Microwave-Assisted Synthesis of 1-Hydroxymethylazoles

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In order to study their antimicrobial activity, series of 1-hydroxymethylazoles were synthesised by condensation reaction of azoles (pyrazole, imidazole, 3,5-dimethylpyrazole, 2-methylimidazole and benzimidazole) with paraformaldehyde. The reactions were carried out under microwave irradiation conditions using tetrahydrofurane (THF) or dimethyl sulfoxide (DMSO) as solvents. Obtaining hemiaminals of azoles using the microwaves assisted procedure has noticeable advantages compared to classical methods: yield increase, substantial reduction of reaction time, solvents consumption and waste minimization. All obtained hemiaminals were characterized by melting points, absorption spectra (FT-IR, ^{1}H-NMR and mass spectra (MS) while the purity was established by HPLC.

Keywords: hemiaminals of azoles, 1-hydroxymethylazole, microwave assisted synthesis, picrates of azoles

It is well known that cyclic secondary amines (as pyrrolidine, piperidine, morpholine, etc.) react with formaldehyde at N-H bond to form 1-hydroxymethyl derivatives [1-10]. Generally azoles are weak bases with aromatic character. Thus we presumed that azoles can have similar reactivity as other heterocyclic compounds to form hemiaminals [11-15].

N.J. Putochin proved that the reaction between pyrrolidine and formaldehyde at stoechiometric ratio 1:1 leads to a mixture of N-hydroxymethylpyrrolidine (hemiaminal) and dipyrrolidinemetane (aminal) [2]. Further studies showed that dipyrrolidinemethane represents 13% in the final product [3].

In 1959 the N-hydroxymethylpyrazole obtained by condensing pyrazole with formaldehyde was first mentioned (the term *hemiaminal* was not yet used). The resulted compound was poorly characterised, only by melting point data (table 1) [3-4].

According to some studies 1-hydroxymethylpyrazole can be obtained by condensation of pyrazole with aqueous solution of formaldehyde. The reaction takes place overnight and the resulted product is separated and purified from ether [15-17].

The increased possibility for metal complexes formation, where the hemiaminal of pyrazole is a perfect ligand, was the subject of many studies [5-7].

From the reaction of imidazole and formaldehyde, in a sealed tube, for 15 min at 120-130°C, a mixture of hydroxymethylimidazole derivatives was obtained. In the resulted mixture, 1-hydroxymethylimidazole (26%), 1,2-dihydroximethylimidazole (18%) and 2,4,5-trihydroxy-methylimidazole (2%) were identified [8].

Some early studies mention that the synthesis in a sealed tube and alkaline conditions affords selective reaction for 1-hydroxymethyimidazole as unique reaction product, which cannot be achieved by working at acidic *p*H. The existent 1-hydroxymethylimidazol ^{1}H-NMR data indicates that the presence of N-CH_2-O protons is to be noticed at 5.39 ppm. [8]

In this study we present a simple and rapid synthesis method of hemiaminals of azoles by condensing azoles (pyrazole, imidazole, 2-methylimidazole, 3,5-dimethyl-imidazole and benzimidazole) with paraformaldehyde under microwave irradiation conditions. (fig. 1)

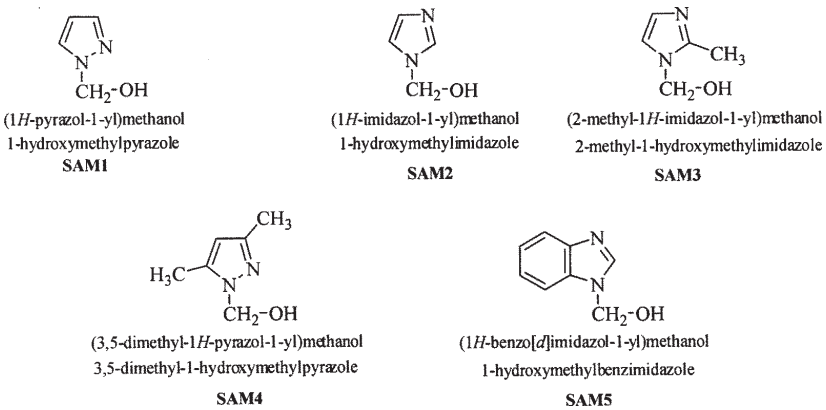

Fig 1. Chemical structure of the hemiaminals prepared by microwave protocols

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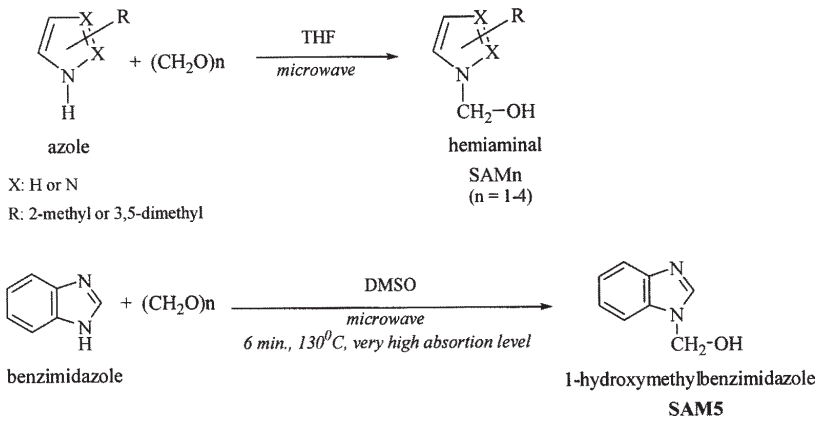


Scheme 1. Microwave synthesis for hemiaminals of azoles

Experimental part

Synthesis and reagents

All microwave reactions were performed using the single-mode Biotage Initiator 2.0.

As a general scheme, the reported 1-hydroxymethyl-azoles were obtained by condensing azole (pyrazole, imidazole, 2-methylimidazole, 3,5-dimethylimidazole and benzimidazole) with paraformaldehyde under specific conditions of microwave reactions (scheme 1).

1-Hydroxymethylpyrazole (SAM1)

50 mmoles pyrazole, 50 mmoles paraformaldehyde, 3.5 mL of tetrahydrofurane (THF) and a magnetic bar were introduced in a reaction vial that was sealed after. The reaction vial was placed in the microwave system, programmed as follows: 30 s pre-stirring and heating at 120°C for 5 min at a very high absorption level. After the reaction took place the mixture was cooled at room temperature and the resulted solid product was washed with tetrahydrofurane and petroleum ether and dried under vacuum.

1-Hydroxymethylimidazole (SAM2)

The microwave assisted synthesis of 1-hydroxy-methylimidazole was carried out following two protocols.

Method a

50 mmoles imidazole, 50 mmoles paraformaldehyde, 1.5 mL tetrahydrofurane (THF) and a magnetic bar were introduced in a reaction vial subsequently sealed and placed in the microwave system. The working parameters were: 30 s pre-stirring and heating at 120°C for 6 min at a very high absorption level. After cooling, the obtained liquid product was extracted with petroleum ether and the solvent was removed by distillation at reduced pressure.

Method b

50 mmoles of imidazole, 50 mmoles of para-formaldehyde, 0.105 g Na_2CO_3, 4.5 mL of tetra-hydrofurane (THF) and a magnetic bar were introduced in a reaction vial which was sealed and placed in the microwave system, programmed to operate as follows: 30 s pre-stirring and heating at 100°C for 6 min at a very high absorption level. The mixture was cooled at 50°C and the liquid fraction was separated from the solid sodium salt by filtration. A white solid with m.p 27°C was formed after complete cooling of the liquid product.

2-Methyl-1-hydroximethyl-imidazole (SAM3)

15 mmoles of 2-methylimidazole (1.68 g), 15 mmoles of paraformaldehyde (0.45 g), 0.5 mL of tetrahydrofurane (THF) and a magnetic bar were introduced in a reaction vial, sealed and then placed in the microwave system, set to operate as follows: pre-stirring for 1 min and heating at 100°C for 6 min at a very high absorption level. The resulting product was cooled and let overnight to crystallize completely. The crystals were washed with tetrahydro-furane and petroleum ether and dried under vacuum. The solid product partially melts at 66°C and completely melts at 106°C.

3,5-Dimethyl-1-hydroymethylpyrazole (SAM4)

50 mmoles 3,5-dimethylpyrazole (4.8g), 50 mmoles of paraformaldehyde (1.5g), 4 mL tetrahydrofurane (THF) and a magnetic bar were introduced in a reaction vial which was then sealed and placed in the microwave system. The operating parameters for the microwave system were: 30 s pre-stirring and heating at 120°C for 5 min at a very high absorption level. The resulting mixture was cooled at room temperature. The white crystals obtained were washed with tetrahydrofurane and petroleum ether and dried under vacuum. The solid product partially melts at 84°C and completely melts at 111°C.

1-Hydroxymethylbenzimidazole (SAM5)

50 mmoles of benzimidazole, 50 mmoles of paraformaldehyde, 4 mL dimethyl sulfoxide (DMSO) and a magnetic bar were introduced in a reaction vial, subsequently sealed and placed in the microwave system. The operating parameters of the microwave system were: 30 s pre-stirring and heating at 130°C for 6 min at a very high absorption level. The mixture was poured onto cold water. The resulted yellowish solid was washed with cold water, collected by filtration and dried under vacuum.

All reagents and chemicals were used as purchased. Paraformaldehyde was a Riedel de Haen product (Germany). Pyrazole, 3,5-dimethylpyrazole, benzimidazole were Merck products (Germany) and 2-methylimidazole was received from Fluka Chemie (Switzerland). The used solvents were: tetrahydrofurane (THF) (LiChrosolv) and dimethyl sulfoxide (DMSO) both of them Merck products.

Characterization

All melting points were measured with a Böetius melting point microscope and are uncorrected.

The purity of obtained hemiaminals was established by High Performance Liquid Chromatography (HPLC) performed on a CECIL CE4300 HPLC system equipped with UV-VIS (DAD) detector. The detection of compounds 1 to 4 was performed at 217 nm wavelength, using MeOH : H_2O (55 : 45) as mobile phase. Compound 5 was detected at 254 nm, with a mobile phase composition of MeOH : H_2O (60 : 40). The first tests were performed with a Nucleosil C18 ODS, 25 cm column (Hichrom), which contains free Si-OH groups that catalyzed hemiaminals

Compound*	Chemical formula	Molecular weights	Yield	Melting point °C		Boiling point °C	Picrate melting point °C	
				found	literature		hemiaminal	azole
SAM1	$C_4H_6N_2O$	98.10	89.80	84.4	89	-	141.3	163.5
SAM2	$C_4H_6N_2O$	98.10	*a.* 93.44	-	-	118 n^{20}_D= 1.5049	200**	210.1
			b. 84.28	27	-	-		
SAM3	$C_5H_8N_2O$	112.13	81.99	66 and 105-107	-	-	212.8	205
SAM4	$C_6H_{10}N_2O$	126.16	90.93	84 and 121	109	-	147-150	165.7
SAM5	$C_8H_8N_2O$	148.16	85.27	160-164	142-143	-	227	220.6

Table 1
CHEMICAL FORMULA, MOLECULAR WEIGHTS, YIELDS (%) AND PHYSICAL DATA OF HEMIAMINALS OF AZOLE

* *SAM1 = 1-hydroxymethylpyrazole; SAM2 = 1-hydroxymethylimidazole; SAM3 1-hydroxymethyl-2-methylimidazole; SAM4 = 1-hydroxymethyl-3,5-dimethylpyrazole, SAM5 1-hydroxymethylbenzimidazole.*

** *In literature 201-202 °C [8]*

back-conversion to the raw materials; therefore it was replaced with a Varian Inertsil 5-ODS-2 column for a better analysis.

The FTIR data have been gathered on samples prepared by embedding the solid compounds in KBr disks and analyzed with a BRUKER VERTEX 70 Fourier Transform Infrared Spectrometer. IR spectra were recorded in the range 4000–400 cm^{-1} with a resolution of 1 cm^{-1} and an accumulation of 25 scans.

The ^{1}H-NMR spectra were recorded with a Varian EM 360 Spectrometer using deuterio-chloroform ($CDCl_3$) as solvent and tetramethylsilane (TMS) as an internal standard.

The mass spectra were acquired using an AB Sciex quadrupole-linear ion trap mass spectrometer mode API 4000 QTrap, equipped with an electrospray ionization interface, operated in positive ions mode. The parameters were: turboionspray voltage - 5000V; nebulizergas - 25 psi; curtain gas - 15, declustering potential - 50V, collision energy from 5 to 25 V, collision extraction potential - 12V, CAD gas – medium. The analyzed compounds were dissolved in methanol at 1 mg/mL and then diluted to 1 µg/mL with H_2O:MeOH 1/1(v/v) before infusion in the ion source at a flow of 10 µl/min (with a help of a Harvard syringe pump).

Results and discussions

Except SAM2*a*, all azole hemiaminals are solid and have distinct melting points. The resulted picrates of 1-hydroxymethylazoles have also distinct melting points compared to the corresponding azole picrates (table 1).

The yields of compounds obtained under microwave condition were between 81.99 - 90.93%.

Purity analysis by HPLC

In case of SAM1 the acquired data indicate the presence of a single major compound corresponding to 1-hydroxymethylpyrazole but also traces of formaldehyde hydrates at low retention time.

The analysis of SAM2*a* indicates the presence of 1-hydroxymethylimidazole as major compound but also the presence of isomers in small amounts is possible. In case of SAM2*b* analyses revealed the presence of two compounds, the hemiaminal being major compound (80.74%).

In the chromatogram of SAM3 two major compounds with close retention times (1.54 min and 1.58 min) and peak areas of 144.1 and 99.7 have been identified, but also a compound with retention time of 2.57 min and peak area of 76.1; the latter was found in the chromatogram of 2-methylimidazole.

The chromatogram of SAM4 showed a major compound, 3,5-dimethyl-1-hydroymethylpyrazole, with retention time at 3.74 min, and traces of formaldehyde hydrates and 3,5-dimethylpyrazole.

Spectral characterization

In table 2 the FTIR and ^{1}H-NMR data which confirm the molecular structure of obtained hemiaminals are presented.

Study of FTIR spectra

The registered IR spectrum of SAM1 indicates the presence of -OH group at 3415 cm^{-1}, $-CH_2-$ group (2923 cm^{-1} and 2854 cm^{-1}) and C-O bond at 1088 cm^{-1}.

In SAM2*a* spectrum two vibration bands were registered corresponding to ν_{O-H}: one weak absorption at 3139.7cm^{-1}

Compound	wave numbers (cm^{-1})*	δ [ppm] ($CDCl_3$)
SAM1	3415 vw; 3229w; 3117w; 3132w; 2974m; 2923m; 2854m; 1520w; 1443w; 1402m; 1282w; 1088 vw; 1057 vw; 1009w; 980m; 774vw	7.54 s [2H]; 7.33 s [1H]; 6.12 s [1H]; 5.50 s [2H];
SAM2	*a.* 3139w; 3118w; 2943w; 2843w; 2685w; 1513w; 1219w; 1073vw; 1035m; 925m; 824m; 731w; 659w;	8.03 s [1H]; 7.40 s [1H]; 6.95 s [2H]; 5.26 s [2H];
	b 3139w; 3118w; 2945w; 2850w; 2691w; 1513w; 1221w; 1070vw; 1034w. 922m; 824m; 733w. 661m	
SAM3	3145w; 3108w; 2967w; 2927w; 2845w; 2712w; 2630w; 2494m; 1505m; 1387m; 1279vw; 1065vw; 993w; 758w; 741vw; 683m	8.80 s [1H]; 6.85 s [1H]; 6.66 s [1H]; 5.29 s [2H]; 2.18 s [3H]
SAM4	3143vw; 3123w; 2983m; 2951m; 2848m; 1555w; 1425m; 1307w; 1069vw; 1037m; 1007w; 985w. 808m; 704m	9.29 s [1H]; 5.77 s [1H]; 5.32 s [2H]; 2.30 s [3H]; 2.21 s [3H]
SAM5	3473m. 3414w. 3100w; 3061m; 3038w; 2945w; 2855m; 1616w; 1510m; 1460w; 1217w; 1092m; 1070vw; 897m; 743vw	7.96 s [1H]; 7.59 m [2H]; 7.30 m [2H]; 5.56 s [2H]; 3.76 s [1H]

Notes: * *vw (very weak) 0–20%, w (weak) 20–40%, m (medium) 40–60%, s (strong) 60–80%, vs (very strong) 80–100% with respect to the strongest peak in the spectrum.*

Table 2
IR VIBRATIONAL WAVE NUMBERS (cm^{-1}) AND ^1H NMR CHEMICAL SHIFTS (ppm)

and another more intense absorption at 3118 cm^{-1}. This suggests that are two different possible O-H groups: one can be C-CH_2-OH and the other N-CH_2-OH. The absorption band of methylene group appears at 2943 cm^{-1} for ν_{CH2as} and at 2844 cm^{-1} for ν_{CH2s}. The heterocyclic ring generates two absorption bands, at 1513 cm^{-1} and at 1461 cm^{-1}. For ν_{C-O} stretching vibration an intense band was registered at 1073 cm^{-1} but also a weak band at 1108 cm^{-1} which indicates the presence of C-CH_2-O- bond.

The *SAM2b* showed almost similar values as SAM2*a*.

The stretching vibration of ν_{O-H} and the absorption band of the heterocyclic ring present identical values of the vibrational wave number. The stretching vibration for ν_{C-O} registers a difference of 3 cm^{-1} less than the hemiaminal obtained by *method a* (1073 cm^{-1} for SAM2*a* compared to 1070 cm^{-1} for SAM2*b*).

The same as above described, two different absorption bands for ν_{CH_2} from N-CH_2-OH and C-CH_2-OH were noticed, corresponding to asymmetrical and symmetrical absorption.

In SAM3 spectrum two absorption bands for ν_{OH} were observed: one at 3145 cm^{-1} and another more intense at 3108 cm^{-1}. The absorption band of ν_{CH_2} was recorded at 2967 cm^{-1} and it could not be found in 2-methylimidazole spectrum. The heterocyclic ring vibration appears at 1505 cm^{-1} and at 1387 cm^{-1} and an absorption band for C-O stretching vibration was recorded at 1065 cm^{-1}.

Due to the stretching vibration of ν_{O-H}, two intense bands can be observed at 3143 cm^{-1} and 3123 cm^{-1} in SAM4 spectrum. The characteristic bands of -CH_3 group appear for ν_{CH3as} at 2951 cm^{-1} and for ν_{CH3s} at 2848 cm^{-1}. For aromatic heterocyclic ring a weak absorption at 1555 cm^{-1} and a medium absorption at 1307 cm^{-1} were noticed. Due to the stretching vibration of ν_{C-O} an intense absorption band at 1069 cm^{-1} is present.

In SAM5 spectrum two absorption bands corresponding to the OH group appear due to the stretching vibration of ν_{O-H}: at 3473 cm^{-1} and at 3414 cm^{-1}, which in case of benzimidazole cannot be noticed.

The presence of benzene ring is indicated by the stretching vibrations of $\nu_{C(Ph)-H}$ on the bands 3100 cm^{-1} (s), 3061 cm^{-1} and 3038 cm^{-1}, by the phenyl stretching ring of ν_{C-C} on the band 1616 cm^{-1} and by the out of plane deformation of γ_{C-H} on the band 794 cm^{-1} . The presence of imidazole is indicated by two signals: stretching vibration of $\nu_{C=N}$ at 1497 cm^{-1} and stretching vibration of ν_{C-N} at 1384 cm^{-1}. The stretching vibration of ν_{C-O} generates an intense absorption band at 1071 cm^{-1}.

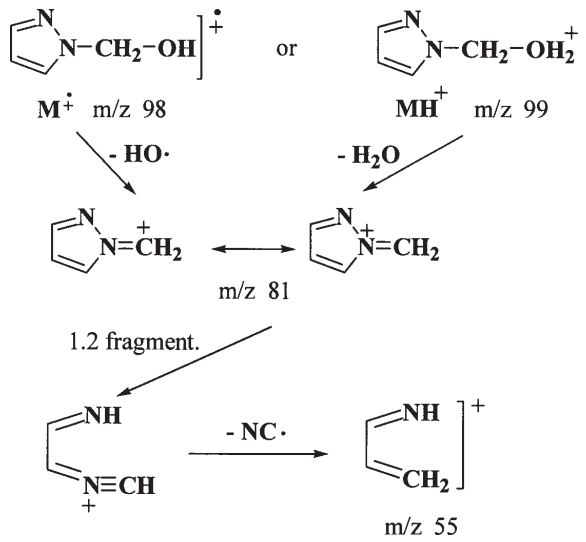
Study of ^1H-NMR spectra

The expected singlet of the methylene group protons from SAM1 structure was recorded at δ 5.50 ppm.

Table 3
THE $[MH]^+$ IONS OBTAINED IN LC-MS POSITIVE MODE AND THE MAIN FRAGMENTS IDENTIFIED IN THE MASS SPECTRA OF SAM_n*

Compound	Exact mass	Observed ion	Main fragments
SAM1	98.05	99	81; 63; 55
SAM2	98.05	99	81.2; 71; 56.9; 55.1
SAM3	112.06	113.1	95; 71; 66,9; 57
SAM4	126.08	127	109; 99; 81.2; 66.9; 57.1
SAM5	148.06	148.36	121.3; 93.1; 65.2; 39.1

**The electroionspray source was operated at 5000 V; the product ion spectra were acquired with collision energy of 17 V.*



Scheme 2. Fragmentation of 1-hydroxymethylpyrazole (SAM1) molecular ion

The ^{1}NMR spectrum of SAM2*b* is identical with SAM2*a* spectrum, which leads to the conclusion that resulted products have similar composition. It was noticed that C-CH_2-O protons where not identified in both SAM2*a* and SAM2*b* products. Only N-CH_2-O protons were recorded at δ 5.30 ppm.

In the case of SAM2*a* the strongly deshielded O-H proton gives a peak at δ 8.03 ppm and the existent heterocyclic protons of C_2 give a peak at δ 7.40. Also the protons of C_4 and C_5 form a singlet at δ 6.95 ppm. The methylene group protons deshielded by the neighbouring atoms present a chemical shift at δ 5.26 ppm.

The ^{1}HNMR spectra support the advanced structure of obtained 1-hydroxymethylimidazole. The –OH group proton form a singlet at δ 8 - 9 ppm and ring protons from C_4 and C_5 give peaks at δ 6.85 ppm and δ 6.66 ppm, respectively. The protons of the methylene group give a singlet at δ 5.29 ppm, and the ones from methyl group at δ 2.18 ppm.

Due to the intermolecular hydrogen bridges the OH proton rises at different values from δ9.5 to 7 ppm in case of SAM4. The only proton of C_4 from the heterocyclic ring appears at δ 5.77 ppm. The methylene protons give a singlet at δ 5.32 ppm and the different deshielded protons of $–CH_3$ groups give signals at 2.21 ppm and at 2.30 ppm respectively.

In SAM5 structure the strongly deshielded proton from C_2 rises to δ 3.76 ppm. Due to the coupling effects of phenyl protons two multiplets appear at δ 7.59 ppm and δ 7.30 ppm. The -CH_2 protons were registered at 5.56 ppm. The proton of -OH group forms a large peak at 7.96 ppm.

Study of the mass spectra

In table 3 the values from the mass spectra of azole hemiaminals are presented.

In the SAM1 mass spectrum the molecular ion with m/z 99 can be identified and it produces a series of fragment ions with m/z: 81; 63 and 55 (scheme 2).

For SAM2, the molecular ion can be identified at m/z 99 and produces a similar series of fragment ions as SAM1 with m/z: 81.2; 71; 56.9 and 55.1.

SAM3 give the molecular ion at m/z 113.1 and fragment ions with m/z: 95; 71; 66.9; 57.

In the SAM4 mass spectrum the molecular ion with m/z 109 can be identified and it produces a series of fragment ions with m/z 99; 81.2; 66.9; 57.1.

The molecular ion of 1-hydroxymethylbenzimidazole was observed at m/z 148.6 and generated main fragments with m/z: 121.3; 93.1; 65.2 and 39.1.

Conclusions

In the present study we showed simple protocols to prepare hemiaminals of azoles using microwave synthesis. Under microwave conditions, hemiaminals of azoles can be prepared in a substantially reduced reaction time and with better yields, by condensing the corresponding azoles with paraformaldehyde.

For further antimicrobial testing [18-19] all hemiaminals were synthesised by this modern procedure and characterized by melting points, absorption spectra (FT-IR, ^{1}H-NMR), mass spectra (MS) and the purity was established by HPLC.

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