Theoretical and multinuclear NMR study of the reaction mechanism of diethyl 2,4,6-trimethyl-1,4-dihydropyridine-3,5-dicarboxylate with N-bromosuccinimide.

The 1,4-dihydropyridine (1,4-DHP) nucleus is the scaffold for important cardiovascular drugs of calcium antagonist class, such as nifedipine, nitrendipine, amlodipine, and nisoldipine [1]. The increasing interest has been devoted to the synthesis of novel 1,4-DHP derivatives owing biological activities which mainly are not related with their calcium L-channel regulating properties. During the last decade new and efficient gene delivery systems based on cationic self-assembling amphiphilic 1,4-dihydropyridine derivatives were investigated and elaborated [2].

Bromination of the methyl groups at positions 2 and 6 of the 1,4-DHP cycle is one of the most important steps in the synthesis of cationic amphiphilic 1,4-DHP derivatives as potential candidates for the development of new gene delivery systems.

In this work the bromination of diethyl 2,4,6-trimethyl-1,4-dihydropyridine-3,5-dicarboxylate with different amounts (from one to six equivalents) of N-bromosuccinimide (NBS) in methanol was studied by multinuclear NMR spectroscopy and quantum chemistry. The study revealed previously unknown intermediates which were possible to register only in the reaction mixture. The experimental findings were confirmed by DFT calculations. The mechanism of the bromination in the 2,6-methyl side chains of 1,4-DHPs was estimated and the structures of the major products and intermediates were confirmed by 1H, 13C, 15N 1D and 2D-NMR experiments.

An increase in the temperature from 25 to 40°C speeds up the reaction rate and does not have an effect on its mechanism.

References

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