	$(\text{MeO})_2\text{SO}_2$ (0.05 eq.), 30 min, 25 °C. Then NaBH_4 (0.1 eq.), -20 °C	0 : 94 : 6
3	$(\text{MeO})_2\text{SO}_2$ (0.02 eq.), 30 min, 25 °C. Then NaBH_4 (0.1 eq.), -20 °C	0 : 83 : 17
4	NaBH_4 (1 eq.), 30 min, -20 °C	0 : 0 : >99
5	$\text{CH}_3\text{OSO}_3\text{H}$ (0.05 eq.), 30 min, 25 °C	17 : 83 : 0
6	$\text{CH}_3\text{OSO}_3\text{H}$ (0.02 equiv.), 30 min, 25 °C	36 : 64 : 0
7	$(\text{MeO})_2\text{SO}_2$ (0.1 eq.), proton sponge (0.1 eq.), 25 °C, 6 h	56 : 44 : 0
8	$(\text{MeO})_2\text{SO}_2$ (0.2 eq.), DTBP (0.5 eq.), 6 h, 25 °C	29 : 71 : 0
9	$(\text{MeO})_2\text{SO}_2$ (0.2 eq.), DTBP (1 eq.), 6 h, 25 °C	40 : 60 : 0
10	$(\text{MeO})_2\text{SO}_2$ (0.2 eq.), anhyd. NaHCO_3 , 2 h, 25 °C	40 : 60 : 0
11	Me_2SO_4 (0.2 eq.), Et_3N (0.2 eq.), MeOH, 30 min, 25 °C	9 : 91 : 0 ^c
12	Me_2SO_4 (0.2 eq.), NaOH (0.2 eq.), MeOH, 30 min, 25 °C	100 : 0 : 0 ^d
13	Me_2SO_4 (0.2 eq.), NaOMe (0.2 eq.), MeOH, 30 min, 25 °C	11 : 89 : 0 ^c
14	Me_2SO_4 (0.2 eq.), pyridine (0.2 eq.), MeOH, 30 min	100 : 0 : 0 ^d
15	$\text{CH}_3\text{OSO}_3\text{H}$ (0.2 eq.), DTBP (0.25 eq.), 18 h, 25 °C	100 : 0 : 0
16	$\text{CH}_3\text{OSO}_3\text{H}$ (0.2 eq.), proton sponge (0.25 eq.), 18 h, 25 °C	100 : 0 : 0
17	$\text{CH}_3\text{OSO}_3\text{H}$ (0.2 eq.), anhyd. NaHCO_3 , 18 h, 25 °C	100 : 0 : 0

^a Reactions were carried out with 2.5 mmol **1**. ^b Yields were calculated by ¹H-NMR using internal standard 1,1,2,2-tetrachloroethane. ^c Base was added before the DMS addition. ^d Base was added 30 min after the DMS addition.



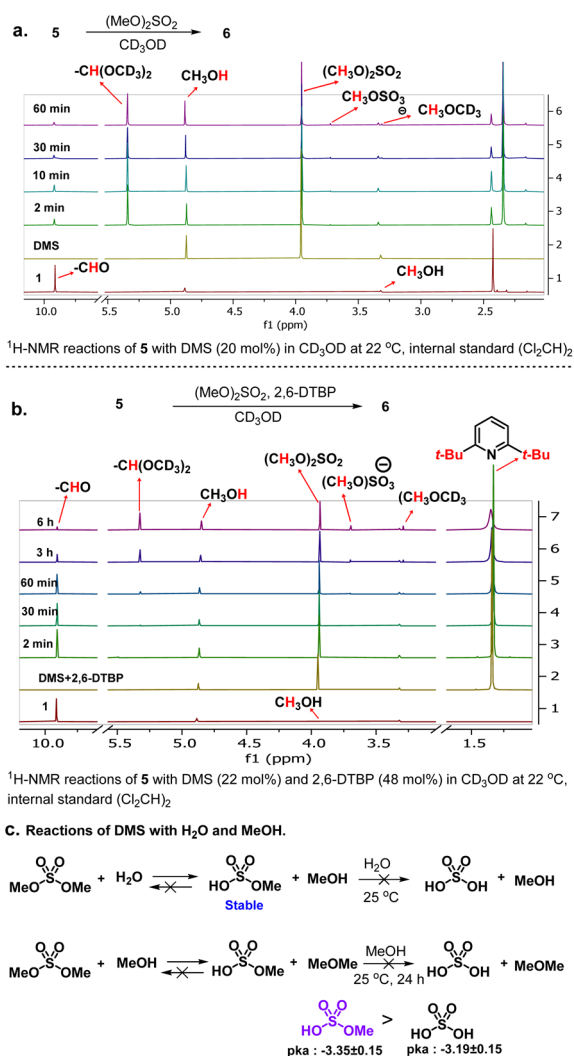


Fig. 1 NMR experiments and DMS reactions.

transformation in the literature. In the first instance, we observed that dimethyl, diethyl, diisopropyl, and di-*n*-butyl sulfates exhibited distinctly different behaviour as Lewis acid-type catalysts in activating carbonyl groups towards acetalization reactions. Dialkyl sulfates demonstrated their catalytic potential in the presence of bases, such as 2,6-di-*tert*-butylpyridine, proton sponge, and anhydrous sodium bicarbonate. This offers tolerance of several acid-sensitive functional groups.^{27–29}

2 Results and discussion

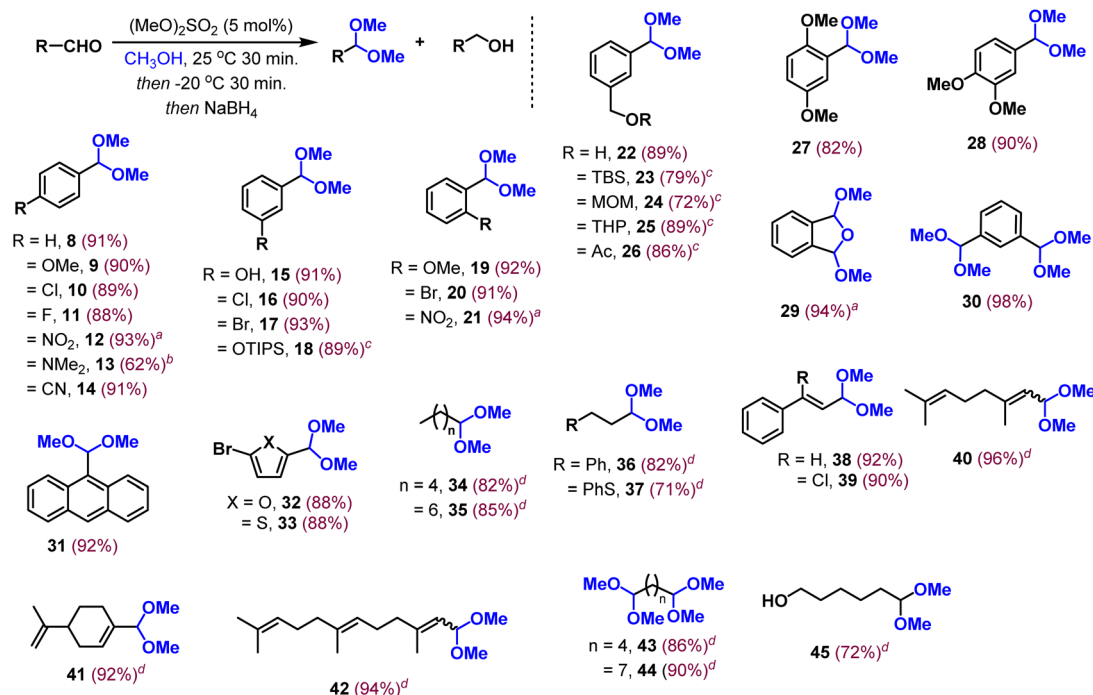
A serendipitous outcome in the reaction of 3-methoxybenzaldehyde (1) to 3-methoxybenzaldehyde dimethyl acetal (3), during NaBH_4 reduction, sparked our curiosity (Scheme 2). The reactions were carried out in a two-step sequence from 3-hydroxybenzaldehyde (1) reacting with dimethyl sulfate (DMS) and a base. The simple aqueous workup did not remove the DMS traces, confirmed by $^1\text{H-NMR}$. Following dissolution of 2 in MeOH and addition of sodium borohydride, yielding acetal 3 in 93% and alcohol 4 in 7%.

However, DMS has previously been used as a reagent for the acetalization of aldehydes, as reported by two individual research groups. Schmitz utilized DMS as a reagent in the presence of aq. NaOH for the conversion of aldehydes to corresponding dimethyl acetal. He proposed that DMS as a methylating agent for aldehyde bis(olate), a hypothetical intermediate expected to be generated from aldehyde in alkaline solution (Scheme 1b).^{30,31} Contrariwise, Langvad emphasized DMS as a water scavenger; it hydrolyze with *in situ* water to produce H_2SO_4 , which catalyzes the acetalization (Scheme 1c).³² Our results demonstrate that both previous proposals are erroneous. We experimentally found that Schmitz's claim, that a base promotes the formation of bis(olate), is not true; in reality, the base is preventing the catalysis by reacting with DMS (entries 11 to 14; Table 1). In addition, DMS was used as a methylating agent in acetal formation reactions;³³ dialkyl amides were converted to α -aminoacetals by treatment with DMS and NaOMe. Also, DMS is used to methylate hemiacetals to get methyl acetals.³⁴ Our study is establishing that, instead of a reagent or H_2SO_4 source, the DMS functions as a Lewis acid-type catalyst involving NCIs through a unique mechanistic pathway (Scheme 1d).

To optimize reaction conditions, 4-methylbenzaldehyde (5) was taken as a test substrate and reacted with methanol under various conditions (Table 1, also see SI, S3). Reaction of aldehyde 5 with DMS (5 mmol) in methanol, followed by NaBH_4 addition, produced acetal 6 and alcohol 7 in 94% and 6% isolated yields. Based on Schmitz's report,^{30,31} initially, we hypothesized that NaBH_4 or its derivatives might assist as base in the acetalization process. To identify the role of NaBH_4 , it was used in absence of DMS, which exclusively yielded the alcohol 7 quantitatively (entry 4). Other potential byproducts of NaBH_4 in MeOH, such as BH_3 (ref. 35) or NaB(OMe)_4 , did not affect the reaction outcome (see SI, S2).³⁶ The acetalization requires as little as 5 mol% DMS (entries 1–3; achieved 86% isolated yield on a 50 g batch), and the NaBH_4 aids in converting the unreacted aldehyde to alcohol. NaBH_4 also quenches the DMS quickly to stop the reaction; longer reaction times led to the backwards reaction towards aldehyde. Separating acetals from unreacted carbonyl compounds is difficult due to their close or similar R_f -values; hence, we continued with NaBH_4 to convert traces of unreacted aldehyde into a more polar alcohol for easier column chromatographic separation.

A time-dependent NMR study (Fig. 1a) showed that acetalization is instantaneous, producing acetal in >80% in less than two minutes. It also revealed that DMS reacts with MeOH slowly in small quantities to give dimethyl ether and methyl bisulfate (MBS, Fig. 1c), in 1 : 1 ratio.³⁷ As MBS is a stronger acid ($\text{pK}_a = -3.4 \pm 0.15$), it can catalyze the reaction when present in traces. To confirm the catalytic nature of MBS,³⁸ we reacted aldehyde 5 with MeOH using catalytic MBS (2 and 5 mol%; entries 5 and 6, Table 1), providing 6 in 64% and 83% yields. These yields are significantly lower compared to DMS (entries 2 and 3) catalysis. To further understand whether the reaction was catalyzed by DMS or proton, a base was introduced into the reaction medium.³⁹ Remarkably, the use of sterically hindered bases such as 2,6-di-*tert*-butylpyridine (DTBP), Proton-Sponge, and



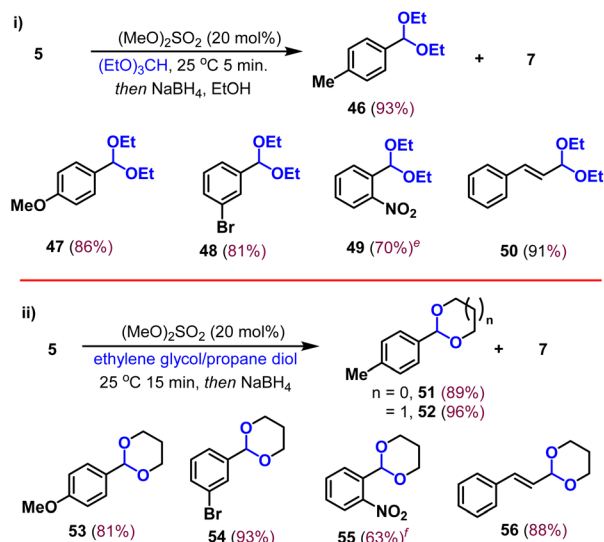


Reactions were conducted with aldehyde (5 mmol), DMS (5 mol%) and NaBH₄ (20 mol%); ^a 3 hours; ^b DMS (50 mol%), 4 h; ^c 0 °C, 3 h; ^d DMS (20 mol%), 3 h.

Scheme 3 Preparation of dimethyl acetals of aldehydes.

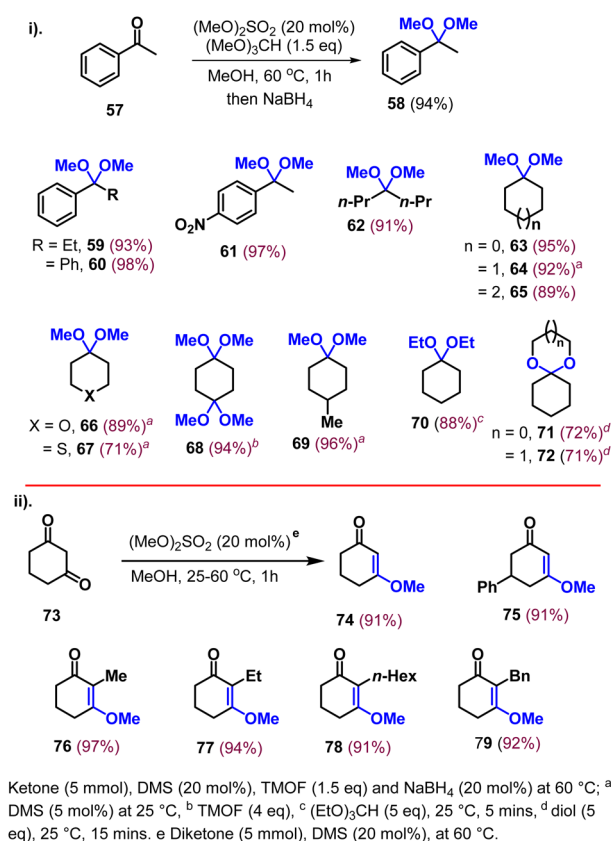
anhyd. NaHCO₃ in excess equivalents to DMS, produced acetal **6** in good yields (entries 7 to 10).⁴⁰

A time-dependent NMR study using DMS and DTBP revealed that, although the reaction was slow, it progressed steadily over 6 hours to reach 94% conversion (Fig. 1b). Strong bases were found to react with DMS; however, when added after DMS into



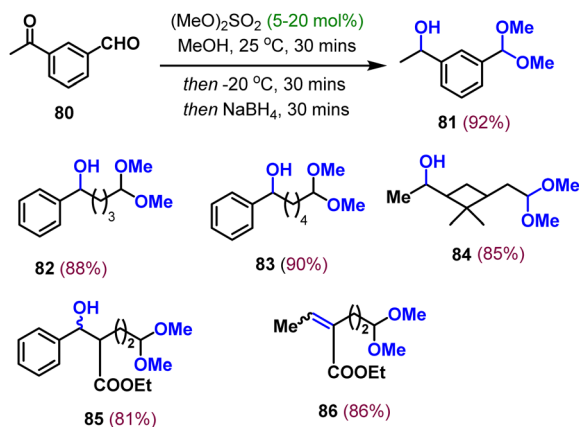
Aldehyde (5 mmol), DMS (20 mol%) and NaBH₄ (20–30 mol%); ^e 30 mins; ^f 1 h

Scheme 4 Reaction of aldehydes with ethanol and ethylene glycol and propylene diol.



Ketone (5 mmol), DMS (20 mol%), TMOF (1.5 eq) and NaBH₄ (20 mol%) at 60 °C; ^a DMS (5 mol%) at 25 °C, ^b TMOF (4 eq), ^c (EtO)₃CH (5 eq), 25 °C, 5 mins, ^d diol (5 eq), 25 °C, 15 mins. ^e Diketone (5 mmol), DMS (20 mol%), at 60 °C.

Scheme 5 Preparation of acetals from ketones and vinylogous esters from 1,3-cyclohexanedione.

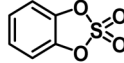


Scheme 6 One-pot selective aldehyde acetalization and ketone reduction.

the reaction mixture, the desired acetal was obtained. In contrast, pre-addition of the base (prior to DMS) did not lead to acetal formation (see entries 11–14). Conversely, MBS (20 mol%), when employed with DTBP or Proton-Sponge or anhyd. NaHCO_3 (entries 15 to 17; Table 1), the starting aldehyde was recovered completely even after 18 h. Collectively, these experiments revealed that DMS itself catalyzes the acetalization effectively. The results also exclude the proton catalysis, even it was found ineffective with MBS and DTBP salt. These results also conclude the acetalization works in the presence of a base. Few reports show base-mediated acetalizations by transition metal catalysts.^{41,42} Base-promoted acetalizations in the presence of alkylating agents, including dimethyl sulfate (DMS), have also been reported.^{43,44} In contrast, our study presents the first example of DMS-catalyzed acetalization promoted in the presence of a base.

Thereafter, the scope of reaction was expanded using various aromatic, hetero aromatic, aliphatic, and α,β -unsaturated aldehydes to provide corresponding dimethyl acetals (8 to 45) in yields ranging from 62 to 94% (Scheme 3). Several acid-sensitive protecting groups, such as silyl, MOM, THP ethers and ester groups, remained intact (18 and 22–26).⁴⁵ 4-*N,N*-Dimethylamino benzaldehyde provided acetal 13 in moderate yields of 62%.⁴⁶ Phthalaldehyde and isophthalaldehyde gave oxalane 29 and bis-

Table 2 Acetalization utilizing different dialkyl sulfates^a

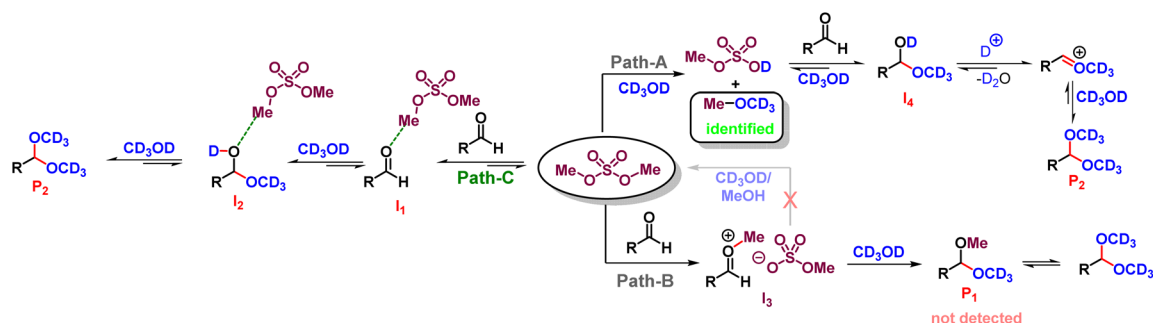
Entry	Conditions	Yield ^b [5 : 6]
1	(EtO) ₂ SO ₂ (0.1 eq.), 30 min	22 : 78
2	(i-PrO) ₂ SO ₂ (0.1 eq.), 30 min	35 : 65
3	(n-BuO) ₂ SO ₂ (0.1 eq.), 30 min	50 : 50
4	 (0.1 eq.), 24 h	0
5	(PhO) ₂ SO ₂ (0.1 eq.), 24 h	0

^a Reactions were carried out with 2.5 mmol 5. ^b Yields were calculated by ¹H-NMR using internal standard.

acetal 30. Conjugated aldehydes produced corresponding acetals without any Michael addition product or unwanted cyclization reactions (38 to 42).

Similarly, diethyl acetals (46 to 50) were produced in 70–93% yields by reacting aldehydes with ethanol, and the reactions were found to be much slower only in ethanol. When triethyl orthoformate was used as an ethanol source (Scheme 4i), corresponding diethyl acetals were produced in good to excellent yields.^{47–49} Similarly, ethylene diol and 1,3-propanediol reacted with aldehydes under mild conditions in the presence of 20 mol% DMS to give cyclic acetals 51 to 56 up to 96% yields (Scheme 4ii).

In the case of ketones, apart from cyclohexanones, other ketones displayed poor reactivity towards acetalization. Acetophenone reacts with MeOH in the presence of catalytic DMS and trimethyl orthoformate additive as water scavenger to promote forward reaction, producing 58 in 94% yield (Scheme 5i). Under similar reaction conditions, several aromatic and aliphatic ketones produced their ketals (59–72) in excellent yields. Cyclic ketones with different ring sizes and heterocyclic ring systems reacted well to produce corresponding dimethyl ketals 63–69, in 71–96% yields. 1,4-cyclohexadione converted to



Scheme 7 Possible mechanistic pathways; Path-A: *in situ* formation of MBS and a Brønsted acid catalysis; Path-B: electrophilic activation by methyl transfer; Path-C: electrophilic activation of the carbonyl through noncovalent interactions.



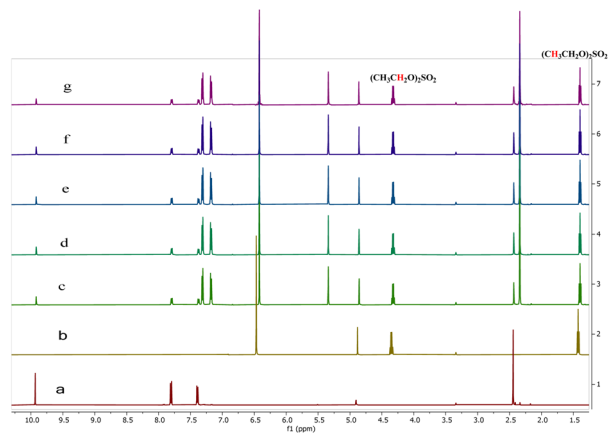


Fig. 2 ^1H -NMR (500 MHz, CD_3OD) reaction with diethyl sulfate catalyst at 25 °C. 1,1,2,2-Tetrachloroethane (1 eq.) used as internal standard; (a) ^1H -NMR of the 4-methylbenzaldehyde (**1**) in $\text{CD}_3\text{-OD}$; (b) ^1H -NMR of the diethyl sulfate (**B**) in $\text{CD}_3\text{-OD}$; ^1H NMR measured for the reaction mixture at (c) 2 min; (d) 10 min; (e) 20 min; (f) 30 min; (g) 1 h; yields were calculated in comparison with internal standard.

bis-ketol **68** in 94% yield (Scheme 5i). Cyclohexanone was reacted with ethanol, ethylene glycol and propylenediol to give corresponding ketals **70** to **72** in very good yields.

Furthermore, an important transformation involving the conversion of 1,3-diketones into corresponding β -methoxy enones was achieved using DMS catalysis.^{50,51} When 1,3-cyclohexanedione reacted with methanol in the presence of catalytic DMS, they furnished corresponding vinylogous esters (**74** to **79**) in yields exceeding 90% (Scheme 5ii).

Based on the biased reactivity of aldehydes over the ketones, one-pot aldehyde protection and ketone reduction were explored (Scheme 6). This method has many advantages, including milder and faster reaction conditions, superior selectivity, and higher yields.^{19,20} 3-Acyl benzaldehyde **80** underwent selective acetalization and reduction by NaBH_4 , resulting in the formation of hydroxy acetal **81** in 92% yield. Similarly, other ketoaldehydes underwent selective conversion to their respective hydroxy acetals **82** to **86**, consistently yielding excellent results. Notably, aldehydes containing β -keto ester functionality displayed remarkable chemo selectivity for ketone reduction, ultimately affording acetals **85** and **86** with high efficiency.

Base medium experiments ruled out the possibility of catalysis being driven by an active proton from MBS (Path A, Scheme 7). An alternative mechanism involving the transfer of a methyl group from DMS to form a methoxonium ion (Path B; Scheme 7) was considered as a secondary pathway, but experimental evidence could not support regenerating DMS from MBS in methanol under ambient conditions. This conclusion is reinforced by our NMR analysis, which showed no exchange of OCH_3 to OCD_3 in DMS (Fig. 1a and 2) or OEt to OCD_3 when diethyl sulfate catalyst was used.

To further investigate the role of the methyl and sulfate groups in DMS's catalytic function, various dialkyl sulfates were tested as catalysts. Diethyl sulfate, diisopropyl sulfate, and di-*n*-

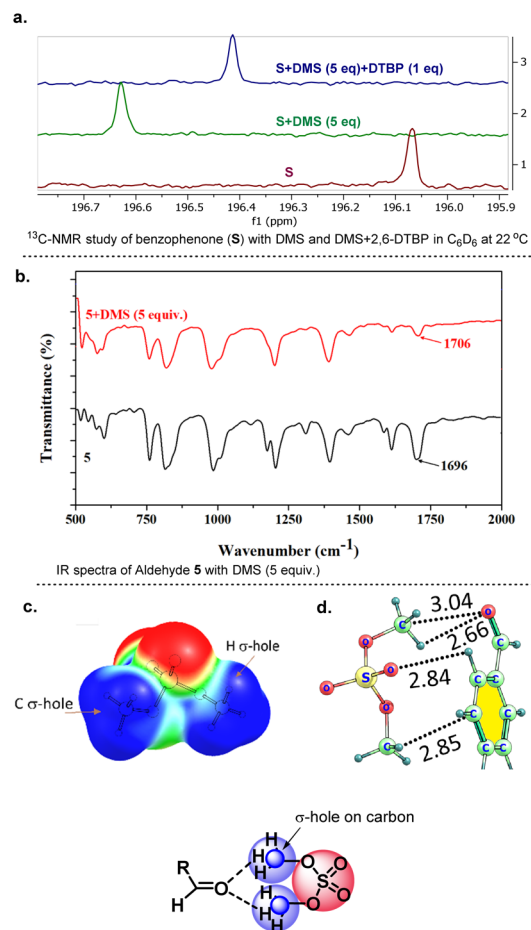


Fig. 3 NMR experiments, IR-study, and DFT calculations.

butyl sulfate promoted acetalization, producing compound **6** in 78%, 65%, and 50% yields, respectively (Table 2). NMR studies indicated that diethyl sulfate remains stable in methanol, yet it still achieved a 78% yield of compound **6** (Fig. 2) within 30 minutes. Conversely, diphenyl sulfate and catechol sulfate did not promote acetalization, even at elevated temperatures and longer reaction times. These findings suggest that the alkyl group bind to sulfate promoting the catalytic acetalization.

Hydrocarbons attached to polar groups (C-X ; X = electron negative atom) can develop a region of positive electrostatic potential on the carbon atom, known as σ -hole.^{52–54} These positive potentials can spread across the C-H groups. These polar hydrocarbons which can establish multiple weak non-covalent interactions (NCIs) with electron donating atoms or groups. Such NCIs include, carbon bonding, non-classical hydrogen bonding, dipole interactions, polarization effects and van der Waals interactions.^{55,56} In a separate study we employed DMS as a catalyst in Friedel-Crafts reactions of aldehydes with indoles, and arenes.⁵⁷ Where we performed DFT studies, that showed positive potentials on the CH_3 groups negative potentials on sulfate groups. These positive alkyl groups, as shown in Fig. 3c, establish multiple NCIs including carbon bonding ($\text{C=O}\cdots\text{C-OSO}_3$) and non-classical hydrogen bonding ($\text{SO}_3\text{-OCH}_2\text{-H}\cdots\text{O=C}$) with carbonyl oxygen.

Collectively these weak attractive NCIs activate the carbonyl group, accounting for the abnormal catalytic behaviour of DMS.^{58,59} The spectroscopic methods supported very weak interactions between DMS and carbonyl group. The ¹³C-NMR of benzophenone showed a slight shift in the carbonyl from 196.1 to 196.6 ppm in the presence of DMS. It was also observed that addition of base to this complex disturbed the interactions shifting the carbonyl peak to a slightly higher field (196.4 ppm, Fig. 3). IR blue shift for $\nu_{\text{C=O}}$ (1696 to 1702 cm^{-1}) supports an $\text{O}=\text{C}-\text{H}\cdots\text{O}=\text{S}$ type interaction.^{60,61} These observations suggest the non-covalent interactions between DMS and carbonyl groups, and supports the non-covalent Lewis acid type nature of DMS in catalytic acetalizations.

3 Conclusions

In summary, we demonstrated the catalytic potential of dimethyl(alkyl) sulfates as Lewis acid-type catalysts in acetalization of carbonyl compounds. Dialkyl sulfates, which are extensively used as alkylating agents in industry and academia are now proven as prospective catalysts. It is understood that electrophilic alkyl (not aryl) of sulfates play a pivotal role in catalytic function. The reaction worked well in the presence of hindered organic bases, and weak inorganic base showing that the acetalization is not promoted by any hindered proton. However, the cooperative effect of hindered proton in the catalysis by DMS cannot be ignored. This study also demonstrates that the previously proposed methods by Schmitz and Langvad suggesting that DMS act as methylating agent and as water scavenger in acetalization of aldehydes are erroneous. The acetalisation was promoted in the presence of base under catalytic conditions. Additional studies are currently in progress to implement this novel catalysis concept in multi-component reactions.

Author contributions

GR wrote the manuscript with the help of all authors. Tanmay conceptualization, data curation, formal analysis, investigation, validation, methodology; Keerthana and Reyno validation, investigation; Rajendar conceptualization, formal analysis, funding acquisition, investigation, project administration, resources, supervision, validation, writing-original draft, and editing.

Conflicts of interest

There are no conflicts to declare.

Data availability

Experimental procedures and spectral data of all compounds are available as SI. See DOI: <https://doi.org/10.1039/d5ra06610g>.

Acknowledgements

This work was supported by Science and Engineering Research Board (SERB), India through SERB-Core Research Grant "CRG/

2020/003737". TS, and RRS acknowledges CSIR-UGC and KS acknowledges IISER-TVM for research fellowship.

References

- 1 L. Albrecht, A. Albrecht and L. Dell'Amico, *Asymmetric Organocatalysis: New Strategies, Catalysts, and Opportunities*, Wiley-VCH, 2022.
- 2 T. Clark, M. Hennemann, J. S. Murray and P. Politzer, Halogen bonding: the sigma-hole. Proceedings of "Modeling interactions in biomolecules II", Prague, September 5th-9th, 2005, *J. Mol. Model.*, 2007, **13**(2), 291–296.
- 3 M. Benaglia, Walter de Gruyter, *Organocatalysis: Stereoselective Reactions and Applications in Organic Synthesis*, 2021.
- 4 S. von Angerer and S. L. Warriner, Category 4, Compounds with Two Carbon Heteroatom Bonds Acetals: Hal/X and O/O, S, Se, Te, *Science of Synthesis*, Thieme Chemistry, 2007, vol. 29.
- 5 T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, New Jersey, 3rd edn, 1999.
- 6 M. Johnny, R. M. Philip and G. Rajendar, *Org. Lett.*, 2022, **24**, 6165–6170.
- 7 M. Johnny and G. Rajendar, *J. Org. Chem.*, 2024, **89**, 7036–7046.
- 8 S. Wang, O. Zhelavskiy, J. Lee, A. J. Argüelles, Y. Y. Khomutnyk, E. Mensah, H. Guo, R. Hourani, P. M. Zimmerman and P. Nagorny, *J. Am. Chem. Soc.*, 2021, **143**, 18592–18604.
- 9 J.-L. Dong, L.-S.-H. Yu and J.-W. Xie, *ACS Omega*, 2018, **3**, 4974–4985.
- 10 P. G. M. Wuts and K. Michigan, in *Greene's Protective Groups in Organic Synthesis*, Academic Press, New York, 5th edn, 2014, pp. 559–643.
- 11 R. G. Cooks, H. Chen, M. N. Eberlin, X. Zheng and W. A. Tao, *Chem. Rev.*, 2006, **106**, 188–211.
- 12 S. Krompiec, M. Penkala, K. Szczubiałka and E. Kowalska, *Coord. Chem. Rev.*, 2012, **256**, 2057–2095.
- 13 H. B. Kagan and J. L. Namy, *Tetrahedron*, 1986, **42**, 6573–6614.
- 14 B. Procuranti and S. J. Connon, *Org. Lett.*, 2008, **10**, 4935–4938.
- 15 L. Myles, R. Gore, M. Špulák, N. Gathergood and S. J. Connon, *Green Chem.*, 2010, **12**, 1157–1162.
- 16 Y. Liu, Q. Chen, C. Mou, L. Pan, X. Duan, X. Chen, H. Chen, Y. Zhao, Y. Lu, Z. Jin, *et al.*, *Nat. Commun.*, 2019, **10**, 1675.
- 17 T. Kawabata, T. Mizugaki, K. Ebitani and K. Kaneda, *Tetrahedron Lett.*, 2001, **42**, 8329–8332.
- 18 M. Kotke and P. R. Schreiner, *Tetrahedron*, 2006, **62**, 434–439.
- 19 A. L. Gemal and J. L. Luche, *J. Org. Chem.*, 1979, **44**, 4187–4189.
- 20 A. L. Gemal and J. L. Luche, *J. Am. Chem. Soc.*, 1981, **103**, 5454–5459.
- 21 S. R. Hanson, M. D. Best and C.-H. Wong, *Angew. Chem., Int. Ed.*, 2004, **43**, 5736–5763.



- 22 E. Chapman, M. D. Best, S. R. Hanson and C.-H. Wong, *Angew. Chem., Int. Ed.*, 2004, **43**, 3526–3548.
- 23 D. R. Edwards, D. C. Lohman and R. Wolfenden, *J. Am. Chem. Soc.*, 2012, **134**, 525–531.
- 24 M. J. Scott and M. N. Jones, *Biochim. Biophys. Acta*, 2000, **1508**, 235–251.
- 25 M. Zubradt, P. Gupta, S. Persad, A. M. Lambowitz, J. S. Weissman and S. Rouskin, *Nat. Methods*, 2017, **14**, 75–82.
- 26 K. Weisenberger, D. Mayer and S. R. Sandler, in *Ullmann's Encyclopedia of Industrial Chemistry*, 2000.
- 27 Base-mediated acetalizations are very rare. A. Clerici, N. Pastori and O. Porta, *Tetrahedron*, 1998, **54**, 15679–15690.
- 28 H. E. Simmons and D. W. Wiley, *J. Am. Chem. Soc.*, 1960, **82**, 2288–2296.
- 29 M. Barbasiewicz and M. Makosza, *Org. Lett.*, 2006, **8**, 3745–3748.
- 30 E. Schmitz, *Angew. Chem.*, 1956, **68**, 375.
- 31 E. Schmitz, *Chem. Ber.*, 1958, **91**, 410–414.
- 32 T. A. Langvad, *Acta Chem. Scand.*, 1954, **8**, 336–338.
- 33 U. Pindur, in *The Chemistry of Acid Derivatives*, ed. S. Patai, Wiley, Chichester, UK, 1992, vol. 2, suppl. B, p. 1005.
- 34 S. von Angerer and S. L. Warriner, *Sci. Synth.*, 2007, **29**, 303–406.
- 35 Y. Zhou, G. Gao, Y. Song and J. Qu, *Synth. Commun.*, 2014, **44**, 1515–1520.
- 36 SI denotes supporting information, and Sx shows the page number.
- 37 J. P. Guzowski Jr, E. J. Delaney, M. J. Humora, E. Irdam, W. F. Kiesman, A. Kwok and A. D. Moran, *Org. Process Res. Dev.*, 2012, **16**, 232–239.
- 38 We did not find any reported methods for methyl bisulfate as a Bronsted acid catalyst for acetalization reactions.
- 39 The nature of the base and its addition sequence is important; NaOH, Et₃N, Py, K₂CO₃, and NaOMe reacted with DMS and prevented acetalization when added before DMS, contradicting Schmitz's bis(olate) hypothesis.
- 40 The addition of a base slows the reaction, as it was expected that the catalyst would interact with the base, demonstrates the disruption of the carbonyl–DMS complex interactions.
- 41 A. Clerici, N. Pastori and O. Porta, *Tetrahedron*, 1998, **54**, 15679–15690.
- 42 T. Kawabata, T. Mizugaki, K. Ebitani and K. Kaneda, *Tetrahedron*, 2001, **57**, 217–229.
- 43 G. R. Newcome, J. D. Saner and G. L. McClure, *Tetrahedron Lett.*, 1973, **14**, 1599.
- 44 H. E. Simmons and D. W. Wiley, *J. Am. Chem. Soc.*, 1960, **82**, 2288–2296.
- 45 These reactions were conducted in anhydrous methanol at 0 °C.
- 46 Substrates with amines substituents react with DMS to form their corresponding methylammonium salts and did not provide any acetalization products.
- 47 Use of ethanol or triethyl orthoformate led to lower yields.
- 48 D. Arnodo, C. Meazzo, S. Baldino, M. Blangetti and C. Prandi, *Chem.–Eur. J.*, 2023, **29**, e202300820.
- 49 E. A. Mensah, S. D. Green, J. West, T. Kindoll and B. Lazaro-Martinez, *Synlett*, 2019, **30**, 1810–1814.
- 50 P. J. Kocienski, *Protecting Groups*, Thieme, Stuttgart, 3rd edn, 2003.
- 51 N. Mohanta, M. B. Chaudhari, N. K. Digrawal and B. Gnanaprakasam, *Org. Process Res. Dev.*, 2019, **23**, 1034–1045.
- 52 T. Brinck, J. S. Murray and P. Politzer, *Int. J. Quantum Chem.*, 1992, **44**, 57–64.
- 53 W. Zierkiewicz, M. Michalczyk and S. Scheiner, *Molecules*, 2021, **26**, 1740.
- 54 B. Mallada, A. Gallardo, M. Lamanec, B. de la Torre, V. Špirko, P. Hobza and P. Jelínek, *Science*, 2021, **374**(6569), 863–867.
- 55 J. J. Novoa and F. Mota, *Chem. Phys. Lett.*, 1997, **266**, 23–30.
- 56 R. Vargas, J. Garza, D. A. Dixon and B. P. Hay, *J. Am. Chem. Soc.*, 2000, **122**, 4750–4755.
- 57 T. Sarkar, A. Das, C. H. Suresh and G. Rajendar, Catalytic Prowess of Dialkyl Sulfates: Cooperative Carbon Bonding and C–H Hydrogen Bonding Driven Friedel–Crafts and Multicomponent Reactions of Aldehydes, manuscript under review.
- 58 E. J. Corey and T. W. Lee, *Chem. Commun.*, 2001, **15**, 1321–1329.
- 59 Further details are provided in our upcoming work on DMS-catalyzed bis-indolyl methanes and xanthene diones.
- 60 A. Borba, A. Gómez-Zavaglia, P. N. N. L. Simões and R. Fausto, *Spectrochim. Acta, Part A*, 2005, **61**, 1461–1470.
- 61 Y. Gu, T. Kar and S. Scheiner, *J. Am. Chem. Soc.*, 1999, **121**, 9411–9422.

