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Development of a Safe and Scalable Amine-to-Nitrone Oxidation: A Key Step in the Synthesis of R107500

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Abstract:

The stepwise optimization towards a safe, reproducible, and high-yielding oxidation of azepine 2 into the prochiral nitrone 4 is described, with emphasis on the elimination of Davis reagent 3. *m*-Chloroperoxybenzoic acid (mCPBA) was found to be an elegant and scalable alternative oxidant regarding safety, yield, and easy workup procedures. Nitrone 4 was obtained in 95% yield and used without purification or isolation in the cycloaddition step to provide oxazolidone 6 in high yield. The process was scaled up successfully to an 800-L scale (60 mol of starting material).

Introduction

Chiral tetracyclic isoxazolidine **7** (R107500)[1] was discovered in the Medicinal Research labs of Johnson & Johnson Pharmaceutical Research and Development, a division of Janssen Pharmaceutica.

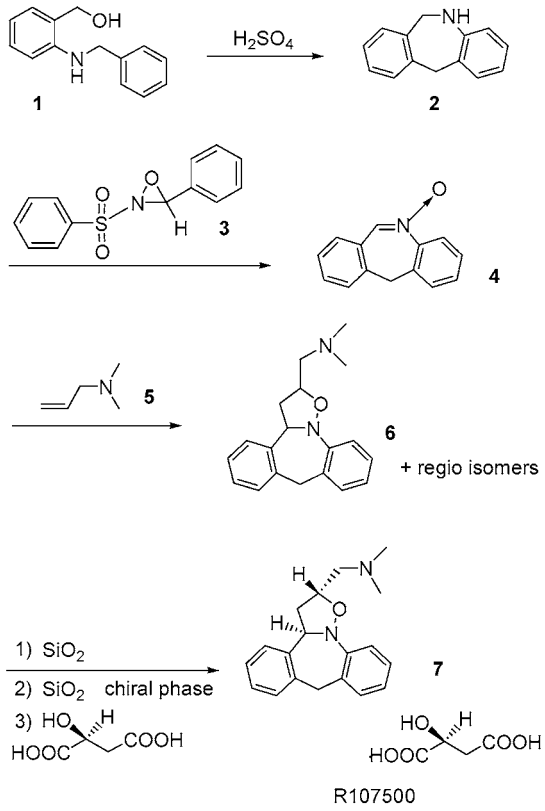
The compound shows affinity for 5-HT_2 receptors, particularly for 5-HT_{2A} and 5-HT_{2C} receptors.[2] Furthermore, in central nervous system(CNS)-related tests on rats, such as the "mCPP (*m*-chlorophenylpiperazine) Test on rats"[1], the "Tail Suspension Test",[3] and the "LSD Drug Discrimination Test",[4] interesting pharmacological activities have been observed. Another interesting property of this compound is that it suppresses amphetamine-induced stereotypical behaviour in rats.

In view of these pharmacological properties, R107500 was selected to be used as an anxiolytic, an antidepressant, and an agent having the potential to overrule the addictive properties of drugs of abuse.

In the discovery synthesis route, the oxidation to convert amine **2** to nitrone **4** was performed with isolated Davis reagent **3**[5−9] (Scheme 1).

The Davis reagent was reported to be a versitale reagent in the oxygenation of various functional groups. Drawbacks on its large-scale synthesis and application, however, are its potential hazards and the formation of a sulfonylimine byproduct. Removal of this byproduct could not be accomplished by crystallization due to instability of the nitrone **4** and had to be performed by column chromatography.

Scheme 1. **Discovery synthesis route**



This oxidation procedure was acceptable to synthesize the first 500 g of drug substance for early toxicology and formulation tests.

However, since larger amounts of drug substance were needed for clinical batches and further testing, this oxidation process was unacceptable, mainly because of safety concerns.

This article will present the development of a safe and scalable oxidation process to convert azepine **2** to the corresponding nitrone **4**.

Discovery Synthesis Route. As outlined in Scheme 1, the synthesis started with the ring-closure of aminobenzylic alcohol **1** with sulfuric acid to provide azepine **2** that was subsequently oxidized with Davis reagent **3**.

Nitrone **4**, which had been purified by column chromatography, underwent cycloaddition with allylamine **5** to give

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(2) Nomenclature as described by Hoyer, D. In *Serotonin (5-HT) in Neurologic and Psychiatric Disorders*; Ferrari, M. D., Ed.; Boerhaave Commission of the University of Leiden: the Netherlands, 1994.
(3) Described in *Arch. Int. Pharmacodyn.* **1977**, *227*, 238−253.
(4) Described in *Drug Dev. Res.* **1989**, *18*, 119−144.
(5) Davis, F. A.; Sheppard, A. C. *Tetrahedron* **1989**, *45*, 5703−5742.
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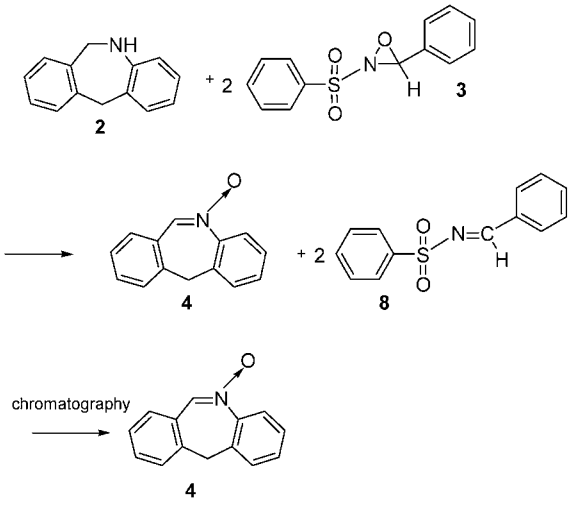
Scheme 2. **Oxidation using isolated Davis reagent**



isoxazolidine **6** as a mixture of all four possible diastereomers, along with small amounts of regio isomers. The *cis*/*trans*-diastereomers were separated on silica gel, whereas the enantiomers were separated using a chiral solid phase. The desired enantiomer **7** was isolated as the (*S*)-malic acid salt.

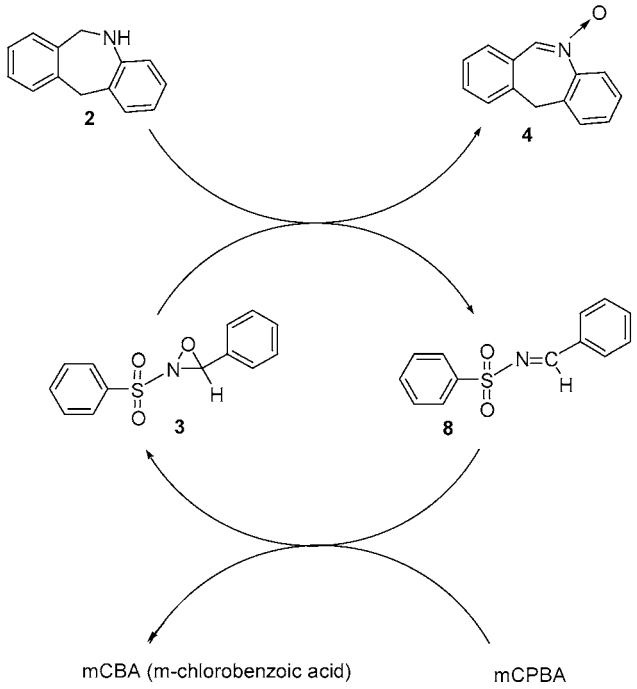
In this synthesis the isolated oxaziridine **3** was used to oxidize amine **2** (Scheme 2).

Davis reagent, prepared by the oxidation of sulfonylimine **8** with mCPBA, according to a literature method,[10] was obtained as a solution in CH_2Cl_2. Evaporation and crystallization from hexane yielded the oxidant as a white solid. One mole of azepine **2** was oxidized with 2 mol of reagent **3** within 2 h at room temperature in CH_2Cl_2. This also resulted in the formation of 2 mol of sulfonylimine **8**, which were separated from nitrone **4** by preparative chromatography.

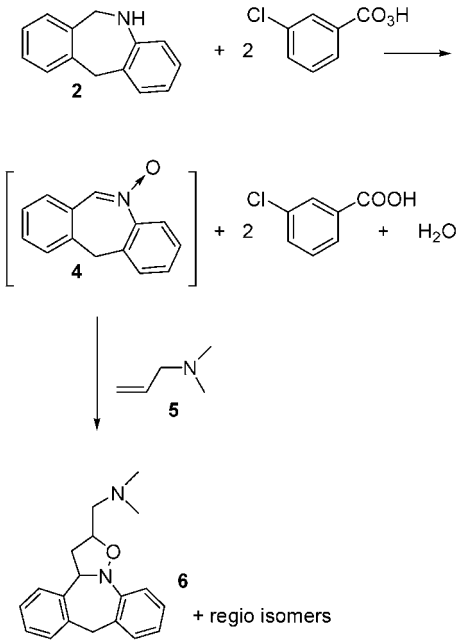
A safety study using differential scanning calorimetry (DSC) revealed the decomposition of oxaziridine **3** at 75 °C after 9 min and at 60 °C after 1.5 h in both air and N_2 atmosphere. In a mini-autoclave, a decomposition with a strong and fast exothermic signal was observed around 80 °C with a strong energy release of 1000 J/g. Therefore, isolation and storage of large quantities were to be avoided. Furthermore, isolated nitrone **4** was found to be thermally unstable. A DSC experiment showed exothermic decomposition starting off at 110 °C. These data prompted us to redesign the oxidation process.

Optimization of the Oxidation Process. Oxidation Using a Catalytic Amount of Sulfonylimine 8. The safety issue was adequately addressed by adding mCPBA to a mixture of amine **2** and a catalytic amount of the sulfonylimine **8** (Scheme 3). The in situ generated oxaziridine **3** oxidized the amino compound **2** to the nitrone **4**. This catalytic version, as depicted in Scheme 3, was tested. Complete conversion could still be obtained using only 5 mol % of the imine **8**, thus avoiding the difficult workup to remove the large quantities of imine.

Scheme 3. **Oxidation using a catalytic amount of sulfonylimine 8**



Scheme 4. **Direct oxidation with mCPBA**



We decided to investigate the direct mCPBA oxidation of the amine **2** because in the catalytic cycle, this could be a competitive reaction for the oxaziridine **3** formation.

Direct Oxidation with mCPBA. mCPBA oxidation worked fine when a solution of the peracid in CH_2Cl_2 was added dropwise to a solution of amine **2** in CH_2Cl_2 (Scheme 4).

Note: only toluene (cycloaddition solvent for compound **6**) was tested as an alternative solvent for CH_2Cl_2, but the reaction was incomplete.

The reaction was completed within 15 min, and the nitrone **4** was formed in 95% yield. This solution, after basic workup to remove the benzoic acid byproduct, was intro-

(10) Davis, F. A. *J. Org. Chem.* **1982**, *47*, 1774−1775.

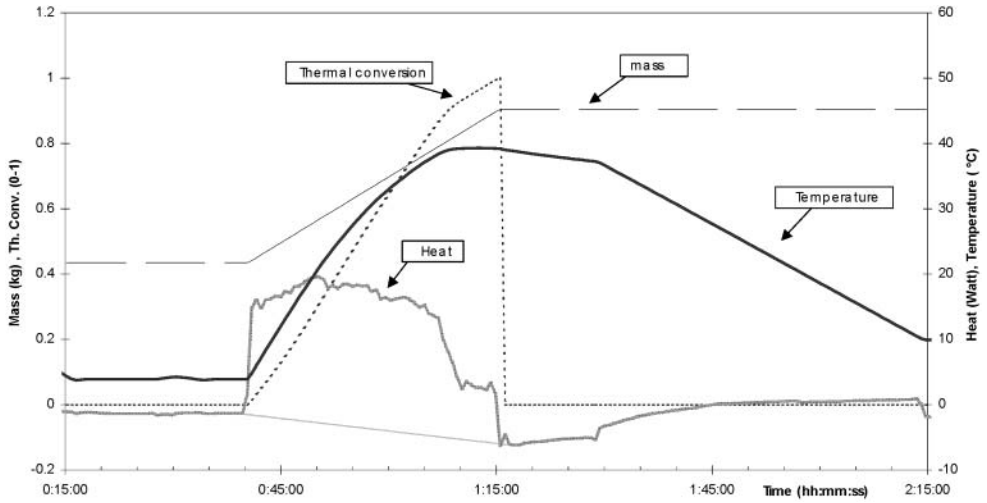


Figure 1. **Dilution: 5 L/mol, adiabatic RC1 experiment**

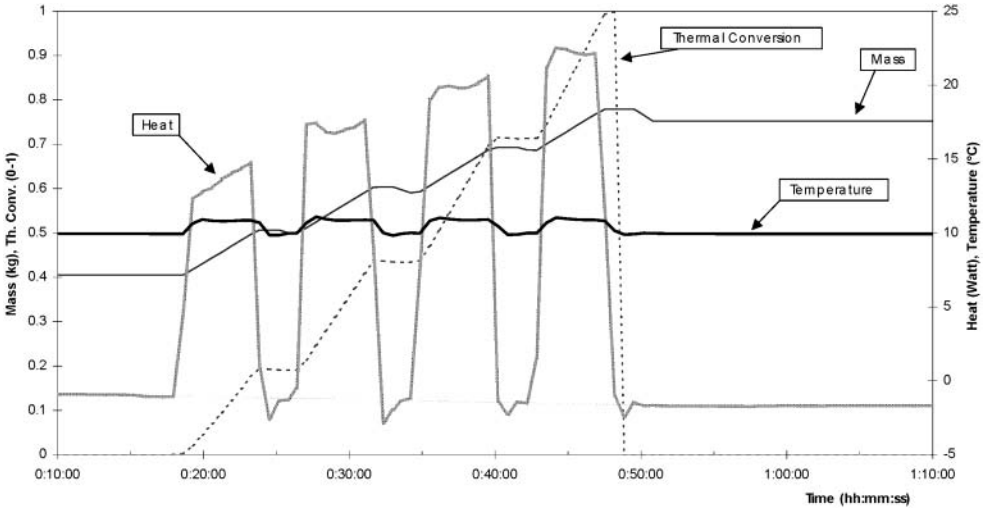


Figure 2. **mCPBA in four portions, isothermal RC1 experiment**

duced in the next step without further purification. By doing so, we avoided the isolation of the nitrone which, in its pure form, was not stable. Moreover, combining steps is time- and labour-saving and therefore economically attractive.

The next project objective was to demonstrate the safety and scalability of this methodology.

Safety Experiments. Two experiments were carried out using a Mettler RC1 reaction calorimeter to determine heat evolution.

RC1 Calorimetric Experiments. The reaction was performed at 0 °C. In adiabatic conditions, the reaction temperature rose by 42 °C at a concentration of 5 L/mol amine **2** and by 24 °C for a more dilute (10 L/mol) solution of amine **2**. Therefore, to avoid exceeding the boiling point of CH_2Cl_2, the diluted concentration was preferred for upscaling (Figure 1).

From the calorimetric experiments we also concluded that the reaction was dose-controlled: when the addition of the mCPBA solution was interrupted, the reaction heat immediately dropped to the baseline, proving there was no accumulation (Figure 2).

These results showed us that this oxidation was a safe and dose-controlled reaction.

Scalability. The oxidation procedure and ratio of reagents, as described in the Experimental Section (experiment C), was successfully scaled up to a 60 M batch in the pilot plant.

The quality and yield of the nitrone **4** from the 60 M batch were comparable with those from the lab-scale results.

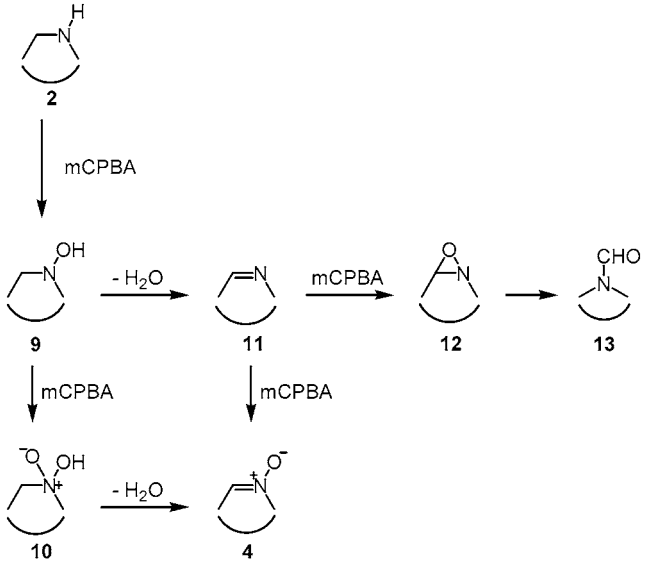
No problems were encountered regarding processability or safety.

It was clear that, in this case, the mCPBA oxidation showed a number of advantages compared to those of the Davis oxidation. The high yield and easy workup and safeness of the procedure made this an excellent alternative for the Davis oxidation.

Reaction Mechanism. The mechanism is thought to proceed in at least two stages via the hydroxylamine intermediate **9** (Scheme 5).

Oxidation may proceed via the hydroxylamine *N*-oxide **10** that dehydrates to the nitrone **4**. Alternatively, dehydration of the hydroxylamine **9** leads to the imine **11** which can be oxidized either to nitrone **4** or to oxaziridine **12** that rearranges into the *N*-formyl compound **13**. The formation of imine **11** as an intermediate was, however, excluded; a separate experiment starting from imine **11** supported this

Scheme 5. **Proposed reaction mechanism**



rationale because compound **13** was isolated and identified[11] as the main product, whereas no nitrone **4** was detected.

Conclusions

The laborious and potentially unsafe Davis oxidation was replaced by a safe, reproducible, and scalable oxidation using mCPBA. The adequate process design allowed us to immediately further process the nitrone in the subsequent reaction step without isolation. The applicability of the concept on a large scale was proven in an 800-L reactor (60 mol of starting material).

Experimental Section

The oxidation was carried out under an inert atmosphere of nitrogen. All solvents and reagents used in this process are commercially available. The structure of the nitrone has been confirmed by proton NMR using a Bruker AM-360 spectrometer with TMS as an internal standard.

HPLC analysis was performed on a HP 1090 instrument using a Hypersil BDS-C18 column, 3 μm particle size (4.0 mm $\times$ 100 mm), and UV detection at 220 nm.

Mobile phase was 10 mM tetrabutylammonium hydrogen sulfate in water/acetonitrile/tetrahydrofuran 85:10:5 (v/v). Flow rate was 1.5 mL/min.

Oxidation of Amine 2 to Nitrone 4. (A) Using Isolated Davis Reagent. To a stirred and cooled solution (ice bath) of amine **2** (19.8 g, 0.102 mol) in 350 mL of CH_2Cl_2 was added oxaziridine **3** (53.5 g, 0.204 mol) portion-wise over 30 min, while maintaining the temperature at $\pm$10 °C. The mixture was stirred for another 2 h at room temperature and evaporated to dryness. Nitrone **4** and sulfonylimine **8** were separated by column chromatography over silica gel (eluent = CH_2Cl_2/CH_3OH 98/2). The pure fractions were collected and evaporated. The residue (17.6 g) was used without further purification (yield 82.5%). ^{1}H NMR (CD Cl_3) δ 3.87 (s, 2H), 7.26−7.46 (m, 7H), 8.11 (dd, 1H, J_1 = 8.1 Hz, J_2 = 1.5 Hz), 8.61 (s, 1H).

(B) In Situ Davis Reagent with Catalytic Amount of Sulfonylimine 8. Benzyltriethylammonium chloride (5.38 g, 0.0236 mol) was added to a stirred solution of *N*-benzylidenebenzene sulfonamide **8** (0.125 g, 0.0005 mol) and amine **2** (1.95 g, 0.01 mol) in 50 mL of CH_2Cl_2. A solution of $NaHCO_3$ (4.87 g, 0.058 mol) in 50 mL of water was added. To this vigourously stirred two-phase system was added a solution of mCPBA (5.7 g, 0.023 mol; containing 24 wt % water and 7 wt % 3-Cl-benzoic acid in 50 mL of CH_2Cl_2) dropwise over a 15 min period at 0−10 °C. The mixture was stirred for another 15 min at 0−10 °C and for 6 h at room temperature. The organic layer was washed with an aquous 10% sodium carbonate solution and evaporated to dryness. The oily residue (2.6 g, yield 124%) contained 60% of the desired nitrone **4** by HPLC (wt/wt %) analysis (retention time 3.88).

(C) Direct mCPBA Oxidation. Amine **2** (68.3 g, 0.35 mol) was dissolved in 1750 mL of CH_2Cl_2 and cooled to 5 °C (ice bath) → solution A.

mCPBA (175.1 g, 0.7 mol; containing 24 wt % water and 7 wt % 3-Cl-benzoic acid) was dissolved in 1750 mL of CH_2Cl_2 and cooled to 5 °C (ice bath) → solution B.

Solution B was added dropwise to solution A over a period of 45 min at 5−10 °C

Note: water from mCPBA (upper layer solution B) was not added.

The mixture was stirred for another 30 min at 10−15 °C.

A sample was taken for in-process control by HPLC analysis. The oxidation was considered complete when the amine **2** content was less than 6%. The reaction mixture was washed with 750 mL of a 10% Na_2CO_3 solution. The layers were separated, and the organic phase was vigourously stirred with 280 mL of 10% aqueous Na_2SO_3 solution for 1 h.

Note: a sample of the organic layer was tested for peroxide content that should be lower than 50 ppm. If not, the Na_2SO_3 treatment had to be repeated.

The organic layer was evaporated to half its volume, and 1050 mL of toluene was added. This mixture was heated to 80 °C, while distilling off the remaining CH_2Cl_2. The mixture was kept at 80 °C until the reflux stopped. The resulting toluene solution (HPLC 95.5%) was processed in the cycloaddition step without purification.

Note: during workup (solvent exchange from CH_2Cl_2 to toluene at 80 °C as described above) we observed no thermal decomposition of nitrone **4** as a solution in toluene, in contrast with the instability of the isolated nitrone **4**.

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