CONDENSATION OF IODO-N-METHYLPYRAZOLE-4-CARBOXYLIC ACIDS

WITH COPPER ACETYLIDES

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4-Iodo-N-methylpyrazolecarboxylic acids condense with substituted copper acetylides to give pyranopyrazoles or γ -lactones [1], while the analogous reaction of o-halobenzoic acids leads to γ -lactones. The reasons for this difference are not entirely clear, and in order to ascertain them it is necessary to obtain additional information on the effect of the structure of the reactants on the direction of the reaction. In this connection we continued to study the direction of the cyclization as a function of the position of the entering acetylenic (iodine atom) and carboxyl groups in the pyrazole ring.

The reaction of 5-iodo-1,3-dimethylpyrazole-4-carboxylic acid (I) with copper n-propyl-(IIa) and phenylacetylide (IIb) in pyridine at 115°C proceeds with closure of the lactone ring and leads to bicyclic products (IIIa, b) in respective yields of 66 and 79%.



The structure of the lactone formed from (I) and (IIa) as being 4-oxo-6-n-propyl-1,3dimethylpyrano[4,3-c]pyrazole (IIIa) unequivocally follows from the data of its PMR spectrum, in which, together with the signals of the N-propyl group (for α -CH₂ a triplet at 2.45 ppm), and of the N- and C-methyl groups of the pyrazole ring, is present the single signal of the unsubstituted proton of the oxygen-containing ring at 6.25 ppm. In the spectrum of the isomeric γ -lactone (III'a) the α -proton of the butylidene group should appear as a triplet [2]. Since it was previously shown that when 4-iodopyrazolecarboxylic acids are condensed the replacement of the propyl radical in (II) by phenyl does not change the direction of the cyclization, the pyran structure of (IIIb) also does not evoke any special doubt. In addition, the closeness in the values of the chemical shifts of the protons of the lactone ring in (IIIb) (δ_{7-H} 6.68 ppm) and in other phenyl-substituted pyranopyrazoles [1] also testifies to the validity of this structure.

Analogous to acid (I), 3-iodo-1,5-dimethylpyrazole-4-carboxylic acid (IV) reacts with (II) to give δ -lactones (V).



The structure of 4-oxo-6-n-amyl-2,3-dimethylpyrano[4,3-c]pyrazole (Vc), obtained in 66.5% yield, is confirmed by its PMR spectrum having a singlet at 5.96 ppm, which corresponds to the ethylenic proton in the ring, and a triplet at 2.37 ppm of the α -CH₂ group of the alkyl substitutent. Compound (Vb) (67% yield) was assigned a δ -lactone structure for the same reasons as (IIIb) (δ_7 -H 6.95 ppm).

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Prod -	Reac- tion time, h	Yield, %	mp, °C	Empirical formula	Found/ Calculated,			60 Cl₃),	PMR spectrum
uct					С	H	N	CHC CHC CHC	ppm
(IIIa)	5	66,0	104-105 (hexane)	$\mathrm{C}_{11}\mathrm{H}_{14}\mathrm{N}_{2}\mathrm{O}_{2}$	<u>64,17</u> 64,06	<u>6,84</u> 6,84	<u>13,62</u> 13,58	1735	3,74 (1-CH _a), 2,44 (3-CH _a), 2,45 t (α -CH ₂), 1,59quintet (β -CH ₂), 0,9 t (γ -CH _a), 6,25 (7-H)
(IIIb)	2,5	78,8	217–218 (EtOH)	$C_{14}H_{12}N_2O_2$	<u>69,81</u> 69,99	<u>5,03</u> 5,03	11,62 11,66	1740	3,80 (1-CH ₃), 2,48 (3-CH ₃), 6,68 (7-H), 7,2-7,8m (Ph)
(Vb)	3	66,6	210–211 (EtOH)	$C_{14}H_{12}N_2O_2$	69,89 69,99	<u>5,11</u> 5,03	<u>11,57</u> 11,66	1735	3,87 (2-CH ₃), 2,62 (3-CH ₃), 6,95 (7-H), 7,3-8,0m (Ph)
(V c)	2,5	67,0	53-54 (petro- leum ether)	C ₁₃ H ₁₈ N ₂ O ₂	66,64 66,44	7,74 7,77	<u>11,96</u> 11,94	1758	3,76 (2-CH ₃), 2,50 (3-CH ₃), 5,96 (-7H), 2,37 t (α -CH ₂), 0,88 t (ω -CH ₃), 1,2-1,8 m [(CH ₂) ₃] *

TABLE 1. Cyclocondensation of (I) and (IV) with Copper Acetylides (II)

*The spectrum of (Vc) was taken in CCl₄ solution.

As a result, the acetylide cyclocondensation of iodo-N-methylpyrazolecarboxylic acids, containing iodine and a carboxyl group on adjacent C atoms, proceeds independently of the position of these substituents with closure of the six-membered lactone ring.

The starting iodo acids (I) and (IV) were synthesized by the oxidative iodination of the methyl esters of dimethylpyrazole-4-carboxylic acids (VI) and (VII) with I_2 and HIO_3 and subsequent saponification. Under these conditions the free N-methylpyrazole-4-carboxylic acids undergo substitutive iodination in the 4 position [3].



EXPERIMENTAL

The PMR spectra were obtained on a Tesla BS-487C spectrometer (80 MHz) using HMDS as the internal standard. The IR spectra were taken on a UR-20 instrument.

<u>1,5-Dimethylpyrazole-4-carboxylic Acid.</u> To 61.5 g of 4-formyl-1,5-dimethylpyrazole [4] in 2 liters of water at 20°C was added 52.4 g of KMnO4 in portions, and at the end of reaction the precipitate was separated and the filtrate was evaporated to small volume and acidified with conc. HCl. The obtained 1,5-dimethylpyrazole-4-carboxylic acid was filtered and recrystallized from water. Yield 42.5 g (62.6%), mp 184-185° [5].

1,3-Dimethylpyrazole-4-carboxylic acid was obtained in a similar manner in 52.1% yield, mp 188-189° (from AcOEt). Found: C 51.12; H 5.74; N 20.16%. C₆H₈N₂O₂. Calculated: C 51.42; H 5.75; N 19.99%.

<u>Methyl Ester of 1,5-Dimethylpyrazole-4-carboxylic Acid (VII).</u> A solution of 58 g of 1,5-dimethylpyrazole-4-carboxylic acid in 1.2 liters of abs. MeOH was saturated with HCl gas at reflux for 10 h, the MeOH was distilled off, and the residue was dissolved in CHCl₃, washed with NaHCO₃ solution, and dried over K₂CO₃. Distillation gave 51 g (79%) of (VII), mp 40-40.5° (from hexane), bp 125-127° (12 mm). Found: C 54.16; H 6.52%. C₇H₁₀N₂O₂. Calculated: C 54.53; H 6.54%. Infrared spectrum (CCl₄, ν , cm⁻¹): 1715 (C=0).

1,3-Dimethylpyrazole-4-carboxylic acid was esterfied in a similar manner to give (VI) in 82% yield, mp 45-45.5° (from hexane). Found: C 54.58; H 6.53; N 18.12%. $C_{2}H_{10}N_{2}O_{2}$. Calculated: C 54.53; H 6.54; N 18.17%. Infrared spectrum (CHCl₃, v, cm⁻¹): 1715 (C=O). PMR spectrum (CDCl₃, δ , ppm): 2.28 (3-CH₃); 3.66, 3.72 (1-CH₃, OCH₃); 7.62 (5-H).

Methyl Ester of 3-Iodo-1,5-dimethylpyrazole-4-carboxylic Acid (IX). A mixture of 23.7 g of (VII), 31.2 g of I₂, and 12.6 g of HIO₃ in 62 ml of 30% H₂SO₄ solution and 170 ml of AcOH was stirred for 5 h at 90-100°, treated with 63 g of AcONa·3H₂O, and the AcOH was vacuum-distilled. The residue was dissolved in CHCl₃, washed in succession with Na₂SO₃ and Na₂CO₃ solutions, and dried over K₂CO₃. We obtained 35 g (81.2%) of (IX), mp 117-118° (from hexane). Found: C 29.92; H 3.37; I 45.25%. C₇H₉IN₂O₂. Calculated: C 30.02; H 3.24; I 45.31%. Infrared spectrum (CHCl₃, ν , cm⁻¹): 1710 (C=O). PMR spectrum (CDCl₃, δ , ppm): 2.50 (5-CH₃); 3.80, 3.85 (1-CH₃, OCH₃).

Ester (VI) was iodinated in a similar manner (reaction time 40 h) to give (VIII) in 30.6% yield, mp 81-82° (from hexane). Found: C 30.07; H 3.25; I 45.28%. $C_7H_9IN_2O_2$. Calculated: C 29.92; H 3.24; I 45.31%. Infrared spectrum (CHCl₃, v, cm⁻¹): 1710 (C=O). PMR spectrum (CDCl₃, δ , ppm): 2.37 (3-CH₃); 3.77, 3.85 (1-CH₃, OCH₃).

<u>3-Iodo-1,5-dimethylpyrazole-4-carboxylic Acid (IV)</u>. A solution of 5.6 g of (IX) in 70 ml of MeOH and 25 ml of 25% NaOH solution was hydrolyzed for a day at 20°, the solvent was vacuum-distilled, and the residue was dissolved in water and acidified with conc. HCl. The precipitate was filtered and recrystallized from EtOH. The yield of (IV) was 4.9 g (91.4%), mp 245° (decompn.). Found: C 27.14; H 2.68; I 47.64%. C₆H₇IN₂O₂. Calculated: C 27.09; H 2.65; I 47.70%. Infrared spectrum (CHCl₃, ν , cm⁻¹): 1722 (C=O); 3532 (OH). PMR spectrum (C₅D₅N, δ , ppm): 2.41 (5-CH₃); 3.50 (1-CH₃); 11.30 (OH).

We obtained (I) in a similar manner in 74.6% yield, mp 222-223° (from benzene). Found: C 27.06; H 2.74; I 47.61%. C₆H₇IN₂O₂. Calculated: C 27.09; H 2.65; I 47.70%. PMR spectrum (C₅D₅N, δ , ppm): 2.58 (3-CH₃); 3.71 (1-CH₃), 10.41 (OH).

<u>Cyclocondensation of Iodo Acids (I) and (IV) with Copper Acetylides (II).</u> The reaction was run the same as described in [1]. At the end of reaction the mixture was poured into ether, the obtained salts were filtered, the solution was washed in succession with aqueous NH_3 and water and dried over K_2CO_3 , the solvent was removed, and the product was recrystallized. The condensation time, yields, and constants of the obtained compounds are given in Table 1.

CONCLUSIONS

The condensation of iodo-N-methylpyrazole-4-carboxylic acids with substituted copper acetylides proceeds with the formation of the δ -lactone ring and leads to pyrano[4,3-c]-pyrazoles.

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