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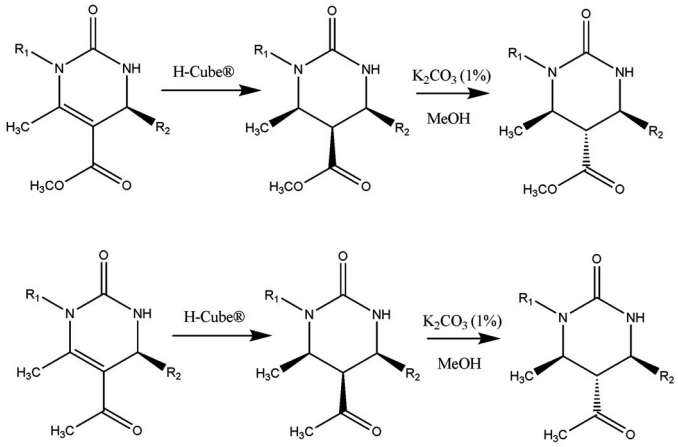
Diastereoselective Hydrogenation of Dihydropyrimidones using H-Cube®

The following application note will give details on how the H-Cube® was used in the reduction of dihydropyrimidones to the corresponding tetrahydropyrimidones in high diastereoselectivity. Reactions were performed at Boston University.

INTRODUCTION



Scheme 1. Hydrogenation of Dihydropyrimidones with H-Cube®

Originally, the above reaction was tried using standard batch hydrogenation equipment, but resulted in multiple hydrogenation products with little or no chemoselectivity or stereoselectivity. The reaction was then performed on the H-Cube® to see if results could be improved. In order to find the optimal reaction conditions a series of catalysts were tested: Pd/C, Pt/Al_2O_3, Pt/C and Raney Ni were tested over a series of temperatures and pressures. The initial results indicated that Raney-Ni provided the best conversions with fewer side reactions. Further optimization of reaction pressure, temperature and solvent gave 90 bar and 45°C as the optimal reaction conditions.

RESULTS AND DISCUSSION

As seen in Scheme 1., the hydrogenation of dihydropyrimidone resulted in the syn addition of the dihydrogen from the opposite face of the R_2 substituent. From LC-MS with ELSD (Evaporative Light Scattering Detector) results the diasteroselectivity was found to be greater than 20:1. The epimerization of the compounds resulted in the thermodynamically more stable isomer via treatment in MeOH with catalytic amount of K_2CO_3. Yields after the two steps were between 76 and 91% for all compounds.

CONCLUSION

These experiments demonstrate the ability of H-Cube® to improve upon standard batch reactors significantly in terms of stereoselective control and yield.

REFERENCE

Lou, S., Dai, P., Schaus, S.E., J. Org. Chem, 2007, 72, 9998-10008

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