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A New Method for the Synthesis of Ald(ket)azines and their Antioxidant Activity

The synthesis of biologically active compounds frequently requires the establishment of specific conditions (such as pressure, temperature, medium, solvent, and catalyst) or the use of expensive equipment. An important task is the search for simple synthesis methods for promising biologically active compounds. This paper presents data on a rapid method for the synthesis of ald(ket)azines (azines) with a variety of biological and physicochemical properties. Hydrazine hydrate reacts readily by condensation with aromatic (heterocyclic) aldehydes or ketones to form azines. The reaction occurs at room temperature in acetic acid. The synthesis is completed in a short period of time, between 5 and 15 seconds, with yields of 32 % to 98 % after recrystallization. The formation rate of ald(ket)azines depends on the reaction medium and the presence of hydrogen donors in the system, and increases with increasing acidity. The investigation did not yield any discernible pattern in the impact of electron-donor or electron-acceptor substituents in the *para*-, *meta*-, or *ortho*-positions at aromatic (heterocyclic) aldehydes or ketones on the azines yield. The synthesized compounds were studied using ^{1}H NMR spectroscopy, chromato-spectrometry, and elemental analysis. The Ferric Reducing Antioxidant Power (FRAP) spectrophotometric method was used to study the antioxidant activity of the compounds obtained. Compounds with an N,N-dimethyl- or N,N-diethyl group in the *para*-position of the aldehyde fragment of azine showed a significant antioxidant effect. The results obtained exceed the antioxidant value of ascorbic acid — an industrially used oxidation inhibitor.

Keywords: condensation reaction, aldazines, ketazines, azines, synthesis, Schiff bases, hydrazinium monoacetate.

Introduction

Schiff bases (imines, azomethines, azines) containing the structural element (–CR=N–) represent a fairly common class of organic compounds with a wide range of practical applications. They possess antidiabetic [1], antitumour [2, 3], antimicrobial [4–7], antifungal [8, 9], cytotoxic [10, 11], luminescent properties [12, 13], and are used as plant growth regulators [14], chemosensors [15, 16], liquid crystals [17] or universal building blocks in organic synthesis [18, 19].

The known methods for azines synthesis are based on the interaction of hydrazine hydrate or its salts with aromatic aldehydes (ketones) in various solvents at different temperatures and stirring [9, 16, 17, 20–27], without solvent [28, 29] (with the addition of iodine/bromine [30], aluminium oxide [31, 32]) or using different catalysts (ruthenium complex [33], nickel [34] or its salts [35], bismuth [36]).

Many of the described methods for azines synthesis have a number of disadvantages, such as special reaction conditions, long reaction time, low yields and the use of expensive catalysts. The aim of our work is to develop a simple and rapid method for the ald(ket)azines synthesis.

Experimental

Materials

General Information: starting hydrazine hydrate (64 %, CAS 7803-57-8), phenylmethanal (≥99.5 %, CAS 100-52-7), 4-bromobenzaldehyde (99 %, CAS 1122-91-4), 4-chlorobenzaldehyde (97 %, CAS 104-88-1), 4-nitrobenzaldehyde (98 %, CAS 555-16-8), 4-methoxybenzaldehyde (≥98 %, CAS 123-11-5), 4-(dimethylamino)benzaldehyde (98 %, CAS 100-10-7), 4-(diethylamino)benzaldehyde (99 %, CAS 120-21-8), 4-hexyloxybenzaldehyde (99 %, CAS 5736-94-7), 4-decyloxybenzaldehyde (CAS 24083-16-7), 2-thiophenaldehyde (98 %, CAS 98-03-3), 2-hydroxybenzaldehyde (≥98 %, CAS 90-02-8), 2-hydroxy-1-naphthaldehyde (CAS 708-06-5), 3-pyridinecarbaldehyde (98 %, CAS 500-22-1), 3-nitrobenzaldehyde (99 %, CAS 202-772-6), acetophenone (≥98 %, CAS 98-86-2), 4-nitroacetophenone (98 %, CAS 100-19-6), 2-hydroxyacetophenone (99 %, CAS 118-93-4), from Aldrich, Acros Organics, were used without purification.

The structure of the obtained compounds was confirmed by ^{1}H NMR spectroscopy, chromato-mass spectrometry and elemental analysis. Mass spectra were recorded on an Agilent Technologies 6890N/5975B chromatography-mass spectrometer (USA); ^{1}H NMR spectra were recorded on a Bruker Advance III 400 (Bruker Corporation, USA) in DMSO-d_6, $CDCl_3$ solvent; ^{1}H chemical shifts are given relative to $SiMe_4$. Elemental analysis was performed on a VARIO EL CUBE elemental analyzer (Elementar, Germany). Melting points were determined on a Stuart SMP40 device (Stuart Scientific, UK).

General Procedure for the Synthesis of Ald(ket)azines **3a-r**

0.04 mol of aldehyde (ketone) **1a-r** and 0.17 mol of acetic acid were mixed until completely dissolved and 0.026 mol of hydrazine hydrate **2** was added dropwise to the resulting solution under stirring. After 5–15 seconds, the precipitate (compounds **3f, g** do not precipitate, they are precipitated by water) was neutralized with ammonia solution (except compound **3k, r**), washed with water, filtered and recrystallized from benzene, chloroform or dimethyl sulfoxide: ethanol mixture (ratio 1:1).

1,2-bis(benzylidene)hydrazine 3a. Yield is 3.03 g (73 %), yellow crystals, m.p. 92–93 °C (92–93 °C [37]). ^{1}H NMR spectrum (400.0 MHz, $CDCl_3$) δ, ppm: 7.39–7.44 m (6H, Ar-H), 7.80–7.85 m (4H, Ar-H), 8.64 s (2H, 2 CH=N). Mass spectrum, m/z ($I_{rel,\ \%}$): 208 (70.3), 131 (100), 104 (26.7), 90 (3.9), 77 (37.5). Found, %: C 80.70; H 5.79; N 13.42. $C_{14}H_{12}N_2$. Calculated, %: C 80.74; H 5.81; N 13.45.

1,2-bis(4-bromobenzylidene)hydrazine 3b. Yield is 6.92 g (95 %), yellow crystals, m.p. 230–231 °C (223–224 °C [28]). ^{1}H NMR spectrum (400.0 MHz, DMSO-d_6) δ: 7.71–7.74 m (4H, Ar-H, *J* 8.0 Hz), 7.83–7.85 m (4H, Ar-H, *J* 8.0 Hz), 8.65 s (2H, 2 CH=N). Mass spectrum, m/z ($I_{rel,\ \%}$): 366 (59.4) $[M]^+$, 209 (100), 183 (18.7), 156 (2.2). Found, %: C 45.90; H 2.71; N 7.62. $C_{14}H_{10}N_2Br_2$. Calculated, %: C 45.94; H 2.75; N 7.65.

1,2-bis(4-chlorobenzylidene)hydrazine 3c. Yield is 5.30 g (96 %), yellow crystals, m.p. 208–210 °C (208–210 °C [37]). ^{1}H NMR spectrum (400.0 MHz, $CDCl_3$) δ, ppm: 7.38–7.42 m (4H, Ar-H, *J* 8.0 Hz), 7.73–7.77 m (4H, Ar-H, *J* 8.0 Hz), 8.56 s (2H, 2 CH=N). Mass spectrum, m/z ($I_{rel,\ \%}$): 277 (51.6) $[M]^+$, 165 (100), 152 (2.3), 138 (28), 111 (29.7). Found, %: C 60.59; H 3.58; N 10.06. $C_{14}H_{10}N_2Cl_2$. Calculated, %: C 60.67; H 3.64; N 10.11.

1,2-bis(4-nitrobenzylidene)hydrazine 3d. Yield is 5.42 g (91 %), yellow crystals, m.p. 312–313 °C (312–313 °C [37]). ^{1}H NMR spectrum (400.0 MHz, DMSO-d_6) δ, ppm: 8.14–8.16 m (4H, Ar-H, *J* 8.0 Hz), 8.33–8.35 m (4H, Ar-H, *J* 8.0 Hz), 8.78 s (2H, 2 CH=N). Mass spectrum, m/z ($I_{rel,\ \%}$): 298 (46.7) $[M]^+$, 176 (100), 149 (6.5). Found, %: C 56.30; H 3.35; N 18.74. $C_{14}H_{10}N_4O_4$. Calculated, %: C 56.38; H 3.38; N 18.79.

1,2-bis(4-methoxybenzylidene)hydrazine 3e. Yield is 5.02 g (94 %), yellow crystals, m.p. 177–179 °C (178 °C [37]). ^{1}H NMR spectrum (400.0 MHz, DMSO-d_6) δ, ppm: 3.84 s (6H, $2CH_3$), 7.03–7.07 m (4H, Ar-H, *J* 8.0 Hz), 7.79–7.83 m (4H, Ar-H, *J* 8.0 Hz), 8.59 s (2H, 2 CH=N). Mass spectrum, m/z ($I_{rel,\ \%}$): 268 (100) $[M]^+$, 161 (65), 134 (21), 107 (3.1). Found, %: C 71.58; H 5.97; N 10.40. $C_{16}H_{16}N_2O_2$. Calculated, %: C 71.62; H 6.01; N 10.44.

1,2-bis(4-N,N-dimethylaminobenzylidene)hydrazine 3f. Yield is 5.73 g (97 %), yellow crystals, m.p. 263–264 °C (263-264 °C [38]). ^{1}H NMR spectrum (400.0 MHz, DMSO-d_6) δ, ppm: 3.02 s (12H, $4CH_3$), 6.78–6.81 d (4H, Ar-H, *J* 12.0 Hz), 7.65–7.68 d (4H, Ar-H, *J* 12.0 Hz), 8.48 s (2H, 2 CH=N). Mass spectrum, m/z ($I_{rel,\ \%}$): 294 (100) $[M]^+$, 174 (21.8). 147 (36), 133 (2.3), 120 (7.5). Found, %: C 73.40; H 7.51; N 19.00. $C_{18}H_{22}N_4$. Calculated, %: C 73.44; H 7.53; N 19.03.

1,2-bis(4-N,N-diethylaminobenzylidene)hydrazine 3g. Yield is 6.86 g (98 %), yellow crystals, m.p. 195–197 °C (193 °C [39]). ^{1}H NMR spectrum (400.0 MHz, $CDCl_3$) δ, ppm: 1.17–1.20 t (12H, $4CH_3$),

3.37–3.42 t (8H, 4CH_2), 6.64–6.66 d (4H, Ar-H, *J* 8.0 Hz), 7.63–7.76 d (4H, Ar-H, *J* 8.0 Hz), 8.52 s (2H, 2 CH=N). Mass spectrum, m/z ($I_{rel,\,\%}$): 350 (100) $[M]^+$, 202 (9.4), 175 (15.6), 161 (20.3), 148 (1.6). Found, %: C 75.31; H 8.58; N 15.94. $C_{22}H_{30}N_4$. Calculated, %: C 75.39; H 8.63; N 15.98.

1,2-bis-(4-hexyloxybenzylidene)hydrazine 3h. Yield is 6.91 g (97 %), yellow crystals, m.p. 120–127 °C (turbid phase), at 128 °C full clearing. ^{1}H NMR spectrum (400.0 MHz, $CDCl_3$) δ, ppm: 0.88–0.92 t (6H, 2CH_3), 1.31–1.36 m (8H, 4CH_2), 1.42–1.50 m (4H, 2CH_2), 1.75–1.82 m (4H, 2CH_2) 3.98–4.01 t (4H, 2 OCH_2, *J* 8.0, 4.0 Hz), 6.92–6.94 d (4H, Ar-H, *J* 8.0 Hz), 7.75–7.77 d (4H, Ar-H, *J* 8.0 Hz), 8.60 s (2H, 2 CH=N). Mass spectrum, m/z ($I_{rel,\,\%}$): 408 (100) $[M]^+$, 231 (89), 206 (2.2), 204 (4.3), 130 (2.1), 41 (45.5). Found, %: C 76.38; H 8.84; N 6.81. $C_{26}H_{36}N_2O_2$. Calculated, %: C 76.43; H 8.88; N 6.86.

1,2-bis(4-decyloxybenzylidene)hydrazine 3i. Yield is 9.15 g (88 %), yellow crystals, m.p. 121–128 °C (turbid phase), at 129 °C full clearing. ^{1}H NMR spectrum (400.0 MHz, $CDCl_3$) δ, ppm: 0.86–0.89 t (6H, 2CH_3), 1.26–1.30 m (16H, 8CH_2), 1.32–1.37 m (8H, 4CH_2), 1.42–1.49 m (4H, 2 CH_2), 1.75–1.82 m (4H, 2 CH_2), 3.98–4.01 t (4H, 2 OCH_2, *J* 4.0, 4.0 Hz), 6.92–6.94 d (4H, Ar-H, *J* 8.0 Hz), 7.75–7.77 d (4H, Ar-H, *J* 8.0 Hz), 8.60 c (2H, 2 CH=N). Mass spectrum, m/z ($I_{rel,\,\%}$): 520 (87.4) $[M]^+$, 287 (100), 260 (10.5), 130 (7). Found, %: C 78.35; H 10.00; N 5.32. $C_{34}H_{52}N_2O_2$. Calculated, %: C 78.41; H 10.06; N 5.38.

1,2-bis(thiophen-2-ylmethylene)hydrazine 3j. Yield is 4.02 g (93 %), yellow crystals, m.p. 158–159 °C (161 °C [40]). ^{1}H NMR spectrum (400.0 MHz, $CDCl_3$) δ, ppm: 7.09–7.11 t (2H, Ar-H, *J* 4.0, 4.0 Hz), 7.39–7.41 d (2H, Ar-H, *J* 8.0 Hz), 7.45–7.46 d (2H, Ar-H, *J* 4.0 Hz), 8.75 s (2H, CH=N). Mass spectrum, m/z ($I_{rel,\,\%}$): 220 (100) $[M]^+$, 137 (7.5), 110 (30.5), 96 (9.8), 83 (5.9). Found, %: C 54.47; H 3.60; N 12.66; S 29.07. $C_{10}H_8N_2S_2$. Calculated, %: C 54.52; H 3.66; N 12.72; S 29.10.

1,2-bis(2-hydroxybenzylidene)hydrazine 3k. Yield is 4.56 g (95 %), yellow crystals, m.p. 224 °C (224 °C [41]). ^{1}H NMR spectrum (400.0 MHz, DMSO-d_6) δ, ppm: 7.00–7.02 d (4H, Ar-H, *J* 8.0 Hz), 7.41–7.45 m (2H, Ar-H), 7.70–7.72 m (2H, Ar-H, *J* 8.0 Hz), 9.00 s (2H, 2 CH=N), 11.08 w.s. (2H, 2OH). Mass spectrum, m/z ($I_{rel,\,\%}$): 240 (100) $[M]^+$, 147 (31.3), 120 (25), 106 (1.6), 93 (16.4). Found, %: C 69.90; H 4.98; N 11.60. $C_{14}H_{12}N_2O_2$. Calculated, %: C 69.99; H 5.03; N 11.66.

1,2-bis((2-hydroxynaphthalen-1-yl)methylene)hydrazine 3l. Yield is 6.56 g (96.5 %), yellow crystals, m.p. 233 °C (233 °C [28]). ^{1}H NMR spectrum (400.0 MHz, DMSO-d_6) δ, ppm: 7.23–7.31 d (2H, Ar-H, *J* 8.0 Hz), 7.45–7.49 t (2H, Ar-H, *J* 4.0, 16.0 Hz), 7.62–7.65 t (2H, Ar-H, *J* 8.0, 8.0 Hz), 7.92–7.94 d (2H, Ar-H, *J* 8.0 Hz), 8.03–8.05 d (2H, Ar-H, *J* 8.0 Hz), 8.61–8.64 d (2H, Ar-H, *J* 12.0 Hz), 9.91 s (2H, 2 CH=N). Mass spectrum, m/z ($I_{rel,\,\%}$): 340 (52.7) $[M]^+$, 184 (0.9), 170 (100), 156 (1.6), 143 (5.3). Found, %: C 77.59; H 4.70; N 8.18. $C_{22}H_{16}N_2O_2$. Calculated, %: C 77.63; H 4.74; N 8.23.

1,2-bis(pyridin-3-ylmethylene)hydrazine 3m. Yield is 1.76 g (42 %), yellow crystals, m.p. 150–152 °C (144–145 °C [42]). ^{1}H NMR spectrum (400.0 MHz, $CDCl_3$) δ, ppm: 7.34–7.37 d.d (2H, Ar-H, *J* 4, 4 Hz), 8.16–8.19 d.t (2H, Ar-H, *J* 4, 2, 2, 2 Hz), 8.63 s (2H, Ar-H), 8.67–8.68 d.d (2H, 2CH=N, *J* 1.6, 1.6 Hz), 8.97 d (2H, 2CH=N, *J* 1.8 Hz). Mass spectrum, m/z ($I_{rel,\%}$): 210 (10.9) $[M]^+$, 132 (100), 105 (10.9), 91 (1.6), 78 (11.7). Found, %: C 68.51; H 4.75; N 26.59. $C_{12}H_{10}N_4$. Calculated, %: C 68.56; H 4.79; N 26.65.

1,2-bis(3-nitrobenzylidene)hydrazine 3n. Yield is 4.70 g (79 %), yellow crystals, m.p. 188–190 °C (192–194 C [28]). ^{1}H NMR spectrum (400.0 MHz, $CDCl_3$) δ, ppm: 7.82–7.84 t (2H, Ar-H, *J* 8, 8 Hz), 8.32–8.39 m (4H, Ar-H), 8.72-8.73 t (2H, Ar-H, *J* 1.8, 1.8 Hz) 8.87 s (2H, 2CH=N). Mass spectrum, m/z ($I_{rel,\,\%}$): 298 (67.8) $[M]^+$, 252 (4.3), 176 (100), 149 (8.7), 130 (26.1), 122 (2.4), 117 (2.2), 103 (25),89 (19.6), 76 (29.3). Found, %: C 56.36; H 3.35; N 18.77. $C_{14}H_{10}N_4O_4$. Calculated, %: C 56.38; H 3.38; N 18.79.

1,2-bis(1-phenylethylidene)hydrazine 3o. Yield is 4.32 g (91.5 %), yellow crystals, m.p. 129–131 °C (123–125 °C [43]). ^{1}H NMR spectrum (400.0 MHz, $CDCl_3$) δ, ppm: 2.32 s (6H, 2CH_3), 7.38–7.43 m (6H, Ar-H), 7.88–7.92 m (4H, Ar–H). Mass spectrum, m/z ($I_{rel,\%}$): 236 (44) $[M]^+$, 221 (100), 159 (20.3), 132 (9.4), 118 (23.4), 104 (9.4), 77 (50). Found, %: C 81.28; H 6.79; N 11.81. $C_{16}H_{16}N_2$. Calculated, %: C 81.32; H 6.82; N 11.85.

1,2-bis(1-(4-nitrophenyl)ethylidene)hydrazine 3p. Yield is 5.93 g (91 %), orange crystals, m.p. 220–221 °C (204 °C [44]). ^{1}H NMR spectrum (400.0 MHz, $CDCl_3$) δ, ppm: 2.35 s (6H, 2CH_3), 8.05–8.07 d (4H, Ar-H, *J* 8.0 Hz), 8.25–8.27 d (4H, Ar–H, *J* 8.0 Hz). Mass spectrum, m/z ($I_{rel,\,\%}$): 326 (48.4) $[M]^+$, 311 (100), 296 (4.7), 204 (14), 177 (4.7), 163 (7.81), 149 (5.5). Found, %: C 58.83; H 4.32; N 17.15. $C_{16}H_{14}N_4O_4$. Calculated, %: C 58.89; H 4.32; N 17.17.

1,2-bis(1-(2-hydroxyphenyl)ethylidene)hydrazine 3r. Yield is 1.77 g (32 %), yellow crystals, m.p. 201–202 °C (197–199 C [45]). ^{1}H NMR spectrum (400.0 MHz, $CDCl_3$) δ, ppm: 6.87–6.91 t (2H, Ar-H, *J* 8.0, 4.0 Hz), 6.99-7.01 d (2H, Ar-H, *J* 8.0 Hz), 7.31–7.35 t (2H, Ar-H, *J* 8.0, 8.0 Hz), 7.58–7.61 d.d (2H, Ar-H, *J* 4.0, 4.0 Hz), 13.07 s (2H, 2OH). Mass spectrum, m/z ($I_{rel,\,\%}$): 268 (100) $[M]^+$, 147 (9.8), 134 (34.7),

120 (15.1), 106 (3), 93 (5.9). Found, %: C 71.59; H 6.00; N 10.42. $C_{16}H_{16}N_2O_2$. Calculated, %: C 71.62; H 6.01; N 10.44.

Procedure for Antioxidant Activity Determination by the FRAP Method

The antioxidant activity (AOA) of ald(ket)azines **3a-r** was determined by the FRAP spectrophotometric method [46].

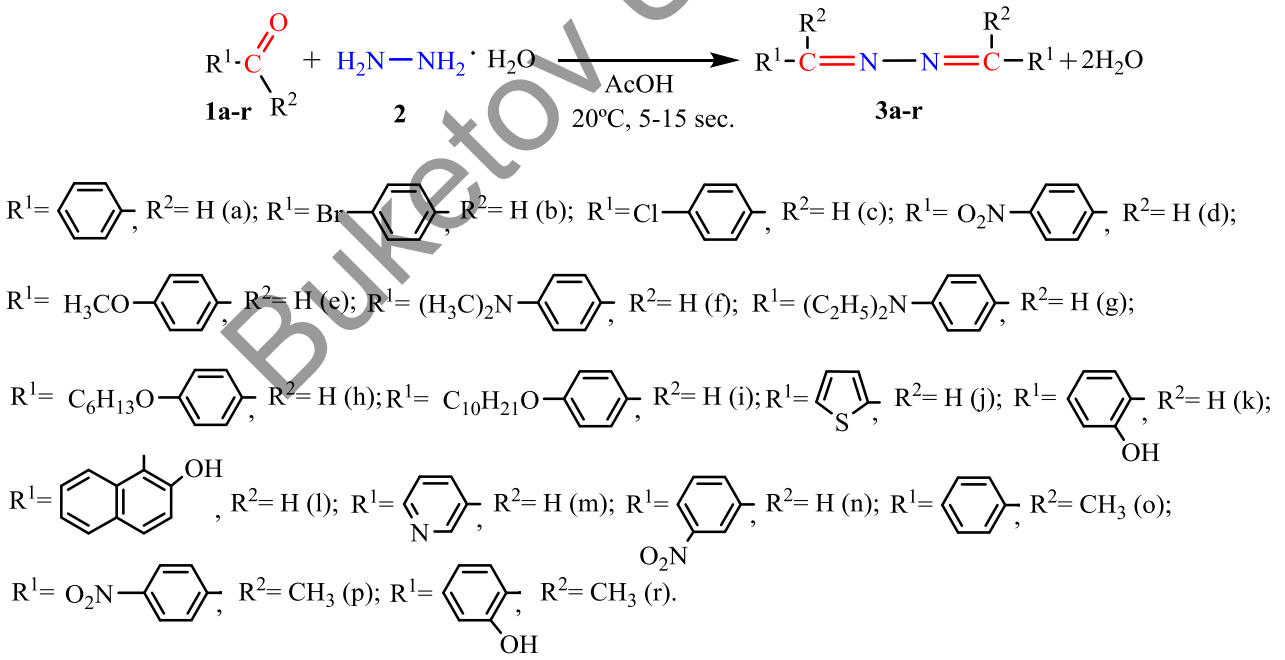
Ascorbic acid (AA), as one of the known antioxidants, was used as a reference [47]. Solutions with AA concentrations of $2.0–3.0\cdot10^{-3}$ mol·L^{-1} were prepared by dissolving an accurate suspension in water on the determination day, and 1.0 mL of organic solvent was added to AA aliquots for analysis. The samples investigated were dissolved in ethanol or DMSO, and the reagent content in the solutions was 4.0×10^{-4} or 1.0×10^{-3} mol·L^{-1}, respectively. The optical density of the solutions was measured on an SF-2000 spectrophotometer (Spektr, Russia) at λ = 510 nm in 10 mm cuvettes against a blank experiment [48]. Aliquots of 0.2–0.4 mL of the reagent solutions were taken for analysis, the corresponding organic solvent was added to the total volume of 1.0 ml, the AOA values were calculated from the calibration graph plotted from the AA content using the formula:

$$\mathbf{AOA} = \frac{\boldsymbol{n}_{AA,\,CG}}{\boldsymbol{n}_r},$$

where $\boldsymbol{n}_{AA,\,CG}$ is the amount of ascorbic acid found from the calibration graph, moles; $\boldsymbol{n}_r$ is the amount of reagent in the aliquot for analysis, moles.

Results and Discussion

The use of methanol [24], ethanol [21], toluene [25] or butanone-2 [17] is known to produce ald(ket)azines after 3, 5, 12 and 24 h, respectively. It has also been reported in the literature that the reaction rate of hydrazones or azines formation depends on the pH of the medium [49–53]. In contrast with the previously mentioned methods for the synthesis of ald(ket)azines, we carried out a reaction in an acetic acid medium (8.5 eq.) involving aromatic or heterocyclic aldehydes (ketones) **1a-r** (2 eq.) and hydrazine hydrate **2** (1.3 eq.) at room temperature (Scheme 1).

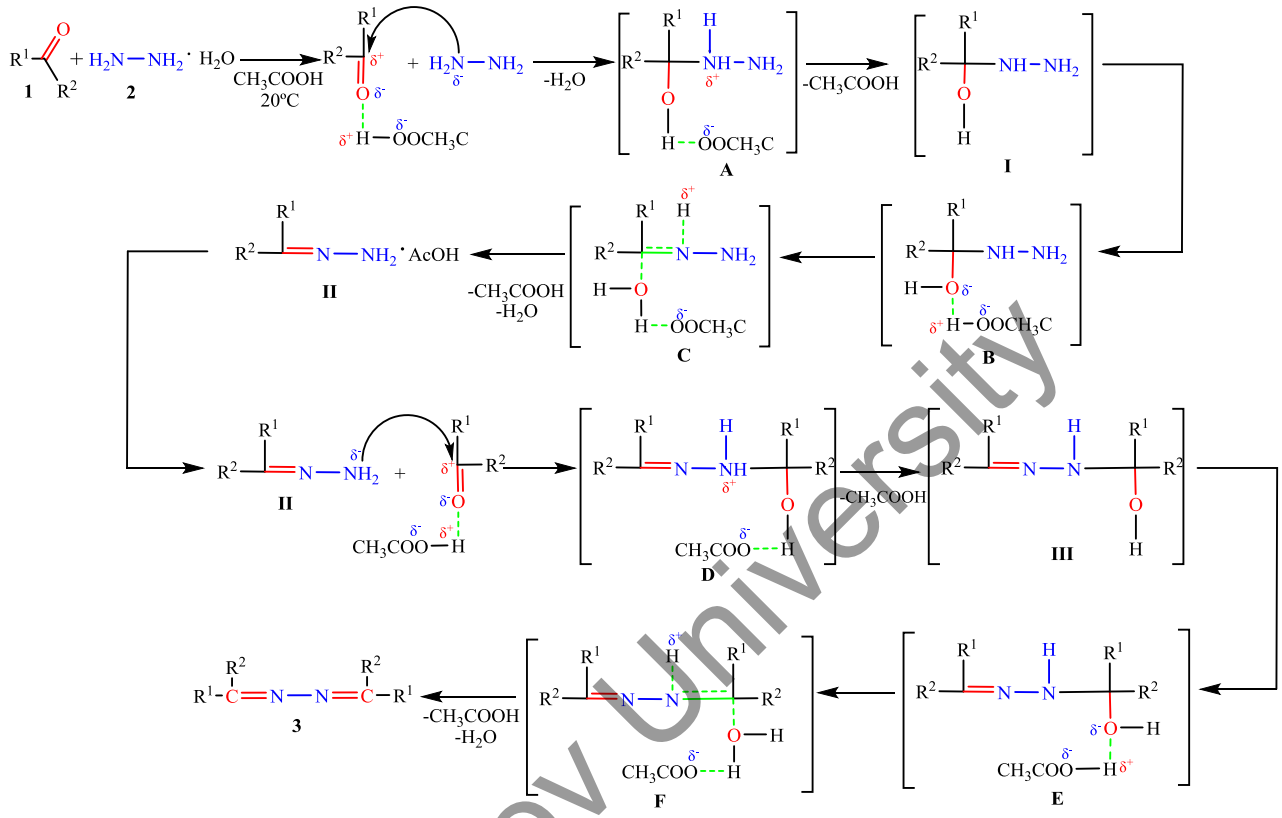


Scheme 1. Synthesis of ald(ket)azines

The azines **3a-e, h-p** formation was observed in 5–15 seconds after dropping hydrazine hydrate into the aldehyde (ketone) and acetic acid solution under stirring. Compounds **3f, g** did not precipitate and were precipitated with distilled water. Compound **3r** was formed as oil, which crystallized after 48 hours. The yield of azines **3a-r** after recrystallization was 32–98 %.

During the experiment, no clear trend of the effect of electron-donating or electron-accepting substituents in *para*-, *meta*- or *ortho*-positions in aldehydes or ketones on the azines **3a-l, o, p** yield was observed. The use of 3-pyridinecarbaldehyde **1m** or 2-hydroxyacetophenone **1r** resulted in lower yields.

The high formation rate of ald(ket)azines **3a-p** is achieved by acid catalysis. The authors [50–52] described the mechanism of hydrazones formation. A similar mechanism for the ald(ket)azines formation can be assumed (Scheme 2).



Scheme 2. Proposed mechanism for the ald(ket)azines formation

During the interaction between aldehydes/ketones **1** and hydrazine hydrate **2** in acidic medium, the protonation of the hydrazine hydrate molecule decreases its nucleophilicity. In contrast, acetic acid promotes an increase in the fractional positive charge on the carbon atom in the carbonyl group, which compensates for the decrease in hydrazine nucleophilicity [50–52]. In addition, at low pH values there is an increase in the rate of hydrazinocarbinols dehydration. This also compensates for the reduced nucleophilicity of hydrazine and allows the final ald(ket)azines to be obtained in a shorter time [50–52].

The mechanism described for the formation of ald(ket)azines is hypothetical, as the reaction may proceed through either one or two amino groups of hydrazine, which requires further study.

AOA values were determined for the obtained compounds **3a-g, j, k, m-r.** The results are presented in the table.

T a b l e

Antioxidant activity of 3a-r compounds determined by the FRAP method

No.	Compound	EtOH, mol·L^{-1}	AOA	DMSO, mol·L^{-1}	AOA
1	*2*	*3*	*4*	*5*	*6*
1	**3a**	0.001	0.12±0.01	0.001	0
2	**3b**	< 0.0004	–	0.001	0.13±0.01
3	**3c**	0.0004	0.36±0.03	0.001	0.11±0.02
4	**3d**	< 0.0004	–	0.0004	0.12±0.01
5	**3e**	0.001	0.16±0.01	0.001	0
6	**3f**	0.0004	**1.70±0.02**	0.001	**1.53±0.05**

Continuation of the Table

1	2	3	4	5	6
7	**3g**	0.0004	**1.18±0.01**	0.001	**1.35±0.04**
8	**3h**	< 0.0004	–	< 0.0004	–
9	**3i**	< 0.0004	–	< 0.0004	–
10	**3j**	0.001	0.43±0.02	0.001	0.23±0.01
11	**3k**	0.001	0	0.001	0.14±0.02
12	**3l**	< 0.0004	–	0.001	–
13	**3m**	0.001	0	0.001	0
14	**3n**	< 0.0004	–	0.001	0
15	**3o**	0.001	0.14±0.01	0.001	0
16	**3p**	< 0.0004	–	0.001	0
17	**3r**	0.001	0.43±0.02	0.001	0.10±0.01
Note: "–" — compound is insoluble.					

The compounds **3a-r** were dissolved in 95 % ethanol or dimethyl sulfoxide. For compounds **3h, i, l** no AOA study was carried out due to their low solubility in both solvents. The AOA for compounds **3b, d, n, p** was studied only in DMSO solution because of their poor solubility in EtOH.

It was found that compounds **3a, e, o** exhibited low AOA in ethanol solution (0.12/0.16/0.14) and in DMSO solution the AOA value was 0.

Moderate AOA values were found for compounds **3c, j, r** in ethanol (0.36/0.43/0.43), in DMSO the AOA values were reduced by more than half (0.11/0.23/0.10).

The significant AOA effect was exhibited by compounds **3f** (1.70±0.02/1.53±0.05) and **3g** (1.18±0.01/1.35±0.04) in ethanol/DMSO solution. The AOA values exceed those of ascorbic acid (reference) by 70/53 % (ethanol/DMSO) for compound **3f** and by 18/35 % (ethanol/DMSO) for compound **3g**.

During the study of the AOA, no specific dependence of its values on the use of different electron-donor or electron-acceptor substituents in ald(ket)azines **3a-r** was revealed, except for compounds containing N,N-dimethyl- or N,N-diethyl groups in the *para*-position of the aldehyde fragment of ald(ket)azine.

Conclusions

The interaction of hydrazine hydrate with aromatic or heterocyclic aldehydes (ketones) in an acetic acid medium results in the rapid formation of ald(ket)azines in quantitative yields. The high rate of the condensation reaction is due to the use of acetic acid, which provides optimal conditions for the reaction to proceed. Our findings indicate that compounds containing N,N-alkyl groups in the *para*-position of the ald(ket)azine aldehyde fragment exhibit antioxidant values that exceed those of ascorbic acid.

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Conflicts of Interest

The authors declare no conflict of interest.

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