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1,2-DIARYL-4-AMINO-4,5-DIHYDRO-5,5-DISUBSTITUTED IMIDAZOLES: BEHAVIOUR IN ACIDIC MEDIUM

LUISA CITERIO, DONATO POCAR, MARIA LUISA SACCARELLO and RICCARDO STRADI*
Istituto di Chimica Organica della Facoltà di Farmacia, Università di Milano, Viale Abruzzi 42, 20131 Milano, Italy

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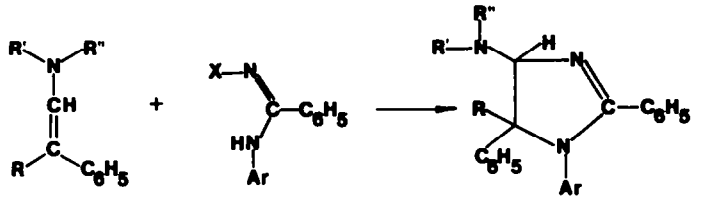
Abstract—The behaviour of 1,2,5-triaryl-4-amino-5-methyl-4,5-dihydro-imidazoles **2a–e** and 1,2,5,5-tetraphenyl-4-morpholino-4,5-dihydro-imidazole **2f** in acidic medium was studied. By heating in 50% H_2SO_4, 1,2,4-triaryl-5-methyl-imidazoles and 1,2,4,5-tetraphenyl-imidazole were obtained. When 5-aryl-5-methyl-derivatives were reacted with various nucleophiles in acidic medium the corresponding 4-substituted imidazolines were formed. Generally, only one isomer (*viz E*) was obtained. The 5,5-diaryl-derivative afforded the 1,2,4,5-tetraphenyl-imidazole even in the presence of nucleophiles.

Recently we reported that *N*-halo-*N'*-aryl-benzamidines react with enamines of general formula **1** affording 1,2-diaryl-4-amino-4,5-dihydro-imidazoles disubstituted at the 5-position **2** in good yield.[1]

In this paper we wish to report our findings about the chemical behaviour of this new class of imidazole derivatives in acidic medium. By treating imidazolines **2a–f** with 50% H_2SO_4 at 130° a complete conversion to the imidazoles **3a–d** was obtained.

The 1,2,4-triaryl-5-methyl-imidazole structure of compounds **3a–c** was assigned on the basis of the preferred anionotropic shift of the phenyl group with respect to the methyl group and confirmed by independent synthesis of imidazole **3a** which was prepared by condensation of *N*-benzoyl-α-anilino-propiophenone with ammonium acetate in boiling acetic acid.

The above aromatization process can also be completed in anhydrous medium by refluxing the imidazolines **2a–f** in 1,1,2-trichloroethane and in the presence of an equimolecular amount of dry triethylammonium chloride.



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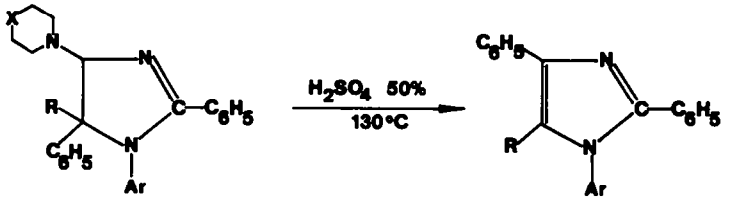
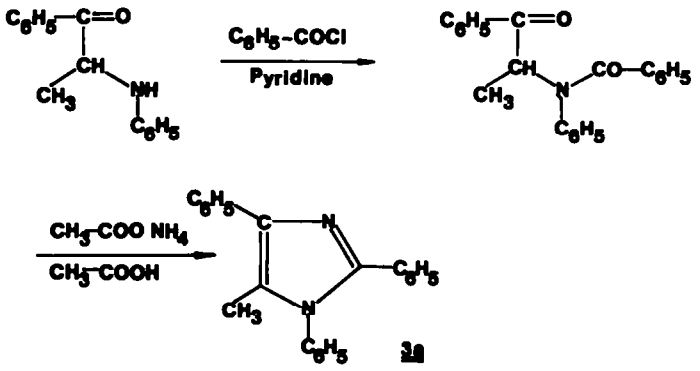
block 1



2 a	Ar = C_6H_5;	R = CH_3;	X = O	**3 a**	Ar = C_6H_5;	R = CH_3
b	Ar = $C_6H_4CH_3$(4);	R = CH_3;	X = O	**b**	Ar = $C_6H_4CH_3$(4);	R = CH_3
c	Ar = C_6H_4F(4);	R = CH_3;	X = O	**c**	Ar = C_6H_4F(4);	R = CH_3
d	Ar = C_6H_4F(4);	R = CH_3;	X = CH_2	**d**	Ar = C_6H_5;	R = C_6H_5
e	Ar = C_6H_4F(4);	R = CH_3;	X = –			
f	Ar = C_6H_5;	R = C_6H_5;	X = O			

block 2



block 3

By employing hydrochloric acid at various concentrations (10–35%) at 80–110° instead of sulfuric acid only imidazoline **2f** afforded the corresponding 1,2,4,5-tetraphenyl-imidazole in almost quantitative yield while the imidazolines **2a–e** were converted into white crystalline compounds whose analytical and spectral data suggested the structure of 1,2,5-triaryl-4-hydroxy-5-methyl-4,5-dihydroimidazole-hydrochlorides **4a–c**. This structure was confirmed by the mass spectrometry study of the free bases.[2]

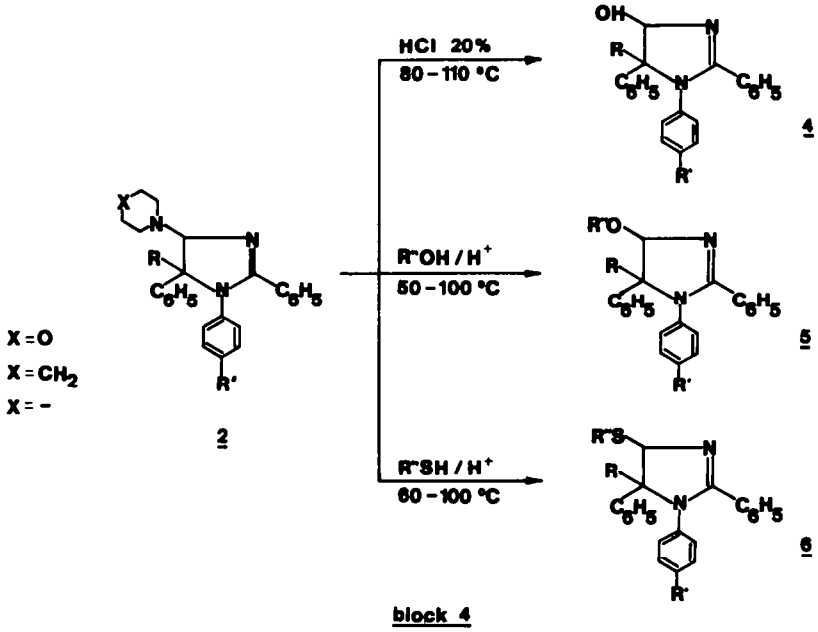
This result shows that it is possible to achieve the exchange of the amine residue with nucleophiles in acidic medium, avoiding the competitive aromatization process. These reactions are both of theoretical and preparative interest owing to the lack of alternative methods for the preparation of such 4-functionalized imidazoline derivatives.

Accordingly, the 4-amino-imidazolines **2a–e** were reacted with several nucleophiles in the presence of an acidic catalyst. Thus, we found that the amino group of such imidazolines is easily replaced with alkoxy-, phenoxy-, alkylthio-, arylthio- and other amino groups in mild conditions and with yields of preparative interest. A typical procedure consists in refluxing the 4-amino-imidazoline in 1,1,2-trichloroethane in the presence of an excess of alcohol or thiol and of an equimolecular amount of triethylammonium chloride.

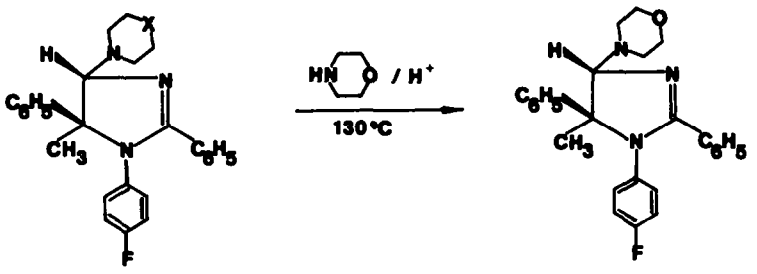
The 4-amino-imidazolines were in the *E*-configuration[1] and in all cases examined (except for the substitution with phenol, as better described below) only one configurational isomer was produced as shown by t.l.c. and ^{1}H NMR of the crude reaction mixture. Only the reaction with phenol affords a mixture of the *E* and *Z* isomers which were separated by column chromatography on silica gel.

Stereochemistry of the substitution. The 4-amino-imidazolines **2a–e** employed in this study are unambiguously in the *E*-form as shown by spectroscopic ^{1}H NMR and mechanistic considerations.[1] Furthermore the *E*-configuration was confirmed by a crystallographic study of this kind of imidazolines.[3]

As already said, the stereochemically pure imidazolines **2a–e** afforded only one of the two possible isomers. In the case of the substitution of the amino group with different amino residue the pro-



block 4



2d : X = CH_2
2e : X = -

block 5

duct was found to have the same configuration (*E*). In the case of the hydroxy-, alkoxy-, phenoxy-, alkylthio and arylthio- derivatives the configuration cannot be assigned with complete confidence from the spectral (IR, ^{1}H NMR) or other physicochemical properties. However, at least for the alkoxy derivatives, the lanthanide induced shift effect with $Eu(fod)_3$ suggests the analogous *E* configuration.

Configurational assignment to **5i** and **5j**. The configuration of the isomers **5i** (m.p. 260°) and **5j** (m.p. 278°) was assigned on the basis of their ^{1}H and ^{13}C NMR spectra.

The ^{1}H NMR spectra show a noteworthy difference between the chemical shifts of the H_4 and the methyl protons: for the isomer melting at 260° these protons resonate at 5.63 and 1.1 p.p.m. respectively whereas in the isomer melting at 278° the same protons resonate at 5.25 and 0.95 p.p.m. respectively. Clearly the phenyl groups are responsible for the observed difference because of the shielding effect of the C_5 phenyl groups on the H_4 and of the phenoxy group on the CH_3 in the *E*-isomer.

The chemical shifts of the ^{13}C of the methyl groups confirm the above stereochemical attributions, since the methyl group of the isomer melting at 260° resonates at 22.7 p.p.m. whereas the methyl of the partner melting at 278° resonates at 20.85 p.p.m. thus evidencing the higher steric constriction of the neighbouring phenoxy group.[4] Another noteworthy feature of the ^{13}C NMR spectra is the wide difference between the C_4 chemical shift whereas the C_5 values are very near.

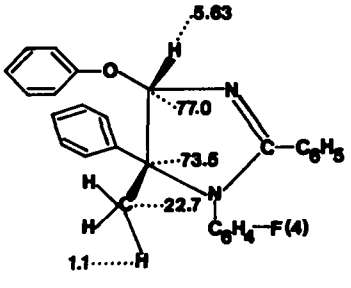
This is probably due to the different inductive effect of the phenoxy groups in the two isomers. The inductive effect of the phenoxy group is presumably higher in the *E*-isomer in which there are no preventions to a complete delocalisation of oxygen atom electrons on the phenyl ring whereas in isomer *Z* such a delocalisation could be hindered by the presence of the phenyl group at C_5. Furthermore, other short- and medium-range non-bonded interactions could be important and may have to be taken into consideration to explain this difference.

DISCUSSION

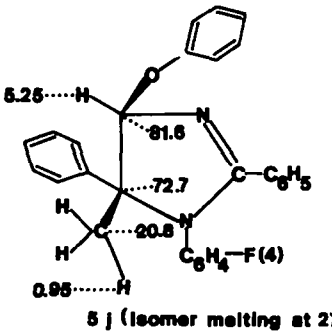
The substitution of the amino residues with nucleophiles occurs most likely through an intermediate carbonium ion because the direct substitution of the protonated amine residue would clearly afford the products with inversion of the configuration.

A difference in the activation energies between the rearrangement and the substitution processes could explain the easier aromatization (with rearrangement) observed for the 5,5-diphenyl derivative.

According to this mechanistical hypothesis the stereoisomer mainly obtained should be the less hindered one. This was confirmed when the nucleophile reacted was an amine or an alcohol. On the same grounds it seems logical to assign the



5i (isomer melting at 260°C)



5 j (isomer melting at 278°C)

block 6

same configuration to the products obtained by exchanging the amino group with hydroxy-, ethylthio- and phenylthio-groups.†

EXPERIMENTAL

M.ps. were taken with a Büchi apparatus and are not corrected. ^{1}H NMR spectra were recorded with both Varian HA-100 and Varian A-60 instruments (Me_4Si as internal standard). IR Spectra were recorded with a Beckmann Acculab 4 spectrometer and Mass spectra with a Perkin Elmer 270 mass spectrometer at an electron energy of 80 e.V. The direct insertion technique was used with a probe temperature of 130–170° and an ion source temperature of 150–200°.

1,2-Diaryl-4-amino-4,5-dihydroimidazoles **2a–f**. The 4-morpholino derivatives **2a**, **2b**, **2c**, **2f** are known compounds.[1] The 4-piperidino- and the 4-pyrrolidino derivatives **2d** (60%, m.p. 197°. Found: C, 78.6; H, 6.9; N, 10.4. Calc. for C, H, N: C, 78.45; H, 6.75; N, 10.15) and **2e** (58%, m.p. 151°. Found: C, 78.10; H, 6.25; N, 10.65. Calc. for C, H, N: C, 78.2; H, 6.50; N, 10.50) were prepared in the same way.

1,2,5-triarylimidazoles **3a–d** *from 4-aminoimidazoles* **2a–f**. *General procedure: Method A.* 1-Aryl-2,5-diphenyl-4-amino-5-methyl-4,5-dihyroimidazoles **2a–f** (2 mmol) were refluxed in 50% aqueous sulfuric acid (10 ml) for 24 h. The cooled solution is diluted with water (50 ml) and the precipitate was filtered and crystallized from ethanol.

Method B. Imidazolines **2a–f** (2 mmol) were refluxed for 15 h in 1,1,2-trichloroethane (20 ml) in the presence of an equimolecular amount of triethylamine hydrochloride. The reaction mixture was cooled at room temperature and the solvent evaporated under reduced pressure. The crude residue was washed with water and extracted twice with chloroform. The organic layer was dried (Na_2SO_4) and freed from the solvent under reduced pressure. The crude residue was crystallized from ethanol.

Preparation of 1,2,5-triphenyl-4-methylimidazole **3a**. α-Benzoylanilius-propiophenone (1.5 g, 4.5 mmol) and ammonium acetate (6.6 g, 8.57 mmol) were dissolved in glacial acetic acid (60 ml) and refluxed for 18 h. The reaction mixture was cooled at room temperature and freed from solvent under reduced pressure; the crude residue was worked up with water (20 ml) until crystallization and filtered. The resulted solid was extracted several times with ether. The collected organic layers were dried (Na_2SO_4), evaporated under reduced pressure and the residue crystallized from ethanol. Yield 1.01 g (73%) m.p. 152°, mixed melting point 151–2°.

1,2-Diaryl-4-hydroxy-4,5-dihydroimidazoles **4a–c** *by hydrolysis of 4-aminoimidazolines* **2a–e**. *Method A:* Aminoimidazolines **2a–e** (2 mmol) were refluxed for 15 h in hydrochloric acid 10–30% (15 ml). The reaction mixture was cooled and the white precipitate was filtered and subsequently treated with aqueous sodium hydrogen carbonate and extracted with dichloromethane. The organic layer was dried (Na_2SO_4) and freed from the solvent under reduced pressure. The crude residue was crystallized from isopropyl ether yielding 78–95% of 4-hydroxy derivatives **4a–c**.

Table 1. Imidazoles **3a–d**

Compound no.	R	Ar	m.p. [°C]	Yield [%]	Found [%] [Required (%)]		
3a	CH_3	C_6H_5	152	80 (A)	85.45	5.45	9.0
				65 (B)	[85.15	5.80	9.05]
3b	CH_3	$C_6H_4CH_3$ (4)	161	85 (A)	85.35	5.95	8.71
				70 (B)	[85.2	6.15	8.65]
3c	CH_3	C_6H_4F (4)	170	90 (A)	80.2	5.1	8.45
				60 (B)	[80.5	5.2	8.55]
3d	C_6H_5	C_6H_5	213 (lit[5])	90 (A) 85 (B)			

Method B: Amino-imidazolines **2a–e** (2 mmol) were refluxed for 18 h in 1,1,2-trichloroethane (30 ml) in the presence of water (0.56 ml) and of an equimolecular amount of triethylamine hydrochloride. The solvent is evaporated and the crude residue washed with sodium hydrogen carbonate solution and extracted with chloroform. The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure. The residue was crystallized from isopropylether yielding 4-hydroxy-derivatives **4a–c**.

1,2-Diaryl-4-alkoxy-4,5-dihydroimidazolines **5a**. *General procedure.* 4-Aminoimidazolines **2a–e** (2 mmol) were refluxed, for the time reported in Table 2, in 1,1,2-trichloro ethane (15 ml) in the presence of the appropriate alcohol (10 ml) and of an equimolecular amount of triethylamine hydrochloride. The reaction solvent was evaporated and the crude residue washed with water and extracted several times with ethylacetate. The organic layer was dried (Na_2SO_4) and freed from the solvent under reduced pressure. The crude product was purified by a chromatography column of silica gel using benzene–THF (90:10) as eluent and recrystallized from the suitable solvent.

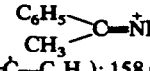
1-(4-Fluorophenyl)-2,5-diphenyl-4-phenoxy-5-methyl-4,5-dihydroimidazoles **5i**, **5j**: *preparation and separation of* E *from* Z-*isomer.* 1-(4-Fluorophenyl)-2,5-diphenyl-4-morpholino-5-methyl-4,5-dihydroimidazole (4.0 g, 9.6 mmol) was refluxed for 13 days in carbon tetrachloride (60 ml) in the presence of phenol (12.0 g, 127.6 mmol) and triethylamine hydrochloride (2.64 g, 13.2 mmol). The solvent was evaporated and the crude residue washed with sodium hydroxide solution and extracted with ethyl acetate. The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure. From the residue, the two products were separated by a chromatography column on silica gel using ether as eluent. The (Z) form crystallizes from isopropyl ether yielding 1.21 g (30%), m.p. 260°; M.S.: *m/e* 422 (24,

† The formation of two isomers in the case of the phenoxy derivatives fits only partially in this picture. However, in this case too, the main product is the *E*-isomer.

Table 2. 4-Substituted imidazolines prepared from 4-amino-imidazolines

Compound	X	R_1	R_2	δ_{H_4}	δ_{CH_3}	R.T. [h]	Crist. solv.	m.p. [°C]	Yield [%]	Found (%) [Required (%)]
4a	O	H	H	5.63 (5.9)	1.58 (1.72)	18	Pr^i_2O	176	85	82.00 6.10 8.50 [81.78 6.09 8.48]
4b	O	CH_3	H	5.67 (5.9)	1.56 (1.7)	18	Pr^i_2O	181	85	80.35 6.3 7.95 [80.7 6.45 8.2]
4c	O	F	H	5.5 (5.65)	1.45 (1.6)	18	Pr^i_2O	179	85	76.15 5.70 7.75 [76.3 5.5 8.1]
5a	O	F	CH_3	5.0	1.43	24	Pr^i_2O	138	75	76.45 5.7 7.7 [76.6 5.9 7.8]
5b	O	F	CD_3	5.0	1.43	24	Pr^i_2O	138	76	P.M. = 347 by MS
5c	O	F	C_2H_5	5.10	1.43	24	L. petroleum	116	78	76.7 5.95 7.4 [77.0 6.2 7.5]
5d	O	F	n-C_3H_7	5.13	1.43	24	L. petroleum	136	80	77.1 6.9 7.1 [77.3 6.5 7.2]
5e	O	F	i-C_3H_7	5.17	1.40	48	MeCN	147	78	77.6 6.2 7.3 [77.3 6.5 7.2]
5f	O	F	n-C_4H_9	5.11	1.40	48	L. petroleum	82	70	77.4 6.6 6.8 [77.6 6.8 6.95]
5g	O	F	t-C_4H_9	5.28	1.37	24	MeCN	142	78	77.55 6.7 6.9 [76.6 6.8 6.95]
5h	O	CH_3	s-C_4H_9	5.16	1.43	36	Pr^i_2O	129	68	84.6 7.75 7.4 [84.8 7.9 7.3]
5i	O	F	C_6H_5	5.63	1.1	300	Pr^i_2O	260	30	79.35 5.75 6.4 [79.4 5.7 6.6]
5j	O	F	C_6H_5	5.25	0.95	300	MeCN	278	50	79.6 5.55 6.8 [79.4 5.7 6.6]
6a	S	F	C_6H_5	5.51	1.6	8	Pr^i_2O	160	60	76.5 5.5 6.3 [76.7 5.25 6.4]
6b	S	CH_3	C_2H_5	5.25	1.6	24	Pr^i_2O	157	80	78.0 6.85 7.2 [77.8 6.7 7.25]

[a] The values in parenthesis refers to the singlets (~5–10%) which could be assigned to H_4 and CH_3 of Z isomers. However, no effort was made to isolate these compounds.

M^+); 407 (3, $M-CH_3$); 214 (8,  C_6H_4F); 209 (100, $C_6H_5O{=}CH{-}N{=}\dot{C}{-}C_6H_5$); 158 (11, $FC_6H_4{-}\dot{N}{\equiv}C{-}C_6H_5$); 106 (16, $C_6H_5{-}O{=}\dot{C}H$); the (*E*) form crystallizes from acetonitrile yielding 2.0 g (50%), m.p. 278°. MS: *m/e* 422 (4, M^+); 209 (100, $C_6H_5{-}O{=}CH{-}N{=}\dot{C}{-}C_6H_5$); 198 (5, $FC_6H_4{-}\dot{N}{\equiv}C{-}C_6H_5$); 106 (11, $C_6H_5{-}O{=}\dot{C}H$).

1-(4-*Methyl-phenyl*)-2,5-*phenyl*-4-*ethylthio*-5-*methyl*-4,5-*dihydroimidazole* (**6b**) *from* 4-*aminoimidazoline* **2b**. 1-(4-methyl-phenyl)-2,5-diphenyl-4-morpholino-5-methyl-4,5-dihydroimidazole (1.0 g, 2.4 mmol) was refluxed in 1,1,2-trichloroethane (20 ml) containing ethanethiol (15 ml) and in the presence of triethylamine hydrochloride (0.66 g, 4.8 mmol). After 24 h, the solvent was evaporated and the crude residue was chromatographed on a silica gel column (benzene/THF; 9:1). The isolated product was recrystallized from isopropylether yielding 0.74 g (80%) of **6b**, m.p. 157°; MS: *m/e* 325 (100, $M-SC_2H_5$); 222 (34, $M-SC_2H_5-C_6H_5CN$); 207 (10, $M-SC_2H_5-C_6H_5CN-CH_3$); 177 (6, $C_2H_5{-}S{=}CH{-}N{=}C{-}C_6H_5$); 104 (12, $C_6H_5{-}\dot{C}NH$); 91 (13, $^+C_6H_4{-}CH_3$).

1-(4-*Fluorophenyl*)-2,5-*diphenyl*-4-*phenylthio*-5-*methyl*-4,5-*dihydro-imidazole* **6a** *from* 4-*aminoimidazoline* **2c**. 1-(4-Fluorophenyl)-2,5-diphenyl-4-morpholino-5-methyl-4,5-dihydroimidazole (3.0 g, 7.2 mmol) was refluxed in carbon tetrachloride (30 ml) containing thiophenol (9.7 ml) in the presence of triethylamine hydrochloride (1.98 g, 14.4 mmol). After 8 h the solvent was evaporated and the crude residue washed with sodium hydroxide solution and extracted with chloroform. The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure. The product crystallised from isopropylether (60%), m.p. 160°; MS: *m/e* 325 (100, $M-SC_6H_5$); 226 (61, $M-SC_6H_5-C_6H_5CN$); 211 (37, $M-SC_6H_5CN-CH_3$); 109 (36, $C_6H_5S^+$).

1-(4-*Fluorophenyl*)-2,5-*diphenyl*-4-*morpholino*-5-*methyl*-4,5-*dihydroimidazole* (**2c**) from 4-amino-imidazolines **2d** *and* **2e**. 1-(4-Fluorophenyl)-2,5-diphenyl-4-pyrrolidino- or 4-piperidino-5-methyl-4,5-dihydroimidazole **2a** and **2d** (1.2 mmol) were refluxed for 24 h in morpholine (20 ml) in the presence of an equimolecular amount of triethylamine hydrochloride. Morpholine was evaporated under reduced pressure and the residue treated with water and extracted with dichloromethane. The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure and the residue crystallised from acetonitrile yielding 0.43 g (87%) of the morpholino derivative **2c**.

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REFERENCES

[1] L. Citerio, D. Pocar, R. Stradi and B. Gioia, *J. Chem. Soc., Perkin I* 309 (1978).
[2] B. Gioia, L. Citerio and R. Stradi, *Org. Mass. Spectrometry* **13**, 319 (1978).
[3] R. Destro, *Acta Cryst.* in press.
[4] F. W. Wehrli and T. Wirthlin, *Interpretation of* ^{13}C *NMR Spectra*, Chap. 2.
[5] A. E. Everest and H. McCombie, *J. Chem. Soc.* **99**, 1756 (1911).