DIRECT PHENYLATION OF ISOXAZOLE RING USING PALLADIUM CATALYSTS: SYNTHESIS OF 4-PHENYLMUSCIMOL

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Muscimol (3-hydroxy-5-aminomethylisoxazole), a potent GABA agonist isolated from Amanitae fungi, was conveniently prepared by modifying 3-hydroxy-5-methylisoxazole, an agricultural chemical. To synthesize more lipophilic 4-phenylmuscimol, direct phenylation of 3-hydroxy-5-methylisoxazole was investigated.

Oxidative coupling of 3-(p-toluenesulfonyloxy)-5-methylisoxazole with benzene in dimethylsulfoxide, in the presence of palladium acetate, cupric acetate and oxygen, afforded 3-(p-toluenesulfonyloxy)-4-phenyl-5-methylisoxazole. The same compound was prepared in a larger scale, using iodobenzene-palladium acetate-hexamethylphosphortriamide as the phenylating system. Palladium on charcoal was also available as the catalyst. Other isoxazoles, e. g. 3-(2-tetrahydropyranyloxy)-methyl-5-(p-chlorophenyl)isoxazole, were phenylated similarly.

Finally, 3-hydroxy-4-phenyl-5-methylisoxazole thus obtained was converted to 4-phenylmuscimol, which showed noGABA agonist activities.