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A modified all-in-one DMSO-activating and base releasing reagent for the Parikh-Doering-type benzylic oxidation reaction

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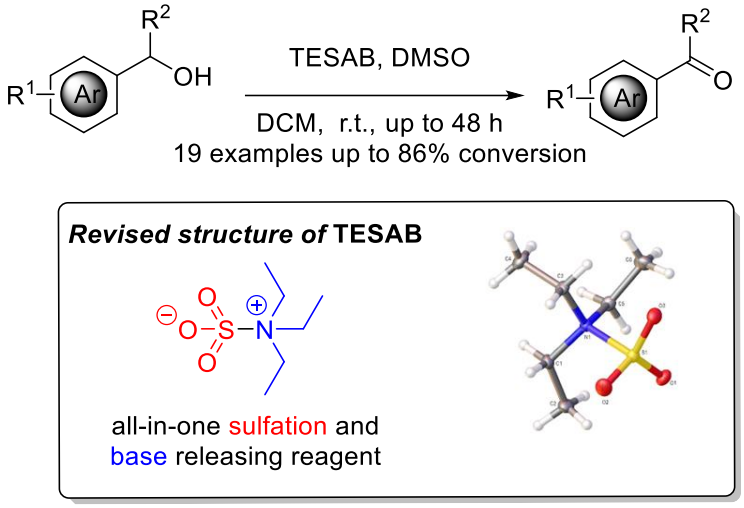
Graphical Abstract



Keywords: Parikh-Doering; DMSO; oxidation, TBSAB, sulfation

Abstract The Parikh-Doering reaction, an example of the series of DMSO-mediated selective oxidation named reaction family, finds ongoing use in natural product synthesis when mild oxidative reaction conditions are required. The original conditions require the use of Py-SO_3 and NEt_3 along with DMSO and DCM. As part of our ongoing interest in sulfating agents, we recently disclosed the novel structure of tributylsulfoammonium betaine (TBSAB) that has a formal *N*-*S* bond (not dative) and may indicate that other $N(_{sp}^3)$ amine-SO_3 complexes have been misassigned.

Herein, we explore a commercial sulfating agent, triethylamine-sulfur trioxide complex, as an all-in-one sulfation and base releasing reagent for a modified Parikh-Doering reaction. Single crystal X-ray crystallography further confirms our hypothesis than triethylamine-sulfur trioxide complex exists as triethylsulfoammonium betaine (TESAB). Employing TESAB as an all-in-one reagent, a range of primary and secondary alcohols were screened for competency. Reactivity was observed for the first time with 1) a non Py-SO_3 sulfating agent and 2) without the need for additional base. Moderate to good yields of aldehydes and ketones can be prepared in an atom-efficient improvement with concomitant removal of toxic pyridine by-products.

Introduction

The Parikh-Doering reaction is a venerable oxidation reaction in organic synthesis [1] and a representative member of DMSO-activated oxidation reactions e.g. Swern, Pfitzner-Moffatt and Corey-Kim. [2-4] The Parikh-Doering reaction exclusively uses pyridine sulfur trioxide (Py.SO_3) which contains a weak SO_3-*N*(sp^2) complex which increases the reactivity of sulfur trioxide compared to *N*(sp^3) amine complex. However, this necessitates the addition of an *N*(sp^3) base to deprotonate the alkoxysulfonium ion intermediate to afford the key ylide intermediate to furnish a DMSO-based oxidation. Furthermore, the release of toxic pyridine could be avoided if an alternative sulfation process could be identified that incorporates a *N*(sp^3) base. Despite these challenges and various superseded oxidation reaction developments, the Parikh-Doering reaction finds widespread use in complex natural product synthesis due to the advantages of non-cryogenic temperatures required, operationally simple, but often requires high loadings and prolonged reaction time. [5-16]

We have recently discovered a novel sulfuryl group transfer reagent with improved organic solubility properties for sulfation of organic substrates, tributylsulfoammonium betaine (TBSAB). [17-23] We identified TBSAB contains a novel *N*-*S* bond (not a dative complex as per Py-SO_3) through single crystal X-ray crystallography.[22] The use of TBSAB would be detrimental for purification purposes in this chemistry when not isolating a sulfated intermediate due to its enhanced lipophilicity. Therefore, we considered whether a similar commercially available reagent $Et_3N.SO_3$ complex could achieve both the desired sulfation of DMSO and release Et_3N *in situ* to deprotonate the alkoxysulfonium ion with increased atom economy (**Chart 1**).

Previous work **The Parikh-Doering reaction (1967)**

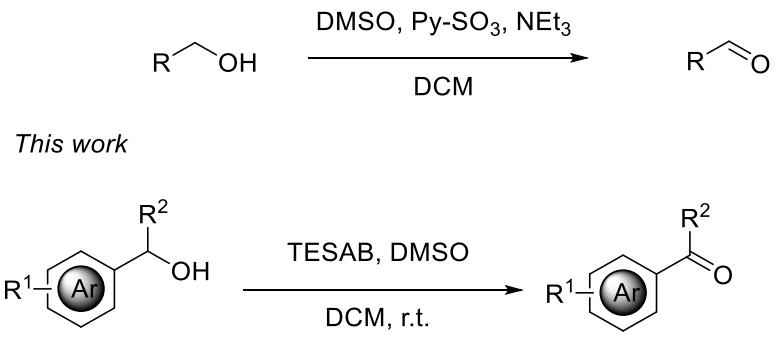


Chart 1. The original report by Parikh and Doering [1] and *this work*.

Results and Discussion

Firstly, we previously hypothesised that *N*(sp^3) amine-sulfur trioxide complexes may exist as formally bonded betaines and set out to determine the single crystal X-ray crystallographic structure of **1** for the first time (**Figure 1**).[24]

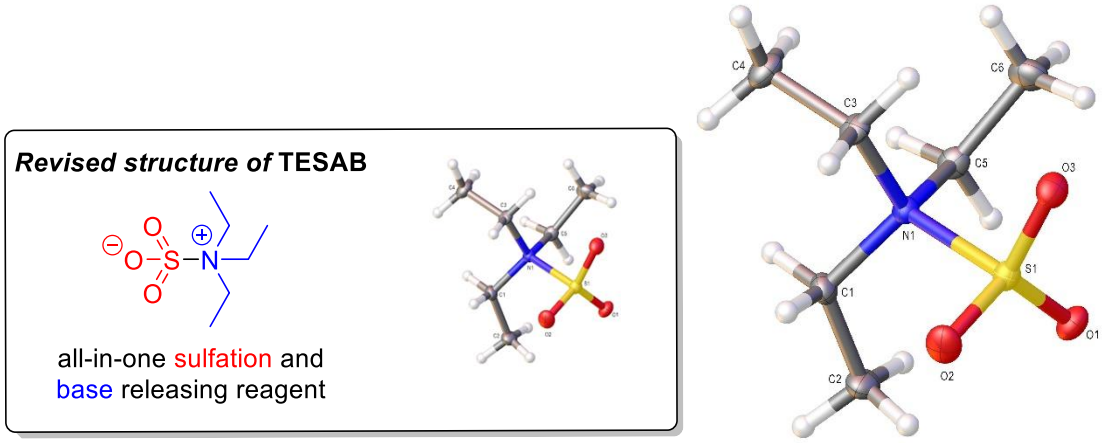


Figure 1. Single crystal X-ray crystallographic structure of reagent **1** (triethylsulfoammonium betaine, TESAB).

Representative crystals of the bulk material of commercial triethylamine sulfur trioxide complex (**1**) were prepared from neat hexanes. Intriguingly, **1** is not a complex but a betaine and should be recharacterized in the literature as triethylsulfonium betaine (TESAB) to account for this misassignment in the literature.

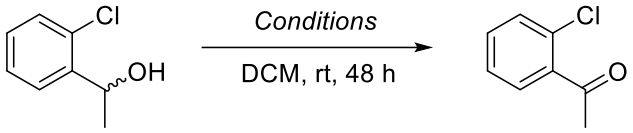
Similarly to TBSAB [22] Et_3NSO_3 (**1**) adopts a *Gauche* conformation within an asymmetric unit cell caused by hydrogen bonding between the methylene hydrogen atoms α to the nitrogen and the oxygens of SO_3. The measured N–S bond length in **1** is 1.8720(12) Å c.f. TBSAB N-S formal bond 1.886(3) Å, a comparable bond length to a single N–S bond (typically: 1.73–1.83 Å *versus* 2.06 Å for a donor–acceptor system) [25-26] suggesting that **1** exists as a betaine in the solid state which enables the revision of the structure to a formal betaine, termed triethylsulfoammonium betaine (TESAB).

A SciFinder^n search (conducted March 2024) returned 178 citations of the previously accepted triethylamine-sulfur trioxide complex but only 7 references to a betaine structure for the complex but not based on any new structural insights.[27-33] Intriguingly, Savel'yanov reported that the related structure of sulfamic acid (NH_2SO_3H) is a zwitterion ($NH_3^+SO_3^-$) based on reaction kinetics experiments and inferred the structure of trimethylamine-sulfur trioxide would be analogous.[34] This compares favourably with related reports to the dielectric properties,[35] gas phase study of dipole moments, [36]. and mechanistic studies.[37] Within the field of ionic liquids, for a related scaffold (*N*,*N*-diethyl-*N*-sulfoethanaminium hydrogen sulfate) a formal bond between the *N* and *S* was proposed based on FT-IR, ^{1}H and ^{13}C NMR spectroscopy and mass spectrum data. [38-40] Taken, together this gives further confidence on *our structural reassignment* for triethylsulfoammonium betaine [TESAB] (*previously* triethylamine-sulfur trioxide complex) with the first single crystal X-ray crystallography reported herein.

Furthermore, a search for "*any*" chemical transformation involving triethylamine-sulfur trioxide complex, returned 43,376 examples but merely two examples for an oxidation reaction. [41-42] Oxidation chemistry with the analogous trimethylamine-sulfur trioxide complex revealed a single report.[43]

In comparison, for a traditional pyridine-sulfur trioxide oxidation reaction there are 369,630 transformations reported of which there are 636 citations specifically employing a Parikh-Doering oxidation.

With this added information to hand, we considered whether the corrected structure of TESAB could function as both a DMSO-sulfating agent and concomitant base source for a modified Parikh-Doering reaction. To this end, 1-(2-chlorophenyl)ethan-1-ol was selected as a hindered benzyl alcohol for optimisation studies (**Table 1**).



Entry	TESAB (Eq.)	Solvent (Eq.)	DMSO (Eq.)	Solvent	Conversion (%)	Product (%)
1	2	40	4	CH_2Cl_2	98	-
2	4	40	4	CH_2Cl_2	95	68
3	6	40	4	CH_2Cl_2	79	76
4	2.5	40	4	CH_2Cl_2	76	-
5	3	40	4	CH_2Cl_2	90	-
6	3.5	40	4	CH_2Cl_2	92	-
7	2.5	40	2	CH_2Cl_2	99	80
8	2.5	40	80	CH_2Cl_2	90	-
9	2.5	80	80	CH_2Cl_2	91	-

Table 1. Optimisation of the conversion of 1-(2-chlorophenyl)ethan-1-ol to 1-(2-chlorophenyl)ethan-1-one (**6**) using TESAB, DMSO, DCM and no additional base.

It should be noted that all cases, a longer reaction time of up to 48 h was required due to the sluggish reactivity of TESAB compared to Py-SO_3. Entries 1-3 demonstrate that excessive TBSAB equivalents e.g. 6.0 eq entry 3 reduces the conversion to the product but minimal impact on isolated yield 76 vs 68% isolated. A screen of intermediate TBSAB equivalents revealed no discernible pattern on reaction conversions (entries 4-6). Reducing the equivalents of DMSO led to an optimal >99% conversion and 80% isolated yield of the ketone was achievable with (entry 7). Entry 8 shows a 40-fold increase in DMSO is tolerated with a modest drop in conversion 90 vs 99%. Entry 9 shows diluting solvent has minimal impact 91 vs 90% conversion. With these optimal conditions in hand, which minimised the excess of TESAB (2.5 eq) and DMSO (2.0 eq) a screen of varying benzyl containing primary and secondary alcohols (**2**) were explored (**Chart 1**).

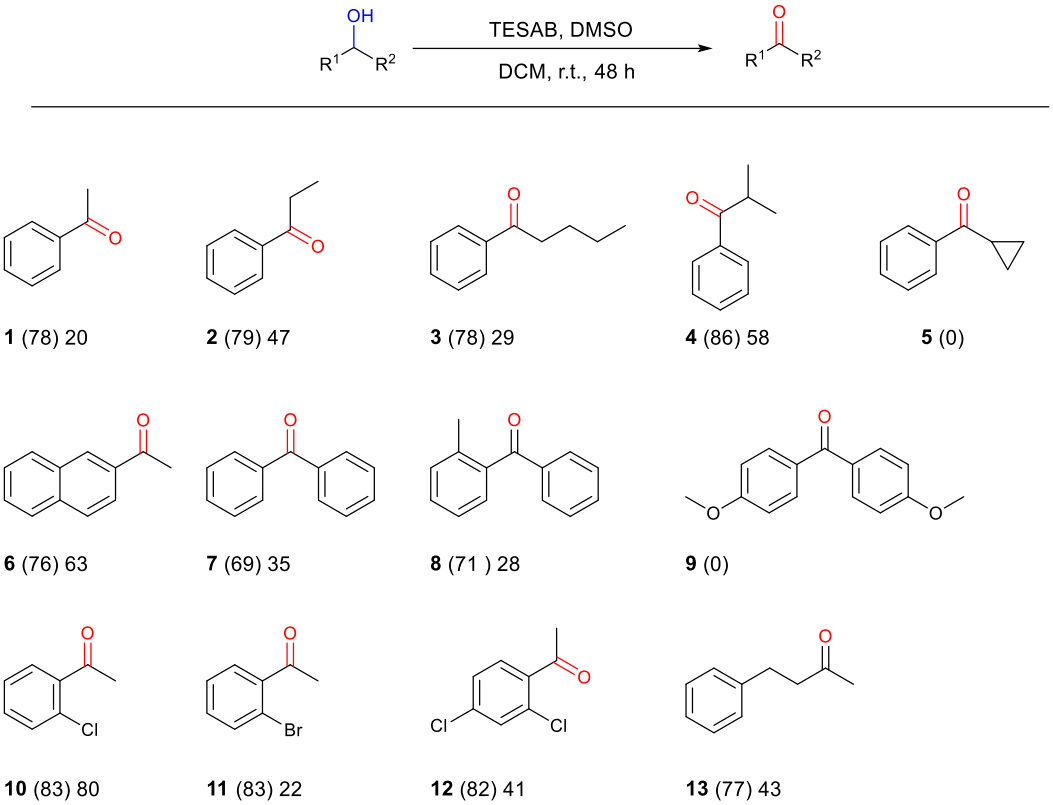


Chart 1. Screen of optimal conditions on a range of secondary benzyl alcohols and a secondary aliphatic alcohol. Percentage conversion as measured by ^{1}H NMR spectroscopy is stated in parentheses alongside isolated yield.

Examples **1**-**13**in **Chart 1** detail examples of converting a secondary alcohol to a ketone using TESAB. It was observed in cases were the reaction proceeded led to a high percentage conversion of the secondary alcohol to the ketone as measured by ^{1}H NMR spectroscopy (69-86%) but the isolated yield was appreciable lower in all cases (20-80%).

Examples **1**-**5** detail the scope of the reaction by elongating the alkyl chain (R^2),and incorporating branched (**4**) and cyclic (**5**) side chains. The reaction is generally tolerant (78-86% conversion to the ketone) with the exception of the non-reactive cyclopropyl derivative (**5**). Example **5**may give rise to deprotonation to the stabilised cyclopentyl anion rather than the desired transformation. Next, variation of the aryl linker was explored (examples **6**-**9**). The steric effect induced by bisaryl substitution was tolerated (69-76% conversion to the ketone) with the exception of the highly electron rich analogue **9** vs **8** (28% isolated vs no conversion, respectively). Exploration of halogen containing benzyl alcohols (examples **10**-**12**) again was tolerated at the *ortho* and *para* positions including the disubstituted example **12**. An example of an aliphatic alcohol oxidation (**13**) returned the ketone in a modest 43% isolated yield.

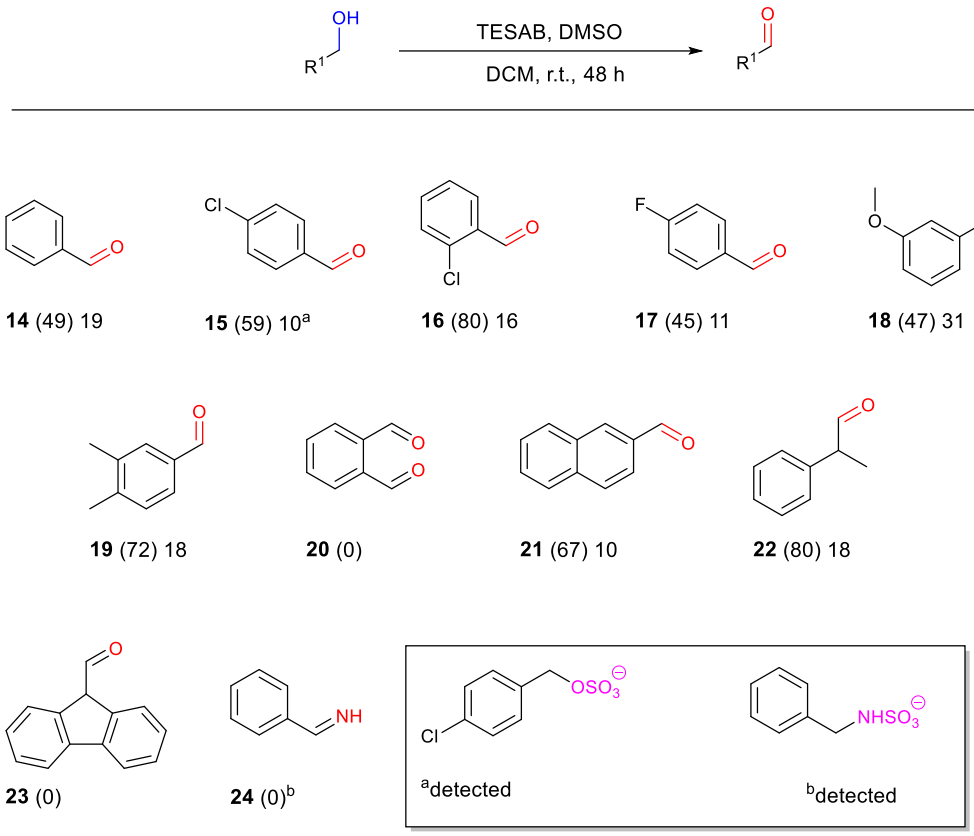
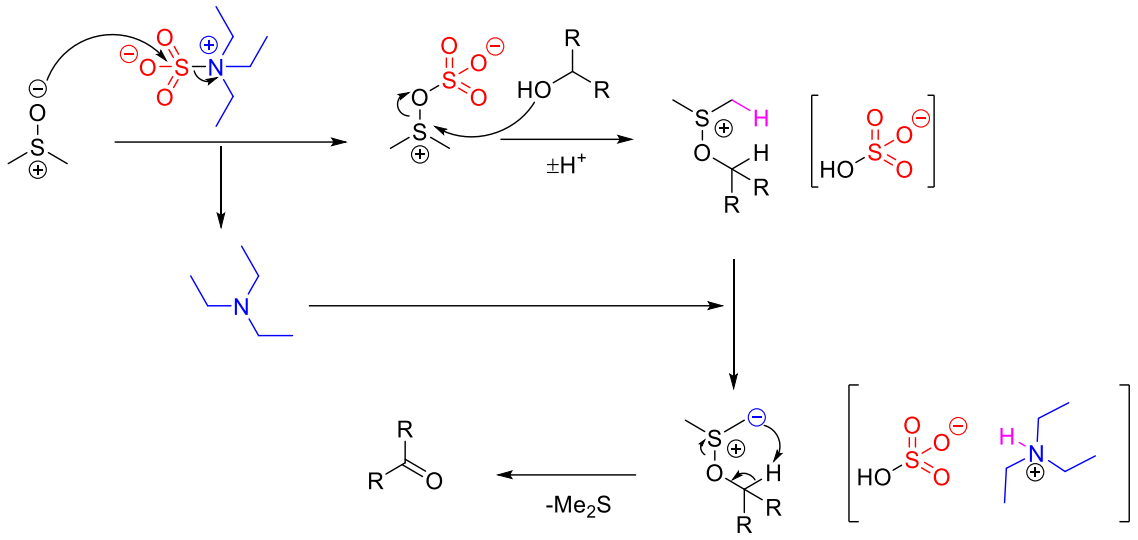


Chart 2. Exploration of the all-in-one TESAB oxidation method on primary alcohols and an amine. Percentage conversion as measured by ^{1}H NMR spectroscopy is stated in parentheses alongside isolated yield. Counterion omitted for clarity on detected side-reaction products.

Chart 2 details primary alcohol to aldehyde oxidation examples and an attempted amine to imine reaction. Examples **14**-**20** detail the effects of substitution on the benzyl ring at the *ortho-meta-para* positions including mildly electron donating and withdrawing effects. With the exception of the bisalcohol (**20**) modest to good conversions to the aldehyde was found. It should be noted that in these cases a large disparity between the percentage conversion to the diagnostic aldehyde ^{1}H NMR spectral signal (9-11 ppm) and the isolated yield was found in all cases, returning at best a 31% isolated yield (**18**).The low boiling point of the aldehyde led to some losses in isolation (and solvent contamination of the final products), combined with the highly reactive nature of the aldehyde product leading to product degradation. Methods to improve isolation included the use of the sodium bisulfite isolation method [44] and preparative TLC over extensive column chromatography. Intriguingly in certain cases the sulfate was formed in preference to the oxidation reaction by comparison to known standards[a].[19]

Examples that varied the R^1 group including a successful naphthyl derivative (**21**), and an unsuccessful fluorenyl example (**23**). The reaction was partially successful with a primary aliphatic alcohol (**22**) but the ^{1}H NMR spectrum indicated a trace of unreacted starting material (supporting information). An example of oxidising a benzylamine to the imine (**24**) was attempted but similar to certain primary alcohols led to sulfamation[b] via comparison to known standards.[21]

Taken together, these findings demonstrate both the scope (**Chart 1**) and limitations (**Figure 1**) of the TESAB method. Based on the revised structure of TESAB we propose the following mechanism (**Scheme 1**).



Scheme 1. Proposed mechanism for how TESAB mediates an all-in-one sulfation and deprotonation to form selectively oxidised products.

Initially, DMSO attacks the sulfuryl group in TESAB breaking the *N-S* bond and revealing triethylamine base and the key, dimethylsulfonio sulfate intermediate. Nucleophilic attack of the dimethylsulfonio sulfate intermediate with an alcohol group leads to the similar intermediate to a classic Parikh-Doering reaction, an alkoxydimethylsulfonium intermediate as the sulfate salt. The triethylamine released from the TESAB reagent in step 1 can now deprotonate the alkoxydimethylsulfonium intermediate, to afford the alkoxy (methyl)(methylene)-λ^4-sulfane which undergoes cyclisation to release dimethylsulfide and the oxidation product (ketone, aldehyde).

Conclusions

In summary, we have discovered 1) that triethylamine sulfur trioxide complex, is in fact a triethylsulfoammonium betaine (TESAB) reagent based on single crystal X-ray crystallography data analysis. And 2) that TESAB can find use as an all-in-one Parikh-Doering oxidation reagent that incorporates both the key sulfuryl activating group for DMSO and releases an *N*(sp^3) base that deprotonates the alkoxydimethylsulfonium intermediate facilitating the first example of a no-additional base required Parikh-Doering reaction.

Acknowledgements

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Supporting information

Compound characterisation, crystallographic data, and traces of ^{1}H and ^{13}C NMR spectra can be found in the accompanying electronic supporting information (PDF).

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