

[Tetrahedron, 56, 8433-8441 (2000)]

[Lab. of Medicinal Chemistry]

Pd/C(en)-catalyzed Chemoselective Hydrogenation with Retention of the *N*-Cbz Protective Group and Its Scope and Limitations.

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A chemoselective method for the hydrogenation of acetylene, olefin, azide, nitro and benzyl ester functionalities with retention of the aliphatic *N*-Cbz group was established. The chemoselectivity was accomplished by using a combination of 5% Pd/C-ethylenediamine [5% Pd/C(en)] and THF (or 1,4-dioxane) as a solvent, and the scope and limitations of this methodology were investigated. Moreover, this method would increase the utility of the *N*-Cbz protective groups in organic synthesis including liquid and solid-phase peptide synthesis.

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[Lab. of Medicinal Chemistry]

Synthesis and Applications of [1-¹⁵N]-Labeled 4,6-Dimethyl-4*H*-[1,2,5]oxadiazolo[3,4-*d*]-pyrimidine-5,7-dione 1-Oxide as a Useful Tool for Mechanistic Investigations.

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[1-¹⁵N]-Labeled 4,6-dimethyl-4*H*-[1,2,5]oxadiazolo[3,4-*d*]pyrimidine-5,7-dione 1-oxide (1-¹⁵N₁) was easily prepared by nitration of commercially available 6-amino-1,3-dimethyl-1*H*-pyrimidine-2,4-dione using ¹⁵N-enriched nitric acid followed by an intramolecular oxidative cyclization with iodobenzene diacetate under mild conditions. On the basis of the experimental results using the labeled N-oxide 1-¹⁵N₁, the formation of 8-phenyltheophylline, 1,3-dimethylalloxazines, and 1,3,7,9-tetramethyl-1*H*,9*H*-pyrimido[5,4-*g*]pteridine-2,4,6,8-tetraone in the thermal reaction of the N-oxide 1 with benzylamine, aniline, or piperidine, and the generation of nitric oxide (NO) or NO-related species in the reaction with N-acetylcysteamine were reasonably explained by considering the initial attack of the employed nucleophiles on the 3*a*-position of 1.

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[Lab. of Medicinal Chemistry]

Reversal of P-Glycoprotein and Multidrug-Resistance Protein-Mediated Drug Resistance in KB Cells by 5-O-Benzoylated Taxinine K.

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5-O-Benzoylated taxinine K (BTK), a newly synthesized taxoid originally from the Japanese yew *Taxus cuspidata*, was examined for its ability to reverse P-glycoprotein (P-gp) and multidrug resistance protein (MRP)-mediated multidrug resistance. BTK reversed the resistance to paclitaxel, doxorubicin (ADM), and vincristine (VCR) of KB-8-5 and KB-C2 cells that overexpress P-gp by directly interacting with P-gp. BTK also moderately reversed the resistance to ADM of KB/MRP cells that overexpress MRP. However, BTK neither inhibited the transporting activity of MRP nor reduced intracellular glutathione levels in KB/MRP cells. BTK shifted the distribution of ADM in KB/MRP cells from punctate cytoplasmic compartments to the nucleoplasm and cytoplasm by inhibiting acidification of cytoplasmic organelles. These two functions of BTK make it able to reverse both P-gp- and MRP-mediated MDR. BTK in combination with ADM should be useful for treating patients with tumors that overexpress both P-gp and MRP.

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[Lab. of Pharm. Synthetic Chemistry]

Asymmetric Synthesis of (+)-Dihydrokawain-5-ol.

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(+)-Dihydrokawain-5-ol was synthesized starting from the major product obtained by a highly diastereoselective Mukaiyama aldol condensation of 3-(*p*-tolylsulfanyl)furaldehyde with a silyl ketene acetal.