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[Lab. of Pharm. Chemistry]

Synthesis and Muscarinic Activity of Novel Aniline Derivatives with a 1-Azabicyclo[3.3.0]octane Moiety.

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In order to develop drugs effective against Alzheimer's disease, we synthesized a series of aniline derivatives having a characteristic cyclic amine, 1-azabicyclo[3.3.0]octane ring, and evaluated their binding affinity for the central muscarinic cholinergic receptor. Among these compounds which showed high affinity to the M₁ receptor, *N*-[2-(1-azabicyclo[3.3.0] octan-5-yl) ethyl]-2-nitroaniline (fumarate, SK-946) showed the highest affinity. The ability of this compound to improve cognitive function was assessed using the passive avoidance test in scopolamine-induced dementia mice.

Some anilines with a 1-azabicyclo[3.3.1]nonane ring were also synthesized by the ring expansion of the 1-azabicyclo[3.3.0]octane ring, and showed a high affinity for the central muscarinic cholinergic receptor.

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A New Entry to Enantioselective Synthesis of α -Methylene- β -hydroxy Ketones by the Chalcogeno-Baylis-Hillman Reaction.

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Chiral hydroxy chalcogenides in the presence of TiCl₄ achieved the asymmetric version of the chalcogeno-Baylis-Hillman reaction. The reaction proceeded under atmospheric pressure for 1h. 10-Methylthioisoborneol achieved the best enantioselectivity. A methoxy derivative of 10-methylthioisoborneol resulted in lower selectivity than that obtained by 10-methylthioisoborneol. A hydroxyl group is required to perform good asymmetric induction. The asymmetric chalcogeno-Baylis-Hillman reaction with a C₂ symmetric bidentate ligand-TiCl₄ complex was also examined. Diol ligands gave the adduct in low to good yields with low or no enantiomeric excess. The adduct was also obtained in low to high yields with low or no enantiomeric excess using bisoxazoline ligands.

[Synlett., 197-198 (1999)]

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The Chalcogeno-Baylis-Hillman Reaction of α,β -Unsaturated Thioester: A New Approach to α -Methylene- β -hydroxy Carboxylic Acid Derivatives.

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Reactions of aldehydes and an α,β -unsaturated thioester with a catalytic amount of Me₂S in the presence of TiCl₄ followed by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene gave α -methylene- β -hydroxy thioesters in good yields. Treatment of the crude product with Ti(O-*i*-Pr)₄ caused transesterification besides dehydrochlorination to give isopropyl acrylates. 1,4-Diazabicyclo[2.2.2]octane and tri-*n*-butylphosphine were ineffective for the Baylis-Hillman reaction of a thioacrylate.

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[Lab. of Pharm. Chemistry]

The Enantioselective Chalcogeno-Baylis-Hillman Reaction Using a Chiral Hydroxy Chalcogenide-TiCl₄ Complex.

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The enantioselective chalcogeno-Baylis-Hillman reaction was investigated by the use of chiral hydroxy chalcogenides in the presence of TiCl₄ under atmospheric pressure. Conformationally flexible sulfides decreased the enantiomeric excess and the reduced Lewis acidity of TiCl₄ by formation of a titanium alkoxide with a hydroxy chalcogenide decreased the chemical yields of adducts. However, a hydroxy group is necessary to induce the high enantioselectivity. The best result was obtained with 10-methylthioisoborneol as a chiral hydroxy chalcogenide.