Improvement of Synthesis Process of the Intermediate of Gemifloxacin

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A novel synthetic route of AMPM (4-amino methyl-3-Z-methoxyimino pyrrolidine methane sulfonate) that is employed as an intermediate in the synthesis of gemifloxacin (Factive), a novel quinolone antibacterial developed by LG Life Science Co. and approved by the US FDA, is reduced from 5 steps to 2 steps. First step is preparation CMBP (4-cyano-3-methoxyimino-1-(N-t-butoxycarbonyl)-pyrrolidne) from BCPO (1-(N-t-butoxycarbonyl)-4-cyano-pyrrolidine-3-one). Second step is chemoselective hydrogenation of CMBP and evaporation.

We performed the experiment to improve yield. We improved the yield and reaction rate by purifying CMBP with Column Chromatography and E-Z isomerization of AMPM filterate by heating. The highest yield was obtained using 1.8eq MSA and 1% Pd/C catalyst on hydrogenation, without layer separation after hydrogenation and at the evaporation temperature of 40℃. With the reduced catalyst, hydrogenation rate and yield are decreased.

The maximum Z-AMPM yield was 56.4% and total yield (containing E-AMPM) is 61.6%.

Through this study, we effectively improved new AMPM process.