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Green Synthesis of Morpholines via Selective Monoalkylation of Amines
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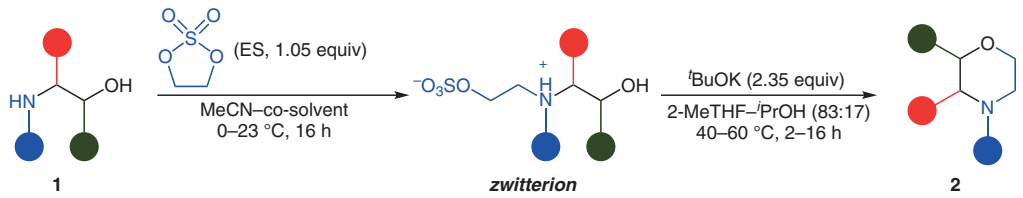
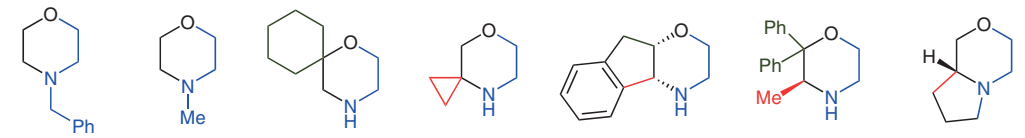
Ethylene Sulfate: A Two-Carbon Synthon for a Modular Synthesis of Morpholines



Examples (yields of zwitterion/morpholine in brackets):



3 (91%/96%) **4** (92%/89%) **5** (77%/94%) **6** (73%/82%) **7** (71%/88%) **8** (54%/62%) **9** (90%/53%)

Significance: Morpholine heterocycles are a prevalent feature in agrochemicals and pharmaceuticals, with the most common approach for their formation being through an annulation reaction of a 1,2-aminoalcohol to form the desired ring system. While conceptually simple, the key challenge to executing this strategy is achieving mono-alkylation of the parent amine, and for this reason an initial acylation reaction is carried out, leading to the formation of morpholinone products, which can then be reduced to the desired parent ring system. However, the additional reduction step presents challenges with functional group tolerance and generation of excess waste, and though alternatives have been developed, these also have intrinsic limitations including reagent cost and limitations in substrate scope. The current report enables a two-step synthesis (that can be carried out in one pot) utilizing ethylene sulfate (ES) as the electrophile, which upon reaction with a 1,2-aminoalcohol forms a zwitterionic intermediate. The latter can often be isolated by crystallization, which then cyclizes upon treatment with base to form the morpholine derivative.

Comment: Model studies evaluated the reaction of ES with *N*-benzylethanolamine in a range of solvents without the addition of an exogenous base to enable crystallization of the zwitterionic product whilst purging residual starting materials and impurities. A broad range of 1,2-aminoalcohols were demonstrated to be successful substrates, providing the desired products in high yields and high purities. Surprisingly, subsequent studies indicated that the formation of the monoalkylated products was not promoted by their selective crystallization, but is instead a function of the reacting nucleophile as well as special properties imparted by ES. Screening of base, solvent, and temperature was carried out to identify the optimal conditions for the cyclization sequence with the reaction applied to a series of diversely substituted and pharmaceutically relevant morpholine derivatives. The sequence was adapted to a one-pot protocol avoiding isolation of the intermediate zwitterion, and was also exemplified on hectogram-scale.

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Category
Synthesis of Heterocycles

Key words
ethylene sulfate
morpholines
zwitterions
monoalkylation

Synfact of the Month