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Scalable and Cost-Effective Synthetic Process for the Preparation of L-3,4-Dihydroxyphenylalanine–Levodopa
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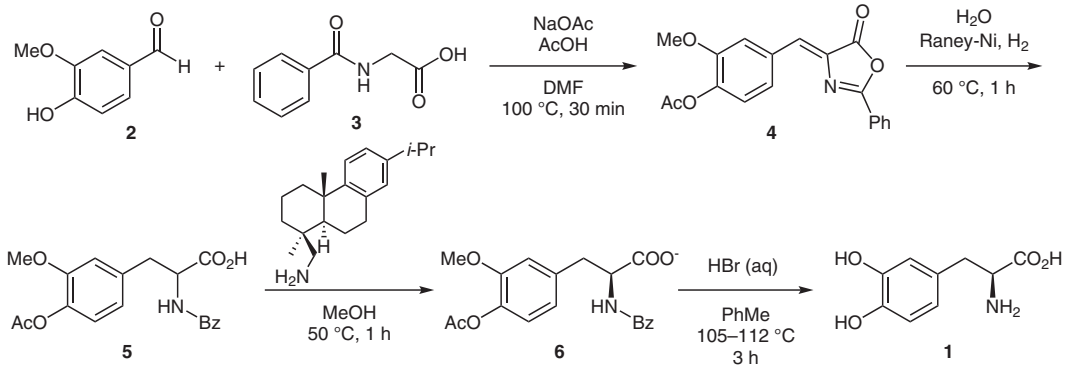
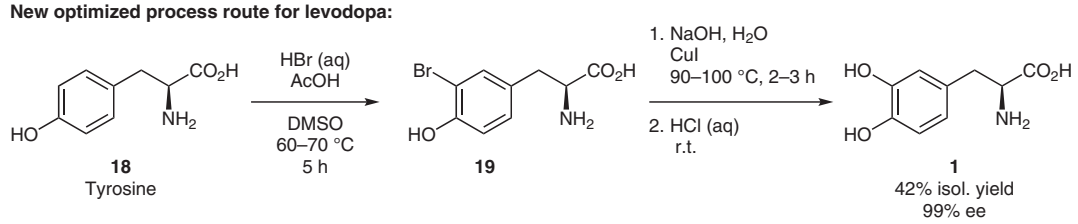
Novel Synthesis of Levadopa Improves Efficiency and Eliminates Use of Pyrophoric Raney Nickel

Hoffmann-La Roche synthesis of levodopa:



New optimized process route for levodopa:



Significance: L-3,4-Dihydroxyphenylalanine, or levodopa, is a key active pharmaceutical ingredient (API) used to reduce motor impairments caused by Parkinson's disease. Hoffman-La Roche previously developed a synthesis of levodopa. However, the process involves several steps. Notably, the route uses the pyrophoric reagent Raney nickel, which is responsible for several serious industrial accidents. Other methods to access levodopa include one developed by Monsanto which uses an expensive rhodium-DiPAMP catalyst, and a process reported by Li et al. which employs toxic sodium cyanide. The authors of this paper report an alternative, commercially scalable synthetic route which aims to eliminate the use of toxic and hazardous reagents while increasing efficiency and reducing cost. The optimized process route takes place in two steps, starting from L-Tyrosine. Bromination using hydrobromic acid is followed by a copper(I)-catalyzed hydroxylation to yield levodopa with 42% isolated yield and 99% ee.

Comment: Differential scanning calorimetry (DSC) was conducted to assess the hazard of employing DMSO in the bromination, which is known to exothermically decompose especially in the presence of halides and acid. The DSC scan indicated only minor exothermic activity, which was likely dampened by the thermal mass of the water and acetic acid in the batch. The authors utilize design of experiments (DoE) to assess which factors impact the yield and purity of the synthesis. The authors used a two-stage optimization approach to test five process parameters in 46 trials for each reaction step. For the bromination, reaction time, temperature, HBr equivalents, DMSO volume, and acetic acid volume were studied. For the hydroxylation, reaction time, temperature, base equivalents, CuI equivalents, and water volume were studied. Optimal synthesis conditions for both reactions were identified via analysis of these results.

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Key words
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ANOVA

Synfact of the Month