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N-Haloamidines. VII[2c]. 4-Amino-5-Chloroimidazoles and 4-Amino-5-Unsubstituted Imidazoles from N-Chloro-N'-Arylbenzamidines and 1,1-Diaminoethenes.

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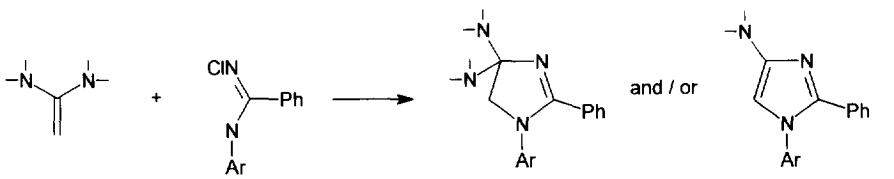
Abstract: N-chloro-N'-arylbenzamidines react with 1,1-diaminoethenes to give in good yields 4-amino-5-chloroimidazoles. The behaviour of these compounds in some nucleophilic substitution reactions and their reduction to 4-amino-5-unsubstituted imidazoles is reported. Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

During the last years we extensively studied the reactivity of N-haloamidines towards enamines.[1] The reaction pathway strongly depends upon the substituents at the enamine double bond and at the N' atom of the N-haloamidine, which determine the product distributions between open chain adducts and widely substituted amino-dihydroimidazoles, amino-imidazoles and imidazoles.[1,2] In the progress of our work we extended the reaction to the 1,2-diaminoethenes which react with N-haloamidines to give diamino-dihydroimidazoles, diamino-imidazoles and amino-imidazoles otherwise difficult to reach.[1,3] As a continuation of our study we thought to extend the reaction to some unsubstituted 1,1-diaminoethenes with the aim to synthesise the 4,4-diamino-4,5-dihydroimidazoles and/or the 4-amino-5-unsubstitutedimidazoles. These latter heterocyclic derivatives, in particular, show interesting pharmaceutical and biochemical properties.[4a-d] Moreover the chemistry of simple 4-amino-5-unsubstitutedimidazoles is relatively unknown probably because of the low stability of these heterocycles.[4]

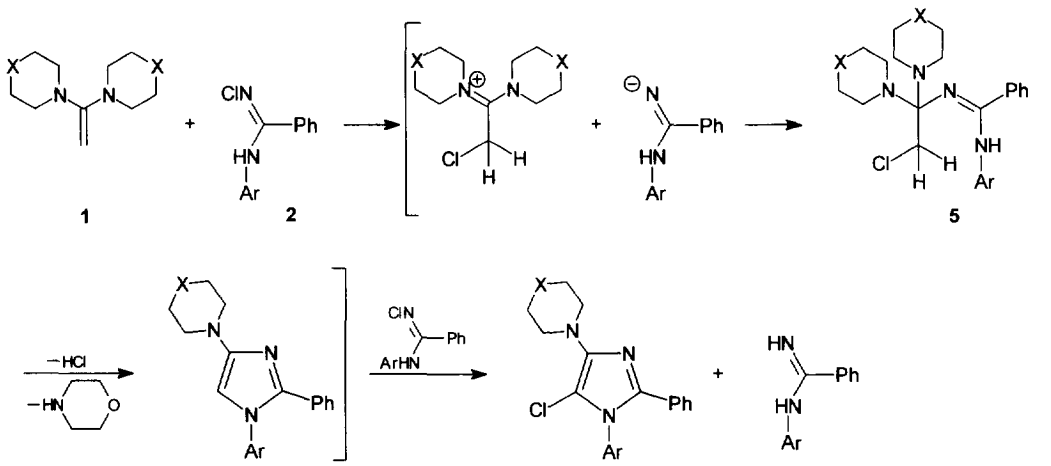


RESULTS AND DISCUSSION

The first experiments were performed using the N-chloro-N'-(4-methylphenyl)benzamidine **1a** and 1,1-dimorpholinoethene **2a** (Scheme 1). The reaction was carried out at room temperature, in dry chloroform , in the presence of pyridine as base and using equimolecular amounts of both reagents. After the complete disappearance of **1a** (12h) the GC analysis of the reaction mixture showed the presence of some unreacted 1,1-diaminoethene **2a** and usual work up of the reaction mixture, followed by column chromatography over silica gel, resulted in the isolation of the 5-chloro-1-(4'-methylphenyl)-4-morpholino-2-phenylimidazole **3a** and the N-(4-methylphenyl)benzamidine **4a** in 30% yield. These results can be rationalised taking into account our previous reports about the mechanism of related reactions.[1a] Also in this case the first stage of the

reaction probably involves the electrophilic attack of the N-chloroamidine upon the unsaturated system of the 1,2-diaminoethene. The intermediate chloro-immonium ion so formed evolves by nucleophilic attack of the amidine anion leading to the open chain intermediate **5** which by heterocyclization with loss of HCl and morpholine affords the 4-aminoimidazole **6**. This compound, unsubstituted in the 5-position and activated towards electrophilic substitution by the presence of an aminic residue at C-4, reacts rapidly with the electrophilic chlorine atom of **1a** giving rise to the final products **3a** and **4a**.

Taking into account these preliminary results, we performed the same reaction with a bimolecular amount of **1a**, with or without pyridine, and in both cases we isolated the same reaction products **3a** and **4a** in 60% yield. On the basis of this experimental evidence a series of different substituted 4-amino-5-chloroimidazoles **3a-h** were synthesised following the same procedure (Scheme 1, Table 1).



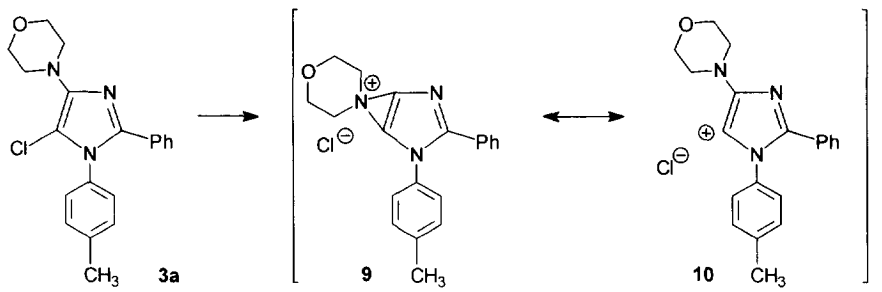
1-4	Ar	X	1-4	Ar	X
a	p-tolyl	O	e	phenyl	O
b	p-tolyl	CH_2	f	4-nitrophenyl	O
c	4-Chlorophenyl	O	g	o-tolyl	O
d	4-Chlorophenyl	CH_2	h	o-xylyl	O

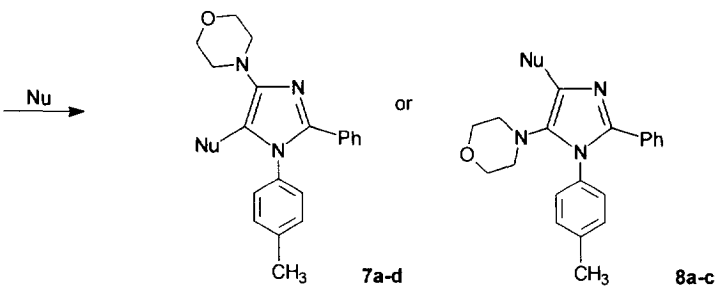
SCHEME 1

The 4-amino-5-chloroimidazoles **3a-h** represent a new class of imidazole derivative. To date similar compounds hare only been detected, by Krowicki and Lown, as by-products during the reduction of the corresponding 2-alkylthio-4-nitroimidazoles with stannous chloride and then isolated as N-acyl derivatives.[4b]

As is well known[5], chlorine at C-5 of imidazoles is normally quite unreactive towards nucleophilic displacement unless the ring is activated by the presence of an electron-withdrawing group in the 2 or 4-position. On the contrary, when we tested the reactivity of the 4-amino-5-chloroimidazole **3a** in some nucleophilic substitutions, the reactions resulted in the chlorine displacement also under mild reaction conditions. Moreover, the reaction products formally can result from the direct substitution of the chlorine atom (imidazoles **7a-d**), or involve also the contemporary migration of the aminic residue at C-4 (imidazoles **8a-c**). The reactions were performed using the reagents and the reaction conditions shown in Scheme 2, and occur in good yield using ethanethiol, morpholine and pyrrolidine or with charged nucleophiles; instead no reaction was observed using methanol or ethanol. The structures of compounds **7** and **8** were assigned on the basis of analytical (C, H, N) and spectral data (^{1}H-NMR, ^{13}C-NMR, MS). In particular, compounds **7a**, **7c**, **7d**,

8b and **8c** show in the EI mass spectra significant fragment ions deriving from cleavage of N1-C2 and C4-C5 bonds. Compound **7b**, which bears the same substituent at C4 and C5 was identified by simple analysis of analytical and spectral data. The structure of compound **8a** was assigned by comparison with the isomeric compound **7a** whose structure was undoubtedly determined by EI mass spectra.





Product	Nu	Solvent	Temp. °C	Yield 7	Yield 8
	MeOH	$CHCl_3$	61	-	-
	EtOH	$CHCl_3$	61	-	-
7a	EtSH	$CHCl_3$	35	65	
7b	Morpholine	$CHCl_3$	61	55	
7c	Pyrrolidine	$CHCl_3$	61	60	
7d	KCN	DMSO	120	40	
8a	EtSNa	DMSO	40	15*	50
8b	MeONa	MeOH	140		60
8c	EtONa	EtOH	140		60

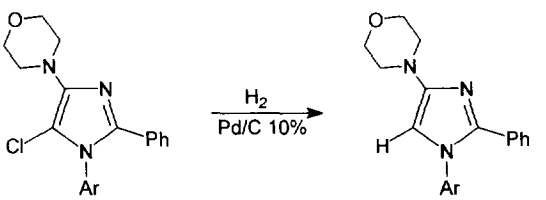
* A little amount of compound **7a** was isolated probably because of the presence of EtSH in the reaction mixture.

SCHEME 2

A reaction mechanism for the formation of compounds **7** and **8** can be postulated to involve the azirinium intermediate **9** with two position (C-4 and C-5 of the imidazole ring) reactive towards nucleophiles, and in equilibrium with the carbonium ion **10**. By the simple analysis of the obtained products, soft nucleophiles react *via* the carbonium ion to give compounds **7**, whereas hard nucleophiles give compounds **8** by direct displacements involving the less hindered position of the azirinium ion. The behaviour of imidazole **3a** in nucleophilic substitution reactions and the products distribution pattern parallel in part that of β-chloro enamines[6] and aziridinium ions[7] whose reactivity with nucleophiles is well documented. To date, however no reports about the chemistry of unstable 1H-azirinium ions are available in the Literature.

The 4-amino-5-chloroimidazoles **3g** and **3h**, having respectively one or two ortho-methyl groups on the N-aryl substituent, require more drastic conditions to undergo nucleophilic displacement and react only when treated at high temperature (160°C) with sodium methoxide in dry methanol to afford 4-methoxy-5-morpholinoimidazoles **8d-e**. This behaviour is probably related with the major "aromatic character" of the imidazole ring due to the non planarity between the heterocycle and the aryl at N-1.

Finally, the synthesis of the 4-amino-5-unsubstituted imidazoles **6**, which were our target compounds, was achieved by catalytic hydrogenation of the carbon-chlorine bond[8] in the 4-amino-5-chloroimidazoles **3a**, **3g** and **3h** (Scheme 3). However, whereas the 4-aminoimidazoles **6g** and **6h**, having one or two methyl groups in the ortho position on the N-aryl substituent, have been easily purified by column chromatography, purification of the 4-aminoimidazole **6a** in the same conditions resulted in the formation of a complex mixture of unidentified products. Compound **6a**, however has been isolated quite pure at the end of the hydrogenation, washed with cold diisopropyl ether and identified by current analytical methods.



3a, 3g, 3h **6a, 6g, 6h**

SCHEME 3

In conclusion, in this work we describe the synthesis of unknown 4-amino-5-chloroimidazoles. These compounds are quite stable to be isolated and characterised but reactive enough to undergo interesting transformations. Moreover we realise the synthesis of some 4-amino-5-unsubstitutedimidazoles. The chemistry of these latter compounds has received little attention probably because of their low stability and will be the subject of further investigations by our group.

EXPERIMENTAL

The N-chloroamidines **1**[2a] and the 1,1-diaminoethenes **2**[9] are known compounds and were prepared according to described methods. All other chemicals and solvents are commercially available and were used without further purification. Merck silica gel (70-120 mesh) was employed for column chromatography. Mps, measured with a Büchi apparatus, are uncorrected. ^{1}H-NMR (200 MHz) and ^{13}C-NMR (50.3 MHz) spectra were recorded with a Gemini-Varian spectrometer, ^{1}H-NMR (60 MHz) spectra were recorded with a Varian A360 spectrometer and EI (70eV) mass spectra with a VG70 SE Q instrument.

4-Amino-1-aryl-5-chloro-2-phenylimidazoles 3a-h. General procedure: A nitrogen flushed solution of appropriate N-chloro-N'-arylbenzamidine **1** (1.5 mmol) and 1,1-diaminoethene **2** (0.82 mmol) in dry chloroform (40 ml) was stirred until no more N-chlorobenzamidine was detectable by tlc (10-24 h). The crude reaction mixture, freed from the solvent under reduced pressure, was then chromatographed over silica gel to give pure imidazoles **3a-h**. Table 1.

5-Ethylthio-4-morpholino-2-phenyl-1-(p-tolyl)imidazole 7a. To a well stirred solution of 4-amino-5-chloroimidazole **3a** (300 mg, 0.85 mmol) in dry $CHCl_3$ (10 ml) were added a solution of ethanthiol (263.5 mg, 4.25 mmol) in dry $CHCl_3$ (10 ml) and then dry triethylamine (86 mg, 0.85 mmnol). The solution was stirred at 35°C for 24 h and then freed from the solvent under reduced pressure. The residue was poured in CH_2Cl_2 (30 ml)/$NaHCO_3$ sat. sol. (30 ml), the organic layer was separated and the aqueous phase extracted twice with

CH_2Cl_2 (15 ml). The combined organic phases, dried over dry Na_2SO_4, were evaporated to dryness and the residue crystallised from diisopropyl ether/petroleum ether 1:1 to give pure **7a**. Table 2.

4,5-Dimorpholino-2-phenyl-1-(p-tolyl)imidazole 7b and 4-morpholino-5-pyrrolidino-2-phenyl-1-(p-tolyl)imidazole 7c. To a well stirred solution of 4-amino-5-chloroimidazole **3a** (300 mg, 0.85 mmol) in dry $CHCl_3$ (10 ml) the appropriate secondary amine (17 mmol) was added. The solution was refluxed for 48 h and then evaporated to dryness. The residue was chromatographed over a silica gel column (eluent cyclohexane/ethyl acetate, 1:1) to give pure **7b** and **7c** respectively. Table 2.

5-Cyano-4-morpholino-2-phenyl-1-(p-tolyl)imidazole 7d. To a stirred suspension of KCN (72 mg, 1.11 mmol) in dry DMSO (10 ml) the 4-amino-5-chloroimidazole **3a** (300 mg, 0.85 mmol) was added. The mixture was stirred at 120°C for 24 h and then poured in CH_2Cl_2 (30 ml)/$NaHCO_3$ sat. sol. (30 ml), the organic layer was separated and the aqueous phase extracted twice with CH_2Cl_2 (15 ml). The combined organic phases, dried over dry Na_2SO_4, were evaporated to dryness and the residue purified by column chromatography over silica gel (eluent cyclohexane/triethylamine, 8:2) to give pure **7d**. Table 2.

5-Ethylthio-4-morpholino-2-phenyl-1-(p-tolyl)imidazole 7a and 4-ethylthio-5-morpholino-2-phenyl-1-(p-tolyl)imidazole 8a. To a stirred suspension of NaSEt (93 mg, 1.11 mmol) in dry DMSO (10 ml) the 4-amino-5-chloroimidazole **3a** (300 mg, 0.85 mmol) was added. The mixture was stirred at 40°C for 24 h and then poured into CH_2Cl_2 (30 ml)/$NaHCO_3$ sat. sol. (30 ml), the organic layer was separated and the aqueous phase extracted twice with CH_2Cl_2 (15 ml). The combined organic phases, dried over dry Na_2SO_4, were evaporated to dryness and the residue purified by column chromatography over silica gel (eluent toluene/ethyl acetate, 8:2) to yield progressively **8a** and **7a**. Table 2.

5-Ethoxy and 5-methoxy-4-morpholino-2-phenyl-1-(p-tolyl)imidazoles 8b-c; 4-methoxy-5-morpholino-2-phenyl-1-(o-tolyl)imidazole and 4-methoxy-5-morpholino-2-phenyl-1-(o-xylyl)imidazole 8d-e. A solution of 4-amino-5-chloroimidazole **3a,3g or 3h** (0.85 mmol) and NaOMe (60 mg, 1.11 mmol) or NaOEt (75 mg, 1.11 mmol) in dry MeOH or EtOH (10 ml) was heated at 160°C in a steel reactor for 24 h. The crude reaction mixture, freed from the solvent under reduced pressure, was purified by column chromatography over silica gel (eluent cyclohexane/triethylamine, 8:2) to yield pure **8b-e**. Table 2.

1-Aryl-4-morpholino-2-phenylimidazoles 6a, 6g and 6h. To a well stirred solution of the appropriate 4-amino-5-chloroimidazoles **3a**, **3g**, or **3h** (0.71 mmol) in dry THF (5 ml) a suspension of K_2CO_3 (112 mg, 0.81 mmol) and Pd/C (10%) (50 mg) in dry THF (10 ml) was added. The mixture was hydrogenated at room temperature and pressure for 30 min (during this period the theoretical amount of hydrogen was consumed), then freed from the solvent under reduced pressure. The residue, dissolved in $CHCl_3$ (20 ml), was washed with $NaHCO_3$ sat. sol. (20 ml) and the organic phase, dried over dry Na_2SO_4, was evaporated to dryness. Compound **6a** was then washed with cold diisopropyl ether, whereas compounds **5g** and **6h** were purified by column chromatography over silica gel (eluent cyclohexane/triethylamine, 8:2). 4-Morpholino-2-phenyl-1-(p-tolyl)imidazole **6a**: yield: 85%. ^{1}H-NMR ($CDCl_3$/TMS, 200 MHz): 2.45 (s, 3H, CH_3); 3.45 (t, 4H, CH_2N); 3.82 (t, 2H, CH_2O); 6.42 (s, 1H, H-5); 7.05-7.42 (m, 7H, arom.); 7.52 (dd, 2H, arom.).^{13}C-NMR ($CDCl_3$/TMS, 50.3 MHz): 21.8 (CH_3); 50 (CH_2N); 66.2 (CH_2O); 104 (C-5); 123 (C-4); 126-141 (aryl-C); 145 (C-2). MS (m/z, %): 319 (M^+, 26); 262 (12); 194 (16); 118 (44); 105 (100). 4-Morpholino-2-phenyl-1-(o-tolyl)imidazole **6g**: yield: 88%. ^{1}H-NMR ($CDCl_3$/TMS, 200 MHz): 1.95 (s, 3H, CH_3); 3.45 (m, 4H, CH_2N); 3.82 (t, 2H, CH_2O); 6.38 (s, 1H, H-5); 7.25-7.45 (m, 7H, arom.); 7.55 (dd, 2H, arom.).^{13}C-NMR ($CDCl_3$/TMS, 50.3 MHz): 18 (CH_3); 50 (CH_2N); 67 (CH_2O); 103 (C-5); 127-144 (C-4, aryl-C); 152 (C-2). MS (m/z, %): 319 (M^+, 291); 261 (100); 193 (70); 117 (86); 104 (68). 4-Morpholino-2-phenyl-1-(o-xylyl)imidazole **6h**: yield: 93%. ^{1}H-NMR ($CDCl_3$/TMS, 200 MHz): 2.00 (s, 6H, CH_3); 3.22 (t, 4H, CH_2N); 3.88 (t, 2H, CH_2O); 6.15 (s, 1H, H-5); 7.05-7.40 (m, 8H, arom.).^{13}C-NMR ($CDCl_3$/TMS, 50.3 MHz): 18.2 (CH_3); 49.7 (CH_2N); 67.1 (CH_2O); 102.4 (C-5); 127-143 (C-4, aryl-C); 152.7 (C-2). MS (m/z, %): 333 (M^+, 100); 276 (87); 208 (57); 130 (70); 117 (62).

Table 1. 4-Amino-1-aryl-5-chloro-2-phenylimidazoles **3a-h**.

3	Eluent for chromatography	Yield, %	m.p., °C (solvent)	Molecular Formula[a]	^{1}H-NMR (60 MHz), $CDCl_3$, δ from TMS
a	cyclohexane/triethylamine 8:2	60	157 diisopropyl ether	$C_{20}H_{20}ClN_3O$ (353.8)	2.30 (s, 3H, CH_3), 3.50 (t, 4H, CH_2-N), 3.90 (t, 4H, CH_2-O), 7.10-7.35 (m, 9H, arom.)
b	ethyl acetate/cyclohexane 1:1	31	137-139 diisopropyl ether	$C_{21}H_{22}ClN_3$ (351.9)	1.70 (m, 6H, CH_2), 2.43 (s, 3H, CH_3), 3.36 (m, 4H, CH_2N), 7.10-7.60 (m, 9H, arom.)
c	cyclohexane/triethylamine 8:2	56	165-167 diisopropyl ether	$C_{19}H_{17}Cl_2N_3O$ (374.3)	3.35 (m, 4H, CH_2N), 3.86 (m, 4H, CH_2O), 7.10 and 7.38 (AA'BB' system, 4H, arom.), 7.23 (s, 5H, arom.)
d	cyclohexane/ethyl acetate 8:2	30	125-127 diisopropyl ether	$C_{20}H_{19}Cl_2N_3$ (372.3)	1.53 (m, 6H, CH_2), 3.30 (m, 4H, CH_2N), 7.10 and 7.38 (AA'BB' system, 4H, arom.), 7.23 (s, 5H, arom.)
e	cyclohexane/triethylamine 8:2	62	145-147 ethyl ether/ethyl acetate 8:2	$C_{19}H_{18}ClN_3O$ (339.8)	3.33 (m, 4H, CH_2N), 4.85 (m, 4H, CH_2O), 7.00-7.50 (m, 10H, arom.)
f	cyclohexane/ethyl acetate 8:2	58	119 ethanol	$C_{19}H_{17}ClN_4O_3$ (384.8)	3.60 (m, 8H, CH_2), 7.03 and 8.12 (AA'BB' system, 4H, arom.), 7.30-7.55 (m, 5H, arom.)
g	cyclohexane/triethylamine 8:2	58	103-105 diisopropyl ether	$C_{20}H_{20}ClN_3O$ (353.8)	1.93 (s, 3H, CH_3), 3.40 (m, 4H, CH_2N), 3.83 (m, 4H, CH_2O), 6.95-7.50 (m, 9H, arom.)
h	cyclohexane/triethylamine 8:2	55	oil	$C_{21}H_{22}ClN_3O$ (367.9)	1.93 (s, 6H, CH_3), 3.40 (m, 4H, CH_2N), 3.83 (m, 4H, CH_2O), 7.15 (m, 8H, arom.)

[a] Microanalyses were in good agreement with calculated values (C ± 0.3, H ± 0.15, N ± 0.3).

Table 2. 4-Aminoimidazoles **7** and 5-Aminoimidazoles **8**.

Product	m.p., °C (solvent)	Elememtal analysis, %[a] C	H	N	EI-MS m/z, (%)	^{1}H-NMR, $CDCl_3$, δ from TMS
7a	90-92 diisopropyl ether/PE 1:1	69.22 (69.62)	6.64 (6.54)	11.07 (10.85)	379 (M^+, 38); 350 (100); 293 (8); 194 (6); 150 (12).	0.95 (t, 3H, CH_3); 2.28 (q, 2H, CH_2); 2.44 (s, 3H, CH_3); 3.52 (t, 4H, CH_2N); 3.84 (t, 4H, CH_2O); 6.95-7.30 (m, 9H, arom.).[b]
7b	160-162 diisopropyl ether/PE 1:1	70.39 (70.41)	6.91 (7.14)	13.99 (14.29)	404 (M^+, 100), 346 (25); 287 (17); 241 (7); 194 (20).	2.44 (s,3H,CH_3); 2.95 (t, 4H, CH_2N); 3.20 (t, 4H, CH_2N); 3.46 (t, 4H, CH_2O); 3.85 (t, 4H, CH_2O); 7.05-7.35 (m, 9H, arom.).[b]
7c	140-142 diisopropyl ether/PE 1:1	74.56 (74.19)	7.31 (7.26)	14.18 (14.42)	388 (M^+, 100); 330 (31); 301 (10); 287 (22); 194 (56); 187 (18).	1.70 (m, 4H, CH_2); 2.45 (s, 3H, CH_3); 3.05 (m, 4H, CH_2N); 3.30 (t, 4H, CH_2N); 3.85 (t, 4H, CH_2O); 7.15-7.38 (m, 9H, arom.).[c]
7d	190-192 diisopropyl ether	72.88 (73.23)	5.76 (5.85)	15.91 (16.22)	344 (M^+, 88), 287 (60); 232 (15); 194 (12); 143 (80); 91 (100).	2.45 (s, 3H, CH_3); 3.65 (t, 4H, CH_2N); 3.85 (t, 3H, CH_2O); 7.10-7.35 (m, 9H, arom.).[c]
8a	113-115 diisopropyl ether	69.45 (69.62)	6.58 (6.54)	11.12 (10.85)	380 (MH^+, 26); 354 (55); 318 (100); 288 (28); 215 (57); 157 (45); 118 (42).	1.28 (t, 3H, CH_3); 2.40 (s, 3H, CH_3); 2.92 (q, 2H, CH_2); 3.45 (t, 4H, CH_2N); 3.85 (t, 4H, CH_2O); 7.12-7.35 (m, 9H, arom.).[b]
8b	152-154 diisopropyl ether/PE 1:1	72.17 (72.21)	6.68 (6.59)	12.00 (12.03)	349 (M^+, 98); 334 (35); 290 (8); 203 (100).	2.45 (s, 3H, CH_3); 2.95 (t, 4H, CH_2N); 3.55 (t, 3H, CH_2O); 4.05 (s, 3H, OCH3); 6.95-7.35 (m, 9H, arom.).[c]
8c	156-157 diethyl ether	72.56 (72.70)	6.78 (6.93)	11.44 (11.56)	363 (M^+, 55); 334 (50); 290 (8); 203 (100).	1.40 (t, 3H, CH_3); 2.45 (s, 3H, CH_3); 3.00 (t, 4H, CH_2N); 3.55 (t, 4H, CH_2O); 4.35 (q, 2H, CH_2); 6.95-7.35 (m, 9H, arom.).[c]
8d	146-148 diisopropyl ether/PE 1:1	71.91 (72.21)	6.69 (6.59)	12.31 (12.03)	349(M^+, 100); 334 (42); 290 (10); 203 (48).	2.04 (s, 3H, CH_3); 2.95 (t, 4H, CH_2N); 3.50 (t, 3H, CH_2O); 4.05 (s, 3H, OCH3); 7.10-7.40 (m, 9H, arom.).[c]
8e	132-135 diisopropyl ether/PE 1:1	72.84 (72.69)	6.88 (6.93)	11.34 (11.56)	363(M^+, 100); 348 (48); 304 (15); 217 (52).	2.00 (s, 6H, CH_3); 2.95 (t, 4H, CH_2N); 3.50 (t, 3H, CH_2O); 4.05 (s, 3H, OCH3); 7.25 (m, 8H, arom.).[c]

[a] Calculated values in parentheses. [b] Recorded at 200 MHz. [c] Recorded at 60 MHz.

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