SYNTHESIS OF NOVEL DIHYDROPYRIMIDINE DERIVATIVES

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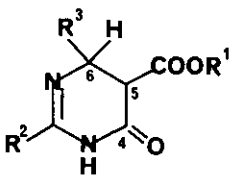
The chemistry of dihydropyrimidine derivatives has not been sufficiently investigated, because of the possibility of ambiguous chemical structures by isomerization or tautomerism and the instability by air oxidation.

Therefore, we have initiated an investigation of the synthesis of dihydropyrimidine derivatives via the cyclization reaction of amidines with α,β-unsaturated carbonyl compounds which do not have a leaving group at the β position. Thus, cyclization of 3-substituted 2-alkoxycarbonyl-2-propenoates or 3-substituted 2-acetyl-2-propenoates with acetamidine, benzamidine, guanidine, or 1,1-dimethylquanidine afforded novel 5,6-dihydropyrimidin-4(3H)-one (1) or 1,4(3,4)-dihydropyrimidine (2). Treatment of (1) with Meerwein reagent or Me_2SO_4-K_2CO_3 gave 4,5-dihydropyrimidine (3) and chlorination of (1) afforded 1,4(3,4)-dihydropyrimidine (4). The chemical structures of (1)-(4) were determined by NMR spectra showing the typical signals. Interestingly, in the crystalline state, the compounds (2) and (4) exist in the 1,4-dihydro form by X-ray crystallographic analysis. In solution, however, the NMR spectra of these compounds are more consistent with a mixture of the 1,4-dihydro and 3,4-dihydro forms.

According to our experiences, no isomerization was observed in these compounds. With some exceptional results, they are fairly stable against air oxidation and sunlight.



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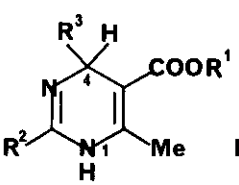

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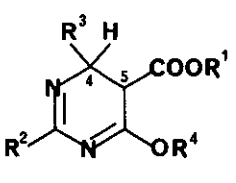

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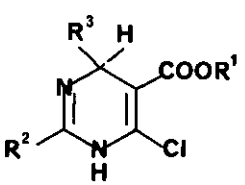

4

R^1= lower alkyl; R^2= Me, C_6H_5, NH_2, NMe_2; R^3= C_6H_5, C_6H_4X, pyridyl, furyl, thienyl, cyclohexyl; R^4= Me, Et; X= NO_2, CN, SMe, S(O)Me, F, Cl, Br, Me, OMe, CF_3.