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CYCLIZATION OF VICINAL ACETYLENYLAMINOPYRAZOLES

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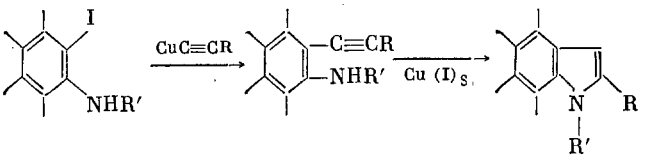
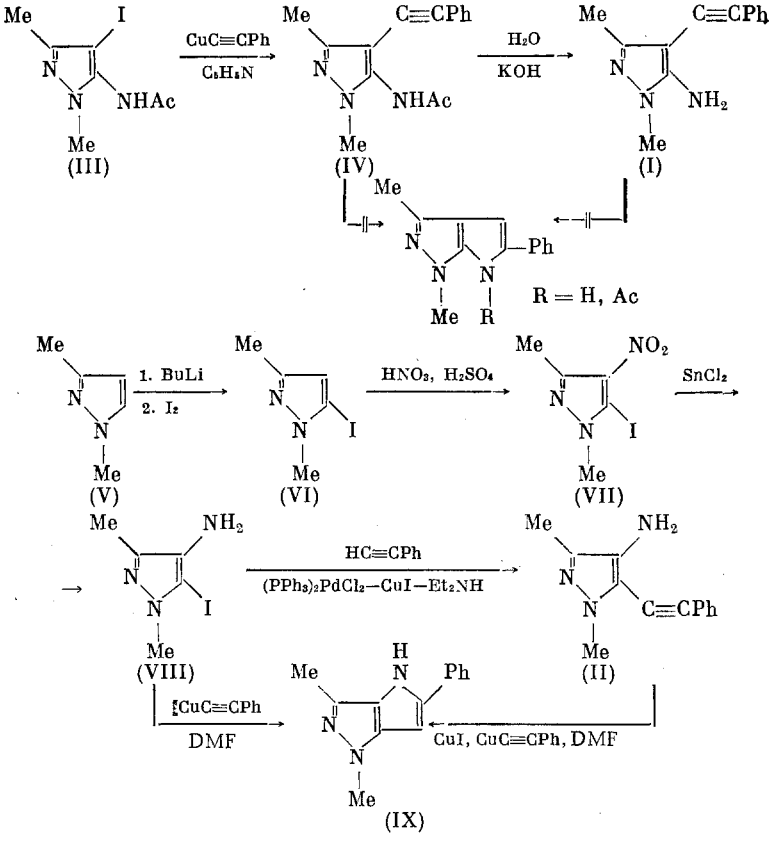
UDC 66.095.252:547.773

In a heterogeneous medium, o-acetylenic derivatives of aromatic amines in the presence of Cu(I) salts are cyclized to indoles [1, 2]. The cyclization is also accompanied by the condensation of o-iodoanilines with copper acetylides if the solvent employed does not assure complete dissolution of the starting acetylide and the CuI formed under the reaction conditions.



The analogous transformations in the series of five-membered heteroaromatic compounds have not been studied.



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 0568-5230/83/3203-0626$07.50

In the present paper we studied the possible cyclization of the isomeric pyrazoles (I) and (II), in which the amino and acetylene groups respectively occupy the 5,4 and 4,5 positions. The synthesis of (I) and (II) is shown in the above scheme.

5-Acetamido-4-phenylethynyl-1,3-dimethylpyrazole (IV) was obtained by condensing (III) [3] with PhC≡CCu in pyridine at 115°C (79.5% yield) and then it was hydrolyzed to amine (I) in 80% yield by refluxing in aqueous alcoholic KOH solution for 7 h. 1,3-Dimethylpyrazole (V) was iodinated in the 5-position via the 5-Li derivative to give (VI) in 60% yield. The nitration of (VI) with $HNO_3 - H_2SO_4$ mixture at 85° gave nitropyrazole (VII) in 80.5% yield, which was reduced with $SnCl_2$ in concentrated HCl at 60° to give aminoiodide (VIII) in 53% yield. The condensation of (VIII) with HC≡CPh as described in [4] gave (II) in 83% yield.

Attempts to cyclize 5-amino-4-phenylethynylpyrazole (I) and its N-acetyl derivative (IV) in the presence of CuI in DMF at 110-145°, or in cyclohexane at 80°, ended in failure. After heating (I) for 30 h in cyclohexane or (IV) for 15 h in DMF we recovered 85-90% of the starting compound. When (I) was heated for a long time in DMF it gradually underwent secondary transformations (partially with the formation of carbonyl-containing products) and substantial tarring. In contrast to (I), its isomer (II) under similar conditions underwent cyclization to 1,3-dimethyl-5-phenylpyrrolo[3,2-c]pyrazole (IX). In DMF the reaction is noticeably accelerated by adding PhC≡CCu. The yield of (IX) reached 65%. The direct cyclocondensation of aminohalide (VIII) with PhC≡CCu in DMF also led to (IX) in 37.5% yield. The difference in the ability of 5-amino-4-phenylethynyl- (I) and 4-amino-5-phenylethynyl-1,3-dimethylpyrazole (II) to cyclize is probably explained by the lower nucleophilicity of the amino group attached to the more electron-acceptor 5 position of the pyrazole ring [5], possibly in combination with the greater strain in general of a condensed system composed of two five-membered rings when compared with a system composed of five- and six-membered rings [6].

EXPERIMENTAL

The PMR spectra were taken at 25° on a Tesla BS-487C spectrometer at a frequency of 80 MHz (internal standard = HMDS), and the IR spectra were taken on a UR-20 instrument.

5-Iodo-1,3-dimethylpyrazole (VI). The metallation of (V) with n-BuLi and subsequent treatment with I_2 under the conditions described for 1-methylpyrazole [7] gave (VI); after distillation at 62-63° (2 mm) and recrystallization from hexane the yield was 60%, mp 58-59°. Found: C 26.97; H 3.22; I 57.00%. $C_5H_7IN_2$. Calculated: C 27.05; H 3.18; I 57.16%. PMR spectrum (CCl_4, δ, ppm): 2.15 (3-CH_3), 3.78 (NCH_3), 6.10 (4-H).

5-Iodo-4-nitro-1,3-dimethylpyrazole (VII). With stirring, to 28.1 g of (VI) in 19 ml of concentrated H_2SO_4 was slowly added a mixture of 57 ml of fuming HNO_3 (d 1.51) and 57 ml of conc. H_2SO_4, and the mixture was stirred at 85° for 45 min, cooled, and carefully poured on ice. The obtained crystals were filtered, washed with water, dried in a desiccator over KOH, and recrystallized from ~400 ml of CCl_4 to give 27.2 g (80.5%) of (VII), mp 150-151°. Found: C 22.44; H 2.30; I 47.14%. $C_5H_6IN_3O_2$. Calculated: C 22.49; H 2.26; I 47.52%. PMR spectrum ($CDCl_3$, δ, ppm): 2.50 (3-CH_3), 3.91 (NCH_3). Infrared spectrum ($CHCl_3$, ν, cm^{-1}): 1345, 1540 (NO_2).

4-Amino-5-iodo-1,3-dimethylpyrazole (VIII). With stirring, to 100 g of $SnCl_2 \cdot 2H_2O$ in 100 ml of concentrated HCl was added in portions 28.6 g of (VII), in such a way that the temperature of the reaction mass did not exceed 60°. The mixture was stirred at 60° for 1 h, cooled, made alkaline with 40% aqueous NaOH solution, and the (VIII) was extracted with $CHCl_3$ and dried over K_2CO_3. The compound (19 g) was purified by recrystallization from a petroleum ether–benzene mixture to give 13.5 g (53%) of (VIII), mp 111-112°. Found: C 25.34; H 3.47; I 53.59%. $C_5H_8IN_3$. Calculated: C 25.33; H 3.40; I 53.54%. Infrared spectrum ($CHCl_3$, ν, cm^{-1}): 3355, 3425 (NH_2).

4-Amino-5-phenylethynyl-1,3-dimethylpyrazole (II). A mixture of 3.8 g of (VIII), 2.2 g of phenylacetylene, 30 mg of CuI, and 60 mg of $Pd(PPh_3)_2Cl_2$ in 50 ml of Et_2NH was stirred in an Ar atmosphere for 3 h at 30° and 3 h at 50° (checked by TLC: Silufol, ether), poured into 0.5 liter of ether, the $Et_2NH \cdot HI$ was filtered, and the solvent was distilled off. The residue in the benzene was filtered through a silica gel bed (h = 30, d = 65 mm) and, having removed the benzene, was recrystallized from petroleum ether to give 2.8 g (82%) of (II), mp 66-66.5°. Found: C 73.78; H 6.22; N 20.20%. $C_{13}H_{13}N_3$. Calculated: C 73.90; H 6.20; N 19.89%. PMR spectrum ($CDCl_3$, δ, ppm) 2.03 (3-CH_3), 2.93 (NH_2), 3.63 (NCH_3), 6.9-7.4 m (C_6H_5). Infrared spectrum ($CHCl_3$, ν, cm^{-1}): 2215 (C≡C), 3375, 3450 (NH_2).

5-Acetamido-4-phenylethynyl-1,3-dimethylpyrazole (VI). A mixture of 25 g of (III) [3] and 22 g of PhC≡CCu in 1 liter of dry pyridine was refluxed in an N_2 atmosphere for 4 h (checked by TLC: anhydrous Al_2O_3, ether), diluted with 1 liter of ether, and the Cu salt was filtered. The solution was filtered through a small bed of anhydrous Al_2O_3, and the ether and pyridine were vacuum-distilled. The residue was dissolved in $CHCl_3$, washed in succession with aqueous NH_3 and water, and dried over K_2CO_3. Recrystallization from toluene gave 18 g (79.5%) of (IV), mp 189.5-190°. Found: C 71.04; H 6.02; N 16.55%. $C_{15}H_{15}N_3O$. Calculated: C 71.12; H 5.97; N 16.59%. Infrared spectrum ($CHCl_3$, ν, cm^{-1}): 1705 (C=O), 2225 (C≡C), 3420 (NH).

5-Amino-4-phenylethynyl-1,3-dimethylpyrazole (I). To 170 ml of 25% aqueous KOH solution was added a suspension of 5.1 g of (IV) in 25 ml of EtOH and the mixture was refluxed for 7 h. Compound (I) was extracted with ether and dried over K_2CO_3; the solvent was removed, and the residue was recrystallized from benzene to give 3.4 g (80%) of (I), mp 118.5-119°. Found: C 73.86; H 6.24; N 19.88%. $C_{13}H_{13}N_3$. Calculated: C 73.90; H 6.20; N 19.89%. PMR spectrum (CCl_4, δ, ppm): 2.01 (NH_2), 2.11 (3-CH_3), 3.45 (NCH_3), 7.1-7.4 m (C_6H_5). Infrared spectrum (CCl_4, ν, cm^{-1}): 2215 (C≡C); 3383, 3460 (NH_2).

Cyclization of 4-Amino-5-phenylethynyl-1,3-dimethylpyrazole (II). A mixture of 0.20 g of (II), 0.05 g of PhC≡CCu and 0.10 g of CuI in 10 ml of DMF was stirred in an Ar atmosphere at 150-155° for 4 h, poured into 200 ml of ether, filtered, washed in succession with aqueous NH_3 and water, and dried over K_2CO_3; the solvent was removed, and the residue was recrystallized from a benzene–petroleum ether mixture to give 0.13 g (65%) of (IX), mp 190-190.5°. Found: C 73.83; H 6.16; N 19.68%. $C_{13}H_{13}N_3$. Calculated: C 73.91; H 6.20; N 19.89%. PMR spectrum ($CDCl_3$, δ, ppm): 2.33 (3-CH_3), 3.79 (NCH_3), 6.24 d (6-H), 7.2-7.8 m (C_6H_5), 8.11 (NH). Infrared spectrum ($CHCl_3$, ν, cm^{-1}), 3485 (NH).

Under analogous conditions, but in the absence of PhC≡CCu, (II) is cyclized to (IX) in 40% yield; isomer (I) and its N-acetyl derivative (IV) do not cyclize. The recovery of (I) is 90% when it is heated with an equimolar amount of CuI [2] in cyclohexane for 30 h at 80°.

Cyclocondensation of 4-Amino-5-iodo-1,3-dimethylpyrazole (VIII). A mixture of 0.9 g of (VIII) and 0.6 g of PhC≡CCu in 20 ml of DMF was refluxed in an N_2 atmosphere for 2 h and then worked up as described for the cyclization of (II). We obtained 0.3 g (37.5%) of (IX).

CONCLUSIONS

1. 4-Amino-5-acetylenylpyrazoles are capable of isomerizing in the presence of Cu(I) salts, with closure of the pyrrole ring and formation of the condensed pyrrolo[3,2-c]pyrazole system.

2. The 5-amino-4-acetylenylpyrazoles, in contrast to the 4-amino-5-acetylenyl derivatives, and also the o-acetylenylanilines, do not cyclize under analogous conditions.

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