

Chiral resolution with supercritical carbon dioxide based on diastereomer salt formation

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The efficient, environmentally benign synthesis of chiral compounds is a key issue in the chemical industry, especially in the pharmaceutical, food or pesticide sectors. Reducing or eliminating the use of organic solvents and simplifying downstream processing can significantly alleviate the environmental impact of chemical technologies. Supercritical carbon dioxide (scCO₂), used as a solvent or reaction medium, addresses both issues.

In our work, we have investigated the resolutions of three racemic compounds: ibuprofen (IBU), *cis*-permethric acid (cPA) and *cis*-chrysanthemic acid (cCA). The former is a widely marketed analgesic and anti-inflammatory agent, the latter two are important precursors in the manufacturing of synthetic pyrethroid-type pesticides. As resolving agents, we have used (*R*)-1-phenylethanamine (PhEA) and (*S*)-2-(*N*-benzylamino)butan-1-ol (BAB). The resolving agents were typically added in half-mole equivalent quantity (according to the Pope–Peachy method), resulting in partial diastereomer salt formation. This was followed by supercritical fluid extraction (SFE) to separate the unreacted enantiomers from the diastereomeric salts.

We have used two experimental approaches, improving on our earlier where the diastereomers were prepared by vacuum evaporation of organic solvent from a solution of the starting materials. The *in situ* method eliminates the use of organic solvents entirely, the starting materials are loaded into a high-pressure reactor and reacted in scCO₂ directly. The antisolvent approach, involves preparing a concentrated solution of the starting materials in an organic solvent, and contacting it with scCO₂, causing the precipitation of the diastereomeric salts. Although the use of organic solvents is reduced, the main advantage of this method is a significant decrease in reaction times.

The *in situ* method was successfully applied to all three racemic compounds at 100–200 bar and 35–55 °C. IBU with PhEA, yielded diastereomers with ~60% enantiomeric excess (ee), albeit with 100–120 h reaction time. cPA and cCA were resolved using BAB, yielding diastereomer salts of >70% ee in <5 h reaction time. Antisolvent resolution was successfully applied to cPA and IBU with PhEA, yielding diastereomers of >90% and >70% ee, respectively in <3 h reaction time.

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