Synthesis of 1-Aryl-4-halo-2-pyrazolin-5-ones by Ascorbic Acid Reduction of 1-Aryl-4,4-dihalo-2-pyrazolin-5-ones

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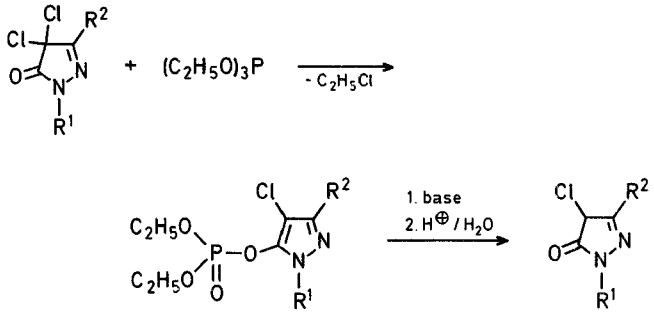
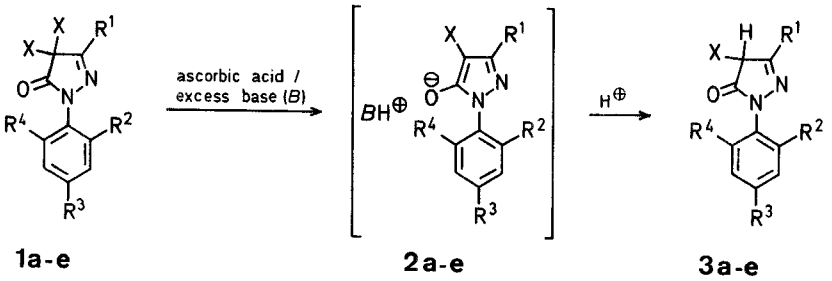
Synthesis of 4-halo-2-pyrazolin-5-ones by direct halogenation is complicated by the fact that the product is often contaminated with 4,4-dihalo derivatives and in many cases this is the major component. If the 3-position is substituted with an anilino or acylamino group, monohalogenation is especially difficult[1]. On the other hand, dichlorination and dibromination proceed smoothly under a variety of conditions.

Selective reduction of 4,4-dichloro-2-pyrazolin-5-one compounds has been accomplished in a two-step process involving first reaction with triethyl phosphite followed by alkaline hydrolysis of the intermediate phosphate ester as shown[1] (Scheme **A**).

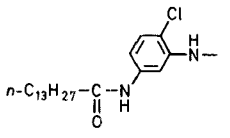
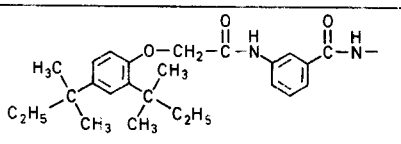
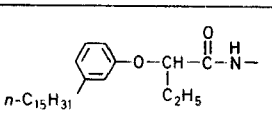


Scheme **A**

Reported here is an improved method whereby 4,4-dichloro- or 4,4-dibromo-1-aryl-2-pyrazolin-5-ones **1** are selectively reduced to the monohalo derivative **2** by reaction with ascorbic acid and an organic base such as triethylamine at 20–30 °C. Acidification then yields the product **3** (Scheme **B**).



1a-e **2a-e** **3a-e**

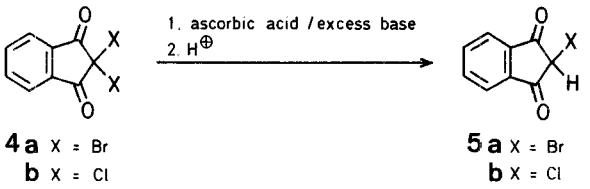
1-3	a	b	c	d	e
R^1			CH_3		CH_3
R^2	Cl	Cl	H	Cl	H
R^3	Cl	Cl	H	CH_3	H
R^4	Cl	Cl	H	CH_3	H
X	Cl	Cl	Cl	Cl	Br
B	$(C_2H_5)_3N$	$(C_2H_5)_3N$	—[a]	—[a]	—[a]

[a] Compound **2** not isolated

Scheme **B**

Compounds **3** are relatively strong acids which in all probability provide the driving force for mild reduction of **1** under alkaline conditions. The intermediate enolate salt **2** resists further reduction under the conditions of the reaction.

Extension of this reaction to other 1,3-unsaturated-2-dihalogenated systems is possible. For example, 2,2-dibromo-1,3-indanedione **(4a)** and 2,2-dichloro-1,3-indanedione **(4b)** are cleanly reduced to the monohalo derivatives **5** (Scheme **C**). However, 2,2-dibromo-1,3-diphenyl-1,3-propanedione gives 1,3-diphenyl-1,3-propanedione in good yield with excess ascorbic acid. Mixtures containing some monobromo product are obtained when an equivalent of ascorbic acid is used.



4a X = Br **5a** X = Br
b X = Cl **b** X = Cl

Scheme **C**

Chlorination or Bromination; General Procedure:
To a solution containing the 1-substituted 2-pyrazolin-5-one (0.05 mol) in acetic acid (100 ml) is slowly added 1,3-dichloro-5,5-dimethylhydantoin or 1,3-dibromo-5,5-dimethylhydantoin (0.05 mol) maintaining the temperature at 20 °C by external cooling. After slurrying for 2 h, the mixture is cooled and the product **1** is collected. Alternatively, the product **1** can be precipitated from the mixture by dilution with water. This can be used as is or recrystallized from methanol to obtain analytically pure material. 1,3-Indanedione is similarly halogenated to give **4a, b**.

Ascorbic Acid Reduction; General Procedure:
To a solution containing ascorbic acid (10 g, 0.06 mol) and triethylamine (50 ml) in methanol (100 ml) is added the appropriate 4,4-dihalo-2-pyrazolin-5-one **1** (0.04 mol). The temperature is maintained at 20–30 °C by rate of addition or external cooling. Solution is obtained upon reaction. After stirring for 15 min, the mixture is acidified by pouring it into cold dilute hydrochloric acid causing

Table. Compounds **1–5** prepared

Substrate	Product	Yield [%]	m.p. [°C] found	m.p. [°C] reported	Molecular Formula[a]
–	**1a**	85	133–135°	–	$C_{29}H_{34}Cl_6N_4O_2$ (683.3)
–	**1b**	93	205–206°	–	$C_{34}H_{35}Cl_5N_4O_4$ (740.9)
–	**1c**	84	66–67°	61°[2]	$C_{10}H_8Cl_2N_2O$ (243.1)
–	**1d**	80[b]	97–100°	–	$C_{36}H_{50}Cl_3N_3O_3$ (679.2)
–	**1e**	85	80–82°	80°[2]	$C_{10}H_8Br_2N_2O$ (332.0)
1a	**2a**	94	136° (dec)	–	$C_{35}H_{50}Cl_5N_5O_2$ (750.1)
1b	**2b**	95	170° (dec)	–	$C_{40}H_{51}Cl_4N_5O_4$ (807.7)
1a	**3a**	92	88° (dec)	–	$C_{29}H_{35}Cl_5N_4O_2$ (648.9)
1b	**3b**	95	125° (dec)	–	$C_{34}H_{36}Cl_4N_4O_4$ (706.5)
1c	**3c**	95	166° (dec)	153°[3]	$C_{10}H_9ClN_2O$ (208.7)
1d	**3d**	88	110–113°	–	$C_{36}H_{51}Cl_2N_3O_3$ (644.7)
1e	**3e**	90	124–127°	128°[2]	$C_{10}H_9BrN_2O$ (253.1)
–	**4a**	88	177–178°	177–179°[4]	$C_9H_4Br_2O_2$ (303.9)
–	**4b**	89	126–128°	124–125°[5]	$C_9H_4Cl_2O_2$ (215.0)
4a	**5a**	95	118–120°	119–120°[4]	$C_9H_5BrO_2$ (225.0)
4b	**5b**	93	114–116°	114°[4]	$C_9H_5ClO_2$ (180.6)

[a] Satisfactory microanalyses obtained: C ±0.5, H ±0.4, N ±0.4, Cl ±0.7, Br +

[b] Ethyl acetate used as a co-solvent.

precipitation of the 4-halo-2-pyrazolin-5-one **3**. In most cases, pouring the mixture into water causes precipitation of the amine salt of the 4-halo-2-pyrazolin-5-one **2**. 2,2-Dihalo-1,3-indanediones **4** are similarly reduced to **5**.

Received: July 27, 1984

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[2] L. Knorr, *Liebigs Ann. Chem.* **238**, 175 (1887).
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[5] T. Zincke, *Ber. Dtsch. Chem. Ges.* **21**, 501 (1888).