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SYNTHESIS OF 6-R-3-(2-AMINOPHENYL)-2*H*-1,2,4-TRIAZIN-5-ONES: RESOURCES AND LIMITATIONS

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Abstract. The novel methods of 6-R-3-(2-aminophenyl)-2*H*-1,2,4-triazin-5-ones synthesis by 2-R-[(3*H*-quinazoline-4-yliden)hydrazono]-α-carboxylic acid esters hydrazinolysis and nucleophylic cleavage of 3-R-2*H*-[1,2,4]triazino[2,3-*c*]quinazoline-2-ones are worked out. It is shown that 2-R-[(3*H*-quinazoline-4-yliden)hydrazono]-α-carboxylic acid esters under hydrazinolysis form (3*H*-quinazoline-4-yliden)hydrazine or 6-R-3-(2-aminophenyl)-2*H*-1,2,4-triazin-5-ones. The reaction direction depends on geometric isomerism of corresponding esters.

Keywords: 6-R-3-(2-aminophenyl)-2*H*-[1,2,4]triazin-5-ones, hydrazinolysis, nucleophylic cleavage.

1. Introduction

Hydrazonocarboxilic acids and their derivatives are representatives of the group of multicenteral reagents, which are extensively used in organic synthesis [1]. 2-R-[(3*H*-quinazolin-4-yliden)hydrazono]-α-carboxilic acids and their esters are interesting reagents used as precursors for their functional derivatives and 3-R-2*H*-[1,2,4]triazino[2,3-*c*]quinazoline-2-ones [2-4]. The authors demonstrated [2-4], that 3-R-2*H*-[1,2,4]triazino[2,3-*c*]quinazoline-2-ones are formed as the result of intermediate [4,3-*c*]izomers rearrangement, which are subjected to recyclization (Dimrot's rearrangement). The authors [2] observed an interesting phenomenon: an attempt of [(3*H*-quinazoline-4-yliden)hydrazono]carboxylic acid's amides formation in the presence of CDI leads to the formation of corresponding amides as well as 3-R-2*H*-[1,2,4]triazino[2,3-*c*]quinazoline-2-ones. It was shown that in this case an important role in the reaction direction belongs to geometric isomerism (*E-*, *Z-)* of 2-R-[(3*H*-quinazoline-4-yliden)hydrazono]carboxylic acids [2]. In view of the abovementioned facts we decided to conduct the subsequent investigation of [(3*H*-quinazoline-4-yliden)hydrazono]carboxylic acids esters behavior under hydrazinolysis conditions.

2. Experimental

2-R-[(3*H*-quinazolin-4-yliden)hydrazono]-α-carboxylic acid esters (**1.1**-**1.8**), 3-R-2*H*-[1,2,4]triazin[2,3-*c*]quinazolin-2-ones (**4.1**-**4.7**) were prepared as reported previously [3, 4]. Other starting materials were commercially available and used without additional purification. All mps were determined in open capillary tubes in a Thiele's apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a Mercury 400 (400 MHz) spectrometer with TMS as internal standard in DMSO-d6 solution. Chemical shifts (δ) are given in ppm downfield. *J* values are in Hz. Mass spectra were determined on a Varian 1200L instrument (EI, 70 eV). LC-MS were determined on an Agilent 1100 instrument (atmospheric pressure chemical ionization – APCI).

(3H-Quinazolin-4-ylidene)hydrazine (**2.1***)*. To a solution of 5 mmol of corresponding esters (**1.1**-**1.4**) in 15 ml of *i*-PrOH hydrazine hydrate (0.75 g, 15 mmol) was added, the resulting mixture was refluxed for 1 h. Upon cooling a precipitate formed was filtered off.

Yield 95.3–98.3 % (of MeOH), mp 455–457 K; ^{1}H NMR: *d* = 5.01 (s, 2H, =N–NH2), 7.47 (t, 1H, H-7), 7.53 (d, 1H, H-8), 7.71 (t, 1H, H-6), 8.34 (s, 1H, H-2), 8.06 (d, 1H, H-5), 9.54 (s, 1H, 3-NH); LC-MS: *m/z* = 161 (MH+), 160 (M), 145 (12), 131 (35), 93 (10), 83 (5);. Anal. calc. for $C_8H_8N_4$: C, 59.99; H, 5.03; N, 34.98. Found: C, 60.02; H, 5.09; N, 35.02.

3-(2-Aminophenyl)-6-R-2H-[1,2,4]triazin-5-ones (**3.1**-**3.7**).

Method A. To a solution of 5 mmol of corresponding 2-aryl-2-[(3*H*-quinazoline-4-ylyden)hydrazono]acetic acid ester (**1.5**-**1.7**) in 15 ml of *i*-PrOH hydrazine hydrate (0.75 g, 15 mmol) was added, the resulting mixture was refluxed for 1 h. Upon cooling a precipitate formed was filtered off and crystallized from DMF-H_2O.

Method B. To a suspension of 20 mmol of corresponding 3-R-2*H*-[1,2,4]triazino[2,3-*c*]quinazoline-2-one (**4.1**-**4.7**) in 30 ml *i*-PrOH hydrazine hydrate (5 g, 100 mmol) was added, the resulting mixture was refluxed for 1 h. Upon cooling the mixture was acidified to pH 4-5; a precipitate formed was filtered off and crystallized from DMF-H_2O.

3-(2-Aminophenyl)-6-phenyl-2H-[1,2,4]triazin-5-one (**3.1**). Yield 41.7 % (method A), 58.7 % (method B), mp 563–565 K; ^{1}H NMR: *d* = 6.64 (t, (1H, *J*=7.4, H-4 Ph), 6.84 (d, 1H, *J*=7.4, H-6 Ph), 7.26 (t, *J*=7.4, 1H, H-5 Ph), 7.72 (d, 1H, *J*=7.4, H-3 Ph), 7.50 (m, 3H, H-3', H-4', H-5' Ph), 8.14 (d, 2H, *J*=8.2, H-2',H-6' Ph), 9.35 (s, 2H, NH_2); ^{13}C NMR: *d* = 109.7 (1-$C_{3\text{-Ph}}$), 115.7 (3-$C_{3\text{-Ph}}$), 117.5 (5-$C_{3\text{-Ph}}$), 128.6 (5-$C_{6\text{-Ph}}$), 128.6 (3-$C_{6\text{-Ph}}$), 128.6 (1-$C_{6\text{-Ph}}$), 128.8 (6-$C_{3\text{-Ph}}$), 128.8 (4-$C_{3\text{-Ph}}$), 128.9 (6-$C_{6\text{-Ph}}$), 128.9 (4-$C_{6\text{-Ph}}$), 128.9 (2-$C_{6\text{-Ph}}$), 130.4 (2-$C_{3\text{-Ph}}$), 133.5 (6-C), 133.6 (3-C), 150.6 (5-C); LC-MS: *m/z* = 265 (M^+); MS (EI): *m/z* (%) = = 264 (5.1), 215 (5.2), 195 (9), 187 (7), 186 (6.3), 163 (5.5), 161 (28.5), 160 (12.8), 134 (5.1), 133 (29.9), 132 (7.1), 120 (7.6), 119 (51), 118 (100.0), 115 (6), 109 (7.2), 105 (9.1), 104 (11.1), 102 (5.1). Anal. calc. for $C_{15}H_{12}N_4O$: C, 68.17; H, 4.58; N, 21.20. Found: C, 68.19; H, 4.58; N, 21.21.

3-(2-Aminophenyl)-6-(4-methylphenyl)-2H-[1,2,4]triazin-5-one (**3.2**). Yield 28.8 % (method A), 52.2 % (method B), mp 531–533 K; ^{1}H NMR: *d* =2.82 (s, 3H, CH_3), 6.63 (t, 1H, *J*=7.4, H-4 Ph), 6.83 (d, 1H, *J*=7.4, H-6 Ph), 7.26 (t, 1H, *J*=7.4, H-5 Ph), 7.28 (d, 2H, *J*=8.2, H-3', H-5' Ph), 7.69 (d, 1H, *J*=7.4, H-3 Ph), 8.06 (d, 2H, *J*=8.2, H-2', H-6' Ph), 9,16 (s, 2H, NH_2); LC-MS: *m/z* = 279 (M^+); MS (EI): *m/z* (%) = 278 (3.2), 171 (17.7), 162 (7.2), 161 (51.5), 133 (36.2), 132 (10.5), 129 (7.3), 119 (41.4), 118 (100), 116 (16.2), 103 (10.6). Anal. calc. for $C_{16}H_{14}N_4O$: C, 69.05; H, 5.07; N, 20.13. Found: C, 69.07; H, 5.08; N, 20.11.

3-(2-Aminophenyl)-6-(4-methoxyphenyl)-2H-[1,2,4]triazin-5-one (**3.3**). Yield 33.9 % (method A), 74.8 % (method B), mp 538–539 K; ^{1}H NMR: *d* =3.82 (s, 3H, OCH_3), 6,63 (t, 1H, *J*=7.8, H-4 Ph), 6,83 (d, 1H, *J*=7.8, H-6 Ph), 7.06 (d, 2H, *J*=8.8, H-3', H-5' Ph), 7.25 (t, H, *J*=7.8, H-5 Ph), 7.70 (d, 1H, *J*=7.8, H-3 Ph), 8.18 (d, 2H, *J*=8.8, H-2', H-6' Ph), 9.20 (s, 2H, NH_2); LC-MS: *m/z* = 295 (M^+); MS (EI): *m/z* (%) = 294 (5.5), 162 (5.8), 161 (56.2), 148 (14), 134 (14.3), 133 (96.5), 120 (7.9), 119 (71), 118 (100), 105 (18), 104 (13.4), 103 (24.7), 102 (13.6). Anal. calc. for $C_{16}H_{14}N_4O_2$: C, 65.30; H, 4.79; N, 19.04.13. Found: C, 65.32; H, 4.78; N, 19.09.

3-(2-Aminophenyl)-6-methyl-2H-[1,2,4]triazin-5-one (**3.4**). Yield 96.5 % (method B), mp 513–514 K; ^{1}H NMR: *d* =2.19 (s, 3H, -CH_3), 6.60 (t, 1H, *J*=7.8, H-4 Ph), 6.80 (d, 1H, *J*=8.1, H-6 Ph), 7.25 (t, 1H, *J*=8.1, H-5 Ph), 7.71 (d, 1H, *J*=8.1, H-3 Ph), 8.44 (s, 2H, NH_2); ^{13}C NMR: δ=17.6 (CH_3), 110.2 (1-$C_{3\text{-Ph}}$), 115.7 (5-$C_{3\text{-Ph}}$), 115.7 (3-$C_{3\text{-Ph}}$), 117.5 (6-$C_{3\text{-Ph}}$), 117.5 (4-$C_{3\text{-Ph}}$), 128.7 (2-$C_{3\text{-Ph}}$), 133.4 (6-C), 133.4 (3-C), 150.2 (5-C); LC-MS: *m/z* = 203 (M^+). MS (EI): *m/z* (%) = 203 (15.4), 202 (100.0), 161 (12), 133 (27.9), 119 (23.1), 118 (64.8).Anal. calc. for $C_{10}H_{10}N_4O$: C, 59.40; H, 4.98; N, 27.71. Found: C, 59.43; H, 5.01; N, 27.73.

3-(2-Aminophenyl)-6-benzyl-2H-[1,2,4]triazin-5-one (**3.5**). Yield 92.4 % (method B), mp 555–557 K; ^{1}H NMR: *d* =3.93 (d, 1H, *J*=6.2, CH_2), 6.59 (t, 1H, *J*=7.8, H-4 Ph), 6.80 (d, 1H, *J*=7.8, H-6 Ph), 7.22 (t, 1H, *J*=7.8, H-5 Ph), 7.30 (m, 5H, H-2', H-3', H-4' ,H-5', H-6' Ph), 7.60 (d, 1H, *J*=7.8, H-3 Ph), 9.12 (s, 2H, NH_2); ^{13}C NMR: δ= 36.7 (CH_2), 109.9 (1-$C_{3\text{-Ph}}$), 115.7 (3-$C_{3\text{-Ph}}$), 117.5 (5-$C_{3\text{-Ph}}$), 126.9 (6-$C_{3\text{-Ph}}$), 128.6 (4-$C_{3\text{-Ph}}$), 128.7 (5-$C_{6\text{-Ph}}$), 128.7 (3-$C_{6\text{-Ph}}$), 128.7 (1-$C_{6\text{-Ph}}$), 129.8 (6-$C_{6\text{-Ph}}$), 129.8 (4-$C_{6\text{-Ph}}$), 129.8 (2-$C_{6\text{-Ph}}$), 129.8 (2-$C_{3\text{-Ph}}$), 133.5 (6-C), 137.1 (3-C), 150.4 (5-C); LC-MS: *m/z* = 279 (M^+). Anal. calc. for $C_{16}H_{14}N_4O$: C, 69.05; H, 5.67; N, 20.13. Found: C, 69.09; H, 5.68; N, 20.17.

3-(2-Aminophenyl)-6-(4-nitrobenzyl)-2H-[1,2,4]triazin-5-one (**3.6**). Yield 82.5 % (method B), mp 537–539 K; ^{1}H NMR: *d* =4.10 (s, 1H, CH_2), 6.59 (t, 1H, *J*=7.8, H-4 Ph), 6.80 (d, 1H, *J*=7.8, H-6 Ph), 7.23 (t, 1H, *J*=7.8, H-5 Ph), 7.60 (m, 3H, H-3 Ph, H-2', H-6' Ph), 8.18 (d, 2H, *J*=8.0, H-3', H-5' Ph), 9.18 (s, 2H, NH_2); LC-MS: *m/z* = 324 (M^+). Anal. calc. for $C_{16}H_{13}N_5O_3$: C, 59.44; H, 4.05; N, 21.66. Found: C, 59.46; H, 4.12; N, 21.72.

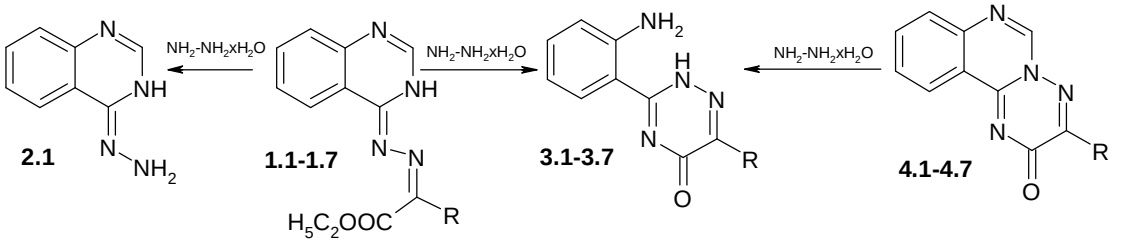
3-(2-Aminophenyl)-6-phenethyl-2H-[1,2,4]triazin-5-one (**3.7**). Yield 59.5 % (method B), mp 465–467 K; ^{1}H NMR: *d* =2.92 (t, 1H, , *J*=8.1, $CH_2C\underline{H_2}$ Ph), 2.95 (t, 1H, *J*=8.1, $\underline{CH_2}CH_2$Ph), 6.60 (t, 1H, *J*=8.1, H-4 Ph), 6.80 (d, 1H, *J*=8.1, H-6 Ph), 7.18 (t, 1H, H-5 Ph, *J*=8.1), 7,24 (m, 5H, H-2', H-3', H-4', H-5', H-6' Ph), 7.60 (d, 1H, *J*=8.1, H-3 Ph), 8.80 (s, 2H, -N$\underline{H_2}$); LC-MS: *m/z* = 293 (M^+); MS (EI): *m/z* (%) =292 (56.4), 277 (5.1), 250 (20.1), 249 (23.3), 246 (11.1), 233 (18.1), 231 (16.5), 221 (10.3), 201 (21.9), 194 (14.3), 189 (5.7), 186 (8.5), 174 (5.5), 172 (6.3), 162 (7.0), 161 (15.0), 147 (8.5), 145 (25.5), 144 (25), 143 (11), 134 (9.8), 133 (10), 132 (16.6), 130 (10.1), 119 (70.2), 118 (100), 116 (8.1), 105 (5.4). Anal. calc. for $C_{17}H_{16}N_4O$: C, 69.85; H, 5.52; N, 19.16. Found: C, 69.86; H, 5.53; N, 19.17.

3. Results and Discussion

Interaction between esters **1.1**-**1.7** and 5-fold excess of hydrazine hydrate in alcohols has certain peculiarities. The ester of 2-[(3*H*)-quinazoline-4-yliden]hydrazonopropionic acid (**1.1**) in the mentioned conditions forms (3*H*-quinazoline-4-yliden)hydrazine (**2.1**). The elongation of aliphatic group, at azometine bond on methylene (**1.2**, **1.3**) or ethylene (**1.4**) fragment gives the same hydrazinolysis product (**2.1**, Scheme 1**)**. Hydrazinolysis of

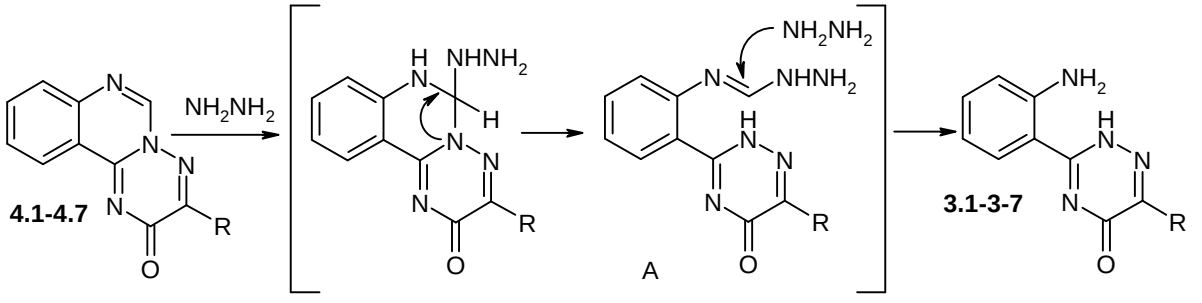
esters **1.5**-**1.7** yields corresponding 6-R-3-(2-aminophenyl)-2*H*-[1,2,4]triazin-5-ones (**3.1**-**3.3**, Scheme 3).

According to the literature [5-7], electron-deficient heterocyclic systems under the action of C-, O- and N-nucleophiles undergo cleavage to the azines or azoles cycles, as well as 3-R-2*H*-[1,2,4]triazino[2,3-*c*]quinazolin-2-ones [3]. We decided to study a possibility of nucleophilic cleavage for compounds **4.1-4.7** by hydrazine hydrate with the aim to expand synthetic potential of 6-R-3-(2-aminophenyl)-2*H*-[1,2,4]triazine-5-one and to explain esters **3.1-3.3** hydrazinolysis mechanism. The results indicated that interactions of compounds **4.1-4.7** with hydrazine hydrate yielded 6-R-3-(2-aminophenyl)-2*H*-[1,2,4]triazine-5-ones (**3.1-3.7**, Scheme 1). Their formation was confirmed by LC/MS, elemental analysis, ^{1}H and ^{13}C NMR, and mass-spectral data. Based on the obtained facts we propose the following reaction mechanism of compounds **4.1-4.7** cleavage: [1,2,4]triazino[2,3-*c*]quinazoline system at the first stage is subjected to nucleophilic attack on C-6 atom with pyrimidine ring opening (intermediate **A**). Exposure of azometine fragment to additional nucleophilic attack yields 6-R-3-(2-aminophenyl)-4*H*-[1,2,4]triazin-5-ones **(3.1-3.7,** Scheme 2).

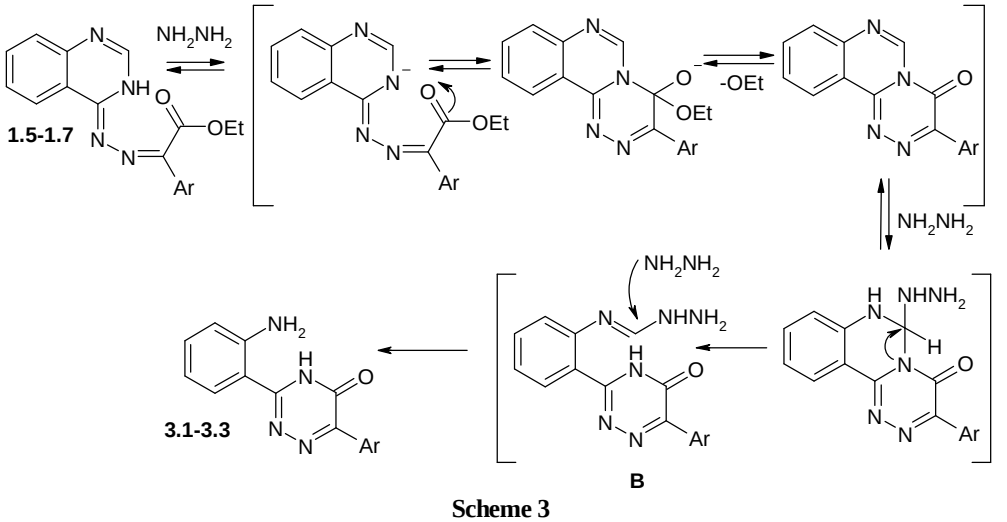


1.1, 3.4, 4.4 R=Me; **1.2, 3.5, 4.5** R=CH_2Ph; **1.3, 3.6, 4.6** R=CH_2Ph-NO_2(p); **1.4, 3.7, 4.7** R=CH_2CH_2Ph; **1.5, 3.1, 4.1** R=Ph; **1.6, 3.2, 4.2** R=Ph-Me(p); **1.7, 3.3, 4.3** R=Ph-OMe(p)

Scheme 1



Scheme 2



Scheme 3

Such an ambiguous direction of hydrazinolysis reaction for esters **1.1-1.7** may be explained by the presence of several electrophilic centers in molecules (in this case, the parallel attacks by nucleophilic reagent are possible) and different configuration of [(3*H*-quinazoline-4-ylyden)hydrazono]carboxylic acids esters [2]. Thus, compounds **1.1-1.4 (***E*-izomers) undergo parallel nucleophilic attacks by hydrazine hydrate on sterically available centers (ethoxycarbonyl group and C-4 of quinazoline cycle) and form **2.1**. Whereas for *Z*-izomers (**1.5-1.7**) a determinant step is nucleophilic attack of N-3-atom on sterically accessible ethoxycarbonyl group. The following nucleophilic attack on C-6 atom leads to pyrimidine cycle cleavage (intermediate **B**). Additional nucleophilic attack on azometine fragment allows to obtain 6-R-3-(2-aminophenyl)-2*H*-[1,2,4]triazin-5-ones **(3.1-3.3,** Scheme 3).

4. Conclusions

In this work the features of interaction between 2-R-[(3H-quinazoline-4-yliden)hydrazono]-α-carboxylic acid esters and 5-fold excess of hydrazine hydrate in alcohols were described. The ambiguous direction of hydrazinolysis reaction for the above mentioned esters may be explained by the presence of several electrophilic centers in molecule and different configurations of [(3H-quinazoline-4-ylyden)-hydrazono]carboxylic acids esters. Preparative methods for synthesis of new 6-R-3-(2-aminophenyl)-2*H*-[1,2,4]-triazin-5-ones *via* hydrazinolysis of corresponding 2-R-[(3H-quinazoline-4-yliden)hydrazono]-α-carboxylic acid esters and nucleophylic cleavage of 3-R-2*H*-[1,2,4]triazino [2,3-*c*]quinazoline-2-ones were also proposed.

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СИНТЕЗ 6-R-3-(2-АМІНОФЕНІЛ)-2*H*-[1,2,4]-ТРІАЗИН-5-ОНІВ: МОЖЛИВОСТІ ТА ОБМЕЖЕННЯ

Анотація. *Розроблено новий метод синтезу 6-R-3-(2-амінофеніл)-2H-[1,2,4]-тріазин-5-онів гідразинолізом естерів 2-R-[(3H-хіназолін-4-іліден)гідразоно]-α-карбонових кислот, а також нуклеофільним розщепленням 3-R-2H-[1,2,4]тріазино [2,3-c]хіназолін-2-онів. Показано, що естери 2-R-[(3H-хіназолін-4-іліден)гідразоно]-α-карбонових кислот під дією гідразину гідрату утворюють (3H-хіназолін-4-іліден)гідразин або 6-R-3-(2-амінофеніл)-2H-[1,2,4]-тріазин-5-они. Напрямок реакції залежить від геометричної ізомерії відповідних естерів.*

Ключові слова: *6-R-3-(2-амінофеніл)-2H-[1,2,4]-тріазин-5-они, гідразиноліз, нуклеофільне розщеплення.*