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Application of a process friendly morpholine synthesis to (*S,S*)-Reboxetine

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ABSTRACT

We report our results on the construction of a morpholine ring system from the corresponding epoxide and amino alcohol. From this study, we were able to convert a previous four-step synthesis into a more efficient two-step process.

The morpholine ring structure is an important heterocycle present in many compounds of biological and pharmaceutical relevance.[1] (*S,S*)-Reboxetine free base **1** is an example of a morpholine-containing compound that displays strong activity against many diseases including neuropathic pain.[2] The initial manufacturing process involved a four-step synthesis from epoxide **2** and was successfully applied to synthesize Reboxetine in its racemic[3] and enantiopure[4] forms. This strategy has also been used in the synthesis of various analogues.[5] The epoxide **2** was converted into the amino alcohol **3** with ammonia followed by reaction with chloroacetyl chloride to form the amide **4**. This compound was converted into the lactam **5** by reaction with a strong base and was subsequently reduced to the morpholine **1** in the presence of a suitable reducing agent (Scheme 1).

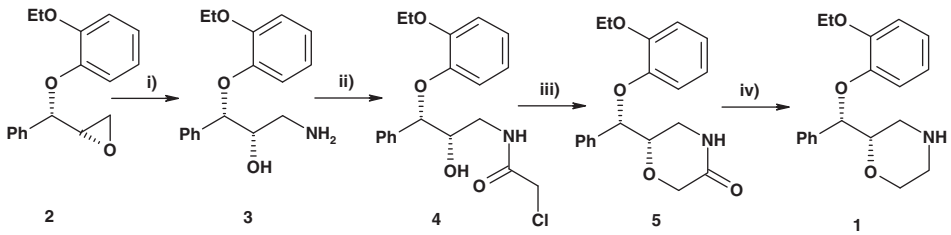
This well-established procedure has some drawbacks for a commercial scale manufacturing process:

(1) The length of the synthesis (four steps) requires time in expensive facilities increasing manufacturing costs and waste produced.
(2) The chlorinated intermediates have a potential toxicity that may also impact workers' health and safety.
(3) The significant aluminium waste produced in the reduction step.
(4) The overall yield is moderate to low (30–40%).

There is scope to optimize the published procedures in terms of yield, stoichiometries, and concentrations. However, these approaches do not address the issues of some of the reagents and by-products, or the throughput and overall step count. Our work therefore focused on the alternative strategies to build the target morpholine ring guided by the SELECT criteria.[6]

The first strategies examined utilized the amino alcohol intermediate **3** as the starting point. We targeted removing 1–2 steps by replacing chloroacetyl chloride by a suitable two-carbon synthon at the correct oxidation level, thus avoiding the lactam reduction stage in the original process. A further chemical step could be removed if the two bonds (N–C and O–C) could be formed in one pot. A large set of conditions, including over 200 reactions, was designed and run in our screening facilities with 10 different reagents (symmetrical and unsymmetrical two-carbon units, see Table 1) and using the most common combinations of solvents and bases for alkylation reactions.

The majority of the reactions did not give the desired product or were lacking in selectivity giving multiple alkylation products. Only the two cyclic substrates gave interpretable reaction profiles. Ethylene carbonate reacted at the carbonyl centre to yield the carbamate **6** that rapidly and quantitatively converted into the oxazolidinone **7** in the presence of a base. The cyclic sulfate, on the other hand, reacted at the desired carbon centre to yield a mixture of mono-alkylated **8** and bis-alkylated **9** products (Scheme 2).



Scheme 1. Reagents: (i) NH_4OH; (ii) THF, chloroacetyl chloride, H_2O, NaOH; (iii) KO*t*Bu; (iv) RedAl or LAH.

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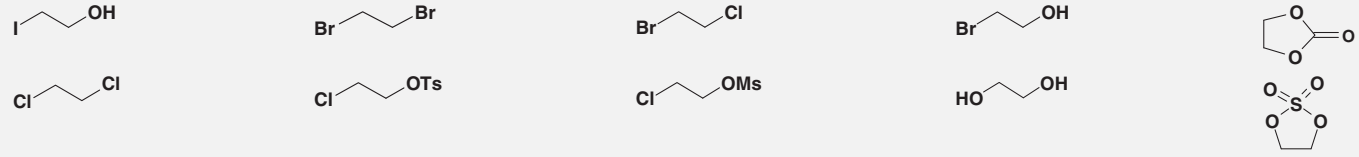
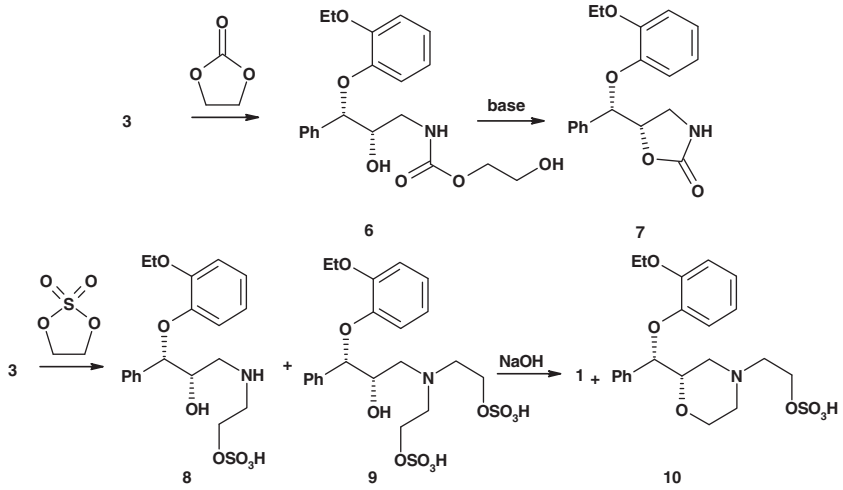
Table 1
List of two-carbon units screened

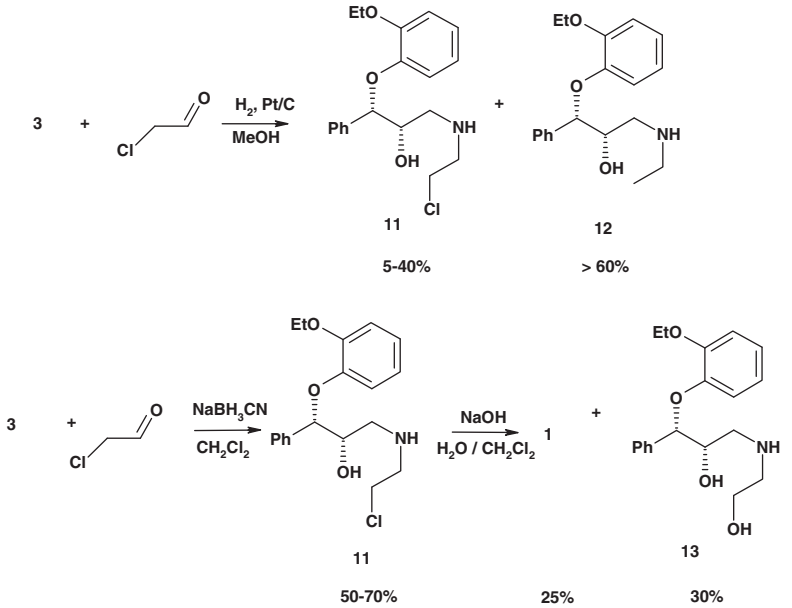




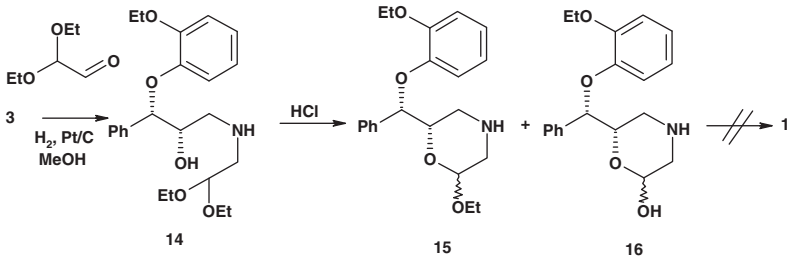
Scheme 2. Reactions of amino alcohol **3** with cyclic substrates.

The resulting mixture of mono-alkylated **8** and bis-alkylated **9** compounds was treated with a base and the formation of the expected morpholines **1** and **10** was observed. After optimization, the selectivity[7] was increased from 57% to 82% by running the chemistry as a flow process: the separate reagent streams were combined in a plug flow reactor before quenching. As the conversion could not be increased above 70% without impacting on the selectivity we looked at alternative strategies to achieve the desired transformations.

We believed that a reductive alkylation of the amino alcohol **3** with chloroacetaldehyde would provide the same type of intermediate **11** and would avoid bis-alkylated by-products. Using heterogeneous hydrogenation conditions we found that only platinum could be used to facilitate this transformation as other metals induced partial or complete loss of the 2-ethoxyphenol fragment. The selectivity was also poor with the major component identified as the fully reduced compound **12**. The amount of desired product **11** could be increased to 70%, this however required the use of toxic sodium cyanoborohydride as the reductant. On treating the crude mixture with aqueous sodium hydroxide, we observed the formation of the desired morpholine **1** as well as the terminal alcohol **13** (Scheme 3).



Scheme 3. Reductive amination of **3** with chloroacetaldehyde.



Scheme 4. An attempted route to Reboxetine via acetal intermediates.

Table 2
Comparison of the bases used: base (5 equiv); 2-AEHS (5 equiv); solvent = methanol; 70 °C

Base	Product[a] **8** (%)	Dimer[a] **17** (%)	Adduct[a] **18** (%)
Imidazole	13	0	87
DBU	92	6	2
Triethylamine	40	15	45
N-Methyl morpholine	21	8	71
2,6-Lutidine	0	0	0
Tetramethyl guanidine	85	5	10
Ethyl diisopropylamine	69	29	2
DABCO	1	0	99

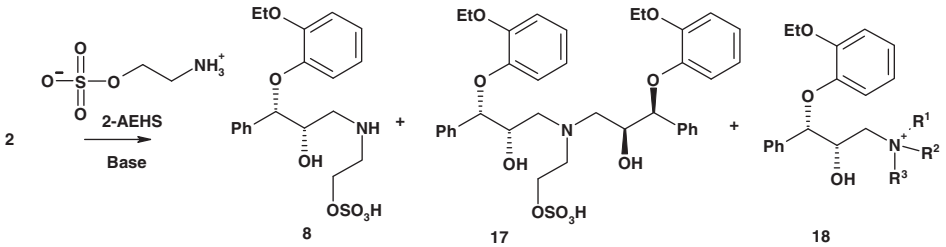
[a] % Area by HPLC, adducts were confirmed by LC–MS.

The use of toxic chloroacetaldehyde and cyanoborohydride could be avoided by switching to the less toxic acetal **3**. In this approach, reductive amination was followed by acid-catalyzed ring-closure and silane reduction.

We were delighted to find that the first step worked well using Pt/C as the catalyst (75% isolated yield) and treatment of the resulting acetal **14** with hydrochloric acid delivered the target intermediate as a 9:1 mixture of acetals **15** and hemiacetals **16** (Scheme 4). The third transformation was well precedented in the literature,[8] typically using triethylsilane with trifluoroacetic acid in dichloromethane. We used this in the design of a reaction screen combining a range of silanes and acids (Lewis and Brønsted). We also screened metal-catalyzed reductions. The most attractive from a process point of view was the use of a specific platinum-based hydrogenation catalyst[9] for reductive etherification as this may allow for telescoping with the first step. Unfortunately, most of the reactions did not yield the desired morpholine, but many impurities instead. Some reaction conditions produced up to 10% of the desired morpholine but they were not reproducible.

The introduction of additional steps could be avoided by reverting to the epoxide intermediate **2** and opening it with a fragment at the correct oxidation state with the leaving group already in place. Clearly 2-aminoethanol hydrogen sulfate (2-AEHS) should facilitate this as it is precedented in the literature, and we had already shown that the sulfate intermediate **8** can be converted into the target molecule.[1,10] 2-AEHS exists as a zwitterion and needs to be activated by deprotonation. We screened a range of bases suitable for this transformation (Table 2), targeting bases strong enough to activate 2-AEHS ($pK_a = 9.25$ in water) and with low nucleophilicity to minimize the formation of by-products **18** due to nucleophilic addition to the epoxide (Scheme 5).

The bases screened confirmed the need for activation of 2-AEHS by deprotonation (no reaction with 2,6-lutidine due to its basicity being too weak) and demonstrated that even relatively non-nucleophilic amines (triethylamine and *N*-methyl morpholine) opened the epoxide to give the undesired adduct **18**. The most suitable base identified for this transformation was 1,8-diazobicyclo-[5.4.0]undec-7-ene (DBU; $pK_a = 11.5$) as this minimized the adduct **18** formation. We also repeated the literature conditions using sodium hydroxide,[10] but with the expectation of high diol impurity formation. The diol **13** and ether by-products were formed when using alcohol/water systems, however, the major impurity was now dimer **17**. To overcome this issue, large excesses of 2-AEHS and sodium hydroxide were needed (see Table 3). With DBU, higher selectivities could be achieved with lower equivalents of 2-AEHS

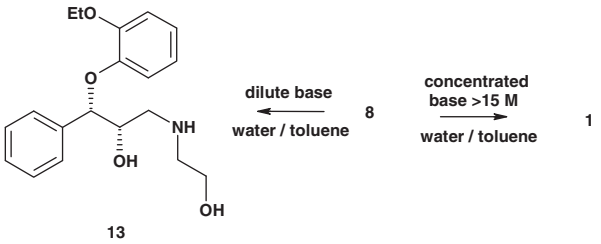


Scheme 5. Epoxide opening with 2-aminoethanol hydrogen sulfate in the presence of a tertiary amine as a base ($NR^1R^2R^3$).

Table 3
Comparison of NaOH and DBU for epoxide opening with different amounts of 2-AEHS and base

Base	2-AEHS (equiv)	Base (equiv)	Epoxide[a] **1** (%)	Product[a] **8** (%)	Dimer[a] **17** (%)	Others[a,b] (%)
NaOH	5	5	3	84	9	4
NaOH	10	10	2	90	5	3
DBU	3	3	0	92	7	1
DBU	5	5	0	96	3	1

[a] % Area by HPLC, conversion measured after 3 h at 65 °C.
[b] Others refer to the sum of all other impurities present. Solvent = water/methanol for NaOH and methanol only for DBU.



Scheme 6. Behaviour of zwitterion **8** in the presence of dilute and concentrated base.

and it was therefore selected as the optimum base. The solvent system was also optimized and resulted in a further decrease of the stoichiometry of base and 2-AEHS. Most of the screened solvents tried gave at least 70% (in situ) product but only the alcohol-based solvent mixtures gave a yield greater than 80% while providing a convenient work-up.

With the target intermediate in hand, the base-mediated ring-closure was explored, by screening a range of bases and solvents. KOH and NaOH were identified as optimum bases in toluene and high concentrations were required to minimize the formation of the diol impurity **13** (Scheme 6).

With other bases in anhydrous systems (typically KO*t*Bu/THF) many side products were observed and the desired morpholine **1** was formed in only 60–70% yield. Amongst the side products, 2-ethoxyphenol and the amino alcohol **3** were observed. We found that the use of solid sodium hydroxide in THF combined with an additive in the solvent (water or alcohol at 1–5% levels) increased dramatically the reaction rate and improved the yield from 65% to 90%.

The effect of water and ethanol was compared and we found that the use of water required very tight control: while 1% water proved beneficial, 3% or more retarded considerably the desired reaction rate and favoured the formation of the amino diol **13**. In comparison, ethanol could be tolerated at higher levels (up to 20% volume in THF) without interfering with the reaction rate and purity profile, typically more than 99% conversion within 3–4 h producing the morpholine **1** in 90–95% yield. Common alcohols were investigated and we found that methanol, isopropanol, *tert*-butanol and *tert*-amyl alcohol gave equivalent results.

This process was successfully scaled up to kilogram-scale delivering (*S*,*S*)-Reboxetine succinate in high yield and chemical purity.[11]

In conclusion, we have explored a number of approaches to synthesize the morpholine ring of (*S*,*S*)-Reboxetine from both the amino alcohol **3** and the epoxide **2**. We have demonstrated that the synthesis described in Scheme 1 can be replaced effectively by a shorter and more efficient two-step process via epoxide opening with 2-AEHS and base-mediated ring-closure using an atypical solid NaOH/THF/EtOH system. The combined transformations delivered (*S*,*S*)-Reboxetine in more than 60% overall yield through a more efficient process both in an environmental and in an economical respect.

Acknowledgements

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References and notes

1. Wijtmans, R.; Vink, M. K. S.; Schoemaker, H. E.; van Delft, F. L.; Blauww, R. H.; Rutjes, F. P. J. T. *Synthesis* **2004**, 641–662.
2. Ellis, A. J.; Junor, R. W. J.; Stoker, M. J.; Whelan, L. J. PCT Int. Appl. WO 2010044016; *Chem. Abstr.* **2010**, *152*, 493509.
3. Henegar, K. E.; Ball, C. T.; Horvath, C. M.; Maisto, K. D.; Mancini, S. E. *Org. Process Res. Dev.* **2007**, *11*, 346–353.
4. Henegar, K. E.; Cebula, M. *Org. Process Res. Dev.* **2007**, *11*, 354–358.
5. Ronald, M.; Tarazi, F. L.; Baldessarini, R. J.; Jarkas, N.; Goodman, M. M.; Seilby, J. P. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 533–537.
6. Butters, M.; Catterick, D.; Craig, A.; Curzons, A.; Dale, D.; Gilmore, A.; Green, S. P.; Marziano, I.; Sherlock, J.-P.; White, W. *Chem. Rev.* **2006**, *106*, 3002–3027.
7. The selectivity in percent is defined as the ratio of **8**/[**9**+**8**] * 100.
8. Srikrishna, A.; Viswajanani, R. *Tetrahedron* **1995**, *51*, 3339–3344; Olah, G. A.; Yamato, T.; Iyer, P. S.; Prakash, J. K. S. *J. Org. Chem.* **1986**, *51*, 2826–2828; Benko, Z.; Shinkle, S.; Van Heertum, J.; Jackson, J.; McQuiston, J.; Webster, J.; Turner, J.; Weimer, M.; Paterson, E. *Chimia* **2003**, *57*, 720–724; Soderquist, J. A.; Kock, I.; Estrella, M. E. *Org. Process Res. Dev.* **2006**, *10*, 1076–1079; Hansen, M. C.; Verdaguer, X.; Buchwald, S. L. *J. Org. Chem.* **1998**, *63*, 2360–2361.
9. Gooßen, L. J.; Linder, C. *Synlett* **2006**, 3489–3491.
10. Brown, G. R.; Forster, G.; Foubister, A. J.; Stribling, D. *J. Pharm. Pharmacol.* **1990**, *42*, 797–799.
11. *Typical reaction conditions: Epoxide opening of* **2**: 2-Aminoethanol hydrogen sulfate (2.50 equiv) was slurried in toluene (2 vol) and EtOH (2 vol). DBU (2.48 equiv) was added and the contents were heated to 65 °C for 1 h. Epoxide (**2**, limiting reagent) in toluene (5 vol) was added dropwise over 1 h and the mixture was stirred for a further 2 h at 70 °C. The reaction mixture was cooled to room temperature and the reaction was quenched with 1.3 M NaOH (3.0 equiv). The product crystallized from the aqueous layer by pH adjustment (with 1.0 M HCl) and was isolated by filtration, washed with H_2O (2 vol) and reslurried in EtOH (6 vol) to give **8** in 74% yield. *Ring closure to* **1**: To a slurry of **8** (limiting reagent) in THF (7 vol) and EtOH (0.21 vol) at room temperature was added NaOH (3.0 equiv). The reaction mixture was heated to reflux for 3 h and cooled to room temperature. H_2O (5 vol) and cyclohexane (4 vol) were added and the phases separated. The solvent was distilled and replaced with EtOH (5 vol) and succinic acid (1 equiv) was added to crystallize the product as the desired salt (82% yield).