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Manuscript Title

Dithioacetalization or Thioetherification of Benzyl Alcohols by 9-Mesityl-10-methylacridinium Perchlorate Photocatalyst

Authors

Milan Pramanik, Khokan Choudhuri, Ashis Mathuri and Prasenjit Mal*

Affiliations

School of Chemical Sciences, National Institute of Science Education and Research (NISER), HBNI, Bhubaneswar, PO Bhimpur-Padanpur, Via Jatni, District Khurda, Odisha 752050, India, E-mail: pmal@niser.ac.in

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Dithioacetalization or Thioetherification of Benzyl Alcohols by 9-Mesityl-10-methylacridinium Perchlorate Photocatalyst

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We report herein the use of 9-mesityl-10-methylacridinium perchlorate as the visible-light photocatalyst for dithioacetalization or thioetherification of benzyl alcohols in one pot using aerial dioxygen as terminal oxidant. EPR analysis and Stern-Volmer quenching studies helped to rationalize the single electron transfer (SET) mechanism.

Towards development of efficient and novel methodologies aerobic oxidation strategies have gained significant attention in synthetic chemistry.[1] Particularly, the oxidation of benzyl alcohols to corresponding carbonyl compounds, selectively, is one of the desirable topics in organic chemistry due to the following implications. The benzyl alcohols are very unreactive because hydroxyl group has bad leaving ability until unless the C-O bond is activated by Lewis acid or catalysis.[2] In addition, oxidation of benzyl alcohols offers corresponding aldehydes or ketones which are more reactive, and prone to be attacked by any other nucleophiles present within the reaction system.[3] So far, many oxidation strategies of benzyl alcohols are documented in literature and most of the methods require stoichiometric use of oxidants. In this context, aerial oxygen is one of the most environmental friendly and sustainable oxidants[4] being served for domino type synthesis.[5]

In last couple of decades, the research area under the umbrella of visible light photoredox-catalysis has become one of the powerful techniques in organic synthesis.[6] Due to the mild nature and having high tolerance ability towards many functional groups, photoredox catalysts are highly popular in organic synthesis.[7] Also, the methodologies by involving single electron transfer (SET) processes have become highly significant to achieve a wide range of synthetic transformations.[8]

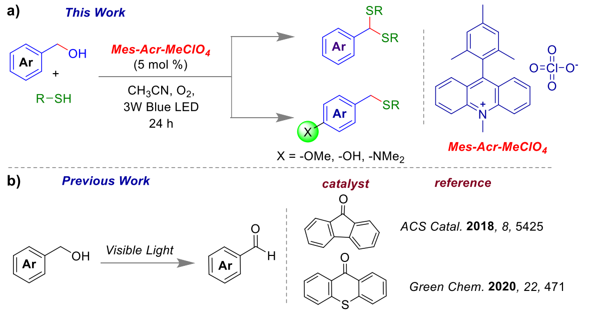

Figure 1. a) Our work based on *in situ* oxidation of benzyl alcohols and followed by C-S bond formation by photocatalysis. b) Known examples on oxidation of benzylic alcohols to benzaldehydes using 9H-fluoren-9-one[9] and 9H-thioxanthen-9-one[10] as photocatalysts.

So, the photolytic studies using benzyl alcohols as alkylating agent or benzyl synthon *via* loss of -OH group is impressive.[2] Therefore, C-S bond forming reactions under mild and sustainable conditions are always desirable.[11] Dithioacetals are excellent protecting groups in synthesis because of their high tolerance ability to acidic or basic condition[12] and also known as directing groups for C-H activation reactions.[13] The photoredox catalyzed oxidation of stable benzyl alcohols to aldehydes are reported by Das's group[9] and Kokotos's group[10] (Figure 1b). Recently, the dithioacetalization reactions are reported from either aldehydes or non-conventional starting materials under inert atmosphere.[14] Contrastingly, many popular routes for synthesis of thioethers mainly relies on either metal or metal free cross coupling reactions.[15] To the best of our knowledge, no reports available for the direct dithioacetalization or thioetherification of benzyl alcohols *via* oxidative functionalization of C-O bonds using any photocatalyst (Figure 1a). We report herein the use of 9-mesityl-10-methylacridinium perchlorate (Mes-Acr-MeClO$_4$) as the photocatalyst[16] and aerial oxygen as the terminal oxidant in acetonitrile using 3W blue LED lights at 30-35 ºC (room temperature).

The ground state reduction potential of Mes-Acr-Me$^+$ (-0.49 V *vs* SCE) comparable to molecular oxygen [$E_{1/2}(O_2/O_2^{\bullet-}) = -0.87$ V *vs* SCE in MeCN].[17] Thus anticipated that excited Mes-Acr-Me$^+$ after SET with benzyl alcohol, would easily reduce molecular

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School of Chemical Sciences, National Institute of Science Education and Research (NISER), HBNI, Bhubaneswar, PO Bhimpur-Padanpur, Via Jatni, District Khurda, Odisha 752050, India, E-mail: pmal@niser.ac.in

† Footnotes relating to the title and/or authors should appear here.

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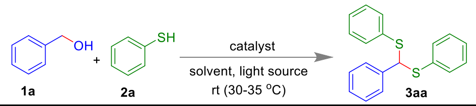
oxygen to its superoxide radical[6b, 9] The reaction condition was optimized using benzyl alcohol **1a** and thiophenol **2a** as model substrates (Table 1) (for details see ESI, Table S1). The compound **3aa** (dithioacetal) was isolated in 32% yield using 5 mol % of 9-mesityl-10-methylacridinium tetrafluroborate (Mes-Acr-$MeBF_4$) as photocatalyst, 0.5 mL thiophenol, 1.0 mL CH_3CN, under aerobic condition for 24 h with 3W blue LEDs. Other photocatalysts like Eosin Y $Ru(bipy)_3(PF_6)_2$ showed inferior results (entries 2-3). Screening of other solvents (DCE, toluene and DMSO) did not produce any better results using Mes-Acr-$MeBF_4$ (entries 4-6). Also, white and green LEDs did not have any better impact (entries7-8). The most suitable condition was identified (entry 9) using Mes-Acr-$MeClO_4$ as photocatalyst under aerobic condition. Poor yield was observed when the reaction was performed for less than 24 h (entry 10). From the reactions no other byproducts like disulfides could be identified except water and the excess thiophenol was recovered using column chromatography.

Table 1. Condition optimization.



Entry	Catalyst	Solvent	Light Source	Yield (%)[a]
1	Mes-Acr-$MeBF_4$	CH_3CN	Blue LED (3W)	32
2	Eosin Y	CH_3CN	Blue LED (3W)	-
3	$Ru(bipy)_3(PF_6)_2$	CH_3CN	Blue LED (3W)	26
4	Mes-Acr-$MeBF_4$	DCE	Blue LED (3W)	29
5	Mes-Acr-$MeBF_4$	Toluene	Blue LED (3W)	-
6	Mes-Acr-$MeBF_4$	DMSO	Blue LED (3W)	-
7	Mes-Acr-$MeBF_4$	CH_3CN	White LED (14W)	31
8	Mes-Acr-$MeBF_4$	CH_3CN	Green LED (26W)	-
9	Mes-Acr-$MeClO_4$	CH_3CN	Blue LED (3W)	96[a]
10	Mes-Acr-$MeClO_4$	CH_3CN	Blue LED (3W)	68[b]

[a]Reaction Condition: **1a** (0.555 mmol, 60 mg), Mes-Acr-$MeClO_4$ (5 mol %, 0.027 mmol, 11 mg) 0.5 mL thiol and 1.0 mL CH_3CN in O_2 atmosphere for 24 h using Blue LEDs, [b]after 12 h.

The substrate scope using various benzyl alcohols is shown in Figure 2a. The benzyl alcohols having electron donating group, such as -Me, -^{i}Pr, -^{t}Bu offered efficient formation of **3aa-3ea** with 76%-96% yield. Substrates having electron withdrawing group, such as -F, -NO_2 were also tolerated well to produce compound **3fa** and **3ga** with 65% and 42% yields, respectively. The optimized reaction condition also showed compatibility with various type of functional groups like -OPh, -SMe to results in **3ha** and **3ia** with 98% and 74% yields, respectively. The dithioacetals **3ja**, **3ka** and **3la** were also synthesized with 72%, 58% and 80% yields. However, heterocyclic benzyl alcohol like 2-thiophenemethanol yielded 68% of **3ta**. The reactions failed with benzyl alcohols having nitrogen based heterocyclic core (supporting information) probably the nitrogen atoms were protonated by the acidic thiophenols and the corresponding benzyl alcohols became photochemically inert.

Furthermore, scopes of the reaction for various thiophenols were tested (Figure 2b). Methyl and methoxy substituted thiophenols led to **3ab** and **3ac** with 84% and 70% yields, respectively. Halo- substituent (X = Br, Cl, F) at para position of thiophenols le to the dithioacetals **3ad, 3ae** and **3ag** in 77%, 94% and 88% yields, respectively. *Meta*-chloro thiophenol yielded 91% of **3af**. The *ortho*-fluoro and *para*–trifluromethyl substituted thiophenols produced dithioacetals **3ah** and **3ai** with 79% and 61% yields, respectively. Aliphatic thiols were also found to be compatible to isolate **3bj, 3bk** and **3ul** with 54%, 62% and 69% yields, respectively. Conversely, 2-mercaptopyridine led to the only homo coupled product 1,2-di(pyridin-2-yl)disulfane (supporting information) possibly due to a stable and non-nucleophilic thiyl radical generation.

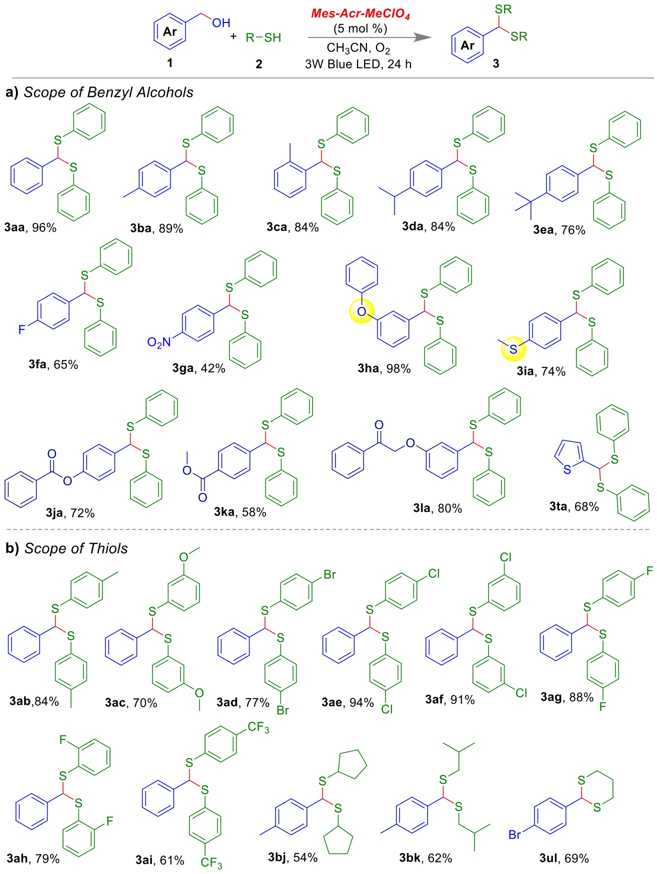


Figure 2. The substrate scopes of a) benzyl alcohols and b) thiols.

Interestingly, thioethers were mainly isolated with *para*-methoxy benzyl alcohols (Figure 3). Possibly, +R effect by the -OMe group at the *para*-position of the aromatic rings of benzyl alcohols led to thioethers over dithioacetals. Similar observations were made with the *para* -NMe_2 and -OH substituted benzyl alcohols. Interestingly, thiophenols having electron rich -Me and -OMe group at -*para, -meta* and -*ortho* positions also afforded thioethers (**4ma-4mc**) exclusively, with 63%-93% yields. 2,4-Dimethoxy benzyl alcohol resulted in **4na** with 81% yield. Notably, when a second methoxy group was introduced at the -*meta* position of *para*-methoxy thiophenol, mixture of thioether **4oa** (53%) and dithioacetal **3oa** (26%) was identified. However, benzyl alcohol **1p** also showed similar reactivity and led to the mixture of thioether **4pa** (52%) and dithioacetal **3pa** (45%). The 3,4,5-trimethoxy benzyl alcohol produced the mixture of **4qa** (29%) and **3qa** (59%). However, 4-dimethylamino benzyl alcohol yielded the thioether **4ra** in

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excellent yield (97%). Vanillyl phenyl sulfide **4sa** could also be derived successfully from vanillyl alcohol with 79% yield. Heteroaromatic furfuryl alcohol led to **4vb** with 59% yield.

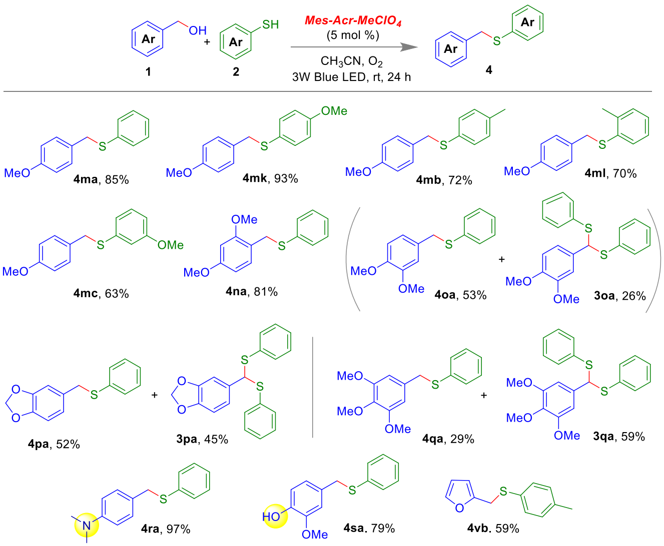


Figure 3. The substrate scopes of benzyl alcohols and thiophenols.

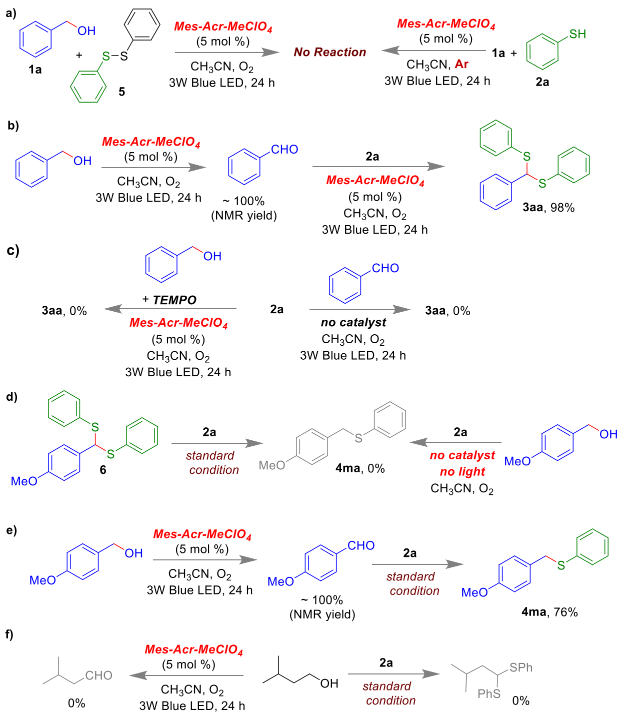
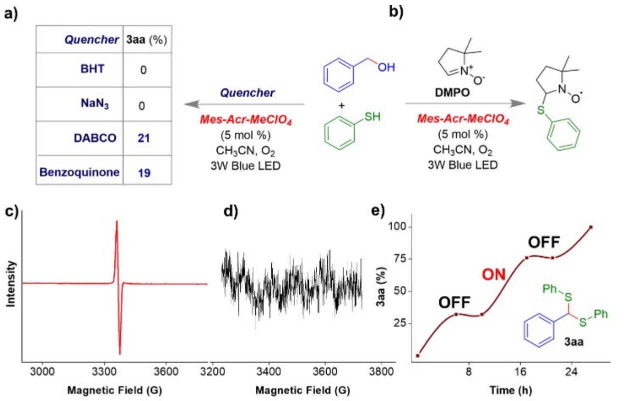


Figure 4. Control experiments.

Control experiments shown in Figure 4 helped to understand the reaction mechanism. The reaction was failed when performed using either diphenyl disulfide **5** instead of thiophenol **2a** or under inert atmosphere (Figure 4a). These evidences confirmed the involvement of aerial oxygen and non-involvement of diphenyl disulfide intermediate during the course of the reaction. The stepwise transformation of benzyl alcohol to dithioacetal **3aa** *via* benzaldehyde has proved that the first step was the oxidation process (Figure 4b). The experiments shown in Figure 4c using TEMPO did not produce the desired product **3aa** which indicated the radical pathway. In addition, the reaction of benzaldehyde and thiophenol was unsuccessful in absence of the photocatalyst (Figure 4c, right hand side), and confirmed the involvement of thiyl radical generated by the photocatalyst. Interestingly, synthesis of thioether **4ma** was unsuccessful from the corresponding dithioacetal **6** (Figure 4d) which possibly supports that reaction was not proceeding *via* the intermediate **6**. Formation of compound **4ma** was also inhibited in absence of catalyst and light. This fact could rule out the possibilities of S_N^2 type reaction between 4-methoxy benzyl alcohol **1m** and thiophenol. The **1m** yielded *p*-anisaldehyde and followed by thioether **4ma** was obtained with 76 % yield (Figure 4e). This fact supported that the reaction proceeded *via* aldehyde as one of the intermediates. Notably, aliphatic alcohol like amyl alcohol neither produced amyl aldehyde nor any thioacetalization product (Figure 4f). This is possibly due to the formation of an unstable alkyl radical intermediate as compared to a stable benzylic radical produced from **8** (Figure 6, *vide infra*).



Quencher	3aa (%)
BHT	0
NaN_3	0
DABCO	21
Benzoquinone	19

Figure 5. a) Quenching experiments (supporting information). b) Scheme of the EPR experiment using DMPO. c) Spectrum under standard condition (g = 2.00293) using DMPO. c) Spectrum in absence of thiophenol. e) Light ON-OFF experiment under standard condition.

Quenching experiments shown in Figure 5a further proved that the reaction proceeded *via* radical pathway. For example, when BHT was added in the reaction system as a radical scavenger, no desired product could be observed. Secondly, NaN_3 and DABCO were employed in the reaction mixture as singlet oxygen quencher. Both of them partially inhibited the reaction indicating requirement of singlet oxygen in reaction pathway. Again, benzoquinone reduced the yield of the products which confirmed the presence of superoxide radical anion in the reaction mechanism. In addition EPR experiments were carried out to detect free radical intermediate (Figure 5b). A sharp EPR signal was observed when DMPO (5,5-Dimethyl-1-pyrroline *N*-oxide) was used as a free radical spin trapping candidate (Figure 5c).[18] On the other hand EPR signal was disappeared in absence of thiophenol (Figure 5d). Furthermore, the light ON-OFF-ON experiments shown in Figure 5e has clearly indicated that reaction did not proceed in absence of light. The Stern-Volmer quenching experiments using fluorescence studies helped to understand that the excited state of the photocatalyst Mes-Acr-$MeClO_4$ was quenched by benzyl alcohol as well as thiophenol (supporting information).

Based on control experiments and literature reports,[9, 14a] a plausible mechanism is outlined in Figure 6. At first, the

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photocatalyst Mes-Acr-MeClO$_4$ (**PC**) was excited to [Mes-Acr-MeClO$_4$]* under the irradiation of visible light and the excited **PC** (**PC***) helped to produce intermediate **7** (radical cation of benzyl alcohol) from benzyl alcohol *via* a single electron transfer (SET) process[19] and itself reduced to **PC**$^{\bullet-}$ (radical anion of the photocatalyst). The intermediate **7** possibly led to the radical intermediate **8** after releasing H$^+$. Following, the **PC**$^{\bullet-}$ generated the superoxide radical which oxidized the intermediate **8** to the corresponding aryl aldehyde and **PC** was regenerated. In a similar manner, thiophenol **2a** is expected to produce thiyl radical **10** (Figure 6a). In the second step (Figure 6b), thiyl radical reacted with benzaldehyde to produce hemithioacetal intermediate **11** with the help of thiophenol **2a**.[14a] Following, hemithioacetal **11** led to ether benzylidene(phenyl)sulfenium **12** or oxonium intermediate **13**, depending upon the substitution at the *para*-position of benzyl alcohol (groups like -OMe or -NMe$_2$ favours the formation of **13**). In the presence of thiyl radical, intermediate **12** was further converted to **14** which led to the product dithioacetal **3aa** *via* one electron reduction by **PC**$^{\bullet-}$. However, the intermediate **13** which is electronic rich, was further transformed into cation radical **15** *via* hydrogen atom transfer (HAT) from thiophenol **2a**.[20] Following, **4ma** was obtained by SET from **PC**$^{\bullet-}$.

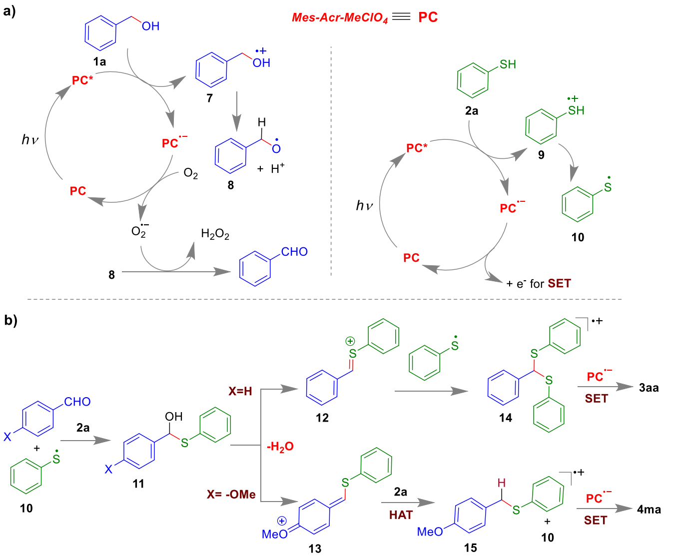

Figure 6. Plausible reaction mechanism.

In summary, we have developed an unprecedented strategy towards the C-S bond formation reaction *via* two step oxidative processes directly from benzyl alcohols under visible light photocatalysis *via* C-O bond functionalization. The Stern-Volmer quenching, light ON-OFF-ON and EPR experiments helped to establish the importance of the photocatalyst and role of aerial dioxygen during the course of the reaction. Mechanistically we have proposed that the reaction proceeded *via* SET process. Various benzyl alcohols and thiophenols were compatible with the standard condition and this fact supports that the methodology is highly efficient. Thus we foresee that this two-step oxidative C-O bond functionalization reaction in a single step would offer a new synthetic route in organic transformations.

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Conflicts of interest

"There are no conflicts to declare"

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9-Mesityl-10-methylacridinium perchlorate as a visible-light photocatalyst is used for oxidative C-O bond functionalization of benzyl alcohols to either dithioacetals or thioethers in presence of aerial oxygen as terminal oxidant.