Rapid Synthesis of Azole Aminals under Microwave Heating Conditions

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A new and rapid synthesis method of azole aminals is described. Starting from pyrazole, 3,5-dimethylpyrazole, imidazole, 2-methylimidazole and benzimidazole in reaction with paraformaldehide under microwave irradiation was successfully obtained the correspondent azole aminals. The performed synthesis provides better yields of pure products compared to the classical methods and significant reduced reaction times (6 min in MW compared to 20 h by classical method). The obtained compounds were characterized by UV-VIS, FT-IR and ^{1}H-NMR techniques while the purity was checked up by HPLC.

Keywords: 1,1'-methandiylbis(1-H-azole), azole's aminals, microwave synthesis

Classical synthesis methods of aminals prepared by reactions of formaldehyde with secondary amines (including saturated heterocycles) are well known and studied [1-5] .

These methods include complex synthesis procedures, long reaction time and purifying methods which conduct to small yields of the pure products [6-8].

Until now it has not been reported the synthesis of azole aminals by condensation reaction of azoles (as secondary amines) with paraformaldehide. Some azole aminals were obtained by the condensation of azoles with dichloromethane [4].

It has been already proved that by reactions of 1,2-dichloromethylether with secondary amines there are obtained aminals (for example dicyclohexilaminal) and not the expected aminoether [9].

Aromatic heterocycles have the necessary basicity to react with formaldehyde to give aminals. For instance, hemiaminals synthesis such as 1-hydroximethyldiazoles (fig.1) in the first step is well known, even if it has not been completely studied [10-12].

Fig. 1. Synthesis of pyrazol-1-yl methanol (hemiaminal)

Considering the chemical properties of diazoles we presumed that the hemiaminal (obtained in the first step) can react on a second reaction step to give the correspondent aminal (fig. 2)

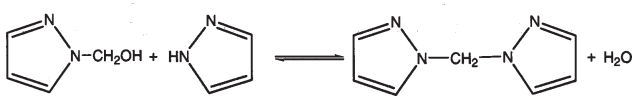


Fig. 2. Synthesis of 1,1'-methandiylbis(1-H-pyrazole) (aminal)

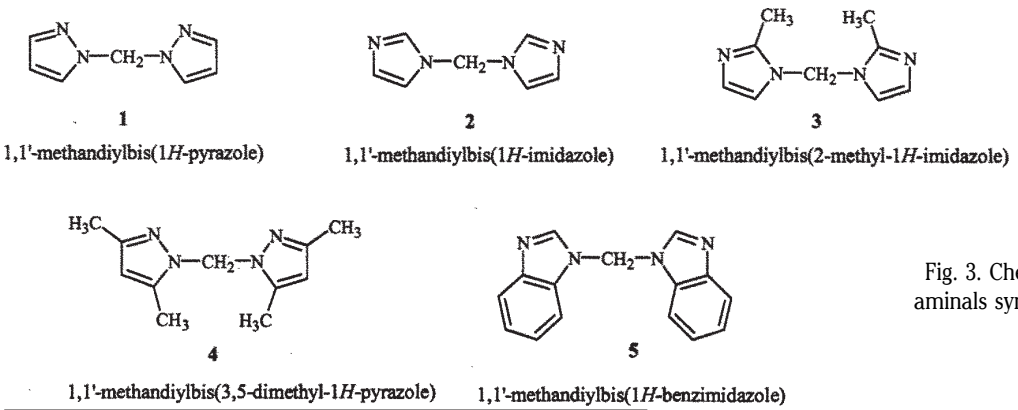
The second step of the reaction is reversible and depends on the stoichiometric ratio and the quantity of water resulting from the reaction [13].

A careful survey of the literature showed that the condensation reaction under microwave irradiation conditions of formaldehyde with N-unsubstituted diazoles in order to obtain azole aminals has not been studied yet.

In this paper we report a novel and rapid synthesis methods of azole aminals starting from: pyrazole, 3,5-dimethylpyrazole, imidazole, 2-methylimidazole and benzimidazole in reaction with paraformaldehyde carried out under microwave heating conditions (fig.3).

Using microwave procedure we obtained the correspondent azole aminals in a significant shorter reaction time (6 min in MW compared to 20 h by classical method) and with better yields in pure products (47.5-92.32% aminals) compared to the classical methods (40.15-75.89% aminals) [13].

The molecular structure of all synthesis products was confirmed by spectrometric ultraviolet–visible (UV–VIS), Fourier transform infrared (FTIR) spectroscopy and nuclear magnetic resonance (^{1}H-NMR) techniques, while the purity was verified by HPLC (Cecil, CE4300, DAD).



1,1'-methandiylbis(1*H*-pyrazole) (1)

1,1'-methandiylbis(1*H*-imidazole) (2)

1,1'-methandiylbis(2-methyl-1*H*-imidazole) (3)

1,1'-methandiylbis(3,5-dimethyl-1*H*-pyrazole) (4)

1,1'-methandiylbis(1*H*-benzimidazole) (5)

Fig. 3. Chemical structure of the azole aminals synthesis by microwave method

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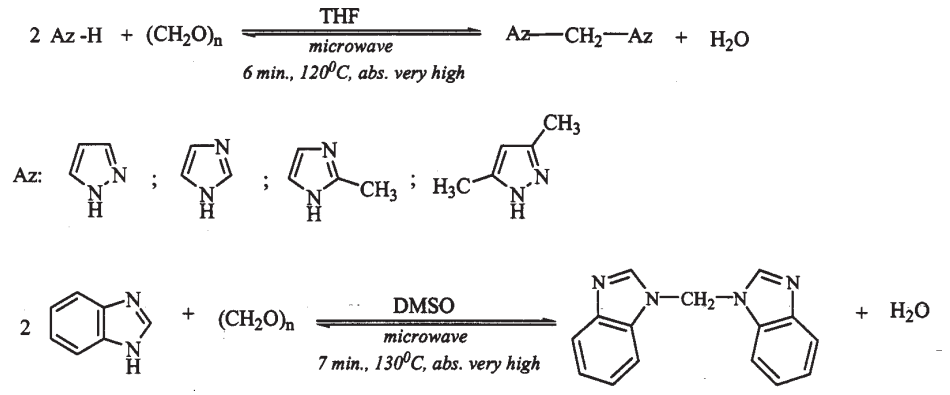

Scheme 1. General scheme of microwave synthetic procedure for azole aminals

Experimental part

Synthesis and reagents

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

As a general scheme, the reported 1,1'-methandiylbis(1-H-azole) were prepared by condensing pyrazole, 3,5-dimethylpyrazole, imidazole, 2-methylimidazole or benzimidazole with paraformaldehyde (scheme 1).

1,1'-Methandiylbis(1-H-azole) synthesis

5 mmoles of azole (pyrazole; 3,5-dimethylpyrazole; imidazole or 2-methyl-imidazole), 2.5 mmoles of paraformaldehyde, 3.5 mL of tetrahydrofurane (THF), used as solvent, and a magnetic bar were added to a reaction vial. In the microwave system the mixture was pre-stirred for 1 min and then was heated and stirred at 120°C for 6 min at a very high absorption level. After the reaction time the mixture was cooled at room temperature. The crystals were washed with cold petroleum ether and dried under vacuum.

1,1'-Methandiylbis(1-H-benzimidazole) synthesis

Except the 1,1'-methandiylbis(1-H-benzimidazole) **5** all the obtained compounds were prepared using tetrahydrofurane (THF) as solvent. The precipitation onto cold water is more practical but is limited of the particularly products solubility.

5 mmoles of benzimidazole, 2.5 mmoles of paraformaldehyde, 3.5 mL of dimethyl sulfoxide (DMSO) used as solvent and a magnetic bar were added to a reaction vial. In the microwave system the mixture was then pre-stirred for 1 min and then heated and stirred at 130°C for 7 min at a very high absorption level. After the reaction time the mixture was cooled to 50°C and poured onto cold water while stirring. The solid product so obtained was washed with cold water and collected by filtration under vacuum.

All reagents were high chemical pure. Paraformaldehyde was a Riedel de Haen product (Germany). Pyrazole, 3,5-dimethylpyrazole, benzimidazole were Merck products (Germany) and 2-methylimidazole was obtained from Fluka Chemie (Switzerland). The used solvents were tetrahydrofurane (THF) a Merck (LiChrosolv) product and dimethyl sulfoxide (DMSO) a Merck product.

Characterization

All melting points were taken on a Böetius melting point microscope and are uncorrected.

Elemental analysis was obtained on a Perkin-Elmer 2400CHN Elemental Analyzer.

The synthesis products purity was establish by High Performance Liquid Chromatography (HPLC) performed on a CECIL CE4300 HPLC system equipped with DAD detector and C18 ODS, 25 cm column eluted with MeOH : H_2O (50 : 50). Due to the fact that the new characterized compounds absorb at higher wavelength than MeOH it was possible to analyze them on a HPLC equipped with UV-VIS (DAD) detector.

The molecular structure of the compounds, deduced from the equations of the synthesis reactions was confirmed by spectral methods. Ultraviolet–visible (UV-VIS) spectra were recorded at wavelengths ranged between 200 and 1000 nm with an SPECORD M40 UV-VIS spectrometer, using methanol as solvent (M^{-4} conc).

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

The samples for IR data have been prepared by embedding the solid compounds in KBr disks and analyzed with BRUKER VERTEX 70 Fourier transform infrared spectrometer. IR spectra were collected in the range 4000–400 cm^{-1} with a resolution 1 cm^{-1} and an accumulation over 16 scans.

Results and discussions

The molecular structures of the microwave synthesis compounds were confirmed by elemental analysis (table 1).

All the obtained aminals are solids with distinctly melting point.

The yields of pure compounds prepared under microwave irradiation were between 47.5-92.32 %.

The azole aminals synthesis carried out under microwave irradiation conditions afforded also beside a considerable shorter reaction time the obtaining of more pure products. The synthesis of compounds **1**-**4** were performed in tetrahydrofurane (THF) medium.

Compound **5** was obtained using dimethyl sulfoxide (DMSO) as a solvent and the obtained mixture could have been treated with water which allowed the crystallization and isolation of 1,1'-methandiylbis(1-H-benzimidazole).

The characterization of the obtained compounds had been done also by their picrates preparation which had distinctly and highest melting points compared to the correspondent aminals (table 1).

In table 2 are presented the UV, IR, ^{1}H-NMR data which confirmed the molecular structure of the synthesis compounds.

Except compound **5**, all the other synthesis compounds (**1**-**4**) do not present chromophores groups in their structures, so they absorbed at shorter wavelengths (λ = 215 nm).

Table 1
ELEMENTAL ANALYSIS AND PHYSICAL DATA OF THE MICROWAVE SYNTHESIS AZOLE AMINALS

Compound no.	Formula	M g/moles	Analysis % C calculated / C found	H calculated / H found	N calculated / N found	Yield (%) of pure compound	Melting point ^{0}C found	Melting point ^{0}C literature	Picrates mp, ^{0}C
1	$C_7H_8N_4$	148.00	56.74 / 56.40	5.44 / 5.21	37.81 / 38.18	54.32	87.5	108	117
2	$C_7H_8N_4$	148.00	56.74 / 56.42	5.44 / 5.64	37.81 / 38.11	92,32	55	168	212
3	$C_9H_{12}N_4$	176.21	61.43 / 61.56	6.86 / 6.85	31.79 / 31.41	56.29	116-118	-	211-212
4	$C_{11}H_{16}N_4$	204.00	64.68 / 64.29	7.69 / 7.21	24.43 / 24.49	60.78	110-112	105	146-148
5	$C_{15}H_{12}N_4$	248.00	72.56 / 72.22	4.87 / 4.53	22.57 / 22.27	47.49	155-159	245	201-203

Table 2
SPECTRAL DATA OF THE MICROWAVE SYNTHESIED AZOLE AMINALS

Compound no.	UV (CH_3OH) λ_{max} (nm)	IR (KBr) λ_{max} [cm^{-1}]	^{1}H-NMR ($CDCl_3$) δ [ppm]
1	210	3153; 3123; 3117; 2948; 2855; 1520; 1443; 1408; 1282; 1088; 1058	7.57 s(4H); 6.27 s(2H); 5.54 s(2H)
2	216	3118; 2945; 2843; 2688; 1513; 1407; 1281; 1221; 1070; 1033; 733; 668	7.60 s(2H); 7.22 s(2H); 6.83 s(2H); 5.17 s(2H)
3	216	3138, 3110, 2957, 2927, 2848, 1564, 1504, 1428, 1277, 1112, 1068, 993, 756, 600	6.83 s(4H); 5.30 s(2H); 2.26 s(6H)
4	216	3202, 3133, 3111, 3040, 2983, 2948, 2925, 2872, 1555, 1424, 1307, 1069, 1029, 1008	5.76 s(2H); 5.43 s(2H); 2.21 s(12H)
5	209; 241; 271; 281	3113, 3062, 3003, 2944, 2862, 2796, 1477, 1458, 1408, 1273, 1245, 1218, 1199, 1068, 745	8.04 s(1H); 7.52 s(4H); 5.70 s(2H)

Compound **5** which has a benzene chromophor ring coupled with an imidazolic ring can absorb to higher wavelengths (λ = 209; 241; 271 and 281 nm).

The IR spectra of the characterized compounds indicate the presence of methylene group band the same for all aminals.

All ^{1}H-NMR spectra show the presence of -CH_2- group at 5.4 ppm resulted from the condensation reaction of azoles with paraformaldehide.

Conclusions

In the present paper we showed that the azole aminals can be obtained in very good conditions by condensation of azoles with paraformaldehyde under microwave irradiation conditions. By these methods the reaction time has been significantly reduced (6 min) compare to classical methods (20 h).

The IR and ^{1}H-RMN spectra support the structure advanced for all the obtained compounds.

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