Preparation of 1-Aryl-4,5- and 5,5-diamino-4,5-dihydropyrazoles and 4- and 5-Amino-1-arylpyrazoles

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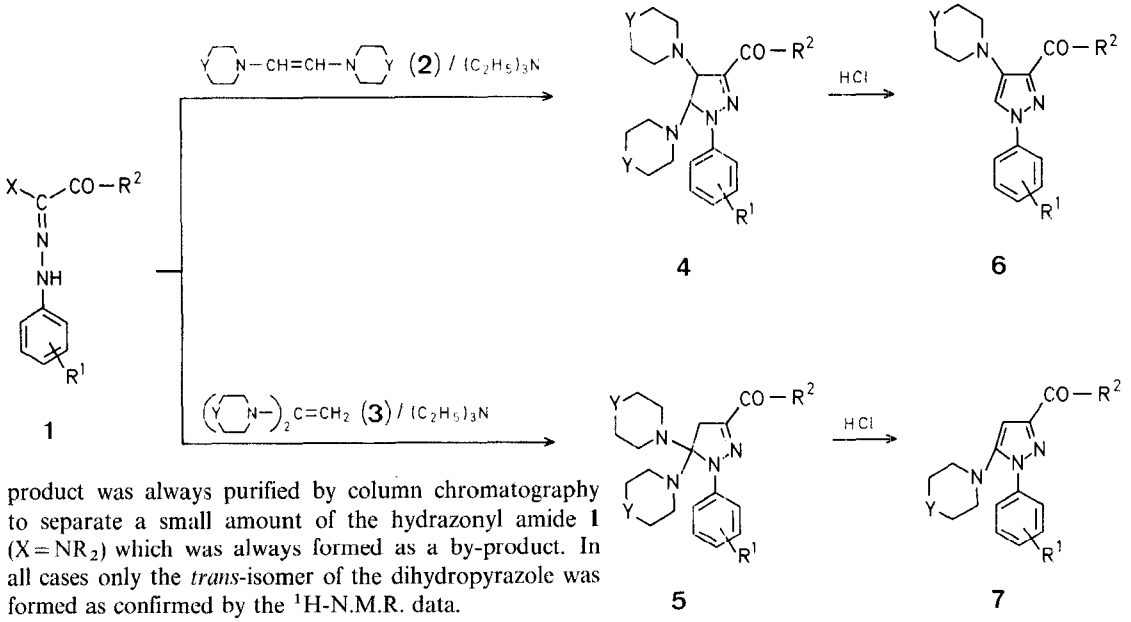
1-Aryl-4,5- and 5,5-diamino-4,5-dihydropyrazoles are a previously unknown class of heterocyclic compounds. We have now studied the preparation of these compounds by the 1,3-dipolar cycloaddition reaction of nitrile imines with 1,2-diaminoethenes and 1,1-diaminoethenes, respectively.

The preparation of the 4,5-dihydropyrazoles **4** was achieved by refluxing the 1,2-diaminoethenes **2** with the hydrazonyl halides **1** (X = Cl) in benzene in the presence of an equimolar amount of triethylamine for several hours. The crude reaction product was always purified by column chromatography to separate a small amount of the hydrazonyl amide **1** ($X = NR_2$) which was always formed as a by-product. In all cases only the *trans*-isomer of the dihydropyrazole was formed as confirmed by the ^{1}H-N.M.R. data.



Owing to their greater reactivity, the 1,1-diaminoethenes **3** could be reacted with **1** (X = Cl) at room temperature. In this case the reaction did not afford by-products and the 4,5-dihydropyrazoles **5** were obtained in almost quantitative yield by simple work-up.

The acid-catalysed amine elimination from the 4,5-dihydropyrazoles **4** affords a convenient preparation of the 4-aminopyrazoles **6**. Compounds **6** were the only reaction products which demonstrates the high regiospecificity of this elimination reaction.

The 5,5-diamino-4,5-dihydropyrazoles **5** undergo deamination more easily and give rise to the 5-aminopyrazoles **7** even on refluxing in trichloromethane for several hours. The elimination takes place more rapidly on refluxing in ethanolic hydrochloric acid.

The 1,1-diaminoethenes[1] and the 1,2-diaminoethenes[2] were prepared according to literature methods. The hydrazonyl halides **1** ($R^1 = H, R^2 = OC_2H_5, CH_3$, and OCH_3) are known compounds[3]. The trifluoromethyl ($R^1 = 3\text{-}F_3C$, m.p. 125°) and the methoxy ($R^1 = 4\text{-}H_3CO$, m.p. 118°) substituted derivatives were prepared in the same way.

Preparation of 1-Aryl-4,5-diamino-4,5-dihydropyrazoles 4; General Procedure:

To a solution of the 1,2-diaminoethene (**2**; 0.01 mol) and triethylamine (1.32 g, 0.012 mol) in dry benzene (50 ml) is added the halide **1** (X = Cl; 0.01 mol). The reaction mixture is refluxed for several hours, (see Table 1), cooled to room temperature, and the precipitated triethylamine hydrochloride filtered off. The filtrate is evaporated under reduced pressure and the crude residue separated by column chromatography on silica gel using benzene/ethyl acetate (1:1) as eluent.

Preparation of 1-Aryl-5,5-diamino-4,5-dihydropyrazoles 5; General Procedure:

To a stirred solution of the 1,1-diaminoethene (**3**; 0.01 mol) and triethylamine (1.32 g, 0.012 mol) in dry benzene (50 ml) is added under nitrogen the halide **1** (X = Cl; 0.01 mol). The mixture is stirred at room temperature for the time shown in Table 1, the precipitated triethylamine hydrochloride is filtered off, and the filtrate washed with water. The organic layer is dried over anhydrous sodium sulfate and the solvent removed in vacuo to give the product **5**.

Table 1. Preparation of 1-Aryl-4,5- and 5,5-diamino-4,5-dihydropyrazoles **4** and **5**

Product	R^1	R^2	Y	Reaction time	Yield (%)	m.p. [from]	Molecular formula[a]	^{1}H-N.M.R. (C_6D_6) δ ppm
4a	H	OC_2H_5	O	10 h	65	109–110° [$(i\text{-}C_3H_7)_2O$]	$C_{20}H_{28}N_4O_4$ (388.5)	4.23 (d, H-4), 4.89 (d, H-5), $J_{4,5}$ = 2.8 Hz
4b	4-H_3CO	CH_3	O	12 h	50	146–147° [$(i\text{-}C_3H_7)_2O$]	$C_{20}H_{28}N_4O_4$ (388.5)	4.25 (d, H-4), 4.72 (d, H-5), $J_{4,5}$ = 3.0 Hz
4c	3-F_3C	CH_3	O	6 h	55	121–122° [$c\text{-}C_6H_{12}$]	$C_{20}H_{25}F_3N_4O_3$ (426.4)	4.17 (d, H-4), 4.63 (d, H-5), $J_{4,5}$ = 3.0 Hz
4d	H	OCH_3	CH_2	4 h	45	99–100° [$(i\text{-}C_3H_7)_2O$]	$C_{21}H_{30}N_4O_2$ (370.5)	4.33 (d, H-4), 4.88 (d, H-5), $J_{4,5}$ = 3.0 Hz
5a	H	OC_2H_5	O	3 h	80	103–104° [$C_6H_6/(i\text{-}C_3H_7)_2O$]	$C_{20}H_{28}N_4O_4$ (388.5)	2.98 (H-4)
5b	4-H_3CO	CH_3	O	4 h	82	127–128° [$C_6H_6/(i\text{-}C_3H_7)_2O$]	$C_{20}H_{28}N_4O_4$ (388.5)	2.98 (H-4)
5c	3-F_3C	CH_3	O	3 h	85	161–163° [$C_6H_6/(i\text{-}C_3H_7)_2O$]	$C_{20}H_{25}F_3N_4O_3$ (426.4)	2.89 (H-4)
5d	H	OCH_3	CH_2	1 h	80	126–128° [$C_6H_6/(i\text{-}C_3H_7)_2O$]	$C_{21}H_{30}N_4O_2$ (370.5)	3.08 (H-4)

[a] All compounds gave satisfactory elemental analyses (C ±0.3%, H ±0.33%, N ±0.32%).

Table 2. Preparation of 4- and 5-Amino-1-arylpyrazoles **6** and **7**

Product	R^1	R^2	Y	Yield (%)	m.p. [from]	Molecular formula[a]	^{1}H-N.M.R. (C_6D_6) δ ppm
6a	H	OC_2H_5	O	90	110–112° [$(i\text{-}C_3H_7)_2O$]	$C_{16}H_{19}N_3O_3$ (301.3)	7.55 (H-5)
6b	4-H_3CO	CH_3	O	85	99–101° [$(i\text{-}C_3H_7)_2O$]	$C_{16}H_{19}N_3O_3$ (301.3)	7.02 (H-5)
6c	3-F_3C	CH_3	O	88	157–158° [C_2H_5OH]	$C_{16}H_{16}F_3N_3O_2$ (335.3)	6.93 (H-5)
6d	H	OCH_3	CH_2	85	113–115° [$(i\text{-}C_3H_7)_2O$]	$C_{16}H_{19}N_3O_2$ (285.3)	7.17 (H-5)
7a	H	OC_2H_5	O	82	128° [C_2H_5OH]	$C_{16}H_{19}N_3O_3$ (301.3)	6.10 (H-4)
7b	4-H_3CO	CH_3	O	78	101–103° [$(i\text{-}C_3H_7)_2O$]	$C_{16}H_{19}N_3O_3$ (301.3)	6.43 (H-4)
7c	3-F_3C	CH_3	O	80	74–75° [$(i\text{-}C_3H_7)_2O$]	$C_{16}H_{16}F_3N_3O_2$ (335.3)	6.38 (H-4)
7d	H	OCH_3	CH_2	88	81–83° [$(i\text{-}C_3H_7)_2O$]	$C_{16}H_{19}N_3O_2$ (285.3)	6.51 (H-4)

[a] All compounds gave satisfactory elemental analyses (C ±0.4%, H ±0.34%, N ±0.3%).

Deamination of Dihydropyrazoles 4 (or 5) to Pyrazoles 6 (or 7); General Procedure:

To a solution of the dihydropyrazole **4** (or **5**) (2.5 mmol) in ethanol (20 ml) is added 37% hydrochloric acid (0.5 ml). The mixture is refluxed for 2 h, the solvent evaporated, and the crude residue washed with saturated sodium hydrogen carbonate solution. The mixture is extracted twice with ether, the organic layer separated, dried over anhydrous sodium sulfate, and evaporated to afford the aminopyrazole **6** (or **7**).

Deamination of 1-Aryl-5,5-diamino-4,5-dihydropyrazoles 5 to 5-Amino-1-arylpyrazoles 7; General Procedure:

Method A: The deamination is carried out as described above for the conversion of **4** to **6**.

Method B: The 5,5-diamino-4,5-dihydropyrazole **5** (2.5 mmol) is dissolved in anhydrous chloroform (20 ml) and refluxed for 3 h. The solvent is evaporated and the solid recrystallised to give **7**.

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