THE SYNTHESIS OF FURO/2,3-c/PYRIDAZINE, A NOVEL HETEROCYCLIC SYSTEM

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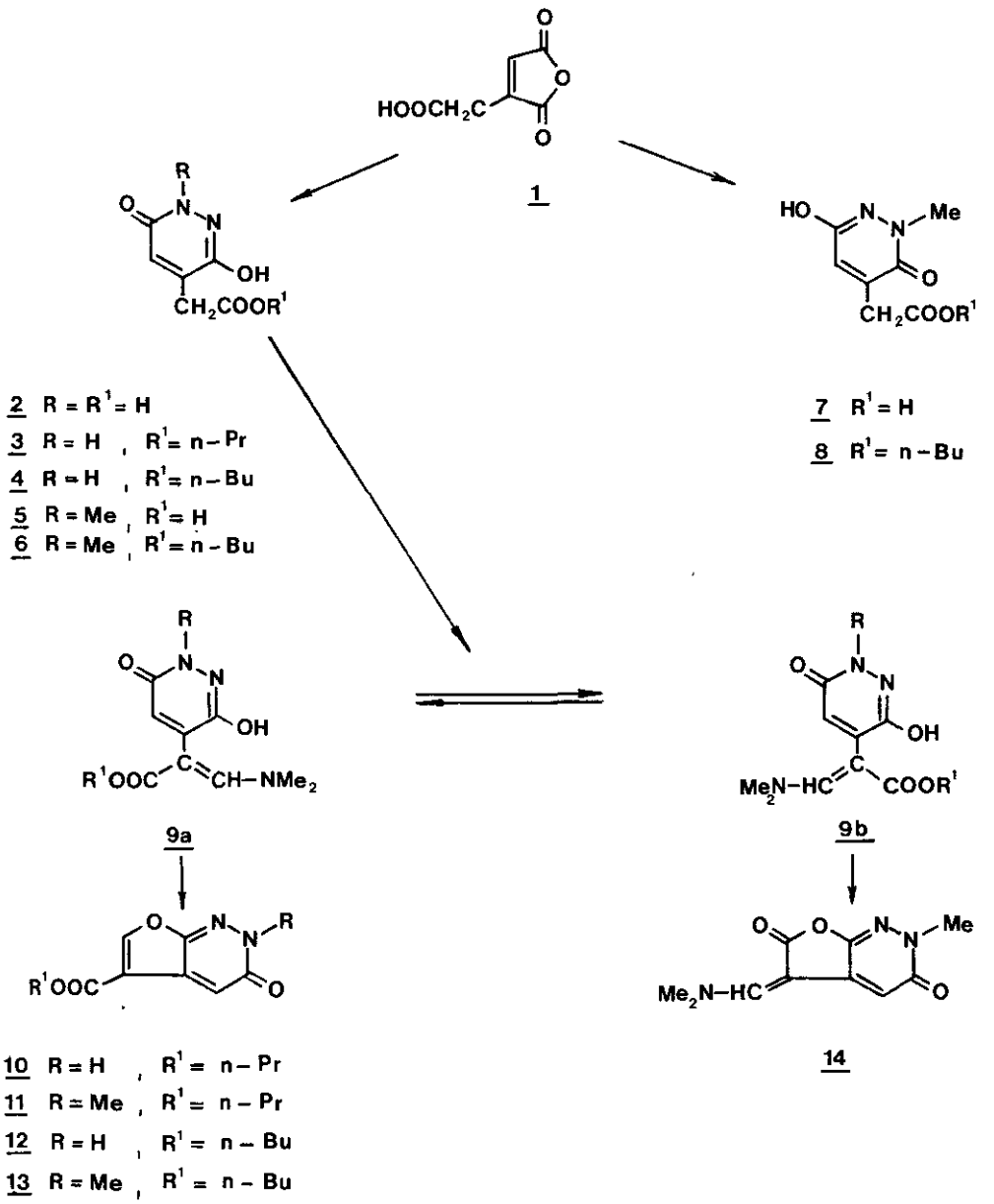
Abstract - A facile one-step synthesis of furo/2,3-c/pyridazines 10-14, derivatives of a novel heterocyclic system, from easily accessible pyridazines 2-6 is described.

There are five possible isomeric furopyridazines, but so far derivatives of only furo/3,4-d/pyridazine, furo/3,2-c/pyridazine and furo/2,3-d/pyridazine are known. The knowledge about these bicyclic systems is very limited, since they have been prepared almost exclusively from not easily accessible ortho-disubstituted furan derivatives[1]. Recently, isomeric furoquinolines, the compounds of major biological and medicinal importance, were prepared by oxidative cyclization of hydroxyquinolines with an allylic group at ortho position[2].

Recently, we have shown that N-heteroaryl formamidines and N-heteroarylformamide oximes are versatile intermediates in the synthesis of various heterocyclic systems, and when in combination with a suitable ortho group, such as NH, SH, and/or OH, various C-C fused azolo- and azinoazines could be prepared[3].

As an extension of these studies we wish to report a facile one-step procedure for the synthesis of furo/2,3-c/pyridazine, derivatives of a novel heteroaromatic bicyclic system, starting from easily accessible pyridazines. Namely, by attempted N- or O-methylation of the compound 3 with N,N-dimethylformamide dimethyl acetal (DMFDMA)[4,5] (1:5 molar ratio, $CHCl_3$, 2 h, 20°C) two products were formed. Separation by column chromatography (silica gel, Merck 0.063-0.200 mm, and a mixture

of chloroform and methanol (9:1) used as the elution solvent) followed by recrystallization from ethyl acetate afforded 5-(n-propoxycarbonyl)furo/2,3-c/pyridazin-3(2H)-one (10) in 11% yield [mp 195°C; m/e 222 (M^+); nmr (DMSO-d_6) δ 0.98 (t, $CH_2CH_2\underline{CH_3}$), 1.66 (m, $CH_2\underline{CH_2}CH_3$), 4.2 (t, $\underline{CH_2}CH_2CH_3$), 6.96 (s, H_4), 7.5 (br. NH), 8.9 (s, H_6); $J_{CH_2CH_2} \simeq J_{CH_2CH_3}$ = 6.5 Hz] and 2-methyl-5-(n-propoxycarbonyl)furo/2,3-c/pyridazin-3(2H)-one (11) in 11% yield [mp 129°C; m/e 236(M^+); nmr($CDCl_3$)



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δ 0.95 (t, $CH_2CH_2\underline{CH_3}$), 1.65 (m, $CH_2\underline{CH_2}CH_3$), 3.62 (s, 2-CH_3), 4.17 (t; $\underline{CH_2}CH_2CH_3$), 6.98 (s, H_4), 8.9 (s, H_6), $J_{CH_2CH_2} \simeq J_{CH_2CH_3}$ = 6.5 Hz]. Similarly, the compound 4[6] gave a mixture of 5-(n-butoxycarbonyl)furo/2,3-c/pyridazin-3(2H)-one (12) in 14% yield [mp 125-128°C; m/e 236 (M^+); nmr (DMSO-d_6) δ 0.94 (t, $CH_2CH_2CH_2\underline{CH_3}$), 1.2-1.8 (m, $CH_2\underline{CH_2}\underline{CH_2}CH_3$), 4.24 (t, $\underline{CH_2}CH_2CH_2CH_3$), 6.94 (s, H_4), 8.0 (br. NH), 8.89 (s, H_6), $J_{CH_2CH_2} \simeq J_{CH_2CH_3}$ = 6.5 Hz] and 5-(n-butoxycarbonyl)-2-methylfuro/2,3-c/pyridazin-3(2H)-one (13) in 14% yield [mp 80-82°C; m/e 250 (M^+); nmr ($CDCl_3$) δ 0.95 (t, $CH_2CH_2CH_2\underline{CH_3}$), 1.2-1.8 (m, $CH_2\underline{CH_2}\underline{CH_2}CH_3$), 3.80 (s, 2-Me), 4.24 (t, $\underline{CH_2}CH_2CH_2CH_3$), 7.10 (s, H_4), 8.75 (s, H_6)]. The treatment of the compound 3 with DMFDMA in 1:1 molar ratio afforded only the compound 10 in 52 % yield. Reaction of cis-aconitic anhydride with methylhydrazine in 1,2-dimethoxyethane (1:1 molar ratio, reflux, 2 h) resulted in the formation of a crystaline product, identified as 5 in 44 % yield, mp 252°C (from water) and an oily residue, which solidified on standing, identified as 7 in 19% yield, mp 210-215°C (from ethanol). On the other hand, cis-aconitic anhydride gave with methylhydrazine sulphate in aqueous solution (reflux, 20 min) the compound 5 as the only product in 64 % yield. The compounds 5 and 7 were converted into the corresponding n-butyl esters 6 in 62 % yield, mp 113°C (from ethanol/water) and 8 in 44% yield, mp 105°C (from ethanol/water), respectively[7]. The compound 6, when treated with DMFDMA in toluene (1:1 molar ratio, reflux, 1 h), was transformed into furo/2,3-c/pyridazine derivative 14 in 58 % yield [mp 290°C (from DMF); m/e 221 (M^+); nmr (DMSO-d_6) δ 3.41 (s, $N\underline{Me_2}$), 3.43 (s, 2-Me), 6.42 (s, $C\underline{H}$=N), 7.75 (s, H_4)].

The compound 8 did not react with DMFDMA under the same reaction conditions.

The formation of furo/2,3-c/pyridazine derivatives 10-14 can be explained through the formation of intermediate 9 a-b (R=H), which first formed in the reaction between active methylene group and DMFDMA, followed by cyclization-elimination reaction in which the hydroxy group at position 3 and either enamine group of the functionalized side chain at position 4 or ester group are involved to give the compounds 10 and 12 or 14. Further methylation of 10 and 12 with an excess of DMFDMA afforded the compounds 11 and 13, respectively.

All new compounds gave satisfactory C,H and N analyses. The scope and limitations of this facile one-step synthesis of furo/2,3-c/pyridazines and other furo-azines in the area of heterocyclic chemistry is under further investigation in our laboratory.

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