A Convenient Synthesis of 2-Aryl-4,5-dicyanoimidazoles and -imidazolines from Diaminomaleonitrile

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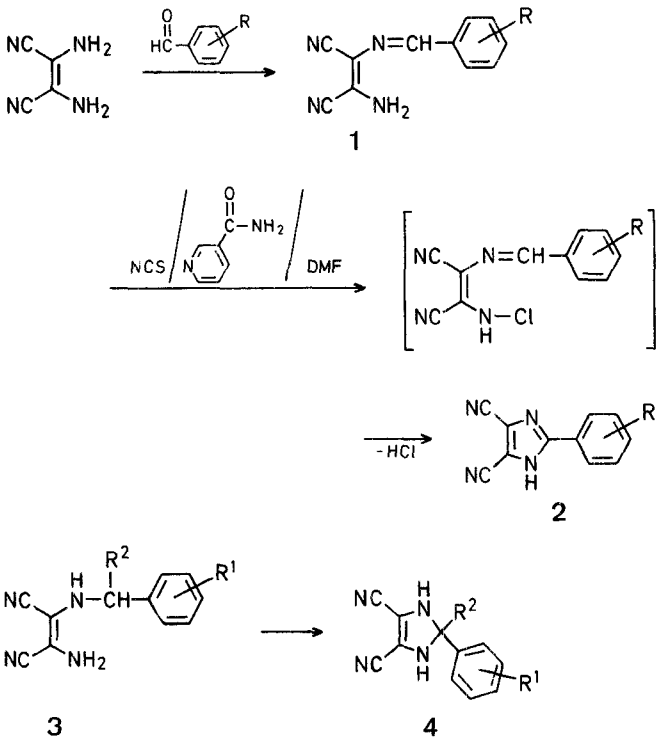
Synthesis of imidazole derivatives is one of the well studied reactions in diaminomaleonitrile chemistry. For the syntheses of 2-alkyl-4,5-dicyanoimidazoles from diaminomaleonitrile, several methods starting from aldehydes[1], ketoesters[2], orthoesters[3], imidates[4], or cyanogen chloride[5] have been reported. The first-mentioned method[1], in which aldehydes are converted to Schiff bases by the condensation with diaminomaleonitrile and then to imidazoles via oxidative cyclization, seems to be the most generally useful as a variety of commercially available aldehydes can be used for the preparation of imidazoles having a desired alkyl substituent. However, the cyclization of Schiff bases employing DDQ or diiminosuccinonitrile in acetonitrile requires long reaction times, varying from 17 h to 4 days under reflux. In this report, we describe a fast and convenient method for the cyclization of Schiff bases **1** to 2-aryl-4,5-dicyanoimidazoles **2** using *N*-chlorosuccinimide under basic conditions.

The cyclization of **1** was accomplished within 3 h by the following procedure. The solution of **1**, nicotinamide, and *N*-chlorosuccinimide in dimethylformamide was stirred for 3 h at 40 °C. The mixture was then poured into water and precipitates formed were isolated by filtration. Recrystallization from appropriate solvents gave products **2** (Table).



Furthermore, we have found that this procedure is available for the syntheses of 2-aryl-4,5-dicyanoimidazolines **4**. When *N*-benzyldiaminomaleonitriles **3**, prepared by reduction of the Schiff bases with sodium borohydride[1], were treated with *N*-chlorosuccinimide and nicotinamide in dimethylformamide, imidazolines **4** were obtained in moderate yields (Table).

On the other hand, Schiff bases derived from diaminomaleonitrile and aliphatic aldehydes, such as pentanal and 3-methylbutanal, afforded less pure products and low yields of imidazoles (5 to 9 %). These results suggest that this reaction requires the presence of an aryl group to facilitate elimination of hydrogen at the α-position, namely, the azomethine hydrogen of **1** and the benzyl hydrogen of **3**, under basic conditions. Although *N*-chloramine intermediates have not been isolated, the cyclization may proceed through the chlorination of the amino group by *N*-chlorosuccinimide and subsequent dehydrochlorination, similar to that reported previously[6].

Table. 2-Aryl-4,5-dicyanoimidazoles **2** and -imidazolines **4** prepared

Product No.	R	R^1	R^2	Yield [%]	m.p. [°C] (solvent)	Molecular Formula[a,b] or Lit. m.p. [°C]	I.R. (KBr) ν[cm^{-1}]
2a	H	–	–	66	220–222° (benzene)	261°[6]	3150, 3080, 2930, 2230, 1455
2b	2-Cl	–	–	64	210–211° (benzene)	211–212°[1]	3270, 2255, 1445
2c	4-H_3CO	–	–	74	225–228° ($CHCl_3$/hexane)	$C_{12}H_8N_4O$ (224.1)	3200, 3120, 2270, 2240, 1618, 1495
4a	–	H	H	80	160–162° (C_2H_5OH/hexane)	$C_{11}H_8N_4$ (196.1)	3410, 3325, 3225, 2240, 2210, 1640, 1610, 1590
4b	–	2-Cl	H	75	172–173° ($CHCl_3$/hexane)	$C_{11}H_7ClN_4$ (230.5)	3380, 3320, 3200, 2230, 2200, 1640, 1600
4c	–	H	CN	78	164–165° ($CHCl_3$/hexane)	$C_{12}H_7N_5$ (221.1)	3450, 3325, 3220, 2240, 1625, 1540, 1405

[a] All products gave satisfactory microanalysis (C ±0.27%, H ±0.28%, N ±0.39%).
[b] The ^{1}H-N.M.R. spectra of the products were in accord with the proposed structures.

2-Phenyl-4,5-dicyanoimidazole (2a); Typical Procedure:
To a solution of *N*-benzylidenediaminomaleonitrile[1] (**1a**, 0.50 g, 2.56 mmol) and nicotinamide (0.37 g, 3.07 mmol) in dimethylformamide (5 ml), *N*-chlorosuccinimide (0.34 g, 2.56 mmol) is added and the mixture is stirred at 40°C. The hydrochloride salt of nicotinamide is gradually deposited from the solution. After stirring for 3 h, the salt is filtered off and washed with acetone. The combined filtrate and washings are poured into water (200 ml). The resulting precipitates are collected and recrystallized from benzene with charcoal treatment to give colourless crystals of **2a**; yield: 0.33 g (66%); m.p. 220–222°C (Lit.[7], m.p. 261°C).

$C_{11}H_6N_4$ (194.2) calc. C 68.04 H 3.09 N 28.87
found 68.31 3.03 29.15

^{1}H-N.M.R. (acetone-d_6): δ = 7.50 (m, 4H); 8.10 ppm (m, 2H).

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A Simple One-Pot Conversion of Alkyl 4-Oxo-1,4-dihydroquinoline-2-carboxylates to 4-Aminoquinoline-2-carboxylates using Reactive Isocyanates

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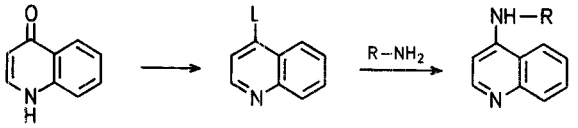
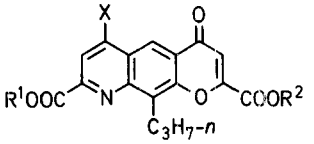
The classic transformation of 4-oxo-1,4-dihydroquinolines to the corresponding 4-aminoquinoline relies on the conversion of the oxygen function to a leaving group, followed by nucleophilic displacement of the leaving group by an amine (Scheme **A**)[1].



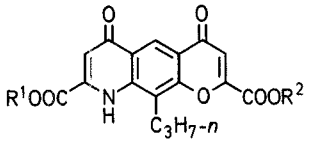
R = H, alkyl
L = leaving group

Scheme **A**

This transformation is inappropriate however when the 4-oxo-1,4-dihydro-quinoline bears other functional groups which react with amines. In particular, attempts at synthesising dialkyl esters (**1**) of 6-methylamino-4-oxo-10-propyl-4*H*-pyrano[3,2-*g*]quinoline-2,8-dicarboxylic acid (minocromil), a promising anti-allergic agent, from the corresponding dihydro-oxoquinoline derivative **2** via the chloroquinoline **3** were unsuccessful.



1 X = NH–CH_3 ; R^1, R^2 = alkyl
3 X = Cl ; R^1, R^2 = alkyl



2 R^1, R^2 = alkyl

We now report a successful new approach to the synthesis of derivatives of 4-aminoquinoline-2-carboxylates from the corresponding 4-oxo-1,4-dihydroquinolines. The reaction of the 4-oxo-1,4-dihydroquinolines, **4a–c**[3], with chlorosulphonyl isocyanate, followed by *in situ* treatment with acid, yields aminoquinoline derivatives, **5a–c** (Method A; Table 1). Surprisingly, we found that in the formation of **5b**, ethyl 4,8-dichloro-3-phenylquinoline-2-carboxylate (*m/e* = 345, 347, 349) was also formed in 23% yield. To minimise such side reactions, we repeated the reaction of **4a–c**, replacing chlorosulphonyl isocyanate by 4-chlorophenoxysulphonyl isocyanate[2], to give on acid work up, **5a–c** in 66–90% yield (Method B; Table 1). In addition we were able to effect a very easy conversion of **4g** to **6**, using chlorosulphonyl isocyanate (Table 1).

We found that simple derivatives of 4-aminoquinoline-2-carboxylates **7a–g**, **8**, **9** could be formed in 65–92% yield (Table 2) by the reaction of **4a–g**[3] with 4-toluenesulphonyl isocyanate, 4-chlorophenoxysulphonyl isocyanate, or trichloroacetyl isocyanate as appropriate (Method C).