A Novel, Regioselective One-Pot Synthesis of 3-Aryl-2-chloroimidazo[1,2-*a*]pyridines and -pyrimidines

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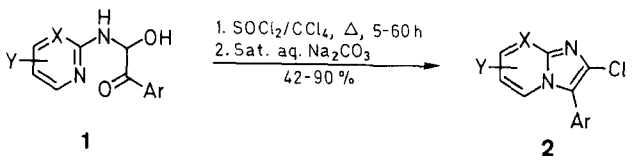
Derivatives of 3-aryl-2-chloroimidazo[1,2-*a*]pyridines and -pyrimidines **2** are prepared in high yields from 2-[(2-aryl-1-hydroxy-2-oxoethyl)amino]pyridines and -pyrimidines **1** by reaction with thionyl chloride, followed by saturated sodium carbonate workup.

The synthesis of imidazo[1,2-*a*]azines has been widely investigated.[1,2] A common feature of most of the reported methods is that C-2 and C-3 of the newly formed imidazole ring, along with the corresponding substituents, are contributed by the reagent used for cyclization. A new strategy for building the C-2-C-3 moiety has been reported recently.[3] However, procedures for the synthesis of imidazo[1,2-*a*]azines with halogen substituents in the imidazole ring are scarce.[4,5] All these methods are based upon electrophilic aromatic substitution on the existing fused imidazole nucleus. Moreover, it is well-known that aromatic halogenation on the imidazo[1,2-*a*]azines yields exclusively the 3-halo derivatives, and only when position 3 is blocked does halogenation occur at position 5.[1,2] To our knowledge only one example of a 2-chloroimidazo[1,2-*a*]azine, namely 2-chloroimidazo [1,2-*a*]pyridine prepared by reaction of imidazo[1,2-*a*]pyridin-2-one with phosphoryl chloride, has been reported.[5] However, it has been reported that 2-chloro-3-nitroimidazo[1,2-*a*]pyridine undergoes, after *N*-methylation, smooth substitution with appropriate nucleophilic reagents yielding some useful mesoionic derivatives of the imidazo[1,2-*a*]pyridinium system.[6]

Recently, we reported that 2-[(2-aryl-1-hydroxy-2-oxoethyl)amino]pyridines and pyrimidines **1**, readily accessible by reaction of 2-aminoheterocycles and arylglyoxals, easily undergo Lewis acid catalyzed intramolecular condensation processes to give bicyclic mesoionic 2-aryl substituted imidazo[1,2-*a*]azine derivatives in high yield.[7] As a part of a general study on the reactivity and synthetic applications of (2-aryl-1-hydroxy-2-oxoethyl)aminoheteroarenes **1**, we report herein a new and totally regioselective one-pot procedure for the preparation of substituted 3-aryl-2-chloroimidazo[1,2-*a*]azines **2** by intramolecular condensation of compounds **1** in the presence of thionyl chloride. 2-Chloro derivatives **2** are of potential interest as precursors for other 2-substituted derivatives and related mesoionic imidazo[1,2-*a*]azinium systems.

The treatment of **1** with an excess of thionyl chloride in carbon tetrachloride as cosolvent at reflux afforded compounds **2** as their hydrochlorides, the free bases being obtained upon reaction with aqueous sodium carbonate (Scheme A). Reaction conditions, yields, and physical and spectroscopic data are collected in Tables 1–3.



1 2

2	X	Y	Ar
a	CH	H	4-$CH_3C_6H_4$
b	CH	5-CH_3	4-$CH_3C_6H_4$
c	CH	6-CH_3	4-$CH_3C_6H_4$
d	CH	7-CH_3	4-$CH_3C_6H_4$
e	CH	6-Cl	4-$CH_3C_6H_4$
f	CH	6-CH_3	4-$CH_3OC_6H_4$
g	CH	6-Cl	4-$CH_3OC_6H_4$
h	CH	6-Cl	Ph
i	CH	6-CH_3	4-ClC_6H_4
j	N	H	Ph
k	N	H	4-$CH_3C_6H_4$
l	N	H	4-ClC_6H_4

Scheme A

Table 1. Imidazo[1,2-*a*]pyridines and -pyrimidines **2** Prepared

Product	Reaction Time (min)	Yield[a] (%)	mp[b] (°C)	Molecular Formula[c]
2a	5	76[e]	oil	$C_{14}H_{11}ClN_2$ (242.7)
2b	5	42[e]	oil	$C_{15}H_{13}ClN_2$ (256.7)
2c	7	68[e]	132–134	$C_{15}H_{13}ClN_2$ (256.7)
2d	5	62[e]	110–112	$C_{15}H_{13}ClN_2$ (256.7)
2e	5	60[e]	146–148	$C_{14}H_{10}Cl_2N_2$ (277.1)
2f	10	90[d]	135–136	$C_{15}H_{13}ClN_2O$ (272.7)
2g	10	80[d]	172–174	$C_{14}H_{10}Cl_2N_2O$ (293.1)
2h	5	84[d]	134–135	$C_{13}H_8Cl_2N_2$ (263.1)
2i	5	90[e]	129–130	$C_{14}H_{10}Cl_2N_2$ (277.1)
2j	20	73[d]	211–213	$C_{12}H_8ClN_3$ (229.6)
2k	20	85[e]	227–228	$C_{13}H_{10}ClN_3$ (243.7)
2l	60	90[e]	178–180	$C_{12}H_7Cl_2N_3$ (264.1)

[a] Yield of isolated product **2** based on **1**. All compounds **2** were recrystallized from MeOH.

[b] Uncorrected, measured with a Büchi 512 apparatus.

[c] Satisfactory microanalyses obtained: C ±0.29, H ±0.07, N ±0.13, Cl ±0.30.

[d] Purified by crystallization.

[e] Purified by flash chromatography using silica gel 60 (230–400 mesh ASTM).

Table 2. ^{1}H-NMR Data of Imidazo[1,2-*a*]pyridines and -pyrimidines **2**[a]

Product	δ				*J*(Hz)					
	H-5	H-6	H-7	H-8	J_{5-6}	J_{5-7}	J_{5-8}	J_{6-7}	J_{6-8}	J_{7-8}
2a	8.09	6.78	7.19	7.54	6.80	1.10	≤0.5	6.80	0.92	9.01
2b		6.50	7.12	7.47				6.96	≤0.5	9.03
2c	7.89		7.06	7.46		1.60	≤0.5			9.18
2d	8.00	6.63		7.31	7.02		0.73		1.83	
2e	8.14		7.19	7.52		1.95	0.85			9.52
2f	7.84		7.06	7.46		1.71	1.10			9.15
2g	8.09		7.18	7.51		1.95	0.85			9.52
2h	8.16		7.19	7.52		1.94	≤0.5			9.60
2i	7.87		7.11	7.48		1.71	0.49			9.15
2j	8.49	6.95	8.56		6.96	2.01		4.15		
2k	8.47	6.95	8.53		6.84	2.07		4.15		
2l	8.43	6.96	8.60		6.90	1.71		4.15		

[a] 300 MHz, $CDCl_3$/TMS. Recorded on a Varian XL-300 and on a Bruker ACE-300.

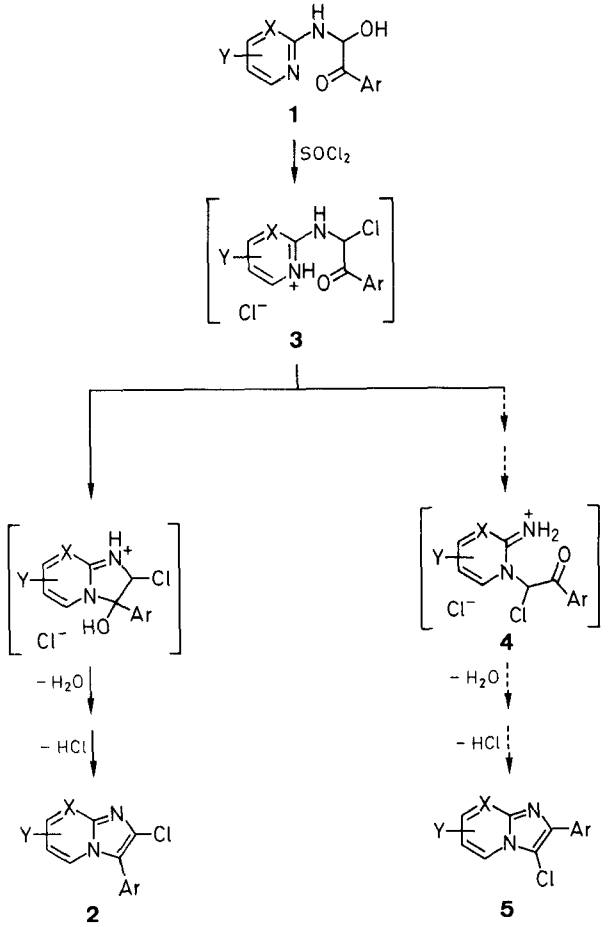
Table 3. ^{13}C-NMR Data of Imidazo[1,2-*a*]pyridines and -pyrimidines **2**[a]

Product	C-2	C-3	C-5	C-6	C-7	C-8	C-9
2a	133.2	119.4	124.8	112.7	122.9	116.8	142.8
2b	134.3	120.0	136.1	113.6	124.8	115.0	144.1
2c	133.0	119.2	120.7	122.5	128.0	116.3	141.9
2d	132.8	118.8	122.3	115.3	136.1	115.3	143.3
2e	134.2	120.1	120.8	121.2	126.0	117.2	141.0
2f	133.0	119.0	120.7	122.4	127.8	116.3	141.8
2g	134.2	120.1	120.9	121.2	126.1	117.4	141.0
2h	134.5	120.2	120.9	121.4	126.4	117.5	141.3
2i	133.6	118.0	120.5	122.9	128.4	116.6	142.2
2j	135.6	118.3	130.5	109.4	150.9	–	145.8
2k	135.2	118.3	130.5	109.2	149.7		145.5
2l	136.1	117.3	130.4	109.6	150.2		146.0

[a] 75 MHz, $CDCl_3$/TMS. Recorded on a Varian XL-300 and on a Bruker ACE-300.

Spectroscopic and analytical data are in accordance with the structures of fused imidazole **2** proposed. Thus, the chemical shifts are the most significant coupling constants are generally in good agreement with those described for related imidazo[1,2-*a*]azines.[8] However, with the available data, it was not possible to distinguish between the two expected regioisomers **2** and **5**, whose formation would have occurred through chloroamine **3** as shown in Scheme **B**. Formation of **5** from **3** would involve previous isomerization to **4** in a process related to some isomerization equilibria of the Chapman-type[9] prior to cyclization. Although less likely, this later possibility could not be discarded a priori. It is known that intermediates related to **4** cyclize with ease, while those related to **3** cyclize only with difficulty.[10] An X-ray crystallographic analysis[11] of compound **2h** confirmed unambiguously the structure and regiochemistry as 3-aryl-2-chloro- and not 2-aryl-3-chloro-substitution and hence the structure as **2** (Figure). Bond distances and angles are given in Table 4.

Derivatives of 3-aryl-2-chloroimidazo[1,2-*a*]pyridines **2a–i** and 3-aryl-2-chloroimidazo[1,2-*a*]pyrimidines **2j–l** were prepared in a simple and regiospecific fashion



Scheme **B**

in good to excellent yields. The method represents a new one-pot synthesis of 2-aryl-3-chloroimidazo-[1,2-*a*]-pyridines and -pyrimidines. The reaction fails with 2-(2-aryl-1-hydroxy-2-oxoethyl)amino derivatives of pyrazines and azoles. In these later cases, only the corresponding intermediate chloroamines **3** were obtained (as their hydrochlorides), and these did not cyclize to the imidazo[1,2-*a*]derivatives even after prolonged reaction times, only decomposition products were obtained.

Table 4. Selected Bond Distances (Å) and Angles (deg) for Compound **2h**.

Cl(2)–C(6)	1.723 (3)	C(9)–N(1)–C(2)	104.6 (3)	Cl(2)–C(6)–C(5)	119.2 (2)
Cl(1)–C(2)	1.714 (2)	C(9)–N(4)–C(3)	107.2 (2)	C(7)–C(6)–C(5)	122.6 (3)
N(1)–C(9)	1.327 (4)	C(5)–N(4)–C(3)	131.0 (2)	Cl(2)–C(6)–C(5)	118.3 (2)
N(1)–C(2)	1.346 (4)	C(5)–N(4)–C(9)	121.6 (2)	C(8)–C(7)–C(6)	119.3 (3)
N(4)–C(5)	1.377 (3)	Cl(1)–C(2)–N(1)	119.3 (2)	C(7)–C(8)–C(9)	120.1 (3)
N(4)–C(9)	1.400 (3)	Cl(1)–C(2)–C(3)	126.4 (2)	N(4)–C(9)–C(8)	118.7 (3)
N(4)–C(3)	1.392 (3)	N(1)–C(2)–C(3)	114.2 (3)	N(1)–C(9)–C(8)	130.4 (3)
C(8)–C(7)	1.346 (5)	N(4)–C(3)–C(2)	103.1 (2)	N(1)–C(9)–N(4)	110.9 (3)
C(8)–C(9)	1.407 (4)	N(4)–C(3)–C(10)	124.4 (2)	C(3)–C(10)–C(11')	120.2 (2)
C(7)–C(6)	1.409 (4)	C(2)–C(3)–C(10)	132.3 (3)	C(3)–C(10)–C(11)	121.1 (2)
C(6)–C(5)	1.359 (4)	N(4)–C(5)–C(6)	117.5 (2)		
C(2)–C(3)	1.376 (4)				
C(3)–C(10)	1.460 (3)				

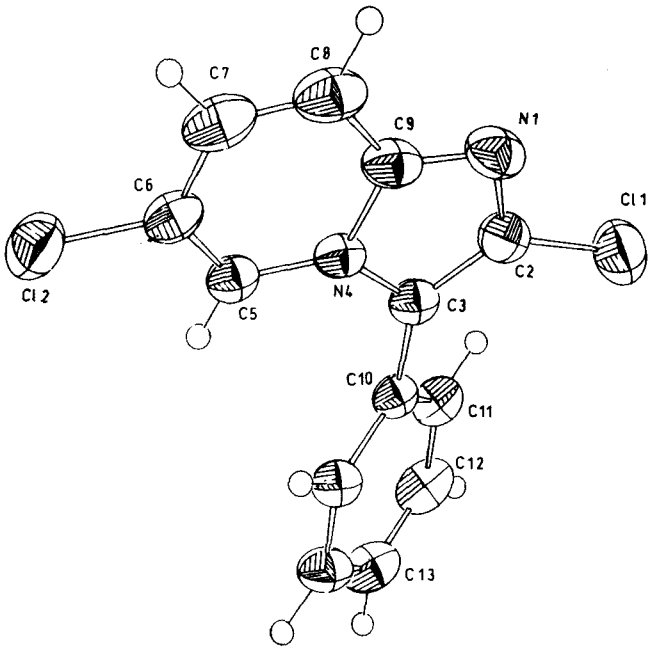


Figure. X-ray crystallographic structure of **2h**

3-Aryl-2-chloroimidazo[1,2-*a*]pyridines and -pyrimidines 2; General Procedure:

$SOCl_2$ (10 mL) is added in one portion to a vigorously stirred suspension of **1**[7] (0.5 g) in CCl_4 (6 mL) at r.t. The solution thus obtained is heated under reflux for the time indicated in Table 1. The solvent is evaporated under reduced pressure and the residue is taken up in CCl_4. The solvent is evaporated again and the resulting residue (solid or oil) is throughly dried *in vacuo* to eliminate traces of $SOCl_2$. The residue is taken up in CH_2Cl_2 (20 mL) and extracted with sat. Na_2CO_3 solution (20 mL). The aqueous phase is extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts are washed with brine (20 mL) and dried ($MgSO_4$). The solvent is evaporated and the crude product is purified by crystallization (MeOH) or flash column chromatography (silica gel, hexane/EtOAc, 3:1) (Table 1).

2h: orthorombic, space group Pbca, Z = 8, a = 11.1958(9), b = 7.737(1), c = 26.978(2) Å, V = 2336(4) Å^3, 4002 reflections were collected in a Euraf-Nonius CAD4 diffractometer using graphite monochromated Mo-kα (0.71069 Å) radiation. The structure was solved by direct and Fourier methods. The final refinements led to R = 0.048.

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(1) Paolini, J.P., in: *Special Topics in Heterocyclic Chemistry*, Weissberger, A.; Taylor, E.C. (eds.), John Wiley and Sons, New York, 1977, p. 1.
(2) Montgomery, J.A.; Secrist III, J.A., in: Katritzky and Rees *Comprehensive Heterocyclic Chemistry*, Vol *5*, Potts, K.T. (ed.), Pergamon Press, Oxford 1984, p. 607.
(3) Podergajs, S.; Stanovnik, B.; Tisler, M. *Synthesis* **1984**, 263.
(4) Paudler, W.W. *J. Org. Chem.* **1976**, *41*, 3549 and references therein.
(5) Paolini, J.P.; Robins, R.K. *J. Heterocyclic Chem.* **1965**, *2*, 53.
(6) Newton, Ch.G.; Ollis, W.D.; Wrigth, D.E. *J. Chem. Soc., Perkin Trans 1* **1984**, 69.
(7) Alcaide, B.; Pérez-Ossorio, R.; Plumet, J.; Sierra, M.A. *Tetrahedron Lett.* **1986**, *27*, 1627.
Alcaide, B.; Plumet, J.; Sierra, M.A.; Vicent, C. *J. Org. Chem.* **1989**, *54*, 5763.
(8) Blewitt, H.L., in: *Special Topics in Heterocyclic Chemistry*, Weissberger, A.; Taylor, E.C. (eds.), John Wiley and Sons, New York, 1977, Chap. II, p. 126.
(9) Stevens, T.S.; Watts, W.E., in: *Selected Molecular Rearrangements*, Van Nostrand Reinhold, New York, 1973, p. 67.
(10) Elliot, A.J.; Guzik, H.; Soler, R. *J. Heterocyclic Chem.* **1982**, *19*, 1437.
(11) The atomic coordinates for this work are available from the Gesellschaft für wissenschaftlich-technische Information mbH. Eckenstein-Leopoldshafen 2. D-7514 Karlsruhe.