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A NOVEL RING TRANSFORMATION OF 5-NITROURACILS INTO 5-CARBAMOYLURACILS VIA THE RETRO-MICHAEL REACTION

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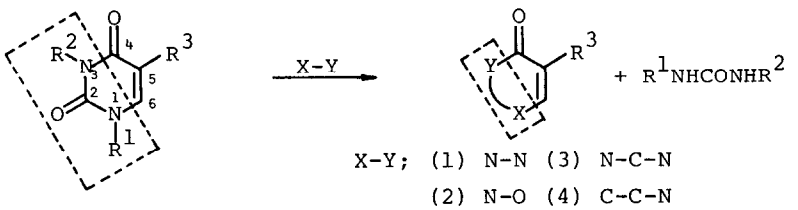
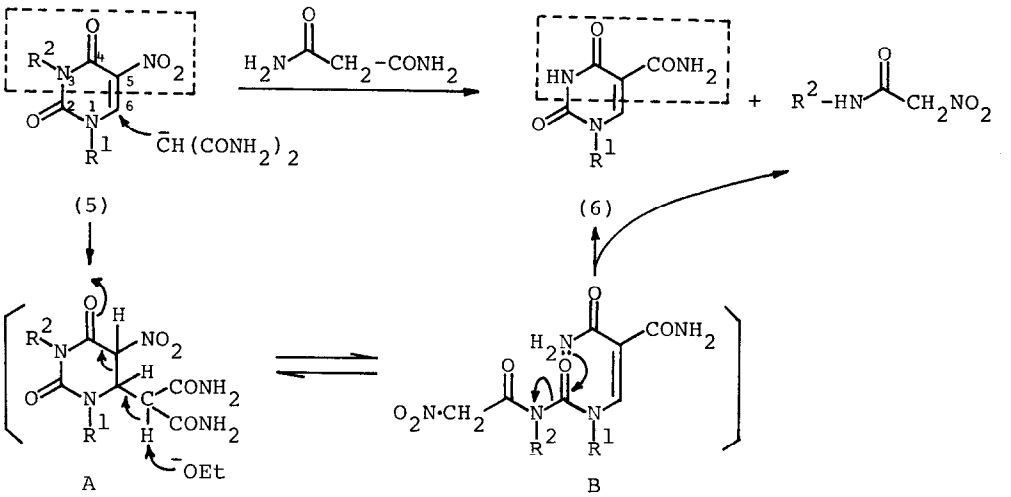
Summary Treatment of 1,3-disubstituted 5-nitrouracils(5) with malonamide in ethanolic sodium ethoxide caused a ring transformation to afford 1-substituted 5-carbamoyluracils(6) in good yields.

Reactions of uracil derivatives with various nucleophiles have been extensively investigated in connection with biosynthesis of thymidilate.[1] Meanwhile, it is well known that uracils are converted into the corresponding pyrazolones(1) and isoxazolones(2) by treatment with hydrazines and hydroxylamines, respectively.[2] Furthermore, reactions of 1,3-disubstituted uracils with 1,3-ambident nucleophiles such as guanidine (N-C-N type) and α-substituted acetamides (C-C-N type) cause a ring transformation to pyrimidines(3)[3] and pyridines(4),[4] respectively, via direct displacement of N_1-C_2-N_3 portion of uracils. We report here a new type of ring transformation of 1,3-disubstituted 5-nitrouracils(5) into 1-substituted 5-carbamoyluracils(6) via the retro-Michael reaction.[5]



Thus, treatment of 1,3-dimethyl-5-nitrouracil(5a; R^1=R^2=CH_3) with malonamide and sodium ethoxide (4eq each) in ethanol at reflux-temperature for 1hr followed by neutralization of the reaction mixture afforded 5-carbamoyl-1-methyluracil (6a; R^1=CH_3, 84%)[6] and N-methylnitroacetamide.[7] The compound(6a) was identical with an authentic sample prepared by hydrolysis of 5-cyano-1-methyluracil[8] with conc. sulfuric acid.

A plausible mechanism is described below. Thus, initial nucleophilic attack of carbanion on C_6 of 5a gives rise to a Michael adduct A. Abstraction of the exocyclic α-proton of A by an ethoxide anion accompanied by scission of the C_5-C_6 bond gives an open-chain intermediate B, which then cyclizes to afford 6a and



N-methylnitroacetamide.

Similar treatment of 1,3-disubstituted 5-nitrouracils(5b; R^1=⟨H⟩, R^2=CH_3) and (5c; R^1=CH_3, R^2=⟨H⟩) with malonamide gave the corresponding 1-substituted 5-carbamoyluracils(6b; R^1=⟨H⟩, 89%) and (6a; R^1=CH_3, 86%). However, the reaction of 5-nitrouracil (5d; R^1=R^2=H) and 1-methyl-5-nitrouracil(5e; R^1=CH_3, R^2=H), which contain dissociable protons, with malonamide did not proceed.

This is the first example of a pyrimidine-to-pyrimidine transformation via direct displacement of N_3-C_4-C_5 portion by 1,3-ambident nucleophile i.e. malonamide which contains an N-C-C fragment.

References and Notes

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