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Research paper

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

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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.

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 resource-conscious 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_2SO_4 using a molar ratio of 2:1 to homogenize the mixture, then the corresponding benzhydrol was gradually introduced (Scheme 1).

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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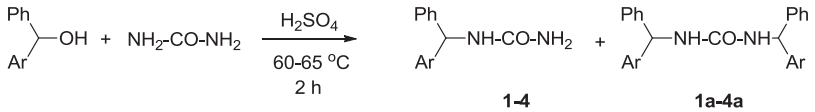
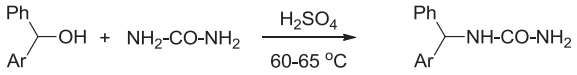
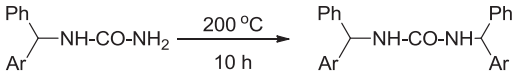


Ar = Ph (**1** (90%), **1a**), o-Cl-Ph (**2** (85%), **2a**), m-Cl-Ph (**3** (80%), **3a**), p-Cl-Ph (**4** (85%), **4a**)



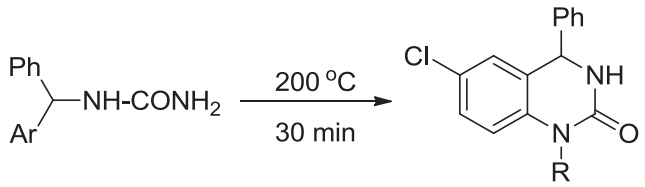
Ar = 2-NH_2-5-Cl-Ph (**5** (77%)), 2-NH(CH_3)-5-Cl-Ph (**6** (78%))

Scheme 1. Urea alkylation by benzhydrol.



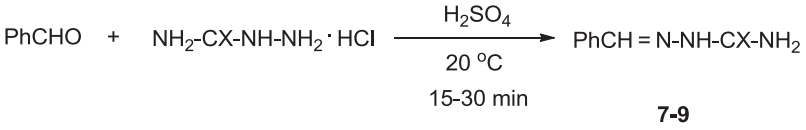
Ar = Ph (**1**, **1a** (92%)), o-Cl-Ph (**2**, **2a** (92%)), m-Cl-Ph (**3**, **3a** (95%)), p-Cl-Ph (**4**, **4a** (89%))

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

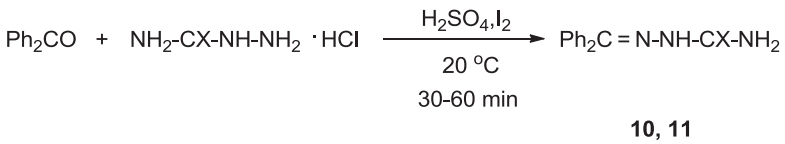


Ar = 2-NH_2-5-Cl-Ph (**5**, **5a** (79%), 2-NH(CH_3)-5-Cl-Ph (**6**, **6a** (74%))

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



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



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

Scheme 4. Preparation of ureas derivatives **7**–**11**.

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 production 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 benzophenone with amino urea and amino thiourea with the formation of hydrazones **10, 11** at high yields (Scheme 4).

3. Conclusion

Thus, we first proposed several methods of solvent-free production of valuable urea derivatives. Compared to conventional approaches, these methods are more environmentally friendly, simple in hardware design and provide high yields of the desired products.

4. Experimental part

Monitoring of the progress of the reaction and purity of the obtained compounds was performed by TLC on Silufol plates UF-254. Detection of spots was carried out with UV light. TLC eluting solvent was benzene: ethanol (9:1). Melting points were determined

on a micro heating table Boetius. The identification of the compounds was performed by comparing the obtained analytical and physical–chemical characteristics with authentic samples.

NMR spectra of ^{1}H were recorded by the spectrometer Bruker AVANCE AV300, internal standard – TMS, solvent – DMSO.

4.1. General procedure for preparation of compounds 1–6

20 mmol of urea was added to 10 mmol of H_2SO_4. The suspension is heated under stirring to 60°C, and 5 mmol of respective benzhydrol was slowly added. The reaction mixture was kept under stirring for 2 h at 60–65°C, identifying the termination of the reaction by TLC, then it was neutralized with aqueous Na_2CO_3 and recrystallized from 55% ethanol.

4.1.1. [(Phenyl)(phenyl)methyl]urea 1

Yield 85%. M.p. 148–150°C, Spectrum ^{1}H NMR (DMSO-d6, 300 MHz) $\delta = 5.59$ (s, 2H, NH_2), 5.88 (d, $J = 8.4$, 1H, CH), 6.99 (d, $J = 8.7$, 1H, NH), 7.19–7.35 (m, 10H, Ar). ^{13}C NMR (DMSO-d6, 75.5 MHz) $\delta = 56.9$; 126.8; 127.1 128.4, 143.9, 157.9 (C = O). Found (%): C, 74.19; H, 6.19; N, 12.04. Calculated (%): C, 74.33; H, 6.19; N, 12.38.

4.1.2. [(2-Chlorophenyl)(phenyl)methyl]urea 2

Yield 78%. M.p. 154–156°C, Spectrum ^{1}HNMR (DMSO-d6, 300 MHz) $\delta = 5.60$ (s, 2H, NH_2); 6.18 (d, $J = 8.1$, 1H, CH); 6.99 (d, $J = 8.4$, 1H, NH); 7.16–7.47 (m, 9H, Ar). ^{13}C NMR (DMSO-d6, 75.5 MHz): $\delta = 56.5$ (CH-NH); 127.0; 128.6; 129.6; 134.1; 140.7; 142.9; 156.8 (C = O). Found (%): C, 64.91; H, 5.15; N, 10.85. Calculated (%): C, 64.61; H, 5.00; N, 10.76.

4.1.3. [(3-Chlorophenyl)(phenyl)methyl]urea 3

Yield 75%. M.p. 137–138°C, Spectrum ^{1}HNMR (DMSO-d6, 300 MHz) $\delta = 5.62$ (s, 2H, NH_2); 5.89 (d, $J = 8.7$, 1H, CH); 7.06 (d, $J = 8.7$, 1H, NH); 7.21–7.38 (m, 9H, Ar). ^{13}C NMR (DMSO-d6, 75.5 MHz): $\delta = 56.4$ (CH-NH); 127.0; 128.5; 129.7; 132.5; 142.3; 146.0; 157.2 (C = O). Found (%): C, 64.38; H, 5.12; N, 10.81. Calculated (%): C, 64.61; H, 5.00; N, 10.76.

4.1.4. [(4-Chlorophenyl)(phenyl)methyl]urea 4

Yield 80%. M.p. 153–154°C, Spectrum ^{1}HNMR (DMSO-d6, 300 MHz) $\delta = 5.62$ (s, 2H, NH_2); 5.88 (d, $J = 8.4$, 1H, CH); 7.03 (d, $J = 8.4$, 1H, NH); 7.21–7.40 (m, 9H, Ar). ^{13}C NMR (DMSO-d6, 75.5 MHz): $\delta = 58.6$ (CH-NH); 127.8; 128.6; 129.3; 133.0; 140.8; 143.5; 157.0 (C = O). Found (%): C, 64.52; H, 5.07; N, 10.49. Calculated (%): C, 64.61; H, 5.00; N, 10.76.

4.1.5. [(2-Amino-5-chlorophenyl)(phenyl) methyl]urea 5

Yield 77%. M.p. 204–206°C, Spectrum ^{1}HNMR (DMSO-d6, 300 MHz) $\delta = 5.10$ (s, 2H, NH_2(Ar)); 5.59 (s, 2H, NH_2); 5.91 (d, $J = 8.7$, 1H, CH); 6.65 (d, $J = 8.4$, 1H, NH); 6.88–6.99 (m, 3H, Ar); 7.25–7.38 (m, 5H, Ar). ^{13}C NMR (DMSO-d6, 75.5 MHz): $\delta = 55.8$ (CH-NH); 116.8; 120.7; 128.5; 141.9; 147.8; 156.8 (C = O). Found (%): C, 60.85; H, 5.14; N, 14.86. Calculated (%): C, 60.97; H, 5.13; N, 15.20.

4.1.6. [(2-Methylamino-5-chlorophenyl)(phenyl) methyl]urea 6

Yield 80%. M.p. 163–164°C, Spectrum ^{1}HNMR (DMSO-d6, 300 MHz) $\delta = 1.15$ (s, 3H, CH_3); 5.34–5.36 (m, 1H, NH-CH_3); 5.59 (s, 2H, NH_2); 5.96 (d, $J = 9.0$, 1H, CH); 6.83–7.12 (m, 3H, Ar); 7.24–7.36 (m, 5H, Ar). ^{13}C NMR (DMSO-d6, 75.5 MHz): $\delta = 30.1$ (CH3); 57.2 (CH-NH); 115.2; 122.3; 127.9; 128.6; 130.1; 141.9; 151.6; 156.8 (C = O). Found (%): C, 62.14; H, 5.34; N, 14.66. Calculated (%): C, 62.16; H, 5.58; N, 14.50.

4.2. General procedure for preparation of compounds 1a-4a

Heat 4 mmol of benzhydro urea **1** (or **2–4**) at 200°C for 10 h, controlling the termination of the reaction by TLC. The reaction mixture was cooled, dissolved in DMSO and precipitated with water.

4.2.1. 1,3-Bis((phenyl)(phenyl)methyl)urea 1a

Yield 92%. M.p. 269–271°C, Spectrum ^{1}H NMR (DMSO-d6, 300 MHz) $\delta = 5.87$ (d, $J = 8.1$, 2H, CH); 6.94 (d, $J = 8.7$, 2H, NH); 7.19–7.34 (m, 20H, Ar). ^{13}C NMR (DMSO-*d6*, 75.5 MHz) $\delta = 56.9$; 126.7; 128.3; 132.2; 143.5; 156.3 (C = O). Found (%): N, 7.20. Calculated (%): N, 7.14.

4.2.2. 1,3-Bis((2-chlorophenyl)(phenyl)methyl)urea 2a

Yield 92%. M.p. 296–298°C, Spectrum ^{1}HNMR (DMSO-d6, 300 MHz) $\delta = 6.18$ (d, $J = 8.1$, 2H, CH); 7.02 (d, $J = 8.4$, 2H, NH); 7.18–7.45 (m, 18H, Ar). ^{13}C NMR (DMSO-*d6*, 75.5 MHz) $\delta = 56.5$; 126.9; 128.1; 132.4; 142.8; 155.8 (C = O). Found (%): N, 6.17. Calculated (%): N, 6.07.

4.2.3. 1,3-Bis((3-chlorophenyl)(phenyl)methyl)urea 3a

Yield 95%. M.p. 272–273°C, Spectrum ^{1}HNMR (DMSO-d6, 300 MHz) $\delta = 5.84$ (d, $J = 8.1$, 2H, CH); 6.99 (d, $J = 8.3$, 2H, NH); 7.20–7.40 (m, 18H, Ar). ^{13}C NMR (DMSO-*d6*, 75.5 MHz) $\delta = 57.0$; 126.7; 127.9; 132.1; 143.0; 155.9 (C = O). Found (%): N, 6.20. Calculated (%): N, 6.07.

4.2.4. 1,3-Bis((4-chlorophenyl)(phenyl)methyl)urea 4a

Yield 89%. M.p. 297–298°C, Spectrum ^{1}HNMR (DMSO-d6, 300 MHz) $\delta = 5.88$ (d, $J = 8.1$, 2H, CH); 6.96 (d, $J = 8.3$, 2H, NH); 7.22–7.40 (m, 18H, Ar). ^{13}C NMR (DMSO-*d6*, 75.5 MHz) $\delta = 57.6$; 126.8; 128.6; 129.3; 132.6; 142.5; 155.9 (C = O). Found (%): N, 6.23. Calculated (%): N, 6.07.

4.3. General procedure for preparation of compounds 5a,6a

Heat 4 mmol of benzhydryl urea **5** (or **6**) at 200°C for 30 min, controlling the end of the reaction by TLC. The reaction mixture is cooled, 25 ml of water added, the precipitate is filtered off and recrystallized from ethyl acetate.

4.3.1. 4-Phenyl-6-chloro-(1H, 3H)-dihydroquinazolinone-2 5a

Yield 79%. M.p. 188–189°C, Spectrum ^{1}HNMR (DMSO-d6, 300 MHz) $\delta = 5.54$ (s, 1H, CH); 6.83 (d, $J = 8.1$, 1H, NHCH); 9.39 (s, 1H, PhNH); 7.15–7.53 (m, 8H, Ar). ^{13}C NMR (DMSO-*d6*, 75.5 MHz) $\delta = 50.8$; 119.7; 123.6; 127.3; 128.4; 128.7; 136.5; 142.1; 155.7 (C = O). Found (%): N, 11.08. Calculated (%): N, 10.83.

4.3.2. 1-Methyl-4-Penyl-6-chloro-(1H, 3H)-dihydroquinazolinone-2 6a

Yield 76%. M.p. 184–185°C, Spectrum ^{1}HNMR (DMSO-d6, 300 MHz) $\delta = 3.3$ (s, 3H, CH_3); 5.55 (s, 1H, CH); 6.83 (d, $J = 8.1$, 1H, NHCH); 7.15–7.53 (m, 8H, Ar). ^{13}C NMR (DMSO-*d6*, 75.5 MHz) $\delta = 50.8$; 119.7; 123.6; 127.3; 128.4; 128.7; 136.5; 142.1; 155.7 (C = O). Found (%): N, 10.64. Calculated (%): N, 10.27.

4.4. General procedure for preparation of compounds 7–9

9 mmol of semicarbazide (thiosemicarbazide or guanilhydrazine) hydrochloride, 0.02 ml of H_2SO_4 and 9 mmol of benzaldehyde is pound in an agate mortar for 15–30 min at the room temperature, controlling the end of the reaction by TLC. Products are recrystallized from ethanol, and, in the case of **9**, washed with benzene.

4.4.1. 2-Benzylidene hydrazine-1-carboxamide 7

Yield 95%. M.p. 214–215°C, Spectrum ^{1}H NMR (DMSO-d6, 300 MHz) $\delta = 6.50$ (s, 1H, CH); 7.31–7.41 (m, 5H, Ar); 7.70 (d, $J = 7.8$, 1H, NH); 7.84 (s, 2H, NH_2). ^{13}C NMR (DMSO-*d*6, 75.5 MHz): $\delta = 127.1$; 128.7; 129.1; 134.8; 143.4 (CH=N); 157.4 (C = O).

4.4.2. 2-Benzylidene hydrazine-1-carbothioamide 8

Yield 96%. M.p. 159–160°C. Spectrum ^{1}H NMR (DMSO-d6, 300 MHz) $\delta = 7.38$–7.39 (m, 3H, Ar); 7.77–7.80 (m, 2H, Ar); 7.99 (s, 1H, CH); 8.01 (s, 2H, NH_2); 8.20 (s, 1H, NH). ^{13}C NMR (DMSO-*d*6, 75.5 MHz): $\delta = 129.3$; 130.7; 131.8; 136.2; 144.2 (CH=N); 180.0 (C = S).

4.4.3. 2-Benzylidene hydrazine-1-carboximidamide 9

Yield 93%. M.p. 135–136°C, Spectrum ^{1}H NMR (DMSO-d6, 300 MHz) $\delta = 7.42$–7.44 (m, 2H, NH_2); 7.84–7.86 (m, 5H, Ar); 8.11 (s, 1H, CH); 12.10 (s, 1H, NH). ^{13}C NMR (DMSO-*d*6, 75.5 MHz): $\delta = 127.8$; 128.9; 130.7; 133.5; 147.1 (CH=N); 155.6 (CH=NH).

4.5. General procedure for preparation of compounds 10, 11

9 mmol of semicarbazide (or thiosemicarbazide) hydrochloride, 0.02 ml of H_2SO_4, 9 mmol of benzophenone and 4 mmol of I_2 are rubbed in an agate mortar for 30–60 min. The end of the reaction was monitored by TLC. The products were recrystallized from ethanol.

4.5.1. 2-(Diphenylmethylene)hydrazine-1-carboxamide 10

Yield 65%. M.p. 163–165°C. Spectrum ^{1}H NMR (DMSO-d6, 300 MHz) $\delta = 6.73$ (s, 2H, NH_2); 7.26–7.35 (m, 5H, Ar); 7.54–7.63 (m, 10H, Ar); 7.89 (s, 1H, NH). ^{13}C NMR (DMSO-*d*6, 75.5 MHz): $\delta = 127.9$; 127.9; 128.7; 138.4; 143.8 (CH=N); 158.5 (C = O).

4.5.2. 2-(Diphenylmethylene)hydrazine-1-carbothioamide 11

Yield 80%. M.p. 170–171°C, Spectrum ^{1}H NMR (DMSO-d6, 300 MHz) $\delta = 7.33$–7.43 (m, 5H, Ar); 7.58–7.70 (m, 5H, Ar); 8.38–8.41 (s, 2H, NH_2); 8.65 (s, 1H, NH). ^{13}C NMR (DMSO-*d*6, 75.5 MHz): $\delta = 128.8$; 129.8; 132.9; 137.1 (CH=N); 181.1 (C = S).

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