The Reaction of 3,5-Dimethylisoxazole with Electrophiles

Choji Kashima*, Yoshihiko Tsuda**, Yasuhiro Yamamoto**,
and Yoshimori Omote*

* Department of Chemistry, Tsukuba University,
Sakura-mura, Niihari-gun, Ibaraki, 300-31

** Department of Chemistry, Tokyo Kyoiku University,
Otsuka, Tokyo, 102

It is well known that the methyl group attached on the heterocycles like picoline is activated by bases. 3,5-Dimethylisoxazole (I), which is easily prepared from 2,4-pentanedione and hydroxylamine hydrochloride, has two methyl groups on the isoxazole ring. First, we tried the deuterium exchange reaction of (I) in methanol-d_4 in the presence of sodium methoxide-d_3. By this reaction, the NMR proton signal of C-5 methyl decreased 215 times as fast as C-3 methyl proton signal and 18 times as fast as C-4 proton signal. From this result, C-5 methyl group of (I) is expected to react regiospecifically with some electrophiles in the presence of base.

Thus, (I) was treated with methyl iodide in the presence of sodium amide in liquid ammonia to give 3-methyl-5-ethylisoxazole in good yield. When (I) was treated with 4 molar amounts of methyl iodide and sodium amide, 3-methyl-5-t-butylisoxazole was obtained as a sole product.

By the same way, (I) was treated with another alkyl halides, aldehydes, ketones, carboxylic esters, aldimines, nitriles, nitrites and nitroso compounds to give the corresponding isoxazole derivatives. It was found that (I) did not react with elect electrophiles having the active methylene protons such as ethyl acetate or cyclohexanone in the presence of sodium amide. However, the reaction of (I) with ethyl acetate proceeded in good yield in the presence of lithium amide. When (I) was treated with α,β-unsaturated carbonyl compounds, the corresponding 1,2-, and 1,4-addition products were obtained.

The conversions of these isoxazole derivatives to β-aminoenones, β-diketones, α,β-unsaturated ketones and isoxazolines were also discussed.