A New, Convenient Synthesis of N^2-Aryl-N^1-alkylformamidines and N^2-Aryl-N^1,N^1-dialkylformamidines

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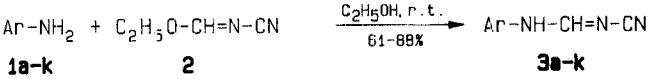
N^2-Aryl-N^1-alkylformamidines are conveniently and rapidly prepared by the reaction of an aromatic amine with ethyl *N*-cyanoformimidate to give the N^2-aryl-N^1-cyanoformamidine. Addition of this intermediate to an excess of an alkyl- or dialkylamine results in the formation of the title compounds in high yield and satisfactory purity. A mechanism for this reaction is proposed and discussed.

Formamidines, derivatives of the unstable imidic acid, have been extensively studied chemically in the past and are now of increasing interest in the medicinal chemistry. Recently, some compounds containing moieties of the formamidine type have been reported to possess pharmacological activity[1,2,3].

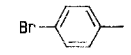
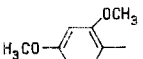
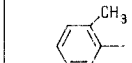
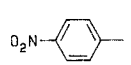
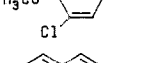
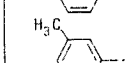
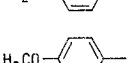
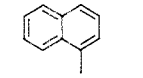
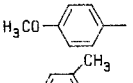
The reaction of an amine with a suitable reactive derivative of a formamide is widely used for the synthesis of formamidines. The activation of the formamide is a necessary prerequisite since the formamide carbon atom is not available for nucleophilic attack by an amine. Imidoyl chlorides[4,5,6,7] (generated by the action of phosphorus pentachloride, phosphoryl chloride, or thionyl chloride) or alkoxy derivatives[8] (generated by the action of triethyloxonium fluoroborate) have been utilized as activated forms of formamides in formamidine syntheses. All these intermediates are rather unstable and difficult to handle and furthermore, despite the strict reaction requirements, they provide the desired compounds in moderate to poor yields and purity, owing to some side-reactions. The reaction of amines with trialkyl orthoformates is another general method for formamidine synthesis[9,10,11,12], with the restriction that only N^1,N^2-symmetrically substituted formamidines are obtained. In some special cases, formamidines have been also prepared by reduction of the corresponding thioureas with Raney nickel[13] or the corresponding amides with sodium borohydride[14].

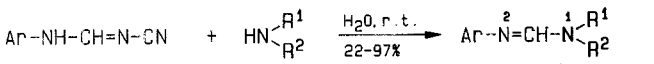
During the synthesis of mifentidine (N^2-isopropyl-N^1-[(imidazol-4-yl)-phenyl]formamidine) and analogues, which represent a new class of antiulcer agents acting as histamine H_2 antagonists[3,15,16], a simple and quick method for the synthesis of N^2-heteroaryl- or -phenyl-N^1-alkylformamidines was needed. All the previously quoted methods proved unsatisfactory when applied to the preparation of these slightly complex formamidines. Long times were needed for their preparation, owing to the tedious synthesis of different reactive intermediates. The yields were poor and, above all, the purity of the compounds was unsatisfactory. The cumbersome manipulations required for the purification and the isolation of the products were the actual limiting step for the classic synthetic methods: it is well known that formamidines are not particularly stable under all the conditions met during the purification processes.

An original method was therefore developed which succeeded in overcoming the above-mentioned drawbacks. The efficiency, the mildness, the applicability, and the scope of



1a-k **2** **3a-k**

1, 3	Ar	1, 3	Ar	1, 3	Ar
a		e		i	
b		f		j	
c		g		k	
d		h			



3a-k **4** **5aa-kd**

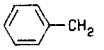
4	R^1	R^2	4	R^1	R^2
a	CH_3	H	g	$H_2C=CH-CH_2$	H
b	C_2H_5	H	h	c-C_6H_{11}	H
c	n-C_3H_7	H	i		H
d	i-C_3H_7	H	j	CH_3	CH_3
e	t-C_4H_9	H	k	$-(CH_2)_4-$	
f	t-$C_4H_9-CH_2$	H			

Table 1. N^2-Aryl-N^1-cyanoformamidines **3a–k**

Product	Yield [%][a]	m.p. [°C]	Molecular Formula[b] or Lit. m.p. [°C]	I.R. (Nujol) [cm^{-1}] ν_{NH}	ν_{CN}	^{1}H-N.M.R. ($CDCl_3$/DMSO-d_6/TMS) δ [ppm]
3a	84	142–143°	144–145°[21]	3190	2200	7.0–7.7 (m, 5H); 8.44–9.02 (s, br. s, 1H); 11.2 (br. s, 1H)
3b	78	104–105°	95–97°[22]	3190	2200	2.25–2.29 (2s, 3H); 7.1–7.7 (m, 4H); 8.40–8.53 (d, br. d, J = 4.6 Hz, 1H); 10.18–10.81 (2d, J = ~4 Hz, ~13 Hz, 1H)
3c	66	161–162°	158–160°[21]	3180	2210	2.31 (s, 3H); 6.9–7.5 (m, 4H); 8.41–9.00 (2d, J = 5 Hz, ~10 Hz, 1H); 10.72–12.19 (br. s, br. d, J = ~10 Hz, 1H)
3d	77	182–183°	183–185°[21]	3190	2210	2.31 (s, 3H); 7.0–7.6 (m, 4H); 8.41–8.88 (2d, J = 5 Hz, ~9 Hz, 1H); 10.72–12.19 (br. s, br. d, J = ~10 Hz, 1H)
3e	68	196–198°	202–204°[21]	3190	2200	7.1–7.6 (m, 4H); 8.48–8.91 (2d, J = 5 Hz, ~9 Hz, 1H); 10.24–10.75 (br. s, br. d, J = ~10 Hz, 1H)
3f	88	185–187°	193–196°[21]	3200	2210	7.1–7.7 (m, 4H); 8.38–8.90 (2d, J = 5 Hz, 10 Hz, 1H); 10.21–10.89 (br. s, br. d, J = ~10 Hz, 1H)
3g	75	143–144°	143–145°[21]	3200	2200	3.77 (s, 3H); 6.90 (d, J = 9 Hz, 2H); 7.25–7.59 (2d, J = 9 Hz, 2H); 8.38–8.81 (br. d, br. s, J = ~4 Hz, 1H); 10.67–11.07 (2 br. s, 1H)
3h	68	167–169°	$C_{10}H_{11}N_3$ (173.2)	3200	2190	2.19–2.22 (2s, 6H); 7.11 (br. s, 3H); 8.51 (d, 1H); 10.15 (br. s, 1H)
3i	61	175–177°	$C_{10}H_{10}ClN_3O_2$ (239.7)	3160	2210	3.90–3.91 (2s, 6H); 6.78 (s, 1H); 7.33–8.02 (2s, 1H); 8.31–8.60 (s, br. s, 1H); 10.27 (br. s, 1H)
3j	63	180–182°	190–192°[21]	3160	2210	7.3–8.2 (m, 7H); 8.68 (s, br. s, 1H); 10.85–11.2 (2br. s, 1H)
3k	82	173–175°	$C_7H_6N_4$ (146.2)	3160	2210	~7.95 (br. m, 2H); 8.70 (d, J = 7 Hz, 2H); 9.32 (br. s, 1H)[c]

[a] Yield of isolated product; purity checked by G.L.C.
[b] Satisfactory microanalyses obtained: C ±0.22, H ±0.18, N ±0.15.
[c] CF_3COOD added.

the reaction are illustrated here by application of this method to the preparation of a series of N^2-aryl-N^1-alkylformamidines.

In the first step the aromatic amine **1** dissolved in a suitable solvent (ethanol is the solvent of choice, but also diethyl ether, tetrahydrofuran, ethyl acetate, or dichloromethane can be conveniently used) is allowed to react with ethyl *N*-cyanoformimidate[17] **(2)** at room temperature. Analogous reactions of **2** (and related compounds) with amines under different reaction conditions have been described[17,18,19,21,22]. Within 1 h under stirring, the N^1-cyano-N^2-arylformamidine **3** crystallizes out and is isolated in a pure form simply by filtration (Table 1). This intermediate is used immediately in the second step of the process but it is sufficiently stable to be stored for several months, if desired. It is added portionwise to an excess of the amine **4** (5 or 6 equiv) at room temperature. The *N*-cyano derivative **3** immediately dissolves and reacts slightly exothermically with the amine to give in a few minutes (usually within 10 min) the corresponding N^2-aryl-N^1-alkylformamidine **5** which can be isolated in moderate to high yields and in a pure form simply by filtration or distillation (Table 2).

This new reaction may be classified within the pattern of the synthesis of formamidines starting from a reactive derivative of a formamide: the Ar—NH—CH=N—CN system possesses suitable features to be envisaged as an activated formamido derivative equivalent. The moiety =N—CN (*N*-cyanoimino) owing to the electron-withdrawing effect of the cyano group, contributes to an exceptionally favourable nucleophilic reactivity at the amidine carbon atom by amines. The lack of electrons at that carbon is even enhanced by the presence of a phenyl ring on the other nitrogen atom.

A possible mechanism is outlined here and can be postulated as follows. The amine **4** would attack the formamidine carbon atom of both tautomeric forms **A** and **A'** of **3**. The low energy transition state is represented by the **B** and **B'** forms which are likely to possess different probability and stability. The $[H—N—CN]^{\ominus}$ species, owing to its good nucleofugacity and its high affinity for a proton, is split as a leaving group from the **B'** form[20]. Cyanamide and N^2-aryl-N^1-alkylformamidine **5** are then obtained in the last step following a simple proton transfer.

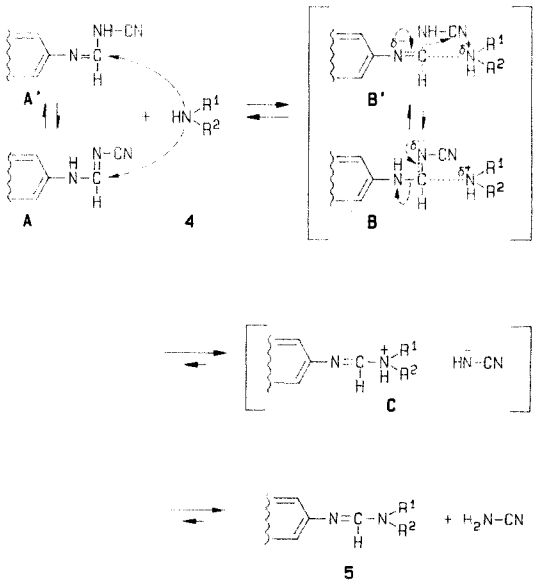


Table 2. N^2-Aryl-N^1-alkylformamidines **5aa–kd**

Reactants	Product	Yield [%][a]	m.p. [°C] or b.p. [°C]/torr	Molecular Formula[b] or Lit. Data	I.R. (Nujol) [cm^{-1}] ν_{NH}	$\nu_{C=N}$	^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm]
3a + **4a**	**5aa**	85	89–90°	88–89°[23]	3220	1680	2.91 (s, 3H); 5.38 (br. s, 1H); 6.8–7.5 (m, 5H); 7.58 (s, 1H)
3a + **4b**	**5ab**	71	62–63°	60–61°[24]	3160	1680	1.19 (t, J = 7 Hz, 3H); 3.32 (q, J = 7 Hz, 2H); 5.5 (br. s, 1H); 6.8–7.4 (m, 5H); 7.55 (s, 1H)
3a + **4d**	**5ad**	90	80–82°	$C_{10}H_{14}N_2$ (162.2)	3180	1680	1.20 (d, J = 6 Hz, 6H); 3.85 (m, J = 6 Hz, 1H); 5.15 (br. s, 1H); 6.8–7.4 (m, 5H); 7.50 (s, 1H)
3a + **4e**	**5ae**	22	88–89°	–[c]	3200	1670	1.30 (s, 9H); 5.83 (br. s, 1H); 6.8–7.4 (m, 5H); 7.70 (s, 1H)
3a + **4f**	**5af**	96	90–92°	$C_{12}H_{18}N_2$ (190.3)	3260	1630	0.91 (s, 9H); 3.03 (s, 2H); ~5.6 (br. s, 1H); 6.8–7.4 (m, 5H); 7.50 (s, 1H)
3a + **4g**	**5ag**	70	51–52°	49–50°[24]	3120	1680	3.91 (d, J = 6 Hz, 2H); 5.0–5.4 (m, 2H); ~5.0–7.0 (br. s, 1H); 5.62–6.25 (m, 1H); 6.8–7.4 (m, 5H); 7.59 (s, 1H)
3a + **4h**	**5ah**	95	116–117°	116°[14]	3220	1620	0.7–2.2 (m, 10H); 3.52 (br. s, 1H); 5.11 (br. s, 1H); 6.8–7.4 (m, 5H); 7.59 (s, 1H)
3a + **4i**	**5ai**	93	76–77°	$C_{14}H_{14}N_2$ (210.3)	3150	1670	4.42 (s, 2H); 5.7 (br. s, 1H); 6.8–7.4 (m, 5H); 7.61 (s, 1H)
3a + **4j**	**5aj**	64	72–73°/0.1	68–71°/0.05[26]	–	1640	2.98 (s, 6H); 6.8–7.4 (m, 5H); 7.48 (s, 1H)
3a + **4k**	**5ak**	62	108–109°/0.06	115–117°/0.05[27]	–	1630	1.91 (m, 4H); 3.50 (m, J = 7 Hz, 4H); 6.8–7.4 (m, 5H); 7.73 (s, 1H)
3b + **4c**	**5bc**	46	100–101°/0.06	$C_{11}H_{16}N_2$ (176.3)	3230	1640	0.92 (t, J = 7 Hz, 3H); 1.57 (m, 2H); 2.27 (s, 3H); 3.28 (t, J = 7 Hz, 2H); 4.78 (br. s, 1H); 6.6–7.3 (m, 4H); 7.41 (s, 1H)
3c + **4d**	**5cd**	82	59–60°	$C_{11}H_{16}N_2$ (176.3)	3210	1640	1.19 (d, J = 6 Hz, 6H); 2.30 (s, 3H); 3.82 (m, 1H); 5.52 (br. s, 1H); 6.6–7.3 (m, 4H); 7.52 (s, 1H)
3d + **4d**	**5dd**	94	92–94°	90–92°[28]	3220	1640	1.21 (d, J = 6 Hz, 6H); 2.30 (s, 3H); 4.59 (br. s, 1H); 3.88 (m, 1H); 6.80 (d, J = 8 Hz, 2H); 7.08 (d, J = 8 Hz, 2H); 7.53 (s, 1H)
3e + **4d**	**5ed**	60	104–105°	$C_{10}H_{13}BrN_2$ (241.1)	3210	1630	1.21 (d, J = 6 Hz, 6H); 3.91 (m, 1H); 4.41 (br. s, 1H); 6.80 (d, J = 8 Hz, 2H); 7.38 (d, J = 8 Hz, 2H); 7.53 (s, 1H)
3f + **4d**	**5fd**	75	82–84°	$C_{10}H_{13}N_3O_2$ (207.2)	3200	1640	1.22 (d, J = 6 Hz, 6H); 3.90 (m, 1H); 4.41 (br. s, 1H); 6.79 (d, J = 8 Hz, 2H); 7.42 (d, J = 8 Hz, 2H); 7.55 (s, 1H)
3g + **4d**	**5gd**	94	96–97°	$C_{11}H_{16}N_2O$ (192.3)	3220	1630	1.19 (d, J = 7 Hz, 6H); 3.75 (s, 3H); 3.87 (m, 1H); 5.05 (br. s, 1H); 6.85 (s, 4H); 7.50 (s, 1H)
3h + **4c**	**5hc**	44	93–95°/0.05	$C_{12}H_{18}N_2$ (190.3)	3230	1650	0.92 (t, J = 7 Hz, 3H); 1.55 (m, 2H); 2.12 (s, 6H); 3.2 (t, J = 7 Hz, 2H); 4.89 (br. s, 1H); 6.7–7.1 (m, 3H); 7.18 (s, 1H)
3i + **4c**	**5ic**	97	113–114°	$C_{12}H_{17}ClN_2O_2$ (256.7)	3210	1630	0.95 (t, J = 7 Hz, 3H); 1.61 (m, 2H); 3.28 (t, J = 7 Hz, 2H); 3.82–3.89 (2s, 6H); ~4.9–5.6 (br. s, 1H); 6.52 (s, 1H); 6.88 (s, 1H); 7.57 (s, 1H)
3j + **4d**	**5jd**	94	80–81°	$C_{14}H_{16}N_2$ (212.3)	3150	1670	1.19 (d, J = 7 Hz, 6H); 4.02 (m, 1H); 4.75 (br. s, 1H); 3.82–3.89 (2s, 6H); ~4.9–5.6 (br. s, 1H); 6.52 (s, 1H); 6.88 (s, 1H); 7.57 (s, 1H)
3k + **4d**	**5kd**	60	213–214°[d]	$C_9H_{13}N_3$ (163.2)	3200	1630	1.17 (d, J = 6 Hz, 6H); ~4.0 (br. s, 1H); 6.85 (d, J = 6 Hz, 2H); 7.68 (s, 1H); 8.37 (d, J = 6 Hz, 2H)

[a] Yield of isolated product; purity checked by G.L.C.
[b] Satisfactory microanalyses obtained: C ±0.22, H ±0.18, N ±0.15.
[c] Ref.[25], m.p. of oxalate salt: 192°C.
[d] m.p. of hydrochloride.

In conclusion, the present method is convenient by virtue of its simplicity of performance, the nature of the reagents used, the purity of the products obtained in high yields, and the short times. In addition it can be used for large scale preparations and it looks promising also when applied to complex or labile substrates. There are only a few restrictions regarding the amine **4**. Amines possessing a high steric hindrance like *t*-butylamine or amines of only slight basicity like aromatic amines cannot be conveniently used in this new process. These two restrictions are indirectly a confirmation of the proposed mechanism.

Melting points were determined on a Büchi apparatus and are uncorrected. The I.R. spectra were recorded on a Perkin-Elmer grating infrared spectrophotometer and the ^{1}H-N.M.R. spectra on a Varian T-60 spectrophotometer. The microanalyses were in good agreement with the calculated values. The aromatic **(1)** and the aliphatic amines **(4)** are commercially available (Aldrich Chemical Co or C. Erba Co).

N^2-Aryl-N^1-cyanoformamidines 3; General Procedure:
To a stirred solution of the aromatic amine **1** (0.1 mol) in ethanol (40 ml) or another compatible solvent, ethyl *N*-cyanoformimidate[17] (**2**; 0.1 mol) is added dropwise at room temperature. In a short time a precipitate forms, the suspension is stirred for 2 h and then filtered (Table 1).

N^2-Aryl-N^1-alkylformamidines 5; General Procedure:
The N^2-aryl-N^1-cyano formamidine **3** (0.1 mol) is added portionwise to an excess (0.5 or 0.6 mol) of the stirred aliphatic amine **4** containing some water (10 ml). A clear solution results from which in a few minutes a white solid crystallizes out. Water (20 ml) is added to the suspension and the white solid is filtered and dried. Compounds **5aj, 5ak, 5bc**, and **5hc** which separate as oily products are extracted into ethyl acetate, isolated, and purified by distillation (Table 2).

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