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Research paper

# New resource-efficient and green synthesis methods for biologically active derivatives of urea

V.V. Shtrykova \*, V. Yu Kuksenok, V.D. Filimonov, S.P. Sidel'nikova

Institute of High Technology Physics, National Research Tomsk Polytechnic University, Lenin Avenue, 30, Tomsk 634050, Russia

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#### Abstract

Developed were highly effective solvent-free processes for preparation of substituted ureas containing pharmacophore substituents (benzhydryl ureas, dihydroquinazolinones, semicarbazones, thiosemicarbazones and guanylhydrazones), consistent with green chemistry principles for environmentally friendly organic synthesis methods.

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Keywords: Solvent-free; Ureas; Semicarbazones; Thiosemicarbazones; Guanylhydrazones

#### 1. Introduction

One of the important options of modern organic synthesis is solvent-free process consistent with the principles of green chemistry for the environmentally sound and resourceconscious organic reactions.

The aim of this work is to develop solvent-free methods for generating a number of urea derivatives of interest as important biologically active compounds [1-5]. There are diverse methods for ureas synthesis [6], but almost none of them are solvent-free methods.

#### 2. Discussion of results

It has been previously shown that one of the methods of obtaining benzhydryl ureas with anticonvulsant properties is the reaction of urea alkylation by benzhydrol in the acetic acid [7]. We have demonstrated that alkylation of urea using different benzhydrols can successfully take place without solvent in the presence of sulfuric acid at 60–65°C with the desired product yields of **1–6** 77–90%. Using this option of the alkylation reaction, urea was mixed with H<sub>2</sub>SO<sub>4</sub> using a molar ratio of 2:1 to homogenize the mixture, then the corresponding benzhydrol was gradually introduced (Scheme 1).

\* Corresponding author. Institute of High Technology Physics, National Research Tomsk Polytechnic University, Lenin Avenue, 30, Tomsk 634050, Russia. Tel.: +7 (3822) 56 38 61; fax: +7 (3822) 56 36 37.

The only by-products of the reaction for ureas 1–4 were corresponding 1,3-di(benzhydryl) ureas 1a-4a in the amount of up to 10%. The desired products 1–4 can be easily separated from 1,3-di(benzhydryl) ureas 1a-4a by recrystallization from aqueous ethanol, wherein the by-products are insoluble. The advantages of this method are most profound in the case of *o*-aminobenzhydryl ureas 5, 6, the preparation of which by alkylation in the acetic acid is accompanied by a large number of difficult to separate by-products, even though the formation of 1,3-disubstituted products was not observed.

We have demonstrated that the resulting benzhydryl ureas **1–4** when heated to 200°C in the absence of solvents undergo disproportionation, giving high yields of 1,3-di(benzhydryl) ureas **1a-4a** (Scheme 2) which are of interest to obtain the corresponding carbodiimides.

Unlike benzhydryl ureas 1–4, *o*-aminobenzhydryl ureas 5, 6 at 200°C undergo rapid cyclization to the corresponding 4-phenyl-6-chloro-(1H, 3H)-dihydroquinazolinones 5a, 6a (Scheme 3) that exhibit various kinds of bioactivity [8].

It should be noted that known methods for producing tetrahydro quinazolinones involve the use of solvents [9].

Thus, *o*-aminobenzhydryl ureas are excellent synthons for tetrahydro quinazolinones production by solvent-free thermal disproportionation reaction.

Our study included also amino derivatives of the respective ureas such as semicarbazones, thiosemicarbazones and guanilhydrazones having various types of biological activity [10–15], and used as building blocks for organic synthesis [16].

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E-mail address: shvv@tpu.ru (V.V. Shtrykova).

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$$\begin{array}{c} Ph \\ \rightarrow \\ Ar \end{array} \rightarrow OH + NH_2-CO-NH_2 \xrightarrow{H_2SO_4} \\ Ar \end{array} \xrightarrow{Ph} \\ \begin{array}{c} Ph \\ \rightarrow \\ OH-CO-NH_2 \\ Ar \end{array} \xrightarrow{Ph} \\ NH-CO-NH_2 + \\ Ar \end{array} \xrightarrow{Ph} \\ NH-CO-NH_4 \\ Ar \end{array} \xrightarrow{Ph} \\ Ar \xrightarrow$$

Ar = Ph (1 (90%), 1a), o-Cl-Ph (2 (85%), 2a), m-Cl-Ph (3 (80%), 3a), p-Cl-Ph (4 (85%), 4a)

$$\begin{array}{c} \mathsf{Ph} \\ \land \\ \mathsf{Ar} \end{array} \rightarrow \begin{array}{c} \mathsf{OH} + \mathsf{NH}_2 \text{-} \mathsf{CO} \text{-} \mathsf{NH}_2 \\ \hline \\ \mathsf{GO} \text{-} \mathsf{GS} \overset{\circ}{\circ} \mathsf{C} \\ 2 \mathsf{h} \\ \end{array} \xrightarrow{} \begin{array}{c} \mathsf{Ph} \\ \land \mathsf{NH} \text{-} \mathsf{CO} \text{-} \mathsf{NH}_2 \\ \hline \\ \mathsf{Ar} \\ \hline \\ \mathsf{S}, \mathsf{G} \end{array}$$

Ar = 2-NH<sub>2</sub>-5-Cl-Ph (**5** (77%)), 2-NH(CH<sub>3</sub>)-5-Cl-Ph (**6** (78%))

Scheme 1. Urea alkylation by benzhydrol.

Earlier, compounds **7–9** were produced by reacting of benzaldehyde with the corresponding hydrazides in a hydroalcoholic solution in the presence of a buffer [10].

We have shown that grinding of benzaldehyde in an agate mortar with various hydrazides in solvent-free conditions and in the presence of a catalytic amount of  $H_2SO_4$  allows produc-

tion of the corresponding hydrazones 7–9 at high yields (Scheme 4).

It was discovered that less reactive benzophenone does not enter into a condensation reaction with amino urea derivatives under these conditions. However, it was also found that the addition of  $I_2$  efficiently catalyses the condensation reaction of



Ar = Ph (1, 1a (92%)), o-Cl-Ph (2, 2a (92%)), m-Cl-Ph (3, 3a (95%)), p-Cl-Ph (4, 4a (89%))

Scheme 2. Preparation of 1,3-di (benzhydryl) ureas.



Ar = 2-NH<sub>2</sub>-5-Cl-Ph (**5**, **5a** (79%), 2-NH(CH<sub>3</sub>)-5-Cl-Ph (**6**, **6a** (74%))

Scheme 3. Cyclization of o- aminobenzhydryl ureas 5, 6.

PhCHO +  $NH_2$ -CX-NH-NH<sub>2</sub>·HCI  $\xrightarrow{H_2SO_4}$  PhCH = N-NH-CX-NH<sub>2</sub> 15-30 min **7-9** 

X = O (7 (74%)), S (8 (78%)), NH (9 (95%))

 $Ph_{2}CO + NH_{2}-CX-NH-NH_{2} \cdot HCI \xrightarrow{H_{2}SO_{4},I_{2}} Ph_{2}C = N-NH-CX-NH_{2}$   $20 \ ^{\circ}C$   $30-60 \ min$ 10. 11

X = O (10 (65%)), S (11 (80%))

Scheme 4. Preparation of ureas derivatives 7-11.

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