The Syntheses of Pharmaceutical Intermediates in Supercritical Fluids

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Reactions such as ammonolyses of esters to amides and of mesylates to amines, asymmetric hydrogenations, and the condensation of trimethylhydroquinone with isophytol to D,L-α-tocopherol in supercritical fluids are reported. Ammonolysis of a mesylate with anhydrous supercritical ammonia can lead to the corresponding amine in high yield (up to 96%), representing an interesting alternative to the normally practiced azide substitution/hydrogenation sequence to introduce an amino function. The synthesis of D,L-α-tocopherol in supercritical carbon dioxide or nitrous oxide by condensation of trimethylhydroquinone with isophytol in the presence of various Brönsted or Lewis acids, especially an imide or its metal salts, as catalysts is an interesting alternative to existing processes.

Introduction

Over the past few years, the investigation of reactions in supercritical fluids (SCFs) has become an important research area for modern synthetic chemistry, including studies of enzymatic reactions, stereoselective syntheses, polymer processing, and hydrothermal waste processing.[1−4] The goal of developing economically as well as environmentally more acceptable chemical processes (achieving the targets and desired results, possibly with "green" chemistry, e.g., replacements of chlorinated solvents) is the driving force for these investigations. As is well-known, supercritical carbon dioxide ($scCO_2$) as a solvent offers many potential advantages over conventional organic solvents, including increased reaction rate, higher selectivity, and facile separation of reactants, catalysts, and products. In addition, carbon dioxide is nontoxic, nonflammable, inexpensive, and readily available in large quantities, and it has a low critical temperature and a moderate critical pressure. With such properties, $scCO_2$ has the potential to replace harmful or regulated organic solvents in industrial syntheses. Reactions in supercritical fluids, especially in $scCO_2$, have recently been reviewed.[5,6] Examples of the application of SCFs in the pharmaceutical industry can be also found, e.g., for controlling particle size.[7,8] However, reports of ammonolyses in $scNH_3$ where NH_3 is not only the reactant but also the solvent are rare for organic syntheses. In this paper, ammonolyses and some other reactions in SCFs carried out in our laboratory for syntheses of pharmaceutical and fine chemical intermediates are reported.

Experimental Section

The detailed experimental procedures were described in our previous publications.[9,10] In general, reactants as well as catalyst (also cosolvent if needed) are charged in an autoclave equipped with a magnetic stirrer, and the autoclave is evacuated and flushed with argon (if necessary, all preparation work is performed in a glovebox, e.g., for hydrogenation). The autoclave is cooled in a dry ice/ethanol bath, and the CF is added (the amount of material is controlled by weighing the autoclave before and after the charging). The autoclave is heated with an oil bath to the desired temperature. After the reaction, the autoclave is cooled in water to room temperature, and the SCF is evaporated. The residue is dissolved in solvent and transferred into a glass flask. After evaporation in vacuo the remaining product is analyzed by GC, ISTD HPLC. Alternatively, the yield is calculated on the basis of the isolated crystals.

Ammonolyses of Esters and Mesylates in Supercritical Ammonia

The well-known hazards of azide reagents and their derivatives, which are associated with their toxicity and explosivity and which require dedicated equipment and precautions for the safe handling of these compounds on an industrial scale, prompted us to investigate azide-free alternatives for the synthesis of amines, especially for larger-scale syntheses. As a short and practical solution, the direct replacement of mesylates by ammonia to give amines and the ammonolysis of esters to amides were investigated.

Generally, most ammonolyses of organic esters, mesylates, or other sulfonates are either carried out in aqueous ammonia solution[11] or in organic solvents saturated with NH_3.[12] Often, the separation of the product from aqueous solution is cumbersome, whereas in organic solvents, the reaction rate and the yield may be low because of the limited concentration of ammonia. Only a few comparable reactions were carried out in anhydrous liquid ammonia.[13] So far, to our knowledge, an ammonolysis of a mesylate or an organic ester in supercritical NH_3 (T_c = 132.5 °C, P_c = 113.5 bar) has only been reported by us.[9]

The following two ammonolyses of esters to the corresponding amides (see Scheme 1) illustrate our approach. Interestingly, under conventional conditions in organic solvents, no reaction was observed, or the reaction rate was so slow that one could only find traces of the desired product after a long reaction time. In NH_4OH (25%), the reactions ran too slowly and were accompanied by more byproducts than in anhydrous supercritical ammonia. Thus, in these two examples, to obtain access to the respective amides, ammonolyses in $scNH_3$ would be the preferred route.

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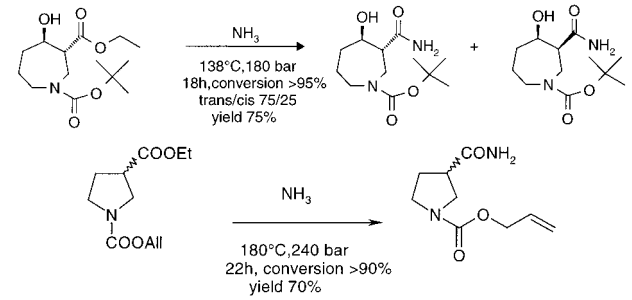
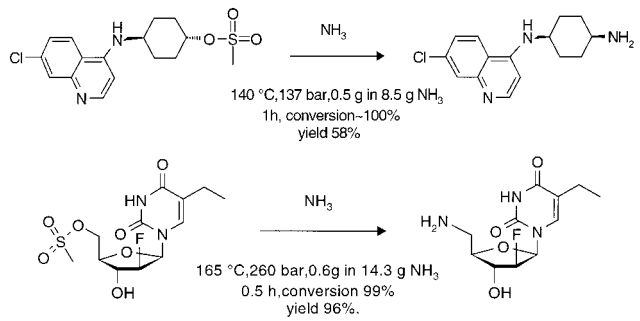
Scheme 1. Ammonolyses of Esters to Amides



Scheme 2. Ammonolyses of Mesylates to Amines



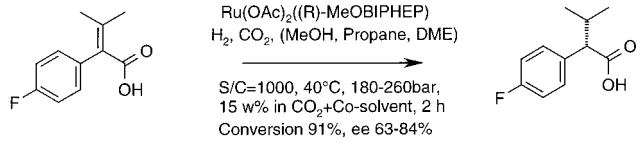
Examples for two ammonolyses of mesylates to the corresponding amines are shown in Scheme 2. The high yield of 96% in the example of the nucleoside mesylate is obtained only under supercritical ammonia conditions; otherwise, more byproducts are observed. Here, the ammonolysis carried out in near- and supercritical ammonia has been shown to be a safe and attractive possibility for the direct introduction of an amino function by substitution of a mesylate, whereby $scNH_3$ is used not only as a reactant but also as a solvent. This may be of importance for the production of the product on a large scale. In this particular case, the use of sodium azide and a subsequent hydrogenation have been eliminated; consequently, the synthesis has been shortened by one step, and the yield increased.

Homogeneous Metal-Complex-Catalyzed, Asymmetric Hydrogenation in $scCO_2$

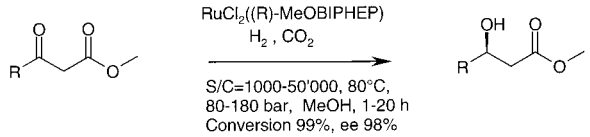
The product (*S*)-2-(4-fluorophenyl)-3-methylbutanoic acid is an important optically active intermediate in the synthesis of a new type of calcium antagonist. In a previous publication, we reported its preparation by an enantioselective, homogeneous, metal-complex-catalyzed hydrogenation under noncritical reaction conditions, where the solvent was MeOH.[14] There, we found that the temperature exhibited a major influence, although the pressure had some effect on the reaction rate and the enantiomeric excess (ee = |%R − %S|), probably because of an increase in the amount of hydrogen dissolved in the MeOH with increasing pressure. We speculated that, if we were to run the reaction in $scCO_2$, the hydrogen partial pressure effect on the ee might become even more significant. It is well-known that the hydrogen amount can be significantly increased when the reaction is carried out in $scCO_2$ because of the indefinite miscibility of the two gases under supercritical conditions.[15] To investigate that possibility, we performed the hydrogenation of 2-(4-fluorophenyl)-3-methylbut-2-enoic acid in $scCO_2$ (Scheme 3).

Indeed, the results demonstrate a pressure effect. The ee is improved from 63% to 84% when the hydrogen

Scheme 3. Hydrogenation of 2-(4-Fluorophenyl)-3-methylbut-2-enoic Acid



Scheme 4. Asymmetric Hydrogenation of a *β*-Keto Ester



pressure is increased from 180 to 260 bar in $scCO_2$ with some MeOH as cosolvent. Propane or dimethyl ether as cosolvents (5−30 wt % in $scCO_2$) did not show any advantage. An explanation for the increase in enantioselectivity with increasing pressure is difficult. It might be that an equilibrium between the two enantiomers exists and that increasing the pressure favors one (in our case, the desired) enantiomer. In comparison with the hydrogenation in methanol (99% yield; 93% ee) the results were, however, disappointing. The drawback of the hydrogenation in $scCO_2$ may be the comparatively lower solubility of the catalyst and the reactant in the "solvent".

The second example of an asymmetric hydrogenation in $scCO_2$ is the synthesis of a *β*-hydroxyester, an intermediate for Xenical (Scheme 4). In comparison to the first example, the reactant is a liquid when the temperature is higher than that of the critical temperature of CO_2. We have found that this property of the substrate improves the mixing performance of the substrate and $scCO_2$ and, hence, the results. Figure 1 shows the results for the hydrogenation of the precursor *β*-keto ester. One can see that, with increasing hydrogen partial pressure in the system, the reaction rate and the ee increase. Without CO_2 but otherwise with the same reaction conditions, the reaction is very slow and the ee is much lower. Most likely, the mass transfer of hydrogen into the liquid reactant or the reaction phase area between hydrogen and the reactant limits the performance of the process. Detailed results of this investigation will be reported elsewhere.

Synthesis of D,L-α-Tocopherol in $scCO_2$ and scN_2O

Vitamin E (D,L-α-tocopherol), an essential food ingredient, is of great importance because of its biological activity and antioxidant properties. Industrial syntheses of D,L-α-tocopherol are based on the condensation of 2,3,6-trimethylhydroquinone (TMHQ) with phytol or phytyl halides, or preferentially with isophytol (IP), whereby Lewis and Brönsted acids, especially zinc chloride with a mineral acid, serve as catalysts.[16] Corrosion caused by the acidic media, contamination of the wastewater with acids and metal ions (e.g., Zn), and then the difficult purification of D,L-α-tocopherol under high vacuum and at ca. 200 °C by distillation are the main problems. The use of supercritical gases as solvents in the condensation and then also for the purification is therefore becoming attractive.[17,18] Scheme 5

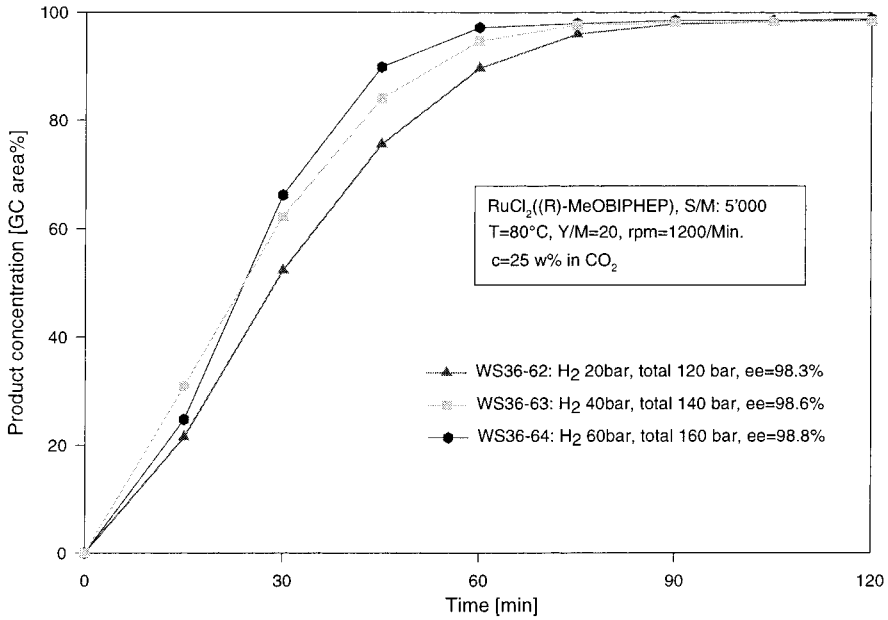
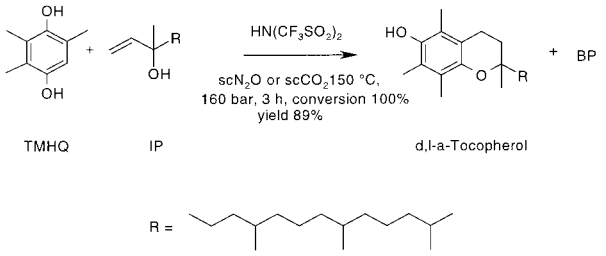
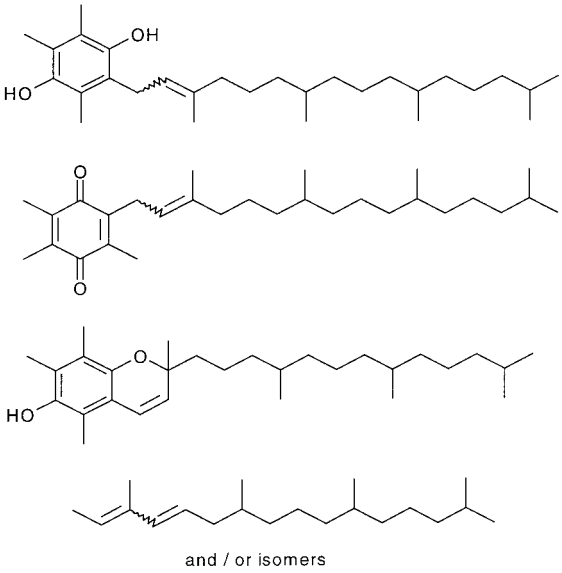


Figure 1. Influence of hydrogen partial pressure on the reaction rate and ee.

Scheme 5. Condensation of TMHQ with IP in SCF



Scheme 6. Observed Intermediate and Byproducts during the Condensation of TMHQ



shows the condensation reaction carried out in our lab and the results.[19]

Some of the observed intermediates and byproducts (BPs), which are also known from the literature, are listed in Scheme 6.[20−22]

Here, various Lewis and Brönsted acids as catalysts were tested for the condensation of TMHQ with IP in supercritical N_2O or CO_2. The best catalyst found was the imide $HN(CF_3SO_2)_2$ or its silver salt. Generally, the yield of D,L-α-tocopherol in scN_2O was as good as the yield in $scCO_2$. Both supercritical fluids are excellent as solvents for the condensation of TMHQ with IP. The addition of cosolvents, e.g., propane, ethanol, or acetone, had no significant effect on the condensation. Details of the kinetic investigation are reported elsewhere.[10]

Conclusions

In SCFs, the temperature and pressure effects on a reaction can be optimally utilized, e.g., enhancing the reaction rate by increasing the temperature and influencing the results of competitive reactions by changing the reactant partial pressure. In contrast, the upper temperature limit and the highest concentration for reactions in organic solvents are given by the boiling point and by the amount of dissolved reactants in the solvents. The ammonolyses of the two esters reported here demonstrate the temperature effect, whereas the homogeneous hydrogenation in $scCO_2$ exemplifies the partial pressure influence on the reaction rate and ee.

Furthermore, the influence of temperature and pressure on the properties of SCFs, such as solubility, viscosity, miscibility, mass-transfer capability, improved diffusion or dispersion coefficient (without surface tension), etc., is shown by the ammonolyses of the mesylates. The beneficial influence on the chemical reaction equilibrium in favor of the desired product is a consequence of the insolubility of the formed products in $scNH_3$.

The use of nonpolar $scCO_2$ (if necessary, with some cosolvents) as an inert "green" solvent, especially for nonpolar substrates, is demonstrated in the synthesis of D,L-α-tocopherol. It may, however, not always be the best solvent, e.g., for polar substrates and catalysts such as that used in the first example of the homogeneous hydrogenation reported here. Nevertheless, one can use advantageously the physical properties of a substrate under supercritical conditions (the substrate is a liquid, so it mixes with $scCO_2$ perfectly), so that the reaction results can be improved, as in the second example of hydrogenation demonstrated here.

Polar $scNH_3$ as a solvent and/or reactant may have important advantages such as those demonstrated in

this paper. It may eliminate the conventional negative solvent effect and increase the reaction rate as well as selectivity; it may also influence the chemical reaction equilibrium and favor product formation. Additional advantages of $scNH_3$ are its stability at higher temperatures, its ease of separation from the product by mere expansion, and, of course, its low costs. The moderately high pressure necessary for supercritical conditions and the unpleasant smell of NH_3 are easily handled on a technical scale. This opens up new possibilities in preparative chemistry, especially for application on a large scale.

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