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NUCLEAR TRANSFORMATIONS BY HYDROGENOLYSIS: SYNTHESIS OF PYRIMIDINONES FROM ISOXAZOLES DERIVATIVES

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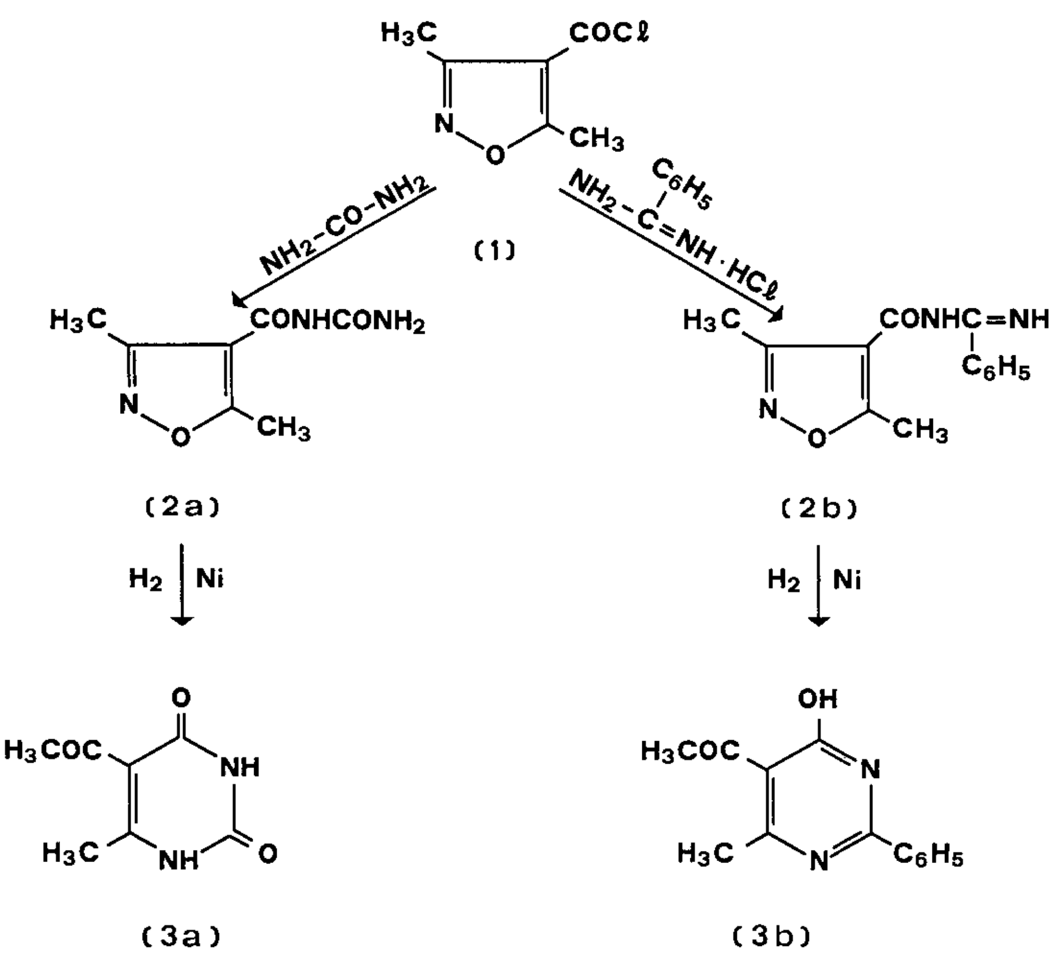
Abstract- Pyrimidinones derivatives are obtained by catalytic hydrogenation of the products resulting from the condensation of 3,5-dimethylisoxazole-4-carboxylic acid chloride with urea (or benzamidine).

The biological interest of compounds (3a,b) is well known and very large is the literature on the argument. Furthermore the compound 3a, synthesized the first time by Lamon[1], is the intermediate to the preparation of drugs[2], whereas compounds similar to 3b are reported as intermediate to amminopyrimidines with a bronchodilatatory activity[3] or as intermediates for the synthesis of agricultural chemicals[4,5].

In our Institute, we already successfully studied the catalytic hydrogenation of isoxazole derivatives, obtaining a large number of heterocycles[6-19].

In the present work, we have obtained 2a, 2b quantitatively by reaction of 1 (Scheme 1) in benzene with urea (or benzamidine). The compound 2a under action of H_2 in presence of Raney nickel brought quantitatively to the known 6-methyl-5-acetyl-2,4(1H,3H)-pyrimidinedione, the structure we confirmed by comparison with the spectral data reported in literature for the same compounds synthesized by different procedure (the mp in mixture with the compound prepared according to Lamon[1] is costant).

In the same experimental condition, product 2b brought quantitatively to 3b,whose structure was confirmed by analytical and spectral data. The ^1H-NMR spectrum of 3b revealed in fact two methyl signal δ 2.30; δ 2.45; δ 7.3-8.2 aromatics and at about δ 12.8 a very broad OH. These data can only be intelligibly interpreted in terms of structure 3b.



SCHEME 1

EXPERIMENTAL

All melting points were determined with a Buchi-Tottoli micro melting point apparatus and are uncorrected. Ir spectra were recorded in nujol mull with a Perkin-Elmer Infrared 137 E spectrometer. Nmr spectra were determined with a Jeol c-60H spectrometer. Chemical shifts are reported relative to internal tetramethylsilane and given in δ value. Splitting patterns are designated as follow: s,singlet;m,multiplet;br,broad;ex,exchangeable. Mass spectra were recorded on a Jeol-JMS-01-SG-2 spectrometer operating with an ionizing electrons beam at 75 eV.

N-(3,5-Dimethyl-4-carboxyisoxazolyl)urea(2a): 1,6 g of 3,5-dimethylisoxazole-4-carboxylic acid chloride and 2,5 g of urea were dissolved in 100 ml of dry benzene. The solution was refluxed for 8 h. After cooling the resulting precipitate was separated by filtration and recrystallized from methanol. mp 209-210°C;yield 70%

Anal. calcd. for $C_7H_9N_3O_3$: C, 45.90; H, 4.95; N, 22.94. Found: C, 46.04; H, 5.03; N,23.26. Ir (cm^{-1}) 3400,3240 (NH_2, NH); 1720,1700 (CO); ms: m/z 183 (M^+).

N-(3,5-Dimethyl-4-carboxyisoxazolyl)benzamidine (2b): 1,6 g of benzamidine hydrochloride in 10 ml of dry ethanol were neutralized with the stoichiometric amount of sodium ethoxide. After filtering the NaCl formed, the solvent was removed under reduced pressure. The residue, dissolved in 50 ml of dry benzene was added of 1.6 g of 3,5-dimethylisoxazole-4-carboxylic acid chloride under magnetical stirring.The resulting precipitate was separated by filtration and recrystallized from ethanol. mp 184°C yield 75%. Anal. Calcd. for $C_{13}H_{13}N_3O_2$: C, 64.18; H, 5.39; N, 17.28. Found: C, 64.39; H, 5.41; N, 17.52. Ir (cm^{-1}) 3300 (NH), 1620-1570 (CO); ms: m/z 243 (M^+).

General procedure for the hydrogenation of (2a) and (2b)

To a solution of (2a) or (2b) (2,5 mmol) in 100 ml of ethanol were added 2 g of W-2 Raney nickel. The resulting mixture was hydrogenate in a Paar apparatus at 45-50 psi at room temperature. After standing overnight the solution was filtered and the solvent removed under reduced pressure. The resulting residue was purified by recrystallization from ethanol.

Hydrogenation of N-(3,5-Dimethyl-4-carboxyisoxazolyl)urea (2a)

6-methyl-5-acetyl-2,4(1H,3H)-pyrimidinedione (3a). A mixture of 460 mg of (2a), 100 ml of ethanol and 2 g of W-2 Raney nickel was hydrogenated at room temperature. After standing overnight, the catalyst was removed and evaporation of ethanol under reduced pressure left white needles with quantitative yield. mp 226-227°C from ethanol. For $C_7H_8N_2O_2$ ms: m/z 152 (M^+).

Hydrogenation of N-(3,5-Dimethyl-4-carboxyisoxazolyl)benzamidine (2b)

6-methyl-2-phenyl-5-acetyl-4-pyrimidinol (3b). A mixture of 600 mg of (3a),100 ml *of ethanol and 2 g of W-2 Raney nickel was hydrogenated at room temperature.After* standing overnight, the catalyst was removed and evaporation of ethanol under reduced pressure left white needles with quantitative yield. mp 264-265°C from ethanol. Anal. Calcd. for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.29; H, 5.30; N, 12.48. Ir (cm^{-1}) 1710,1670 (2 CO); ms: m/z 228 (M^+); nmr (DMSO-d_6): 2.30(3H,s,CH_3); 2.45(3H,s,CH_3); 7.30-8.20(5H,m,C_6H_5); 12.80(1H,br,ex with D_2O).

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