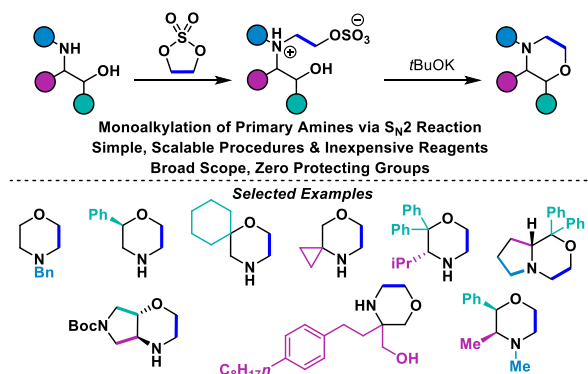# Green Synthesis of Morpholines via Selective Monoalkylation of Amines
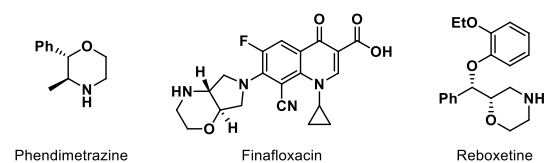
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ABSTRACT: Morpholines are common heterocycles in pharmaceutical and agricultural products, yet methods to synthesize them from 1,2-amino alcohols are inefficient. We report the simple, high yielding, one or two-step, redox neutral protocol using inexpensive reagents (ethylene sulfate and *t*BuOK) for the conversion of 1,2-amino alcohols to morpholines. Key to this methodology is the identification of general conditions that allow for the clean isolation of monoalkylation products derived from a simple S_N2 reaction between an amine and ethylene sulfate. Experiments suggest that the degree of selectivity is dependent upon the structure of reacting 1,2-amino alcohol as well as the unique properties of ethylene sulfate. This method can be used for the synthesis of a variety of morpholines containing substituents at various positions, including 28 examples derived from primary amines and multiple examples contained in known active pharmaceutical ingredients. We have conducted multiple examples on >50 g scale. We have also demonstrated the formal synthesis of a morpholine from a simple primary amine using ethylene sulfate. Overall, while this new methodology has many environmental and safety benefits relative to the traditional methods used to prepare morpholines from 1,2-amino alcohols the most striking feature is the facile selective monoalkylation of a variety of primary amines. We have also explored various reactions beyond those related to the synthesis of morpholines, including obtaining proof-of-principle that ethylene sulfate can be used for the synthesis of piperazines and as a 2-carbon electrophile for fragment couplings.

Monoalkylation of Primary Amines via S_N2 Reaction. Simple, Scalable Procedures & Inexpensive Reagents. Broad Scope, Zero Protecting Groups. *Selected Examples*

Scheme 1. Various Morpholine Containing Drugs

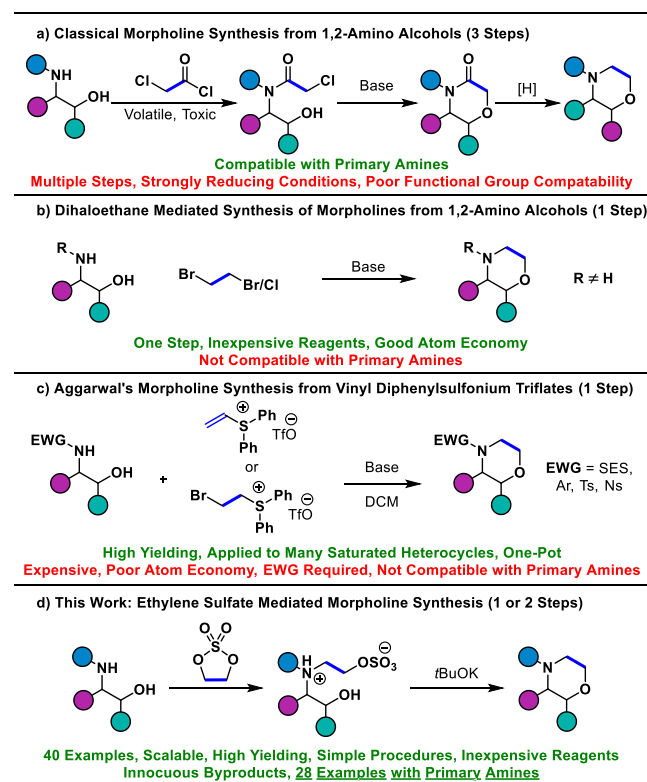Phendimetrazine   Finafloxacin   Reboxetine

Morpholines are commonly found in pharmaceutical[1–4] and agrochemical[5] compounds (Scheme 1). Specifically, morpholines are the 9th most common heterocycle in new small-molecule drugs approved by the FDA during 2013 – 2023.[6] Many methods have been reported for the synthesis of morpholines.[7–20] A common approach is the conversion of a 1,2-amino alcohol into a morpholine via an annulation reaction. While this is conceptually simple and utilizes the plethora of methodologies[21–27] for the synthesis of 1,2-amino alcohols there are few examples of these transformations which directly afford the morpholine. A more common synthetic approach is an annulation of 1,2-amino alcohols with chloroacetyl chloride or related carboxylic ester derivatives containing a leaving group alpha to the carbonyl (Scheme 2a). Typically, this consists of two steps to synthesize a morpholinone (amide bond formation & cyclization) followed by a boron or aluminum hydride mediated reduction.[2,3,10] Thus, three steps are required to add two methylenes to a 1,2-amino alcohol. The morpholinone is the most common synthetic intermediate because it bypasses the true challenge of these annulation reactions: achieving monoalkylation of the parent amine. Unfortunately, the morpholinone approach generates a significant amount of waste while adding relatively little mass and complexity to the molecule, is not compatible with several of the 12 principles of green chemistry,[28] and has poor functional group tolerance due to the strongly reducing conditions that are required.

There have been numerous attempts to make annulation reactions for the synthesis of morpholines more practical. There are literature reports on the use of 1-bromo-2-chloroethane for the synthesis of morpholines, but these appear to be limited to benzo-fused morpholines derived from 2-aminophenol derivatives or to 1,2-amino alcohols derived from secondary amines (Scheme 2b).[29–31] Ethylene oxide can be used for the synthesis of morpholines from amines. However, ethylene oxide is low boiling, highly toxic,[32] and potentially explosive;[33] it is, therefore, difficult to use except in dedicated facilities. Substituted epoxides can be used in the synthesis of morpholines from 1,2-amino

alcohols but require further activation of the amino diol to enable cyclization.[9]

Scheme 2: Comparison of various methods for the synthesis of morpholines from 1,2-amino alcohols

a) Classical Morpholine Synthesis from 1,2-Amino Alcohols (3 Steps)

Compatible with Primary Amines
Multiple Steps, Strongly Reducing Conditions, Poor Functional Group Compatability

b) Dihaloethane Mediated Synthesis of Morpholines from 1,2-Amino Alcohols (1 Step)

R ≠ H

One Step, Inexpensive Reagents, Good Atom Economy
Not Compatible with Primary Amines

c) Aggarwal's Morpholine Synthesis from Vinyl Diphenylsulfonium Triflates (1 Step)

EWG = SES, Ar, Ts, Ns

High Yielding, Applied to Many Saturated Heterocycles, One-Pot
Expensive, Poor Atom Economy, EWG Required, Not Compatible with Primary Amines

d) This Work: Ethylene Sulfate Mediated Morpholine Synthesis (1 or 2 Steps)

40 Examples, Scalable, High Yielding, Simple Procedures, Inexpensive Reagents
Innocuous Byproducts, 28 Examples with Primary Amines

The Aggarwal group has reported a major advance in this area using one of two related reagents ((2-Bromoethyl)diphenylsulfonium triflate and Diphenyl(vinyl)sulfonium triflate) for the high yielding, one-pot conversion of 1,2-amino alcohols and 1,2-diamines to the corresponding morpholines and piperazines (Scheme 2c)[34,35] However, despite the elegant approach, these reagents remain quite expensive particularly when it is considered that only 6.3% of the mass of the reagent ((2-Bromoethyl)diphenylsulfonium triflate) is incorporated into the desired morpholine or piperazine. While this ratio is higher for Diphenyl(vinyl)sulfonium triflate, one must consider that it is synthesized from the bromoethyl derivative. A related reagent was also reported by the Ritter group, but this compound is also quite expensive.[36] Aside from the cost of the reagents there is one major limitation of these methodologies: neither primary amines nor secondary alkyl amines were demonstrated for the synthesis of morpholines. Electron-withdrawing substituents (e.g., aryl) or difficult to remove protecting groups (e.g., sulfonamides) appear to be required, meaning primary amines cannot be used in this methodology. Thus, these methodologies all avoid the main challenge for annulation reactions: achieving monoalkylation of a primary amine.

We became interested in finding an inexpensive reagent that can be used on large scale for the synthesis of morpholines from a variety of 1,2-amino alcohols, including those with primary amines, without generating large amounts of

waste and/or toxic byproducts. Furthermore, we wanted to solve the principal limitation of these annulation reactions, namely achieving monoalkylation of free primary amines because this remains a largely unsolved problem in organic synthesis.[37] Furthermore, morpholines derived from an 1,2-aminoalcohol containing a primary amine will afford a morpholine containing a free N-H bond which allows for facile derivatization.

We were intrigued by a report from Dow that ethylene sulfate (ES), which is now inexpensive (<$1/g from multiple vendors in the US) and widely available because it is used as an additive in lithium-ion batteries,[38] cleanly reacts with a variety of nucleophiles, including primary and secondary amines, to afford monoalkylation products; one of these products was cyclized to form a tetrahydroquinoxaline.[39] Despite this remarkable reactivity there appear to be very few follow-up studies on this reagent for the alkylation of amines. A related cyclic sulfate, 1,3-propylene sulfate, was shown to also alkylate amines selectively; the corresponding salts could be cyclized to form azetidines.[40] The Sharpless group has also prepared many vicinal diol cyclic sulfates derived from their dihydroxylation methodologies and has undertaken a thorough evaluation of their reactivity[41] including examples for the synthesis of epoxides and aziridines.[42] Based on these collective reports, we hypothesized that ES could be used as a two-carbon electrophile for the synthesis of morpholines from 1,2-amino alcohols (Scheme 2d). We were able to find one example where researchers at Pfizer attempted to use ES in the synthesis of the morpholine contained within Reboxetine[43,44] but ultimately chose a different synthetic approach because an adequate combination of conversion and selectivity could not be achieved (1.3:1 mono to bis alkylation at an unspecified conversion to 4.6:1 mono to bis alkylation at 70% conversion). However, detailed experimental conditions were not reported by the group at Pfizer. The difference in selectivity between the two reports are striking; the most apparent change in experimental conditions is the absence of exogenous base in the conditions reported by Dow and the presence of added base in the conditions reported by Pfizer. To the best of our knowledge these are the only two examples of 6-membered heterocycles synthesized via a cyclization of a vicinal dinucleophile onto a cyclic sulfate.

We were intrigued by the enticing reactivity of ES and decided to evaluate it for morpholine annulation. N-Benzyl ethanolamine (1a) was chosen as the model substrate to evaluate the addition to ES in various solvents. These experiments were conducted in the absence of an added base to force the crystallization of the zwitterionic product (1z), which would help to remove unreacted starting materials and other impurities. While product 1z was detected by reverse phase LCMS, some reactions produced poor quality solids which were nearly impossible to stir or filter. However, we discovered that by including an alcohol or water as a co-solvent (typically in 5-10 vol%) the resulting reactions could occur to nearly full conversion with only 1.05 equiv of ES while maintaining better physical characteristics than reactions performed without alcohol and/or water as co-solvents. Furthermore, 1z could be isolated in

Scheme 3: The scope of 1,2-amino alcohols evaluated in the addition to ethylene sulfate
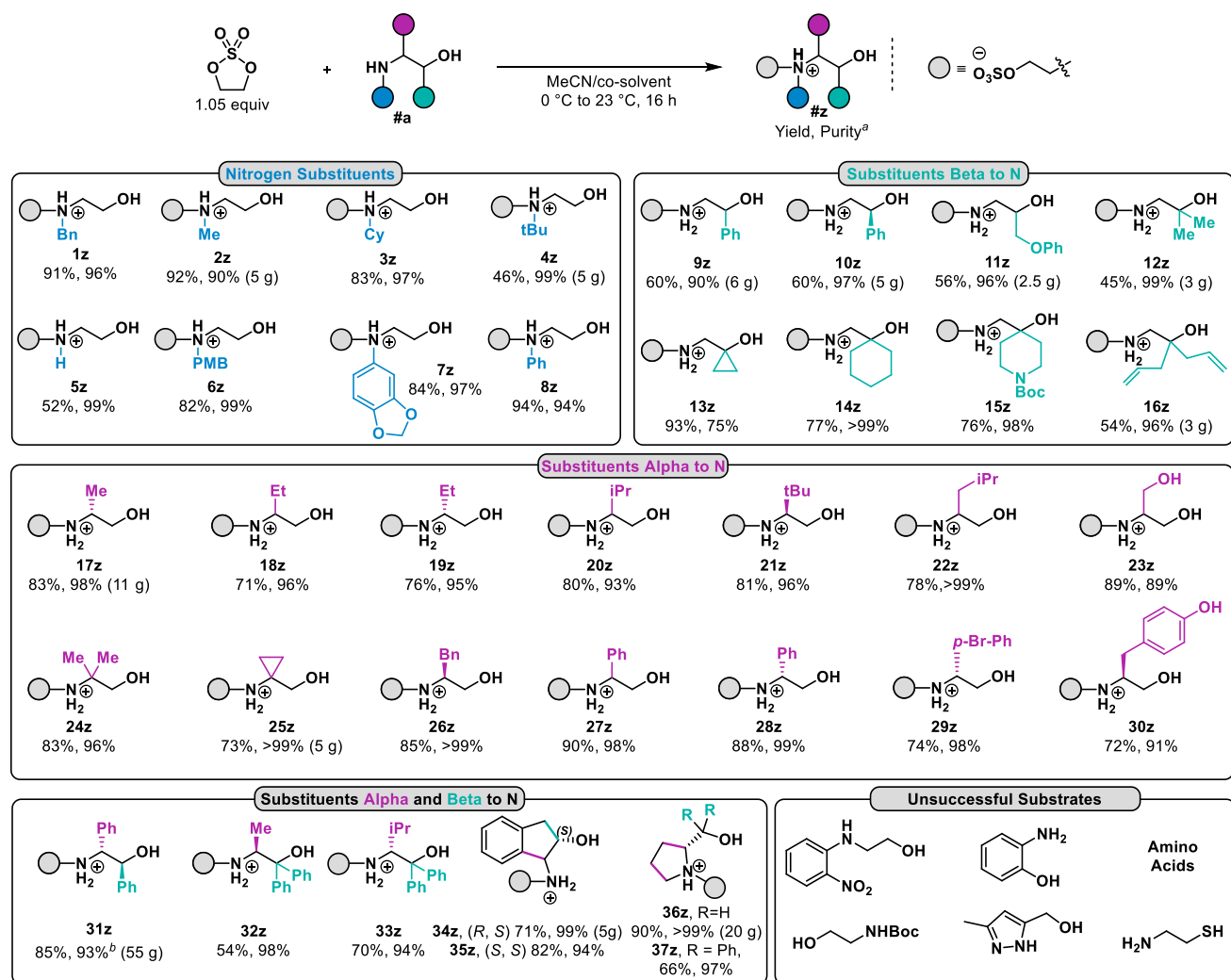
*a*Purity of the isolated zwitterion products was determined by NMR using 1,3,5-trimethoxybenzene as an internal standard. *b*The purity after correction for 6% water content is 99%.

high yield and purity by simply filtering the reaction mixture. For the complete set of solvent screening data and important safety-related information on the handling of ES please refer to the Supporting Information.

We evaluated the reactivity of a variety of commercially available 1,2-amino alcohols towards ES with our standard conditions. Scheme 3 shows the results of the substrate screening, which was performed on 6.5 mmol scale unless otherwise indicated. The zwitterion products are insoluble in most organic solvents and cannot be purified by column chromatography or readily analyzed by TLC on silica gel. Therefore, we have determined the absolute purity by quantitative ¹H NMR analysis against an internal standard; all reported yields for the salt formations are corrected for purity. For simplicity, the reported yields are from the conditions which give the highest combination of yield and purity; the data from other solvents is included in the Supporting Information. Impurities found in the solids vary from compound to compound but typically include unreacted starting material, residual solvent or water, minor amounts of the bis-alkylation products, and ES

degradation products. The presence of ES degradation products and starting material in selected reactions is described in greater detail in Scheme 5.

A variety of monoalkylation zwitterion products **1z – 8z** were isolated from reactions of N-substituted ethanolamines with ES. In most cases these products were isolated in >80% yield, although **4z** and **5z** were isolated in modest yield. However, most of the morpholines that would be formed after cyclization of these zwitterions (see below) could be synthesized from morpholine via alkylation with alkyl halides, reductive amination, or by Buchwald-Hartwig amination. Therefore, it was important to establish the effect of substituents alpha and beta to nitrogen on this methodology to determine if more complex morpholines could be synthesized from primary amines via selective monoalkylation. Reactions containing 1,2-amino alcohols with substituents beta to nitrogen generally afforded high purity zwitterion (**9z - 16z**) products, but these compounds were isolated in lower yield than compounds containing substituents at other positions. For example, **10z** was isolated in a modest 60% yield, but **28z** was isolated in 90%

yield. This is a rather large difference for the two constitutional isomers. Because racemic and enantioenriched materials can crystalize differently we have included products derived from both racemic and enantioenriched 1,2-amino alcohols. For example, a single phenyl group beta to nitrogen afforded the racemic (**9z**) or enantioenriched (**10z**) addition product in similar yield, although the enantiopure salt was isolated in higher purity. A phenoxymethyl group at this position was also tolerated, but the product **11z** was isolated in low yield. The zwitterions derived from a 1,2-amino alcohol containing geminal dimethyl (**12z**) or diallyl (**16z**) substituents were also isolated with high purity, albeit modest yield. A cyclopropane containing zwitterion **13z** was isolated in high yield but with low purity. The presence of 6-membered spirocycles positioned beta to nitrogen afford the corresponding zwitterions in high isolated yield and excellent purity (**14z** and **15z**). A large variety of 1,2-amino alcohols containing substituents alpha to nitrogen (including several derived from amino acids) were also evaluated under the standard reaction conditions and generally produced the corresponding zwitterions in good yield and purity (**17z** to **30z**). A reaction containing L-Alaninol was conducted on 11 g to afford **17z** in good yield and high purity. Similar results were obtained from reactions in which the methyl substituent was replaced with an ethyl, isopropyl, isobutyl, *tert*-butyl, phenyl, or benzyl group. Zwitterion **23z**, which contains a hydroxymethyl group, was isolated in good yield and reasonable purity. A *p*-phenol and *p*-bromo aryl group was also tolerated at these positions, which would allow for further functionalization of the aryl groups once cyclized to morpholines. We concluded the evaluation of 1,2-amino alcohols by looking at those which are commercially available and contain multiple substituents at the alpha and beta positions to nitrogen (**31z** - **37z**). Several densely functionalized zwitterions were isolated in moderate to high yield, typically with good to excellent purity even when conducted on large scale (**31z**, 55 g scale; **36z**, 20 g scale).

Of the 37 zwitterions we isolated, only 3 were obtained in less than 90% purity by simple crystallization and filtration. While most of the yields in Scheme 3 are obtained from reactions in MeCN/IPA, end users of this methodology may need to evaluate a few solvents to obtain the best combination of yield and purity for their compounds. See the Supporting Information for full information on yield and purity for zwitterion formation. In several instances (**7z, 12z, 14z, 25z**, and **30z**) the starting 1,2-amino alcohols were purchased and utilized as the HCl salt. These can be used in the ES addition after *in situ* freebasing with aqueous sodium hydroxide and filtering to remove NaCl.

Despite the broad scope that we have demonstrated, not all 1,2-amino alcohol derivatives were found to be suitable in this methodology. For example, highly electron deficient nitrogen centers, such as those present in Boc-carbamates and nitroaromatics containing aminoethanol groups, do not react to form isolable products under these conditions. A hydroxypyrazole reacted but formed a mixture of products, which we presume to be regioisomers resulting from the reaction of ES with each of the two pyrazole tautomers.

Amino acids do not afford the intended ES addition adducts, presumably because the amine of the amino acid exist as the protonated form in solution and is non-nucleophilic; carboxylate salts are known to be competent nucleophiles for the addition to ES and we have been unable to convert free-based amino acids to the corresponding ES addition products.[39] Thioethanolamine reacted to form a mixture of products that we have not identified.

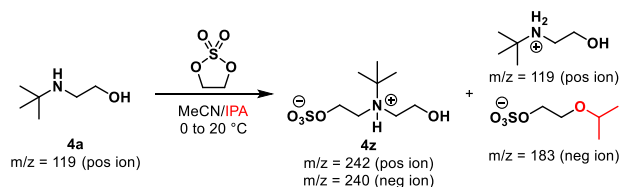**Scheme 4. Experiments to Probe Selectivity for Monoalkylation.**
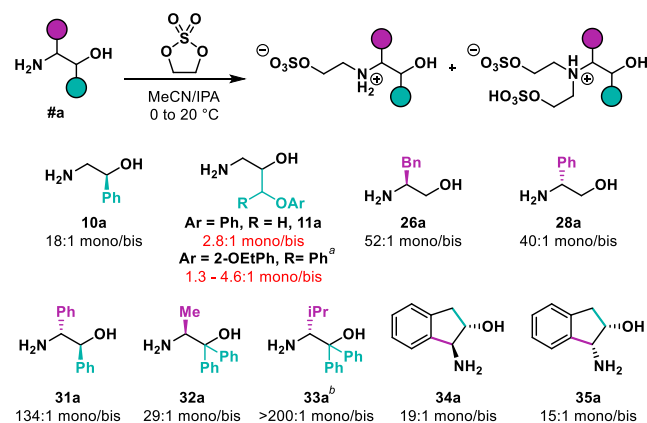
[a]See reference 43. [b]A signal for the bisalkyation product was not observed.

The good isolated yields of pure products shown in Scheme 3 implies that the alkylation of the 1,2-amino alcohols occur preferentially for monoalkylation relative to bisalkylation. We conducted several experiments to probe the origin of this selectivity. Nine of the 1,2-amino alcohols containing UV chromophores were allowed to react with ethylene sulfate under identical conditions. The HPLC profile of the reactions were then compared to establish a selectivity for the formation of mono- and bisalkylation products. These results are summarized in Scheme 4. Surprisingly, we observed a significant amount of variability in selectivity, which indicates at least some of the observed selectivity is due to substrate control. The presence of bulky substituents close to the amine seems to qualitatively, although imperfectly, correlate with selectivity; a similar trend between steric bulk around nitrogen and purity corrected yield can also be observed from Scheme 3. Importantly, **11a** bears a strong resemblance to the 1,2-amino alcohol which was previously found to afford poor selectivity in a reaction with ES.[43]

The origin of this substrate control could be based upon the steric or electronic environment around the amine or upon the reaction physical properties (i.e., does the monoalkylation product crystallize from the reaction mixture and prevent further alkylation). To assess whether the selectivity originates from selective crystallization of the monoalkylated zwitterion we conducted the alkylation of **28a** in the presence of 1.1 equiv of TEA. Nearly identical selectivity for monoalkylation (40:1) was observed despite the fact the reaction remained homogeneous. This result clearly indicates that selective formation of monoalkylation products is not dependent upon selective crystallization of the zwitterion. However, this selective crystallization is obviously required for some 1,2-amino alcohols to
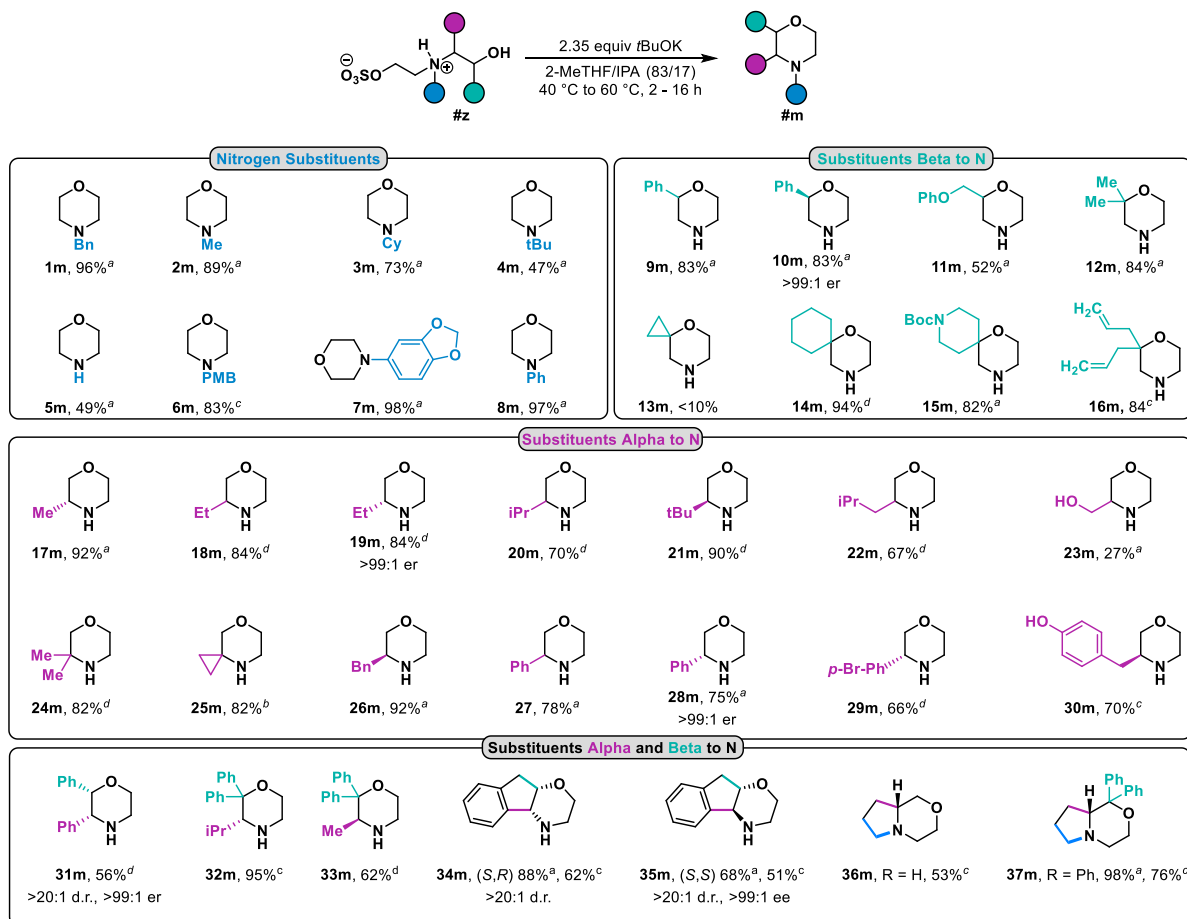
isolate the monoalkylation zwitterion products in high purity. We then conducted a reaction between **28a** and dimethylsulfate under the same conditions as the experiments with ES. In this case poor selectivity was observed (2:1:1 mono/bis/tris alkylation). Thus, the unique selectivity observed in reactions between 1,2-amino alcohols (and presumably other amines) and ES is dependent upon both the structure of the reacting nucleophile as well as special properties imparted by the electrophile.

Scheme 5. Identification of ethylene sulfate degradation products

4a
m/z = 119 (pos ion)

MeCN/IPA
0 to 20 °C

4z
m/z = 242 (pos ion)
m/z = 240 (neg ion)

m/z = 119 (pos ion)

m/z = 183 (neg ion)

The alkylation of an amine by an alkyl sulfate is likely highly favored thermodynamically, which makes the detection of starting material in some of the reactions surprising. To understand the presence of starting material, the reaction to form **4z** was analyzed by LCMS (Scheme 4).

Compounds **4a** and **4z** do not possess a chromophore but the molecular ions are visible in positive ion mode of the mass spectrum. In negative ion mode signals with masses consistent with **4z** and a new compound (m/z = 183) derived from the addition of IPA to ES were observed. The addition of IPA to ES would generate an equivalent of acid which would protonate a molecule of **4a**, rendering it non-nucleophilic. An analogous methanol addition side product was also observed in reactions conducted in MeCN/MeOH. Based on this observation the reactions to form **2z** and **4z** were re-evaluated in the absence of an alcohol co-solvent. The yield for the formation of **2z** was increased from 70% to the 92% yield presented in Scheme 3. However, the yield and purity for formation of **4z** was not improved by switching from MeCN/IPA to pure MeCN. Nonetheless, it is recommended to evaluate pure MeCN as solvent for reactions of highly basic and/or poorly nucleophilic amines. A second potential cause for the presence of "unreacted" starting material is when the starting amines acts as the base required to enable a second alkylation of the zwitterion products. Thus, reactions which occur to low conversion are also likely to contain a significant amount of bisalkylation products. Indeed, the reaction of **11a** with ES discussed above occurs to only 73% conversion.

Scheme 6. Cyclization of ethylene sulfate addition products to morpholines

[a]GC , HPLC, or ¹H NMR yield of the shown compound; [b]GC, HPLC, or ¹H NMR yield of a derivative of the shown compound; [c]Isolated yield of the shown compound; [d]Isolated yield of a derivative of the shown compound

With several zwitterion products in hand, we turned our attention towards the cyclization step. A variety of solvents (2-MeTHF, THF, CPME, MeOH, IPA, Toluene), bases (Li/Na/K *t*-Butoxide, *t*-Pentoxide, Methoxide, and HMDS), and temperatures (20, 40, 60, and 80°C) were screened for the cyclization of **1z** to **1m**. A mixture of 2-MeTHF and IPA was chosen for solvent and *t*BuOK for the base. Reactions were conducted at 60 °C for 2 – 16h. The synthesis of morpholines from zwitterions **1z** – **37z** was evaluated under these conditions; the results are shown in Scheme 6. In some instances, isolated yields are reported, whereas in other cases GC, ¹H NMR, or HPLC yields are reported. Some of the morpholines were derivatized (via tosylation, benzoylation, or HCl salt formation) to simplify isolation (e.g., morpholines that lack chromophores were tosylated or benzoylated to simplify purification by column chromatography). In other cases, novel morpholines were converted to known compounds to simplify characterization. In the cases where the compounds were derivatized the yields include cyclization and derivatization. The isolation details are reported in the Supporting Information.

Cyclization of zwitterions containing substituents only on nitrogen typically occurs in good yields. Reactions of zwitterions with N-benzyl (**1m**), N-methyl (**2m**), N-cyclohexyl (**3m**), N-*p*- methoxybenzyl (**6m**), N-benzodioxole (**7m**), and N-phenyl (**8m**) substituents all produce products in good yield. This contrasts with the zwitterions containing N-H or N-*t*-Bu substituents, which react to form products in modest yield. A variety of substituents beta to nitrogen, including aryl, alkyl, geminal dialkyl, and spirocycles, were also well tolerated during cyclization (**9m** – **12m** and **14m** – **16m**). However, when the cyclization of **13z** to **13m** was attempted an extremely messy reaction profile was observed. We speculate that the cyclopropanol decomposed when heated in the presence of base.[45]

Cyclization also proceeds well for compounds containing substituents alpha to nitrogen (**17m** to **30m**), with only one being formed in poor yield (**23m**, 27%). Unlike the cyclopropanol containing zwitterion **13z**, the cyclopropylamine containing zwitterion **25z** cyclized to form **25m** in good yield. Several zwitterions containing substituents at both the alpha and beta positions relative to nitrogen were also cyclized to morpholines, although the yields vary from compound to compound. We attribute the greater yield for the formation of **37m** relative to **36m** to the Thorpe-Ingold effect.[46] In several cases the enantiopurity of the morpholine products was measured and in all these cases the compounds were isolated with >99:1 chiral purity. However, it is likely morpholines containing stereocenters adjacent to more electron-withdrawing substituents, such as an ester or nitrile, would undergo some degree of racemization or epimerization under our standard conditions.

While the morpholines in Scheme 6 are reflective of typical building blocks often used in the SARs of potential new medicinal and agricultural products we also wanted to demonstrate this methodology for the synthesis of known pharmaceutically relevant compounds (Scheme 7). When **38a** was subjected to the standard ES alkylation and cyclization conditions **38m**, which is a fragment in the

commercial antibiotic Finafloxacin, was isolated in 58% overall yield for the two steps. Similarly, the cis diastereomer of phendimetrazine **39m**, a stimulant appetite suppressant, was isolated in 70% overall yield after our two-step sequence, starting with **39a** (ephedrine). The one-pot conversion of Fingolimod, a treatment for multiple sclerosis, to the corresponding morpholine, is shown in Scheme 9.

## Scheme 7. Synthesis of pharmaceutically relevant morpholines
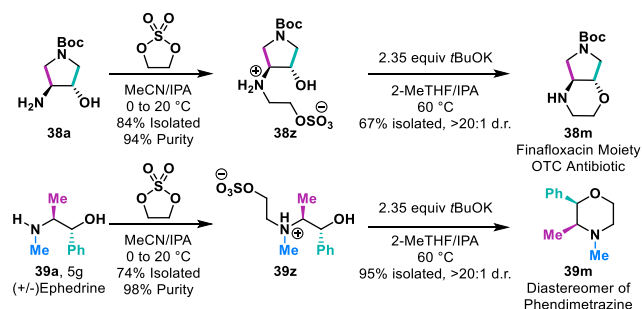
Scheme 8. Morpholine Synthesis using 1,2-Propylene Sulfate
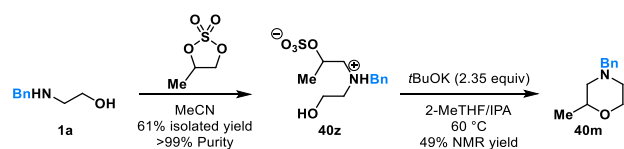
We considered that more complex cyclic 1,2-sulfates could be used to afford more elaborate morpholines and tested the current conditions in a reaction between the commercially available 1,2-propylene sulfate and **1a** (Scheme 8). The reaction occurred to 87% conversion and produced a 27:1 mixture two signals which correspond to mass of **40z**; we presume a mixture of products arising from substitution of the primary vs secondary position of the cyclic sulfate was formed. The compound was isolated in 61% yield, with >99% purity (after correcting for 8% residual solvent). The cyclization was conducted under our standard conditions to afford **40m** in 49% NMR assay yield. We have not explored further transformations using this reagent.

Scheme 9. One-pot conversions of 1,2-amino alcohols into morpholines
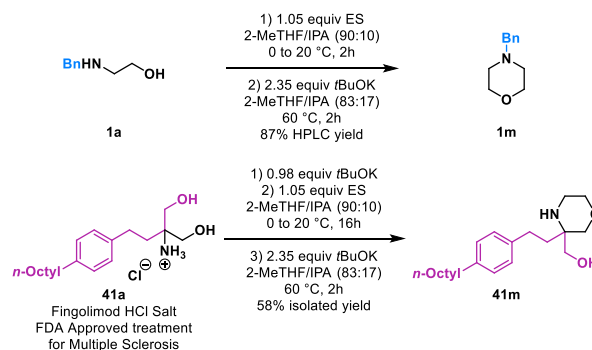
The isolation of the zwitterion intermediates allows an end user the opportunity to remove impurities whether they

are present in the 1,2-amino alcohol or are formed during the ES alkylation. However, this is also a potential limitation because not all 1,2-amino alcohols may form crystalline zwitterion products. Therefore, the formation of **1m** from **1a** was evaluated in a one-pot reaction under modified conditions (Scheme 9). The ES addition was conducted in a 9:1 mixture of 2-MeTHF/IPA; complete conversion to **1z** was observed by HPLC in <2h. Additional IPA and *t*BuOK were added, and the mixture was heated to 60 °C. After 2h we observed a 95% conversion of **1a** to **1m** and obtained an 87 % yield, as determined by HPLC. These conditions were then applied to the HCl salt of Fingolimod, which is currently used as a treatment for multiple sclerosis. After *in situ* free basing with *t*BuOK, the ES alkylation was conducted in the same manner as described above. Even though freebased Fingolimod is only partially soluble in the reaction solvent we observed the formation of the zwitterion product by LCMS, albeit much more slowly than **1a**. After stirring the ES alkylation overnight, *t*BuOK and IPA were added and the mixture was heated to 60 °C. Compound **41m**, which has also been shown to be a potential therapeutic for multiple sclerosis and may lead to fewer adverse side-effects because it is more selective than Fingolimod,[47] was isolated in 58% yield.

Scheme 10. Large Scale Synthesis of Morpholine 1m
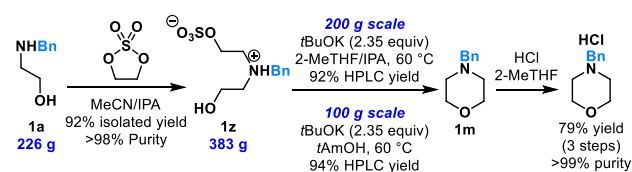
An important attribute for this methodology is ease with which it is scaled under practical conditions. In all cases the ES addition reactions were conducted on at least 6.5 mmol scale, which corresponds to a minimum of 0.4 g (for ethanolamine), and in 13 cases they were conducted on multigram scale. Typically, higher yields (~3 – 5%) are observed when these reactions are conducted on larger scale, which can be attributed to the lower handling losses and improved mixing with larger stir bars or overhead stirrers. To further demonstrate the scalability, the ES addition to N-Benzylethanolamine **1a** was also conducted on 1.5 mol (226 g) scale (Scheme 10). This reaction afforded 383 g of **1z**, (92% yield, 98% purity). The cyclization was then conducted in a clean reactor on 200 g scale, affording a 92% HPLC assay yield after workup (see the Supporting Information for details). The crude oil was then converted to the HCl salt, which was isolated in 79% overall yield (3 steps) and 99% purity (after correcting for ~7 wt% 2-MeTHF in the solid).

The cyclization reactions undergo a characteristic change in physical properties (suspension to solution to thick suspension/gel to slurry). It was found that a stir bar with very high agitation rates was usually able to mix the reaction mixture after thickening on small scale. When the reaction was conducted on 200 g scale with an overhead stirrer mixing of the entire reaction mixture was not possible except with very high agitation rates. In the initial stage of the cyclization the internal temperature increases rapidly from

~20 to ~45 °C from the dissolution of *t*BuOK and freebasing of the zwitterion. Importantly, this temperature increase does *not* coincide with the thickening of the reaction mixture. Furthermore, significant self-heating is not observed thereafter meaning that localized temperature spikes should not occur because of the poor mixing that occurs due to thickening. While this poor agitation may not be a significant concern to end users looking to apply the methodology on small scale, end users looking to apply methodology on large scale should take special considerations for this aspect. We evaluated various additives (dioxane, diglyme, 18-crown-6, water) and were initially unable to find one which results in acceptable conversion and physical properties. However, during the final stages of manuscript preparation it was discovered that conducting the cyclization reaction in pure *t*BuOH or *t*AmOH results in an easily stirred suspension throughout the entire reaction and affords **1m** in 96% and 94% and HPLC yield, respectively. The cyclization of **1z** was conducted on 100 g scale in *t*AmOH and afforded a 94% HPLC assay yield of **1m** (Scheme 9). The physical properties were much improved over the previous large-scale batch; the reaction was easily stirred with a stir bar throughout the entire reaction. We also found that increasing the amount of *t*BuOK from 2.35 to 2.80 equiv prevents gelling of the reaction mixture in 2-MeTHF/IPA without impacting the yield, although we have not tested the efficacy of this on large scale.

Overall, this methodology has environmental and safety benefits relative to the traditional 3-step conversion of 1,2-amino alcohols to morpholines using chloroacetyl chloride. First, this two-step protocol eliminates one step (and the waste associated with it) relative to the three-step protocol. Because the ES mediated approach is redox neutral the aluminum/boron hydride mediated reduction associated with the chloroacetyl chloride approach is eliminated. Although certain hydride reducing agents can be used on scale in pharmaceutical R&D, their use is disfavored because some are pyrophoric, they can evolve hydrogen gas, often require low temperature and lengthy workups, and can be expensive. Whereas DCM, which has recently been restricted by the United States Environmental Protection Agency,[48] is commonly used in the chloroacetyl chloride approach, this ES method uses MeCN for the alkylation (with or without an alcohol co-solvent) and 2-MeTHF/IPA or *t*AmOH for the cyclization. In GSK's published solvent selection guidelines[49] DCM is considered a "red" solvent, whereas MeCN are 2-MeTHF are considered "yellow" solvents, and alcohols (except MeOH) are generally considered "green" solvents. Both ES and chloroacetyl chloride are highly reactive and toxic electrophiles and should be handled with care. However, ES is a solid whereas chloroacetyl chloride is a volatile liquid. Thus, accidental exposure risk is likely lower for ES than for chloroacetyl chloride. Finally, this methodology produces waste with quite low toxicity (K_2SO_4 and *t*BuOH). Collectively, these criteria establish that the ES mediated approach is greener than the classical method for the preparation of morpholines from 1,2-amino alcohols because it directly achieves monoalkylation of the amine.

While the synthesis of morpholines is the focus of this paper, we considered the same strategy could also be used for the synthesis of piperazines, which are among the most common of all heterocycles in small molecule drugs.[4,50] When we attempted the ES addition to ethylenediamines containing alkyl substituents on one of the amines crystalline products were not formed. However, we were able to isolate the alkylation product from the reaction of **42a** with ES (Scheme 11). The cyclization of **42z** occurred at slightly elevated temperatures relative to the conditions for the synthesis of morpholines but formed the product in 68% NMR yield. We plan to further evaluate the scope of this transformation in the future.

### Scheme 11. Synthesis of a piperazine via ES
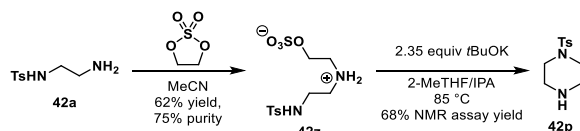
The ease with which monoalkylation products are isolated from reactions of amines with ES warrants some additional considerations about the synthetic possibilities (Scheme 12). For instance, we considered that in some cases the 1,2-amino alcohol that an end user would select as a starting material may not be readily available and decided to evaluate the feasibility converting a benzylamine to a morpholine. We found that benzylamine adds to ES under our standard conditions to afford the zwitterion **43z** in 75% isolated yield. This compound was then hydrolyzed in a mixture of aqueous sulfuric acid and toluene at 100 °C for 6h to afford a 91% HPLC yield of **1a**, which we have already shown can be converted to **1m** in 87% yield. Thus, we have completed the formal synthesis of **1m** from benzylamine in 4 steps with an overall yield of 59%. Additionally, the conversion of beta aminosulfates to aziridines has previously been demonstrated, including **43z** to **44** in 60% yield.[51] Thus, we have also demonstrated the formal synthesis of N-benzylaziridine in two steps from benzylamine in 45% yield. Finally, we considered that ES could be useful as a surrogate for reductive amination or alkylation in cases where the corresponding aldehyde or electrophile would not be readily available. We found that thiophenol readily displaced the sulfate to afford **45** in 82% NMR assay yield. We anticipate that a variety of nucleophiles will be capable of displacing the sulfate group, which could make this a valuable transformation for designing PROTAC linkers.[52]

In summary, we have shown that monoalkylation products from reactions between ES and a variety of substituted 1,2-amino alcohols are readily isolated in good yield and high purity. These zwitterions are readily cyclized into morpholines, including pharmaceutically relevant compounds, which can be isolated in high yield even on large scale (>100 g). We have also demonstrated the proof-of-principle that 1,2-propylene sulfate can be used, have performed the ES zwitterion formation and cyclization in one pot, and completed the synthesis of a piperazine from ES and a protected ethylenediamine. Because the reagents for these transformations (ethylene sulfate and *t*BuOK) are inexpensive and the conditions are practical and environmentally friendly, we expect this methodology will see widespread adoption for the synthesis of morpholines. Moreover, since this protocol enables facile monoalkylation of some primary amines we anticipate a variety of useful synthetic methodologies will be inspired by this chemistry.

Scheme 12. Derivatization of an ES addition product
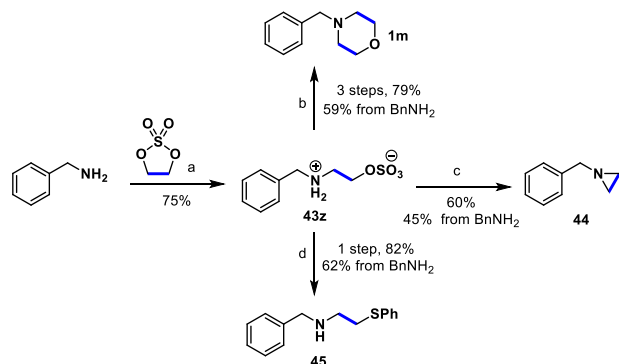
Conditions: a) MeCN/IPA (9:1), 0 to 20 °C, 1.05 equiv ES; b) i. Aq. H₂SO₄/Toluene, 100 °C (91%), ii. See Scheme 3, iii. See Scheme 6; c) Aq NaOH/Toluene, reflux[51]; d) *t*BuOK, PhSH, NMP, 60 °C

ASSOCIATED CONTENT

Supporting Information. Detailed experimental procedures and characterization data for all new compounds are reported in the Supporting Information.

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The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript.

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