Benefits of Using MSAA in Various Applications

Abstract

This technical whitepaper highlights methanesulfonic anhydride's application as a mesylating (and amino-group-protecting) agent, including situations where MSAA would be more useful than methanesulfonyl chloride (MSC) and tosyl chloride. Also discussed herein is MSAA's application as an additive to electrolytic solutions for secondary lithium-ion batteries.

Background

Methanesulfonic anhydride (MSAA; CAS# 7143-01-3) is a solid supplied in crystal powder form, with an off-white[1], light gray-to-brown[2], hue. The compound has melting and boiling points of ~65–70 °C and 125 °C, respectively[1,2]. Pictured in Figure 1, MSAA possesses, similarly to methanesulfonyl chloride (MSC), methyl ends with relatively acidic protons ($pK_a \leq \sim 6.7$)[3,4,5,6,7]. In the presence of a good base (e.g., TEA's conjugate acid $pK_a \approx 10.8$), MSAA deprotonation would occur faster[4] than the base's S_N2-like[8,6] attack (e.g., by pyridine, $pK_a \approx 5.2 < 6.7$) on one of MSAA's electrophilic sulfurs to yield, through the ensuing E1cB[9] or E2-like[6] elimination of methanesulfonate (i.e., mesylate)—its charge balanced by protonated base's—a sulfene intermediate[3,7,10]. This highly-reactive[11] electrophile's "playing host" to amino or hydroxy groups acting as nucleophiles, and subsequent proton transfer, would then yield [methane]sulfonamides—which are versatile[12] amino protecting groups—and mesylates, respectively[1,3,9]. Because the latter, having bromide-like reactivity for follow-up substitution or elimination reactions, are better leaving groups than chlorides, sulfene generation and S_N2-like attack on MSAA's (MSC's) electrophilic S-atom would be faster with MSAA than MSC[3,7,10]. Thus, MSAA could be considered the better activating agent[7]. In comparison, *p*-toluenesulfonyl chloride (TsCl) has more limited reactivity due to its greater steric hindrance for a nucleophilic attack thereon[13] and lacking MSAA's α-hydrogens (and the associated sulfene-generating ability)[4,7,9]. MSAA also has better atom economy than TsCl[7,14].

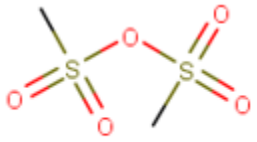

Figure 1. Structure of MSAA.

However, MSAA would be particularly advantageous for preparing alkyl mesylates having alkyl iodide and/or bromide substituents (i.e., halomesylates). Whereas MSAA's mesylate ion by-product is functionally non-nucleophilic, chloride ion is more nucleophilic than Br^- and I^- in polar aprotic solvent and can displace bromides—and thus mes/tosylates—and iodides in S_N2 reactions[3]. Even when coordinated with (i.e., charge-balanced by) protonated base, Cl^- is sufficiently nucleophilic for alkyl chloride formation provided the charge-balanced compound is soluble, as is true with triethylammonium chloride in DCM[15,16,17]. Once formed, alkyl chloride by-product would be a less reactive substrate for follow-up displacement reaction—e.g., it was functionally non-reactive to S_N2 attack by 2,6-dimethylpiperidine[18]—while higher temperatures for accelerating chloride reactivity might be undesirable for various reasons (e.g., safety, elimination by-product formation)[3,19]. The α-carbon of alkyl mes/tosylates would be more susceptible to S_N2 Cl^- attack in the presence of an electron-withdrawing inductive effect, such as that seen with deactivated benzyl alcohols or pyridine methanols having EWGs (e.g., $—NO_2$) on their α-carbons and/or aromatic rings[20].

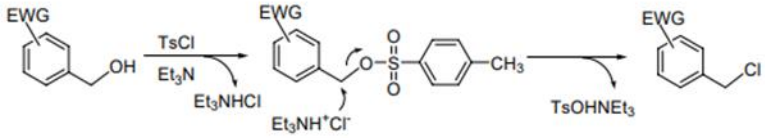

Figure 2. S_N2 reaction formation of EWG-containing benzyl chlorides (TsCl is arbitrary, MSC works too)[3,20,21].

For pyridine methanols, the N-atom's electron distribution distortion of the π-bonding system and σ-bonds would also contribute to a destabilizing inductive effect with the nitrogen not being bonded to the aforementioned α-carbon[20]. Meanwhile, even activated (i.e., with EDGs on the α-carbon and/or ring) benzyl alcohols could yield 31–38% benzyl chloride by-product after 12 hours of mes/tosylation at 15 °C due to EDG-induced stabilization of the α-carbocation formed by the mes/tosylate leaving on its own in an S_N1 reaction[20]. MSAA would also be advantageous for forming mesylates subjected to displacement by S_N2 intramolecular attack of nucleophilic neighboring groups (e.g., tertiary amine). This is because the resulting three-membered rings (e.g., aziridinium ion), being strained and having a good leaving group, would be quite susceptible[3] to S_N2 Cl^- ring-opening attack[17,22,23]. Finally, not limited to just the above compound types, longer —OH-activation reaction times for obtaining higher conversion without greater selectivity of alkyl chloride formation could be employed using MSAA[16,24].

First identified in 1995[25,26] as a potential additive to electrolyte (e.g., $LiPF_6$) solutions for secondary (i.e., rechargeable) lithium-ion batteries (LIBs), MSAA has found renewed interest in patent filings over the past decade with the expansion of LIBs into applications (e.g., EVs, energy storage systems) requiring, as well as existing applications (e.g., phones, computers) desiring, higher performance under a wider range of operating conditions[27]. When added together with an anodic SEI-forming additive (e.g., VC), MSAA has synergistically improved storage (e.g., swelling reduction) and cycling (e.g., capacity retention) characteristics to ensure excellent high-temperature (e.g., 60 °C) LIB performance overall[28,29]. MSAA can also significantly reduce the film impedance and internal resistance increases introduced at ⁻30–⁻10 °C and/or by VC—thereby improving low-temperature power and discharge capacity performance[29,30,31,32]. This suppression (and resulting performance improvement), which was not shown by MSAA's longer alkyl chain relatives (e.g., ethanesulfonic, butanesulfonic anhydride), has been attributed to MSAA having the fewest alkyl carbons[29]. It is for this resistance reduction property with simultaneous improvement of high-temperature performance that has led to MSAA being called an innovative additive[29]. Lastly, like the above advantages, considerable improvement of high-load discharge capacity (e.g., 87.2% at a 20C rate) at 60 °C was achieved because of MSAA and VC electrochemical reduction during initial charging to form a low-impedance, thermally-stable anodic hybrid SEI[28,29]. MSAA as an electrolytic solution additive with which other additives (e.g., LiFSI) can be paired, in addition to its [methane]sulfonylating use, are presented in more detail below.

Representative Cases of MSAA as a Value-added Differentiator

Usage 1: Activating (and Amino-Protecting) Agent

For its reactions with hydroxy or amino groups, slow (e.g., drop-wise[33]) addition of ≥ 1.1–1.2 eq.[34,35] MSAA to stirred solutions of intermediate, base (e.g., DIPEA, DMAP), and/or solvent (e.g., DCM, THF, MeCN) controlled within −5–10 °C[34,36] would account for potential hydrolysis via trace moisture and control generated exotherm[37]. From the standpoint of safety, a more detailed procedure at 100-gram scale operation may be found in the patent literature[38]. In the absence of desired solvolysis reaction, MSAA could also be diluted with toluene co-solvent (e.g., 2 vol. eq.) for a more controlled rise to the predominantly used [methane]sulfonylating temperature range of 0–25 °C, with yield generally increasing *within that range* alongside temperature[3,37]. When activating secondary alcohols, 0–10 °C would, particularly with one of the aforementioned bases stronger than pyridine, be a safer range for minimizing *in situ* β-elimination reaction product formation to give just one reason[3,39].

MSAA-based activation (including for pyridine-*N*-oxides at 75 °C**)** *and* protection reactions have been run at kilogram-scale in pharmaceutical intermediate synthesis[40,41,42]. Tertiary alcohol activation via MSAA was used to prepare fragrant ingredients for perfume compositions[43]. Mesylation using MSAA helped produce electrolytic solution additives (instead of MSAA itself being an additive) for LIBs[34]. This is in contrast to MSC and TsCl, whose Cl^- by-product would lead to battery capacity deterioration[44]. Bismaleimides for curable resin compositions used in electronic circuit boards and semiconductor devices

were synthesized under solvent reflux temperature with MSAA as the activating agent and subsequent cyclization[45,46]. A solvent-free one-pot method for Friedel-Crafts acylation of deactivated benzenes that is suitable for further scale-up and generates minimal waste (no halogenated or metallic components) involves MSAA reaction with carboxylic acids generating, in the absence of base, methanesulfonic acid (MSA) catalyst *in situ*[1,47].

Usage 2: Film-forming Additive in Electrolytic Solutions Applied to Electrodes

As a $LiPF_6$ non-aqueous solution additive, MSAA at 0.5–1.5 wt.% of the solution content has been preferred for preventing electrode impedance increase and capacity reduction with repeated cycling—though up to 5 wt.% is usable[28,29,30,48]. Mixing cyclic carbonate (e.g., EC, PC) and chain carbonate (e.g., DMC, EMC) aprotic solvents in a 1:2–3 mass or 3:7 volume ratio has—without inhibiting MSAA's performance—ensured dissolution of $LiPF_6$ and additives, high Li^+ conductivity, and a low-enough viscosity for high Li^+ mobility[29,30,34,48]. When added, unsaturated/fluorine-containing cyclic carbonate (e.g., VC, FEC) content below the range of ~0.3–3 wt.% could lead to a thin anodic SEI, formed mostly from MSAA, having insufficient self-repairing ability during cycling[28,29,49]. However, an MSAA : (VC + MEC + VEC) mass ratio of $\geq$ 0.2 has been recommended for boosting, via MSAA, the high-temperature performance originally improved by additive (e.g., VC)[29]. One preparation method suitable for industrial large-scale production involves ultrasonic 10–50 °C mixing of the electrolytic solution components[48].

According to a patent noted to be suitable for practical use, besides the improvements (excluding low-temperature) already mentioned in this whitepaper, MSAA and VC $LiPF_6$ solutions for graphite-powder/NMC cells yielded high-capacity LIBs with improved continuous charge and overcharge characteristics[28]. Compared to just MSAA and VC, adding MSAA along with VC, MEC, and VEC gave additional improvement in capacity retention after 60 °C storage of graphite/NMC333, graphite/LFP, and graphite/$LiCoO_2$ cells with improved impedance performance ($^-$10 °C) for at least the first two LIB categories[29]. With LFP cells, the improvement effect for at least high-temperature cycling was noted to be better than the combination of VC with 1,3-propanedisulfonic anhydride[29]. A different patent[30] utilizing LiFSI's (3:7 molar ratio to $LiPF_6$) thermal stability[50] and preferential reduction for carbon-powder/NMC622 pouch cells gave an LIB with 5.76 W at $^-$30 °C. Synergistic improvement of 60 °C performance was also achieved due to MSAA shielding the cathode from $LiPF_6$'s thermal decomposition products[30]. In all three of the above patents, MSAA was noted to be more preferred than its longer alkyl chain relatives (e.g., ethanesulfonic, butanesulfonic anhydride) for yielding desired LIB improvements (or at least the best combination of them). Lastly, compared to previous patents involving thiophene additives, MSAA and 3 wt.% 1,4-butane sultone improved LIB cycle performance at > 4.4 V while keeping the improved low-temperature discharge performance of this paragraph's above two patents[48]. By forming a uniform, compact SEI film on the NCM523 cathode, MSAA inhibited $LiPF_6$'s oxidation from increased ternary material charge cut-off voltages; meanwhile, for the artificial-graphite anode, FEC, VEC, and 1,3-propane sultone were other usable film-forming additives[48].

Varsal Advantage

Varsal is a leading producer of extremely-high-purity MSAA. We are differentiated from the competition as Varsal's proprietary manufacturing logistics processes allows us to produce consistent, stable, extremely-high-purity material—leading to maximal yield and product quality for Varsal's customers.

Extremely high purity in MSAA is important because of the several ways MSA impurities could adversely affect desired reactions. For instance, in the activation of secondary alcohols, while extra base could lead to greater formation of undesired *in situ* E2 product, adding it would be necessary for neutralizing initial MSA impurities[3]. Otherwise, there would be an increased risk for by-product formation based on a substituent's sensitivity (e.g., BOC deprotection) to reaction with MSAA's MSA by-product. Even if no such reaction occurred, this MSA could react with alcohols in subsequent process steps to form alkyl

sulfonates exhibiting genotoxicity and/or carcinogenicity in the eventual final drug substances[51,52]. However, even if the original MSA impurities did preferentially react with base given lower pK_a (⁻1.9) compared to MSAA's α-hydrogens, mesylation could still be slower practically-speaking due to having less base to work with—particularly when using a weaker and less basic nucleophile (e.g., pyridine)[3]. When adding a catalytic amount of DMAP to accelerate this mesylation involving pyridine, MSA could be particularly damaging in neutralizing some of this catalyst at the reaction outset given DMAP's greater basicity[53]. Thus, while every situation might be different, the fact that MSA is acidic enough to plausibly introduce potential reaction variations is reason enough to minimize this impurity content.

Varsal is able to serve a wide variety of end-markets and applications, as our intimate knowledge of the manufacturing process allows us to custom-manufacture various grades of MSAA tailored to our customers' requirements. Please contact us at info@varsal.com to learn more about how Varsal can help you solve your complex chemical and specialty intermediates challenges!

[1] "Sulfur-Container Reagents." L. Paquette.
[2] "Methanesulfonic anhydride." Chemical book.
[3] "Organic Chemistry, Sixth Edition." M. Loudon and J. Parise.
[4] "Why do tosylation and mesylation of alcohols follow different mechanisms?" Stack Exchange.
[5] "Organic sulfur mechanisms." King, et al.
[6] "The Role of Sulfene Intermediates." Truce and Campbell.
[7] "Synthesis of Carbonates." M. Bratt.
[8] "Can carboxylic acids act like nucleophiles?" Stack Exchange.
[9] "Organic Chemistry." Clayden, et al.
[10] "Mayr's Database Of Reactivity Parameters." Mayr.
[11] "Glycosyl Methanesulfonates." K. D'Angelo.
[12] *Org. Synth.* **2012**, *89*, 34-43
[13] "Applications for the Activation of Hydroxyl." I. Awheda.
[14] "Novel compound." Tani, et al.
[15] "TEA-HCL Solubility." Reddit.
[16] "Synthesis of Tosyl- and Nosyl-Ended Polyisobutylenes." Pasztoi, et al.
[17] "Novel derivatives of anaplastic lymphoma kinase inhibitors." Radaram, et al.
[18] "Process to prepare amino acid derivatives." Fox and Meek.
[19] "Elimination Reactions." J. Ashenhurst.
[20] "Treatment of Alcohols." Ding, et al.
[21] "Synthesis of a [18F]-labeled ceritinib analogue." Perera, et al.
[22] "Compounds for use." Thiele, et al.
[23] "Synthesis of asymmetric halomesylate mustards." Yang, et al.
[24] "Spontaneous conversion of O-tosylates." Kurteva, et al.
[25] "Electrolytes for Lithium." Xu, et al.
[26] "Electrolyte for lithium secondary battery." Shima, et al.
[27] "Enabling the Low-Temperature Cycling of NMC." Cho, at al.
[28] "Nonaqueous electrolyte and lithium secondary battery." Onuki, et al.
[29] "Non-aqueous electrolyte and lithium ion secondary battery." Qiao, et al.
[30] "Lithium secondary battery." Jung, et al.
[31] "Why does low temperature affect the battery?" Grepow.
[32] "Analysis of Vinylene Carbonate." Pritzl, et al.
[33] "GLP-1 receptor agonists and uses thereof." Aspnes, et al.
[34] "Oxiranyl ester derivatives." Garcia, et al.
[35] "Electrolyte for rechargeable lithium battery." Yi, et al.
[36] "Anti-viral compounds." Bellizzi, et al.
[37] "Developing a Commercially Viable Process." Yamgar and Sawant.
[38] "Synthesis of cyclopentaquinazolines." Kerschen, et al.
[39] "Methods for producing paricalcitol." Bader, et al.
[40] "Synthesis of mcl-1 inhibitor." Stewart, et al.
[41] "HMG-CoA reductase inhibitors and method." O'Connor, et al.
[42] "Process for preparing halogenated azaindole compounds using boroxine." Bultman, et al.
[43] "Organic compounds." Kraft.
[44] "Detection method for chlorine ion content." Liao, et al.
[45] "Manufacturing method of resin impregnated material." Ashi, et al.
[46] "Bismaleimide compound, photosensitive resin composition using same." Yamamoto, et al.
[47] "Greener Friedel−Crafts Acylations." M. Wilkinson.
[48] "Non-aqueous electrolyte." Zou, et al.
[49] "Nonaqueous electrolyte secondary battery." Chiyou, et al.
[50] "Lithium ion battery electrolyte." Zhao, et al.
[51] "A Detailed Study of Sulfonate Ester Formation." Teasdale, et al.
[52] "Dual Analyte Determination and Validation of Trace Levels." Rao, et al.
[53] "Tosylates And Mesylates." J. Ashenhurst.