2-Imidazolines; Part I. An Improved Synthesis of 1-Aryl- and 1-Acyl-4,5-diamino-4,5-dihydroimidazoles

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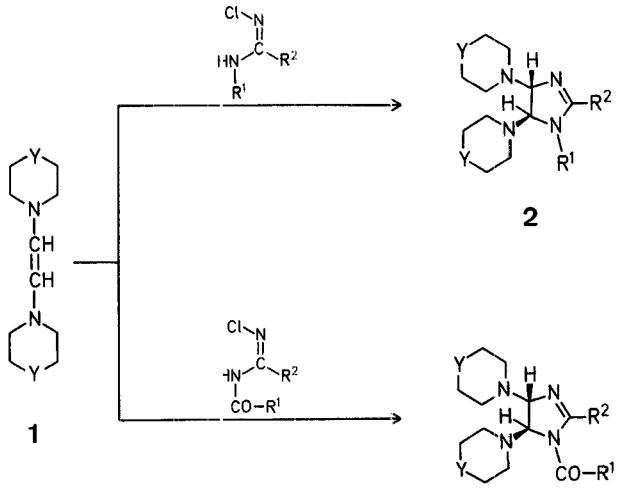
Recently we reported the preparation of *trans*-1-aryl-4,5-diamino-4,5-dihydroimidazoles[1] **2** and *trans*-1-acyl-4,5-diamino-4,5-dihydroimidazoles[2] **3** by reacting 1,2-diaminoethenes **1** with *N*-chloro-*N'*-arylamidines and *N*-chloro-*N'*-acylamidines, respectively, as depicted in Scheme A.



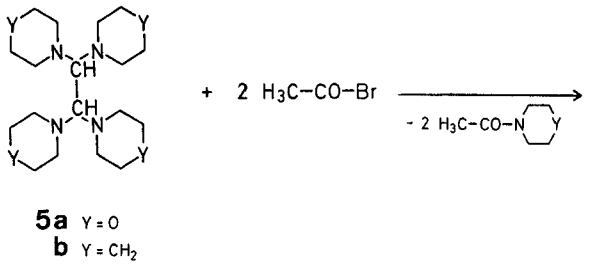
Scheme A

0039-7881/79/0832-0594 $ 03.00

Although this reaction was of preparative interest on a laboratory scale (2–3 g) some problems arise when larger amounts are necessary. There are two main reasons for this: first, the large-scale preparation of 1,2-diaminoethenes is not practicable; second, the *N*-chloroamidines, under the reaction conditions employed, react in part intramolecularly, giving rise to variable amounts of by-products which often must be separated by chromatographic techniques.

Considering the growing biological interest[3] in these imidazole derivatives we have developed a new, practicable, and less expensive synthesis which makes possible the preparation on a scale of several hundred grams. We wish to report these results in this paper.

The diimmonium dibromide **4**, which is easy to prepare by reaction of the readily available 1,1,2,2-tetraaminoethane **5** with acetyl bromide[4], reacts quickly at room temperature either with *N*-arylamidines **6** or with *N*-acylamidines **7** affording imidazolines **2** and **3** in good to high yields and without any purification problems.



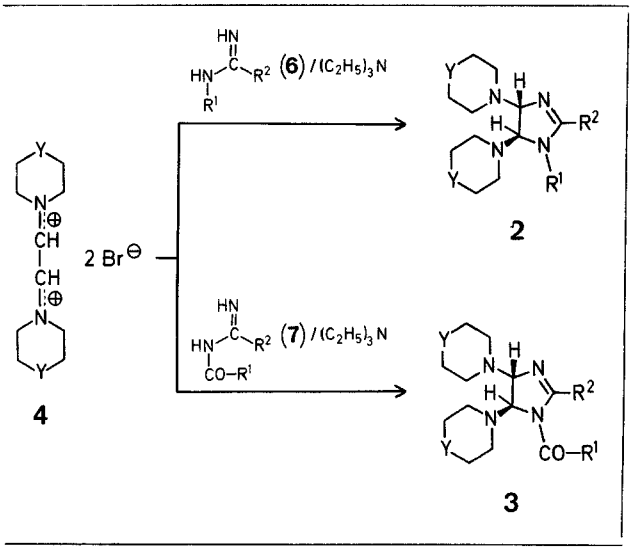
Scheme **B**

Some experiments carried out without isolating the diimmonium dibromide **4** showed that the overall yields are not lowered, but isolation and purification of the products are more complex.

Some of the amidines **6** and **7** are known compounds and different methods of preparation have been described[5,6,7]. The unknown derivatives employed in this work, namely **6**, R^1 = 4-Cl C_6H_4, $R^2 = C_6H_5$, m.p. 112–115°; **7**, R^1 = 2,4-di-Cl C_6H_3, $R^2 = C_6H_5$, m.p. 129–130°, were obtained by the methods described for *N*-phenylbenzamidine[8] and *N*-benzoylacetamidine[7], respectively.

1-Aryl- and 1-Acyl-4,5-diamino-4,5-dihydroimidazoles 2a–f and 3a–h, respectively; General Procedure:

To a stirred solution of acetyl bromide (1.6 mol) in dry dichloromethane (300 ml), cooled at −15°, a suspension of 1,1,2,2-tetramorpholinoethane (**5a**) or 1,1,2,2-tetrapiperidinoethane (**5b**) (0.8 mol) in dry dichloromethane (500–1200 ml) is added dropwise through a dropping funnel. During the addition period the temperature of the reaction mixture is kept in the range −10 to +10°. A fine orange or yellow crystalline precipitate is thus formed. The stirring is continued for 2.5 h at room temperature, then stopped, and the reaction mixture centrifuged at 4000–5000 r/min, the supernatant liquid is decanted and the solid washed with fresh dry dichloromethane, recentrifuged, and freed again from the supernatant liquid.



This operation is repeated twice more to complete the elimination of acetylmorpholine or acetylpiperidine. The solid residue is then suspended in dry dichloromethane (2000 ml) and the suspension transferred in a 10 litre, four-necked, round-bottom flask equipped with a mechanical stirrer, a thermometer, a dropping funnel, and a calcium chloride filled drying tube. The amidine **6** or **7** (0.7 mol)

Table 1. 1-Aryl- and 1-Acyl-4,5-diamino-4,5-dihydroimidazoles **2a–f** and **3a–h**

Product	R^1	R^2	Y	Yield[a] [%]	m.p.	Molecular formula[b] or Lit. m.p.	
2a	C_6H_5	C_6H_5	CH_2	88	193°	192°[1]	
2b	4-F C_6H_4	C_6H_5	CH_2	85	187° (dec.)	$C_{25}H_{31}FN_4$	(406.5)
2c	4-Cl C_6H_4	C_6H_5	CH_2	88	192–195°	$C_{25}H_{31}ClN_4$	(423.0)
2d	4-F C_6H_4	C_6H_5	O	90	189°	189°[1]	
2e	4-Cl C_6H_4	C_6H_5	O	92	202–205°	$C_{23}H_{27}ClN_4O_2$	(427.0)
2f	C_6H_5	CH_3	O	76	103°	$C_{18}H_{26}N_4O_2$	(330.4)
3a	C_6H_5	C_6H_5	CH_2	78	132°	130°[2a]	
3b	4-Cl C_6H_4	C_6H_5	CH_2	76	137°	$C_{26}H_{31}ClN_4O$	(451.0)
3c	2,4-di-Cl C_6H_3	C_6H_5	CH_2	70	162°	$C_{26}H_{30}Cl_2N_4O$	(485.5)
3d	C_6H_5	C_6H_5	O	85	178–180°	178°[2a]	
3e	4-Cl C_6H_4	C_6H_5	O	88	168°	168°[2a]	
3f	4-F C_6H_4	C_6H_5	O	86	136°	134°[2a]	
3g	C_6H_5	CH_3	O	72	151° (dec.)	151° (dec.)[2a]	
3h	$C_6H_5CH_2O$	C_6H_5	O	68	148°	149°[2b]	

[a] Yield based on amidine.

[b] The microanalyses of all new compounds were in satisfactory agreement with the calculated values (C ±0.31, H ±0.16, N ±0.21).

Table 2. Spectroscopic Properties of New Compounds **2** and **3**

Product	^{1}H-N.M.R. ($CDCl_3$): δ [ppm]
2b	1.58 (m, 12H, CH_2 CH_2 CH_2); 2.65 (m, 8H, CH_2 N CH_2); 4.44, 4.71 (AB-system, 2H, H-4 and H-5, J_{AB} = 3.0 Hz); 6.75–7.85 (m, 9H_{arom})
2c	1.52 (m, 12H, CH_2 CH_2 CH_2); 2.6 (m, 8H, CH_2 N CH_2); 4.37, 4.64 (AB-system, 2H, H-4 and H-5, J_{AB} = 2.6 Hz); 7.0–7.8 (m, 9H_{arom})
2e	2.7 (m, 8H, CH_2 N CH_2); 3.74 (m, 8H, CH_2 O CH_2); 4.4, 4.67 (AB-system, 2H, H-4 and H-5, J_{AB} = 2.6 Hz); 6.85–7.75 (m, 9H_{arom})
2f	2.0 (d, 3H, CH_3, $J_{CH_3\ H\text{-}4}$ = 0.9 Hz); 2.68 (m, 8H, CH_2 N CH_2); 3.75 (m, 8H, CH_2 O CH_2); 4.43 (2q, 1H, H-4, $J_{H\text{-}4\ H\text{-}5}$ = 3.6 Hz, $J_{H\text{-}4\ CH_3}$ = 0.9 Hz); 4.71 (d, 1H, H-5, $J_{H\text{-}4\ H\text{-}5}$ = 3.6 Hz); 7.12–7.7 (m, 5H_{arom})
3b	1.52 (m, 12H, CH_2 CH_2 CH_2); 2.62 (m, 8H, CH_2 N CH_2); 4.6, 4.82 (AB-system, 2H, H-4 and H-5, J_{AB} = 3.0 Hz); 7.05–7.82 (m, 9H_{arom})
3c	1.55 (m, 12H, CH_2 CH_2 CH_2); 2.68 (m, 8H, CH_2 N CH_2); 4.52, 5.2 (AB-system, 2H, H-4 and H-5, J_{AB} = 2.0 Hz); 6.84–7.6 (m, 8H_{arom})

and dry triethylamine (1.6 mol) in dry dichloromethane (4000 ml) are added dropwise to the vigorously stirred mixture in 15–30 min. During this period the temperature rises from 20 to 35°. Stirring is continued at room temperature for 1 h. The reaction mixture is washed twice with water; the organic layer is separated, dried with sodium sulfate, and freed from the solvent under reduced pressure to give imidazolines **2** and **3** (see Tables).

Support of this work by the RORER Italiana is gratefully acknowledged.

Received: February 23, 1979

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0039-7881/79/0832-0596 $ 03.00