Synthesis and Structure of Heterocyclic Compounds. 1-Amino-2,4-Disubstituted Imidazoles

Giovanni Cerioni, Maria Teresa Cocco, Cenzo Congiu and Antonio Maccioni

Istituto di Chimica Farmaceutica e Tossicologica,
Universita di Cagliari, 09100 Cagliari, Italy

Received March 27, 1981

A synthesis of 1-aminoimidazoles by reaction between α-halogenoketones and *N*-acetylamidrazones is described. Structure and position of substituent groups in the synthesized aminoimidazoles were established by spectroscopical methods.

J. Heterocyclic Chem., **18**, 1379 (1981).

The scope of this research was the synthesis and the study of some 1-aminoimidazoles which have potential antibacterial and antifungal properties. The synthesis of some 1,2-diaminoimidazoles (1,2) and 1-aminoimidazoles (3,4) have been described in the literature.

The synthetic methods follow two main routes: reaction between *N*-acetylamidrazones and α-halogenoketones or reaction between oxazoles and hydrazine. In the latter case the structure of the 1-aminoimidazole can be inferred from the known structure of the starting oxazole, but the yields are generally very low and, furthermore, this method is not always applicable. In the former case, the formation of two isomers can be foreseen depending upon whether the lone pair of N-2 or N-3 of the starting acetylamidrazone is the nucleophilic species. (For amidrazones nomenclature, see reference 5). It is known that amidrazones are not very stable in basic condition whereas they are much more stable in an acidic medium (6). This major stability of the protonated form in comparison to the free base can be explained in terms of resonance, as has been demonstrated in the case of amidines (7), a very similar class of compounds. The non-protonated amidrazones can be thought as hybrids between structures I and II.

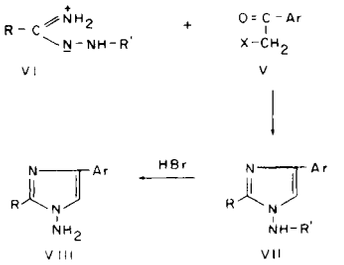
I II

In the case of the protonated compound, the charge delocalization increases the stability of the system, so that, in the reactive state, both structures (III and IV) could be equally interesting.

III IV

When the synthesis has been performed in a basic medium, because of the excess of amidrazones, the 1-amino-4-arylimidazole derivative has always been obtained.

Scheme I



VI V VIII VII

The first step of the reaction is nucleophilic substitution by the N-2 atom. Glover (4), in order to establish the position of the phenyl group in compounds of type VII, transformed them in the parent quaternary 1-amino-3-methylimidazolium salts, which, after deamination, yielded the corresponding trisubstituted imidazoles. They were, afterwards, compared with authentic samples obtained by other routes (8,9). Otherwise the position of the phenyl group was assigned by tentative analogy.

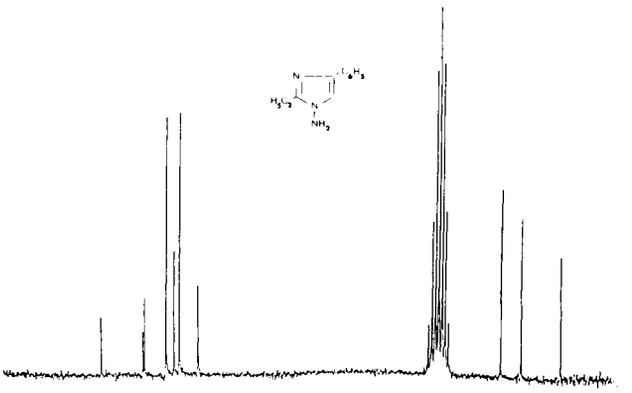


Figure 1. ^{13}C nmr spectrum of 1-amino-2-ethyl-4-phenylimidazole (VIIIa) in deuteriodimethylsulfoxide.

We determined the structure of 1-aminoimidazoles by their ^{13}C nmr spectra and by this method it has been possi-

0022-152X/81/071379-04$02.25

Table I

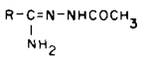
1-Aminoimidazoles Carbon-13 Chemical Shifts, (deuteriochloroform, ppm/TMS)

Compounds	C-2	C-4	C-5	C-1'	C-2'	C-3'	C-4'	CH_2	CH_3
VIIIa	150.46	137.97	116.73	134.46	124.71	128.52	126.57	19.51	12.49
VIIIa (a)	154.54	140.26	121.89	135.59	125.14	128.62	126.60	22.53	14.26
VIIIb	147.29	137.44	117.30					32.73	
VIIIb (a)	150.10	139.70	120.84					34.79	

(a) Final chemical shifts values after last amount of $Yb(dpm)_3$.

Table II

N-Acetylamidrazones

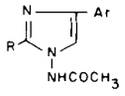


Compounds	R	Yield %	mp °C	Molecular Formula	Elemental Analysis Calcd./Found C	H	N
VIa	Et	70	151 (a)	$C_5H_{11}N_3O$	46.49	8.58	32.54
					46.63	8.59	32.55
VIb	$C_6H_5CH_2$	75	185 (a)	$C_{10}H_{13}N_3O$	62.80	6.85	21.98
					62.70	6.83	21.93
VIc	EtOOC-CH_2	65	145 (b)	$C_7H_{13}N_3O_3$	44.91	7.00	22.45
					44.77	6.98	22.37
VId	NC-CH_2CH_2	68	165 dec (c)	$C_6H_{10}N_4O$	46.74	6.54	36.34
					46.58	6.56	36.29

(a) From ethanol. (b) From acetonitrile (c) From ethanol/dimethylsulfoxide.

Table III

N-Acetylaminoimidazoles



Compounds	R	Ar	Yield %	mp °C	Molecular Formula	Elemental Analysis Calcd./Found C	H	N
VIIa	Et	C_6H_5	50	190 (a)	$C_{13}H_{15}N_3O$	68.10	6.59	18.33
						68.00	6.61	18.28
VIIb (4)	$C_6H_5CH_2$	C_6H_5	55	228-232 (b)	$C_{18}H_{17}N_3O \cdot HBr \cdot \frac{1}{2}H_2O$	54.50	5.20	10.50
						54.40	5.21	10.50
VIIc	$C_6H_5CH_2$	$C_6H_4pNO_2$	60	230-231 (c)	$C_{18}H_{16}N_4O_3$	64.27	4.80	16.66
						64.06	4.79	16.68
VIId	EtOOC-CH_2	C_6H_5	55	205-210 dec (d)	$C_{15}H_{17}N_3O_3$	62.70	5.96	14.63
						62.58	5.95	14.66
VIIe	EtOOC-CH_2	C_6H_4pBr	50	236 (a)	$C_{13}H_{16}BrN_3O_3$	49.19	4.40	11.47
						49.35	4.39	11.44
VIIf	NC-CH_2CH_2	C_6H_5	55	145 (c)	$C_{14}H_{14}N_4O$	66.12	5.55	22.04
						66.10	5.53	21.97

(a) From acetonitrile. (b) From propanol. (c) From ethanol (d) From chloroform.

ble to establish the position of substituents in the 1-aminoimidazole ring with small and easy-to-recover amounts of product.

First of all we assigned all the signals (10) in the spectra and then the positions of the substituent groups, exploiting the capability of the amino group to form contact

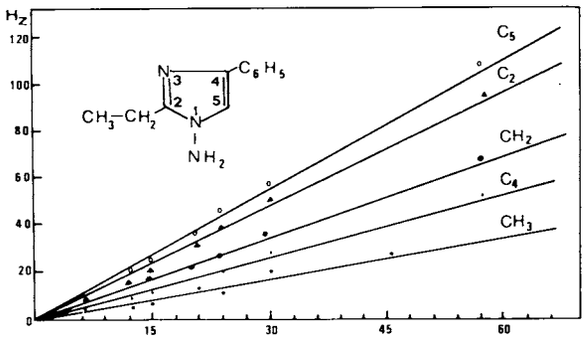


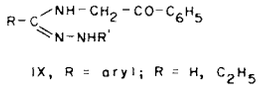
Figure 2 Dependence of the chemical shifts (Hz) of carbons of 1-amino-2-ethyl-4-phenylimidazole (substrate) versus the $Yb(dpm)_3$/substrate values.

Table IV

IR and NMR Data of Compounds VIIa-f

Compound	Ir cm^{-1} C=O	in KBr NH	H-NMR (Deuteriodimethylsulfoxide)
VIIa	1720	3300	1.25 (t, 3H, CH_3CH_2, J = 7.4 Hz), 2.10 (s, 3H, CH_3CO), 3.60 (q, 2H, CH_2, J = 7.4 Hz), 7.40-8.10 (m, 6H, ArH), N-H variable.
VIIb	1730	3310	2.14 (s, 3H, CH_3), 4.22 (s, 2H, CH_2), 7.27-7.75 (m, 10H, ArH), 8.15 (s, 1H of the imidazole ring).
VIIc	1690	3220	2.10 (s, 3H, CH_3), 3.90 (s, 2H, CH_2), 7.24 (s, 5H, C_6H_5-CH_2), 8.12 (s, 1H), 8.07 (q, 4H, C_6H_4, J = 9.1 Hz).
VIId	1675	3285	1.20 (t, 3H, CH_3CH_2, J = 7.1 Hz), 2.02 (s, 3H, CH_3CO), 3.23 (s, 2H, CH_2COOEt), 4.11 (q, 2H, CH_2CH_3, J = 7.1 Hz), 7.11-7.79 (m, phenyl and H-5).
VIIe	1690	3310	0.95 (t, 3H, CH_3CH_2, J = 7.1 Hz), 1.83 (s, 3H, CH_3CO), 3.16 (s, 2H, CH_2COOEt), 4.12 (q, 2H, CH_2CH_3, J = 7.1 Hz), 7.20 (q, 4H, ArH, J = 6.30 Hz).
VIIf	1680	3310	2.02 (s, 3H, CH_3CO), 3.24 (s, 4H, CH_2CH_2), 7.20-7.96 (m, phenyl and H-5).

complexes with the shift reagents (11). In fact upon treatment of the samples of 1-aminoimidazoles with increasing amounts of $Yb(dpm)_3$ it was possible to draw a straight line variation of chemical shifts as a function of the ratio $Yb(dpm)_3$/substrate. (Figures 1 and 2). The slopes of these straight lines as is well known are only dependent on the distance of the carbon atom under examination and the complexation site. From Figure 2 it is readily seen that the slopes for C-2 and C-5 are very similar to each other and are steeper than all the others, while the slope of C-4 is even more gentle than the slope of the CH_2 group. The phenyl carbon atoms are so distant from the complexation site that, as a matter of fact, they do not exert any influence on the slope when treated with the shift reagent. We have obtained real evidence that C-5 of the imidazole ring bearing the proton is nearest to the amine group, which is the complexation site. When the reaction between α-halogenoketones and *N*-acetylamidrazones is carried out in an acidic medium there is no closure of the imidazole ring but rather open chair products of type IX are obtained. Also for these compounds the structure has been determined by ir, nmr and ms.



IX, R = aryl; R = H, C_2H_5

In this case, as expected, there is nucleophilic substitution by the N-3 atom and at the same time hydrolysis of the acetyl group.

EXPERIMENTAL

The infrared spectra were recorded on a Perkin-Elmer model 325 spectrophotometer using pressed potassium bromide disks. The nmr spectra were recorded on a Varian FT 80-A instrument in deuteriodimethylsulfoxide and compared with an internal standard. Mass spectra were measured with an "Hitachi" Perkin-Elmer RMU-6D spectrometer at 70 eV. Microanalyses for C, H and N were carried out on a Perkin-Elmer model 240 Elemental Analyzer. Melting points were uncorrected and obtained on a Tottoli apparatus.

General Method of Obtaining *N*-Acetylamidrazone Compounds (VI).

Compounds VIa-d (Table II) have been prepared starting from the parent iminoester hydrochlorides (12-14). A solution of the acetohydrazide (0.1 mole) in the minimum quantity of absolute ethanol was added to a stirred cooled ethanolic solution of a mixture of the parent iminoester hydrochloride (0.1 mole) and triethylamine (0.1 mole). The solution was stirred overnight at room temperature which after cooling deposited a solid which was filtered off and washed with light petroleum (bp 40-70°). Afterwards it was recrystallized from the proper solvent.

Compounds VIIa-f (Tables III and IV) have been prepared by heating under reflux for about 3 hours, a solution (ethanol or acetonitrile) of the amidrazone (0.1 mole) and the α-halogenoketone (0.05 mole). After cooling the deposited solid (the amidrazone hydrobromide) was filtered off. Concentration of the filtrate yielded the 1-acetylaminoimidazoles which were purified by recrystallization. (See Table III).

1-Amino-2-ethyl-4-phenylimidazole (VIIIa).

A solution of *N*-acetamidoimidazole in 20% hydrobromic acid was heated under reflux for about 2 hours. The acid was evaporated off and the residue dissolved in water. Basification with 10% sodium hydroxide precipitated the *N*-amino compound which was crystallized from methanol mp 126-127° (yield 80%); nmr (deuteriochloroform): δ 1.31 (t, 3H, $-CH_2CH_3$, J = 7.03 Hz), 2.78 (q, 2H, $-CH_2-CH_3$, J = 7.03 Hz); 7.08 (s, 1H-5); 7.18-7.72 (m, 5H, ArH), NH variable; ir (Nujol): 3390 cm^{-1} (b).

Anal. Calcd. for $C_{11}H_{13}N_3$: C, 70.56; H, 7.00; N, 22.44. Found: C, 70.32; H, 7.02; N, 22.36.

3-Benzoylmethylbenzylamidrazone Hydrobromide (IXa).

A mixture of amidrazone hydrobromide (0.1 mole) and α-halogenoketone (0.1 mole) dissolved in alcohol (1-propanol or 2-propanol) was boiled under reflux for about 4 hours. After partial evaporation of the solvent and cooling, the deposited solid was recrystallized from one of the propyl alcohols, mp 220-230° dec (yield 78%); nmr (deuteriodimethylsulfoxide): δ 4.0 (s broad, 4H, CH_2Ar, $-CH_2CO$); 7.26-7.40 (m, 6H, ArH); 7.9-8.1 (m, 4H, ArH); NH, NH_2 variable; ir (potassium bromide): 3400 cm^{-1} (NH) 1670 cm^{-1} (C=O).

Anal. Calcd. for $C_{16}H_{17}N_3O \cdot HBr$: C, 55.18; H, 5.21; N, 12.06. Found: C, 55.04; H, 5.21; N, 12.10.

3-Benzoylmethyl-1-ethylbenzylamidrazone Hydrobromide (IXb).

A mixture of amidrazone hydrobromide (0.1 mole) and α-halogenoketone was heated under reflux in ethanol for 3 hours. From the cooled solution a solid precipitated. After recrystallization from 1-propanol it had mp 197-198° (yield 60%); nmr (deuteriodimethylsulfoxide): δ 0.97 (t, 3H, $-CH_2CH_3$, J = 7.1 Hz); 3.26 (q, 2H, $-CH_2CH_3$, J = 7.1 Hz); 4.07 (s, 2H, CH_2CO); 4.78 (s, 2H, $-CH_2Ar$); 7.38 (m, 6H, ArH); 7.90 (m, 4H, ArH); NH variable; ir (potassium bromide): 3200 cm^{-1} (NH); 1660 cm^{-1} (C=O); ms: m/e 295.

Anal. Calcd. for $C_{18}H_{21}N_3O \cdot HBr$: C, 57.45; H, 5.89; N, 11.16. Found: C, 57.38; H, 5.88; N, 11.15.

Acknowledgement.

We thank the C. N. R. Rome for support.

REFERENCES AND NOTES

(1) A. Heitzhem, O. Peters and H. Beyer, *Chem. Ber.*, **100**, 3418 (1967).

(2) H. Beyer, H. Heitzhem and H. Monek, *ibid.*, **101**, 3151 (1968).

(3) W. Hafner and H. Prigge, German Offen., 1,293,643, 19 Nov. 1970; *Chem. Abstr.*, **74**, 22838j (1971).

(4) E. E. Glover, K. T. Rowbottom and D. C. Bishop, *J. Chem. Soc., Perkin Trans. I*, 2927 (1972).

(5) H. Rapoport and R. M. Bonner, *J. Am. Chem. Soc.*, **72**, 2783 (1950).

(6) G. Ponzio, *Gazz. Chim. Ital.*, **40**, 433 (1910).

(7) M. J. S. Dewar, "The Electronic Theorie of Organic Chemistry", Clarendon Press, Oxford, England, 1949.

(8) P. G. Haines and E. C. Wagner, *J. Am. Chem. Soc.*, **71**, 2793 (1949).

(9) F. Asinger, H. Offermans and P. Krings, *Ann. Chem.*, **719**, 145 (1968).

(10) J. B. Stothers "Carbon 13 NMR Spectroscopy", Academic Press, New York, 1972.

(11a) R. Von Ammon and R. D. Fischer, *Angew Chem. Int. Edit. Engl.*, **11**, 675 (1972); (b) I. Ya. Slonin and A. Kr. Bulai, *Russian Chem. Rev.*, **42**, 904 (1973); (c) B. C. Mayo, *Chem. Soc. Rev.*, 49 (1973); (d) A. F. Cockerill, G. L. O. Davies, R. C. Harden and D. M. Rackham, *Chem. Rev.*, **73**, 553 (1973); (e) O. Hafer in "Topics in Stereochemistry", Vol. 9, N. E. Allinger and E. L. Eliel eds., J. Wiley and Sons, New York, 1976, p 111.

(12) S. M. MacElvain and J. W. Nelson, *J. Am. Chem. Soc.*, **61**, 1825 (1942).

(13) S. M. MacElvain and C. L. Stevens, *ibid.*, **68**, 1917 (1946).

(14) S. A. Glickam and A. C. Cope, *ibid.*, **71**, 43 (1949).