NOVEL AMINATION OF 6-ARYL-3(2H)-PYRIDAZINONES WITH HYDRAZINE

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Abstract - Treatment of 6-aryl-3(2H)-pyridazinones with hydrazine hydrate gave 4-amino-6-aryl-3(2H)-pyridazinones

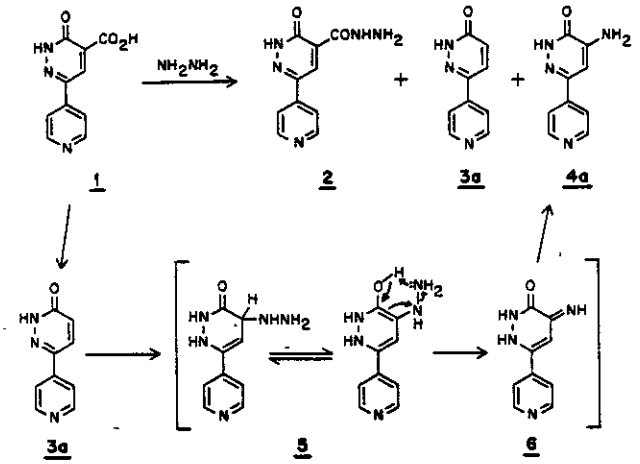
During the preparation of 2,3-dihydro-3-oxo-6-(4-pyridinyl)-4-pyridazinecarboxylic acid hydrazide (2)[1] by the reaction of hydrazine hydrate with 2,3-dihydro-3-oxo-6-(4-pyridinyl)-4-pyridazinecarboxylic acid (1)[1], small quantities of 6-(4-pyridinyl)-3(2H)-pyridazinone (3a)[1] and 4-amino-6-(4-pyridinyl)-3(2H)-pyridazinone (4a)[1] were also isolated. The formation of this unexpected product 4a under these conditions prompted us to investigate this reaction.

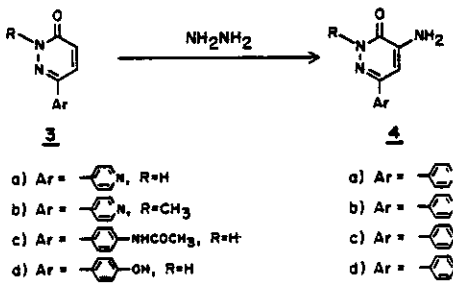
The possibility of the rearrangement of 2 to 4a was ruled out by the fact that 2 was recovered unchanged after treatment with hydrazine hydrate under similar conditions. A proposed mechanism to explain this reaction involves the intermediate 5 which undergoes extrusion of ammonia to give 6 which is a tautomeric form of 4a. The intermediate 5 is formed by the addition of hydrazine to 3a which is produced by the decarboxylation of 1. The formation of 4-amino-6-aryl-3(2H)-pyridazinones 4 by the reaction between hydrazine hydrate and 6-aryl-3(2H)-pyridazinones 3 is consistent with this mechanism. A precedent[2] in favor of this mechanism is provided by the formation of phenylglyoxal monohydrazone (10) by the reaction of hydrazine with phenacyl bromide (7) as shown in the flow chart.

Treatment of 1,2-dihydro-3,6-pyridazinedione (11) with hydrazine hydrate gave 1,2-dihydro-4-hydrazino-3,6-pyridazinedione (14) instead of 4-amino-1,2-dihydro-3,6-pyridazinedione (13). This may be due to the replacement of the amino group by a hydrazino group. The melting point we obtained for 14 is not in agreement with the reported[3,4] melting points. However, our elemental analysis, and nmr and mass spectral data are consistent with 14. As expected, H-5 is rapidly exchanged with deuterium in deutereotrifluoroacetic acid.

EXPERIMENTAL

Melting points were determined in open capillaries in an oil bath and are uncorrected. The nmr spectra of all the compounds except 14 were obtained on varian HA-100 spectrometer in deutereotrifluoroacetic acid using tetramethylsilane as the internal standard and chemical shifts are reported in parts per million and are given in





a) Ar = 4-pyridyl, R=H
b) Ar = 4-pyridyl, R=CH_3
c) Ar = 4-$NHCOCH_3$-phenyl, R=H
d) Ar = 4-OH-phenyl, R=H

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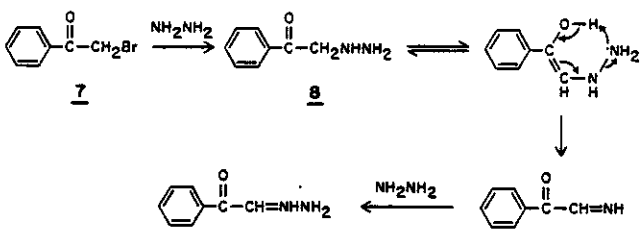

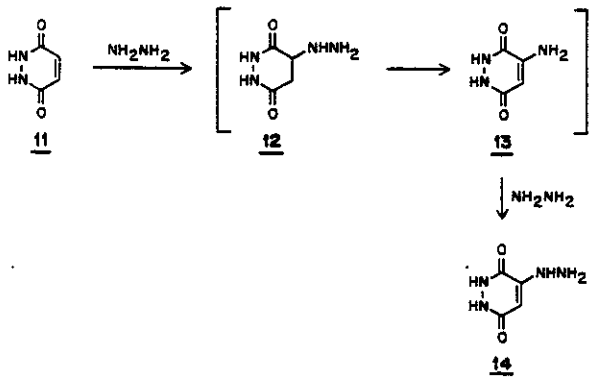

δ units.

The general procedure for the preparation of 4-amino-6-aryl-3(2H)-pyridazinones 4 is illustrated by the following example.

4-Amino-6-(4-pyridinyl)-3(2H)-pyridazinone (4a). A mixture of 2 g (0.01 mol) of 6-(4-pyridinyl)-3(2H)-pyridazinone (3a)[1] and 15 ml of hydrazine hydrate was heated on a steam bath for 48 h and then evaporated to dryness under reduced pressure. The residue was treated with 15 ml of water and then neutralized by acetic acid. The resulting tan solid was collected and recrystallized from methanol to yield 1.6 g (74%) of 4a, mp 305-307 °C; ms: m/e 188 (M^+); ^{1}H-nmr: 11.6 (s, 3H, exchanged), 8.99, 8.59 (4H, pyridine) and 7.4 (s, 1H, H-5). Anal. calcd for $C_9H_8N_4O$: C, 57.44; H, 4.29; N, 29.77. Found: C, 57.47; H, 4.19; N, 29.79.

4-Amino-2-methyl-6-(4-pyridinyl)-3(2H)-pyridazinone (4b). This compound was prepared from 2-methyl-6-(4-pyridinyl)-3(2H)-pyridazinone (3b)[1] in 70% yield, mp 232-235 °C (acetonitrile); ms: m/e 202 (M^+); ^{1}H-nmr: 11.52 (s, 2H, exchanged), 8.92, 8.63 (4H, pyridine), 7.38 (s, 1H, H-5) and 4.17 (s, 3H, $-NCH_3$). Anal. calcd for $C_{10}H_{10}N_4O$: C, 59.40; H, 4.98; N, 27.71. Found: C, 59.51; H, 5.03; N, 27.94.

4-Amino-6-(4-aminophenyl)-3(2H)-pyridazinone (4c). This compound was prepared from 6-(4-acetamidophenyl)-3(2H)-pyridazinone (3c)[5] in 30% yield, mp 306-309 °C (dimethylformamide); ms: m/e 202 (M^+); ^{1}H-nmr: 11.55 (s, 5H, exchanged), 7.99, 7.84 (4H, aromatic), and 8.34 (s, 1H, H-5). Anal. calcd for $C_{10}H_{10}N_4O$: C, 59.39; H, 4.98; N, 27.71. Found: C, 59.58; H, 5.07; N, 27.40.

4-Amino-6-(4-hydroxyphenyl)-3(2H)-pyridazinone (4d). A longer reaction time (165 h) was required to prepare 4d (41%) from 6-(4-hydroxyphenyl)-3(2H)-pyridazinone (3d)[5], mp > 330 °C (dimethylformamide); ms: m/e 203 (M^+); ^{1}H-nmr: 11.45 (4H, exchanged), 7.70, 7.22 (4H, aromatic) and 7.27 (s, 1H, H-5). Anal. calcd for $C_{10}H_9N_3O_2$: C, 59.10; H, 4.46; N, 20.68. Found: C, 58.79; H, 4.57; N, 20.42.

Reaction of 2,3-dihydro-3-oxo-6-(4-pyridinyl)-4-pyridazinecarboxylic acid (1) with hydrazine. A mixture of 80 g (0.37 mol) of 2,3-dihydro-3-oxo-6-(4-pyridinyl)-4-pyridazinecarboxylic acid (1)[1], 250 ml of hydrazine hydrate and 800 ml of ethanol was stirred and heated under reflux for 65 h and then stripped. The brown solid residue was stirred in 300 ml of water and the resulting mixture was acidified with acetic acid. The tan solid that separated was filtered, washed with water and then added to 500 ml of boiling dimethylformamide. The resulting mixture was stirred for a few min and then chilled. The pale yellow solid was collected, washed with methanol and dried to yield 30.4 g (36%) of 2, mp > 320 °C; ms: m/e 231 (M^+); ^{1}H-nmr: 12.2 (s, 4H, exchanged), 9.44 (s, 1H, H-5), 9.11 and 8.9 (4H, pyridine).

The filtrate from above was treated with charcoal and concentrated to dryness. The solid residue was recrystallized from dimethylformamide to afford 9.8 g (14%) of 4a, mp 305-307 °C.

The mother liquor left after the isolation of 4a was stripped to dryness and the residue was recrystallized from ethanol to give 4.2 g (7%) of tan crystals of 3a, mp 223-225 °C; ms: m/e 173 (M^+); ^{1}H-nmr: 12.2 (s, 1H, exchanged), 9.1, 8.7 (4H, pyridine), 8.45 (d, 1H, H-4, J = 6 Hz) and 7.66 (d, 1H, H-5, J = 6 Hz).

Reaction of 2,3-dihydro-3-oxo-6-(4-pyridinyl)-4-pyridazinecarboxylic acid hydrazide (2) with hydrazine hydrate. A mixture of 5 g (0.02 mol) of 2 and 20 ml of hydrazine hydrate was heated on a steam bath for 48 h and then evaporated to dryness under reduced pressure. To the residue was added 25 ml of water and the resulting mixture was acidified with acetic acid. The yellow solid was filtered, washed with methanol and dried to give 4.1 g (82%) of a product which was the identical with the starting material 2.

1,2-Dihydro-4-hydrazino-3,6-pyridazinedione (14). A mixture of 22.4 g (0.2 mol) of 1,2-dihydro-3,6-pyridazinedione (11) and 100 ml of hydrazine hydrate was heated on a steam bath for 144 h and then stripped. The brown solid residue was dissolved in 200 ml of 10% aqueous sodium hydroxide and the resulting solution was treated with charcoal. The brown filtrate was acidified with acetic acid whereupon a yellow solid crystallized which was filtered, washed with water and dried to give 23.2 g of 14, mp 225-229 °C (lit. [3,4] mp 214-216 °C, > 300 °C); ms: m/e 142 (M^+); ^{1}H-nmr (DMSO-d6): 6.2 (s, small peak, H-5) and 6 (s, large peak, H-5); ^{13}C-nmr (DMSO-d6); 159.5 (s, C=O), 137.9 (s, = C-NH-NH_2) and 88.5 (s, O=C-CH=), partial off resonance spectrum displayed a doublet at 88.5, confirming the presence of a carbon atom bearing a hydrogen atom. Anal. calcd for $C_4H_6N_4O_2$: C, 33.80; H, 4.26; N, 39.43, Found: C, 34.15; H, 4.41; N, 39.38.

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