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Heterocyclization Reactions of 4-Hydrazinoquinazoline with Dicarboxylic Acid Anhydrides

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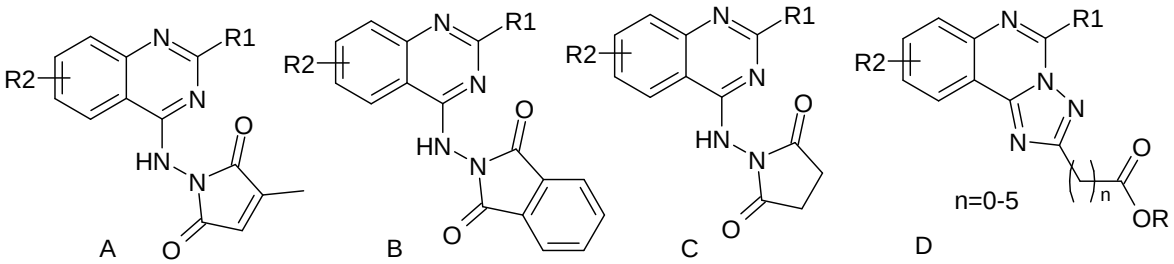
Abstract. An interaction of 4-hydrazinoquinazoline with dicarboxylic acid anhydrides is investigated. Carrying out the reaction in mild conditions proper hydrazidoacids were synthesized. The reaction in the glacial acetic acid medium is accompanied with the cascade of tandem transformations because of dehydration of an above intermediate hydrazidoacids. Instead, the reaction of campharic, endic, phthalic anhydrides and its hydrogenated analogues with rigid framework carcass, results in the formation of proper imidoaminic structures. An interaction of 4-hydrazinoquinazoline with a succinic and glutaric acid anhydrides, and also the heterocyclization of monoethyl ether of oxalic acid 2-(4(3*H*)-quinazolinyliden)hydrazide is accompanied with the formation of 2-R-[1,2,4]triazolo[1,5-*c*]quinazolines *via* Dimroth-like rearrangement of the expected [4,3-*c*] series.

Introduction

Products of heterocyclisation of 4-hydrazinoquinazoline with dicarboxylic acid anhydrides have been attracted a considerable interest during last years. A literature search showed that 2-R-4-hydrazinoquinazolines with citraconic anhydride form novel orally active inhibitors (A) of AP-1 and NF-κB mediated transcriptional activation as therapeutic agents for treating inflammatory mediated

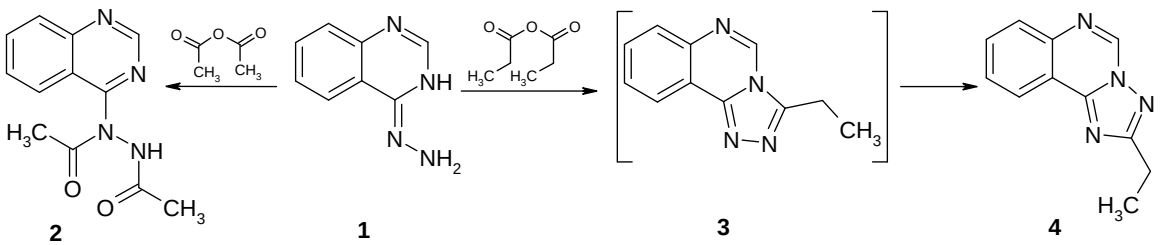
conditions [1]. Some biologically active aminoimides B and C were obtained by the reaction of proper 4-hydrazinoquinazolines with succinic and phthalic anhydrides [2]. However, only B was characterized by the ^{1}H NMR spectrum and possible formation of the isomeric structures was not considered by the authors [2]. On the other hand, heterocyclization of the appropriate N-acyl derivatives in the same conditions has been reported to give *s*-triazolo[1,5-*c*]quinazolines (D) [3, 4]. This prompted us to study the regioselective reactions starting from 4-hydrazinoquinazoline and dicarboxylic acid anhydrides.



Results and Discussions

The starting compound **1** can act as a 1,1-NN-, 1,2-NN- or 1,4-NNCN-bifunctional nucleophilic reagent. Earlier we reported that interaction of 4-hydrazinoquinazoline (**1**) with aliphatic anhydrides is not obvious. Thus, usage of the acetic acid led to the N,N'-diacetyl compound **2** whereas propionic anhydride gave 2-ethyl-[1,2,4]triazolo[1,5-*c*]quinazoline (**4**) *via* Dimroth-like rearrangement of the initially formed [4,3-*c*] system **3** (Scheme 1) [5].

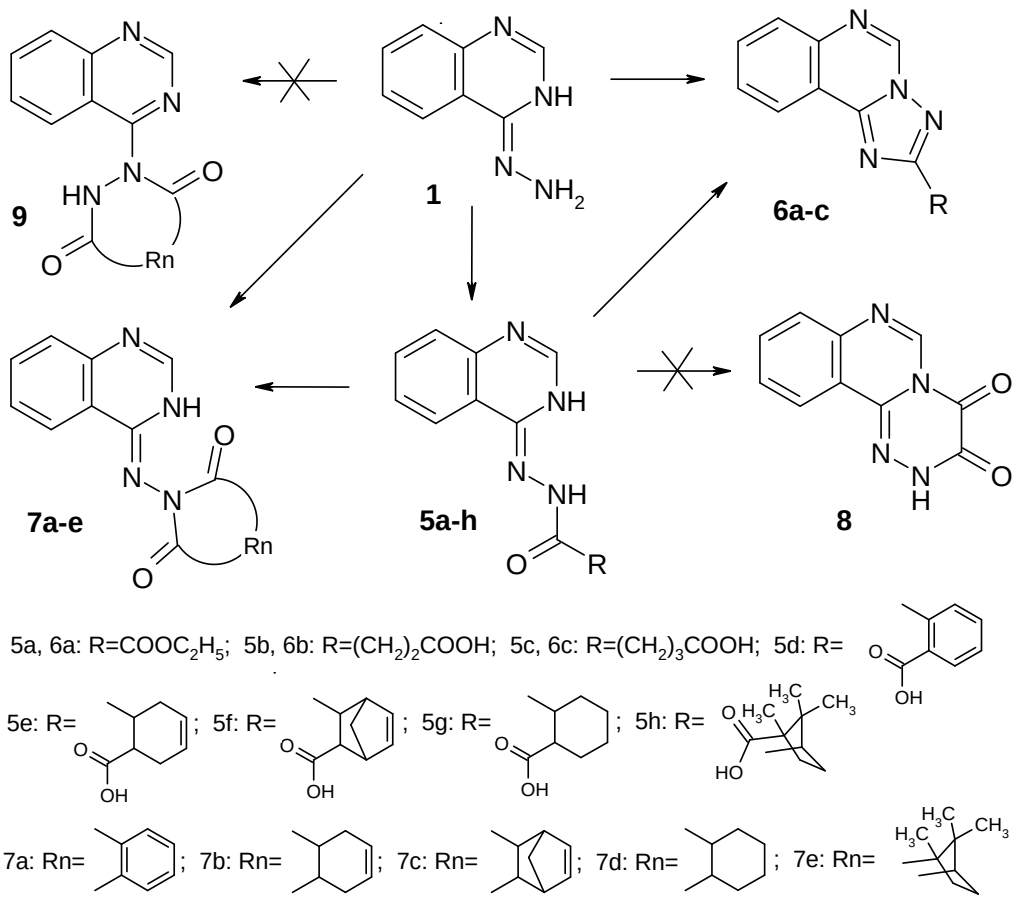
Scheme 1



First we studied the room temperature reaction of **1** with dicarboxylic acid anhydrides in the dioxane or 2-propanol which accompanied with ring-opening process. As a result, expected N-acyl derivatives **5b-g** were isolated in good yields

(Scheme 2). However, camphoric anhydride interacted in the alcoholic medium at 60ºC, probably due to the low electrophilic properties and steric hindrances. Monoethyl ether of oxalic acid 2-(4(3*H*)-quinazolinyliden)hydrazide (**5a**) was obtained from chloroanhydride of monoethyl oxalate by the conventional method (Scheme 2).

Scheme 2

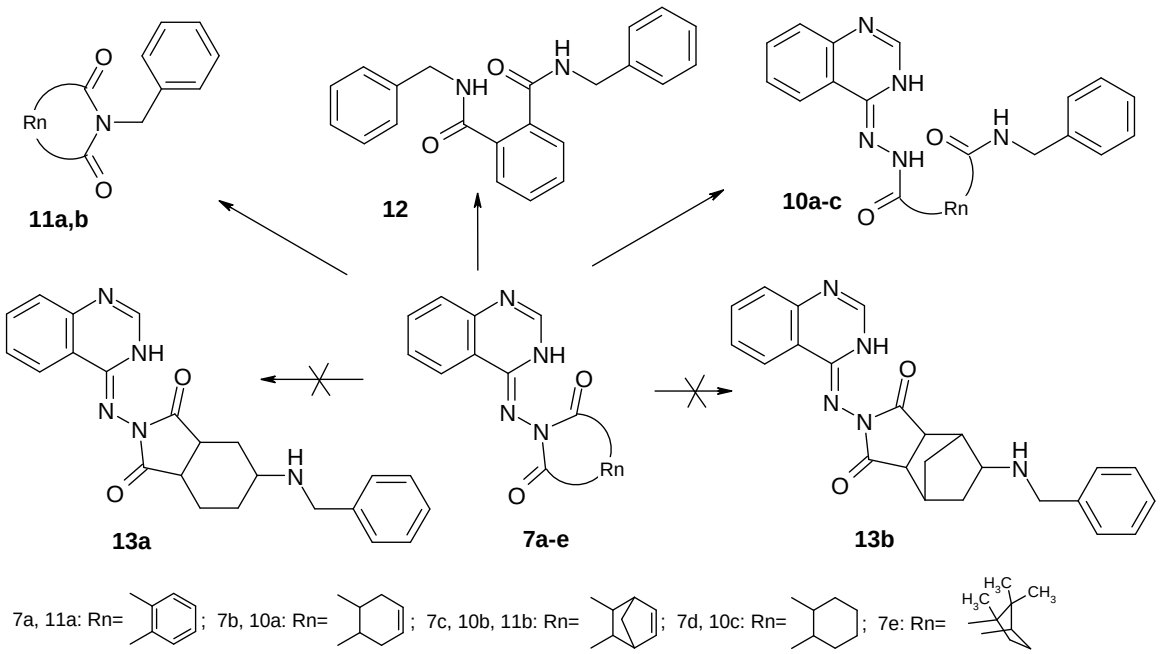


When **1** was heated with dicarboxylic acid anhydrides in glacial acetic acid another products were isolated (Scheme 2). Thus, an interaction of **1** with succinic and glutaric anhydrides led to appropriate acids **6a-c** with *s*-triazolo[1,5-*c*]quinazoline skeleton. The reaction passway probably includes formation of N-acyl derivatives, its cyclocondensation and further isomerization to the [1,5-*c*] series. A facile Dimroth-like rearrangement of the intermediate [4,3-*c*] isomers with alkyl substituents in triazole ring was described previously [5]. Proposed structures **6a-c** were supported by the LC/MS and ^{1}H NMR spectra. Thus, an

unusually downfield singlet of H-5 at 9.52-9.27 ppm was observed. Such strong de-shielding is caused by the ring current of the tricyclic system. Finally, EIMS of derivative (**6b**) exhibited an appropriate *m/z* value 242 for $M^{\cdot+}$ with characteristic mass fragmentation pattern.

Hydrazide **5a** undergoes the same cyclization to the ether **6a**. Possible formation of triazinoquinazoline **8** was excluded based on the spectral data. Nevertheless, camphoric, endic, phthalic anhydrides and its hydrogenated analogues with rigid framework carcass results in the formation of proper imidoamines **7a-e** (Scheme 2). Its structures were deduced from the LC/MS, EIMS and ^{1}H NMR spectra. However, possible formation of ensembles **9** can not be excluded on the basis of obtained data.

Scheme 3



In the next step we attempted to perform nucleophilic transformations of imidoamines **7a-e** (Scheme 3). It was expected that supposed compounds **7** in contrast with **9** would be entered into the reaction. We have found, that **7b-e** with benzylamine formed subsequent benzylcarbamoyl derivatives **10a-c**. The reaction of **7a** with benzylamine under different conditions gave phthalic acid benzylimide (**11a**), or dibenzylamide (**12**), or its mixtures with the starting imidoamine **7a**. Only compound **7e** did not enter into the reaction probably because of steric hindrances.

The structures of the synthesized compounds were deduced from the LC/MS and ^{1}H NMR spectra.

To resume, an interaction of 4-hydrazinoquinazoline with dicarboxylic acid anhydrides is investigated. Carrying out the reaction in mild conditions proper hydrazidoacids were synthesized. The reaction in the glacial acetic acid medium is accompanied with the cascade of tandem transformations because of dehydration of an above intermediate hydrazidoacids. Instead, the reaction of campharic, endic, phthalic anhydrides and its hydrogenated analogues with rigid framework carcass, results in the formation of proper imidoaminic structures. An interaction of 4-hydrazinoquinazoline with a succinic and glutaric acid anhydrides, and also the heterocyclization of monoethyl ether of oxalic acid 2-(4(3*H*)-quinazolinyliden)hydrazide is accompanied with the formation of 2-R-[1,2,4]triazolo[1,5-*c*]quinazolines *via* Dimroth-like rearrangement of the expected [4,3-*c*] series.

Experimental Procedures.

4-Hydrazinoquinazoline (**1**) was prepared as reported [6]. The other starting materials were commercially available and used without additional purification. All mps were determined in open capillary tubes in a Thiele's apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Mercury 400 (400 MHz) spectrometer in DMSO-d_6 solution. Chemical shifts (δ) are given in ppm downfield from internal $SiMe_4$. *J* values are in Hz. LC/MS were determined on an Agilent 1100 instrument. Mass spectra were determined on a Varian 1200L instrument (EI, 70 eV). The purity of all compounds prepared was checked by ^{1}H NMR and LC/MS. For all compounds, satisfactory elemental analyses were obtained.

Monoethyl ether of oxalic acid 2-(4(3*H*)-quinazolinyliden)hydrazide (5a).

To a suspension of 1.6 g (10 mmol) 4-hydrazinoquinazoline (**1**) in dioxane (10 mL) was added 1.11 g (11 mmol) triethylamine. To a resulting mixture was added dropwise 1.5 g (11 mmol) monoethyl ether of oxalic acid chloroanhydride in

dioxane (10 mL) with stirring during 3 hours. Obtained mixture poured into saturated solution of sodium acetate. A crystalline precipitate formed was filtered off and recrystallized from DMF-H_2O (1:2).

Dicarboxylic acid 2-(4(3*H*)-quinazolinyliden)hydrazides (5b-f)

To a suspension of 1.6 g (10 mmol) 4-hydrazinoquinazoline (**1**) in dioxane or ethanol (10 mL) at the room temperature and with stirring was added an appropriate dicarboxylic acid anhydride (11 mmol). The reaction mixture stirred for 12 hours at the room temperature. The resulted precipitate was filtered and recrystallized from H_2O (**5b,c**), 2-propanole-H_2O (**5e**), dioxane (**5f**).

1,2-Cyclohexanedicarboxylic acid 1-[2-[4(3*H*)-quinazolinyliden]hydrazide] (5g)

To a solution of 0.8 g (5 mmol) 4-hydrazinoquinazoline (**1**) in methanol (15 mL) was added 0.85 g (5.5 mmol) 1,2-cyclohexanedicarboxylic acid anhydride and heated at 50°C to a formation of solution. The solvent was removed in vacuo and the residue was treated with water. Thus obtained solid was filtered.

1,2,2-Trimethyl-1,3-cyclopentanedicarboxylic acid 1-[2-[4(3*H*)-quinazolinyliden]hydrazide] (5h)

To a suspension of 1.6 g (10 mmol) 4-hydrazinoquinazoline (**1**) in 2-propanole (10 mL) was added 2.0 g (11 mmol) camphoric anhydride and heated at 60°C to a formation of clear solution for 1 hour. The reaction mixture stirred for 12 hours at the room temperature. The reaction mixture was diluted with water (100 mL). Obtained solid was filtered off and recrystallized from dioxane-H_2O (1:2).

Ethyl [1,2,4]triazolo[1,5-*c*]quinazolin-2-carboxylate (6a)

A solution of **5a** (2.0 g, 7.68 mmol) in glacial acetic acid (15 mL) refluxed for 3 hour. The reaction mixture was cooled and diluted with diethyl ether. Obtained solid was filtered off and washed well with diethyl ether.

[1,2,4]Triazolo[1,5-*c*]quinazolin-2-alkylcarboxylic acids (6b,c), 4-imidoaminoquinazolines (7a-e)

To a solution of 1.6 g (10 mmol) 4-hydrazinoquinazoline (**1**) in glacial acetic acid (15 mL) was added 11 mmol of an appropriate dicarboxylic acid anhydride.

The resulted mixture was refluxed for 6-7 hours, concentrated under reduced pressure. On cooling was added diethyl ether, precipitate was filtered and washed with ether. Recrystallyzation from 2-propanole (**6c**), dioxane (**7c**), dioxane-H_2O (**7a**), acetic acid-H_2O (**7b**) afforded title derivatives.

6-(Benzylcarbamoyl)cyclohex-3-enecarboxylic acid 2-[4(3*H*)-quinazolinyliden]hydrazide (10a)

To a suspension of 0.35 g (1.19 mmol) (**7b**) in 8 mL ethanol was added 0.13 g (1.19 mmol) benzylamine. The resulting mixture stirred at a room temperature for 24 hours to a complete dissolving of a starting compound. The solvent removed under reduced pressure, the residue was treated with water. Thus obtained solid was filtered off and recrystallized from 2-propanole-H_2O (2:1).

3-(Benzylcarbamoyl)bicyclo[2,2,1]hept-5-ene-2-carboxylic acid 2-[4(3*H*)-quinazolinyliden]hydrazide (10b)

To a suspension of 0.52 g (1.7 mmol) (**7c**) in 10 mL ethanol was added 0.18 g benzylamine and heated for 5 min until the reaction mixture became clear. The solvent removed under reduced pressure. Thus obtained oily residue recrystallized from 2-propanole-H_2O (4:1).

2-(Benzylcarbamoyl)cyclohexylcarboxylic acid 2-[4(3*H*)-quinazolinyliden]hydrazide (10c)

To a suspension of 0.6 g (2 mmol) (**7d**) in 10 mL ethanol was added 0.25 g (2 mmol) benzylamine. The resulting mixture stirred at a room temperature for 96 hours to a complete dissolving of a starting material. The solvent removed under reduced pressure, the residue was treated with water. Thus obtained solid was filtered off and recrystallized from 2-propanole-H_2O (1:1).

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