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Catalytic aminomethylation of aliphatic and aromatic amines using (thio)urea†

Regina R. Khairullina

Institute of Petrochemistry and Catalysis of Russian Academy of Sciences, 141 Prospekt Oktyabrya, Ufa 450075, Russian Federation;

* Correspondence: reginessa@gmail.com; Tel. +796-7734-7240

† Presented at the title, place, and date.

Abstract: To continue our research on catalytic aminomethylation, we studied the effect of catalysts on this reaction involving aliphatic and aromatic amines. We have developed an effective method for the production of cyclic and acyclic carbamide-containing compounds. It is based on the reaction between amines and 1,3-bis[dimethylamino(hydroxy)methyl](thio)urea, prepared in situ from urea or thiourea and bis(dimethylamino)methane or formaldehyde in the presence of $NiCl_2 \bullet 6H_2O$, or $CuCl_2 \bullet 2H_2O$, and $SmCl_3 \bullet 6H_2O$ as catalysts.

Keywords: aminomethylation; cyclic and acyclic N-containing compounds; amines; catalyst

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1. Introduction

Aminomethylation of amines with formaldehyde and NH acids (Mannich reaction) is still a universal method for introducing a C-N bond in the construction of nitrogen heterocycles [1–3]. However, this approach has a number of limitations - reactions are carried out at elevated temperatures and low selectivity for the formation of target heterocycles.

We recently demonstrated the catalytic aminomethylation of primary amines with N,N′-bis[(dimethylamino)methyl](thio)urea using Cu-, Ni- and Sm-containing catalysts [4 –6].

Alkylamines undergo catalytic aminomethylation reactions with N,N′-bis[(dimethylamino)methyl](thio)ureas to form 1,3,5-triazinan-2-ones(thiones), while regioisomeric aminobenzamides lead to cyclic and acyclic compounds

Interest in compounds with a urea fragment is due to their wide spectrum of activity. Urea derivatives have antimicrobial, antitumor, antioxidant and antibacterial activity [7–11], and are promising as synthons in the synthesys of alkaloids with antitumor causes, NO synthase inhibitors, growth stimulants of Saccharomycetes [12–14], as well as sorbents for ions and precious metals [15,16].

In addition, urea and its derivatives are used in agriculture as growth stimulants to improve the quantity and quality of crops [17–19].

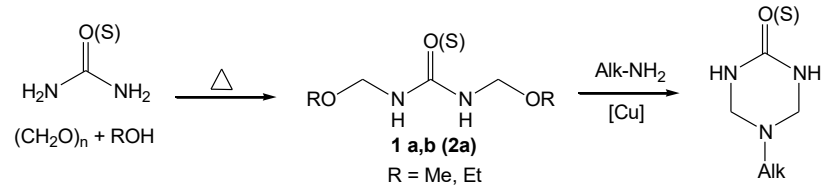
In order to expand the boundaries of this reaction and obtain target products in high yields, we studied three approaches to the catalytic aminomethylation of alkylamines and arylamines.

2. Results and discussion

As a result, in this work, N,N′-bis[(methoxy(ethoxy))methyl]ureas (**1a,b**) and N,N′-bis[(methoxy)methyl]thiourea (**2a**) were obtained in yields of 58 – 91 % condensation of (thio)urea with paraformaldehyde at a ratio of (thio)urea: paraformaldehyde = 1:2 in methyl and ethyl alcohol at 70°C.

Catalytic aminomethylation of alkylamines N,N′-bis[(alkoxy)methyl](thio)ureas **1a,b** (**2a**) in the presence of 5 mol.% $SmCl_3 \cdot 6H_2O$ under conditions **1a,b** (**2a**): alkylamine = 1:1, 70° C led to 1,3,5-triazinan-2-ones(thiones) **3 a–f** with yields of 36–54%, respectively.

The reaction of alkylamines with **1a,b** (**2a,b**) obtained in situ is carried out more efficiently, yielding the target **3a–f** with yields of 41–67%, respectively.



[Cu] = $CuCl_2 \cdot 2H_2O$;

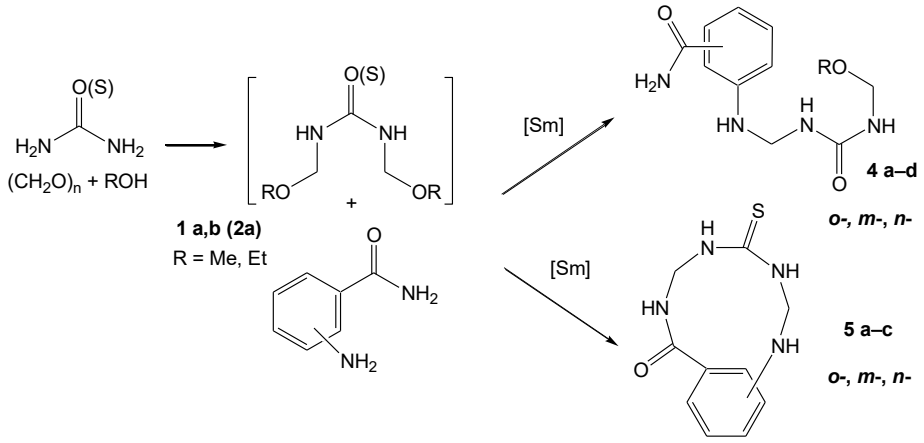
C=O, R = *cyclo*-C_6H_{11} (**3a**); C=O, *R* = *t*-Bu (**3b**); C=O, R = $HO(CH_2)_2$ (**3c**); C=S, R = *cyclo*-C_6H_{11} (**3d**); C=S, *R* = *t*-Bu (**3e**); C=S, *R* = $HO(CH_2)_2$ (**3f**).

The choice of catalysts was determined by positive results in the aminomethylation of alkylamines and aminobenzamides [4–6].

It should be added that the target 1,3,5-triazinanones **3a–f** were obtained previously with yields of 22–50% from the catalytic aminomethylation of alkylamines with (thio)urea and bis(dimethylamino)methane through the stage of formation of N,N′-bis[(dimethylamino)methyl] (thio)ureas [4].

Positive results on the synthesis of **3a–f** were used in the development of an effective approach for the preparation of target N-carbamoyl-substituted benzamides by condensation **1a,b (2a,b)**, obtained in situ with regioisomeric aminobenzamides.

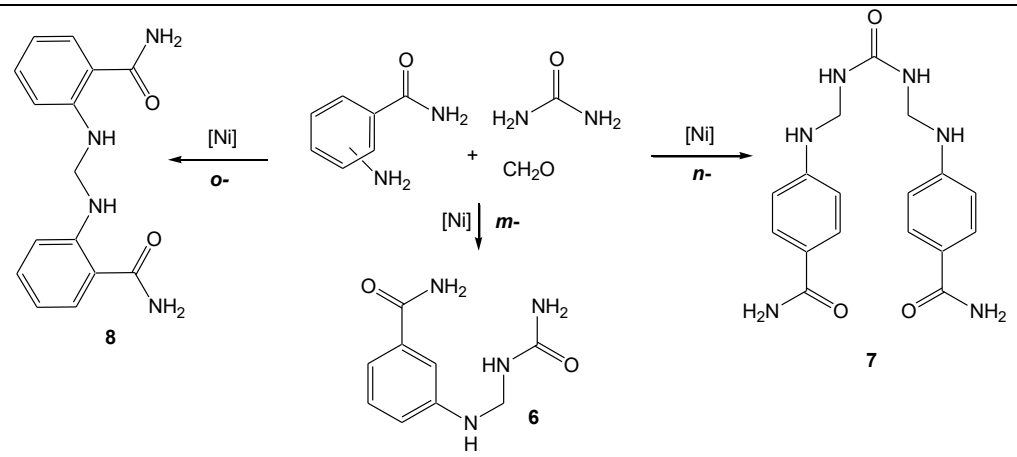
In a medium of methyl or ethyl alcohols at the ratio aminobenzamide: 1a,b: $[Sm(NO_3)_3 \cdot 6H_2O]$ = 1:1:0.1 at 70 °C, benzamide derivatives with a terminal alkoxy group **4 a-d** are formed in yields of 52–69%.



Catalytic aminomethylation of aminobenzamides with **2a,b**, obtained in situ under the developed conditions, gives cycles **5 a–c** in yields of 47–61%, respectively.

At the next stage of studying the reaction, catalytic aminomethylation of regioisomeric aminobenzamides with of formaldehyde (37% aqueous solution) and urea in the absence of solvents was carried out.

Thus, the reaction of urea with formaldehyde and aminobenzamides under the conditions (aminobenzamide: CH_2O: urea: $[NiCl_2 \cdot 6H_2O]$ = 1:2:1:0.1, 70 °C, 8 h) led to compounds **6** and **7** with yields of 25 and 18%, respectively.



2-Aminobenzamide gave heme diamine 8 in 41% yield.

Under the developed conditions, catalytic aminomethylation of aminobenzamides with thiourea and formalin led to the formation of condensed cycles 5 in yields of 14–22%, respectively.

3. Conclusions

Thus, by catalytic aminomethylation of regioisomeric aminobenzamides using N,N′-bis[methoxy(ethoxy)methyl](thio)ureas obtained in situ in the presence of salts of d- and f-elements, the most effective approach for the synthesis of cyclic and acyclic benzamides derivatives with (thio)urea fragment.

4. Experimental Part

One-dimensional (**1**H, **13**C), homo- (COSY) and hetero- (HSQC, HMBC) NMR experiments were carried out on a Bruker Avance 400 spectrometer (400.13, 100.62 MHz, respectively) according to standard procedures, the solvent was DMSO-*d***6**. Mass spectra of compounds 2a, 3, 5, 6, 8 were obtained on a Bruker MALDI TOF/TOF AUTOFLEX III instrument. The preparation of samples for registration of mass spectra was carried out according to the "dry drop" method. A solid-state UV laser with a wavelength of 355 nm was used as a source of laser radiation. Mass spectra of compounds 4, 7 were obtained on a Q-TOF MaXis impact mass spectrometer (Bruker) by electrospray ionization (direct injection, eluent acetonitrile–water–formic acid, 95 : 5 : 0.1, eluent flow rate 5 μL/min) in the positive ion registration mode (capillary potential –3.5 kV, pressure on the nebulizer— 2.0 bar). The flow rate of the drying gas (nitrogen) is 6 L/min, the temperature of the drying gas is 200 °C. Melting points were determined on a RNMK 80/2617 device. The progress of the reaction was monitored by TLC on Sorbfil plates (PTSH-AF-V), developed with iodine vapor. Silica gel KSK (100–200 μm) was used for column chromatography.

Aminomethylation of urea with paraformaldehyde and alcohols. (Thio)urea (10 mmol), methyl or ethyl alcohol (250 mmol), paraformaldehyde (25 mmol) were stirred for 8 h at a temperature of ~70 °C. By removing the solvent, N,N′-bis[methoxy(ethoxy)methyl](thio)urea (**1a,b, 2a**) is obtained.

***N,N′*-bis(methoxymethyl)urea (1a)**. Yield 90%, resinous substance. ^{1}H NMR spectrum, δ, ppm: 3.14 s (6H, OC<u>H</u>$_3$), 4.44 d (4H, MeO-C<u>H</u>$_2$-NH, ^3J 8.0 Гц), 6.96 t (2H, N<u>H</u>, ^3J 8.0 Гц). ^{13}C NMR spectrum, δ, ppm: 54.75 (O<u>C</u>H$_3$), 72.28 (HN-<u>C</u>H$_2$-OMe), 157.71 (<u>C</u>(O)).

***N,N′*-bis(ethoxymethyl)urea (1b)**. Yield 58%, wet snow, mp 48–54 °C. ^{1}H NMR spectrum, δ, ppm: 1.05 t (6H, C<u>H</u>$_3$, ^3J 8.0 Гц), 3.37 quartet (4H, OC<u>H</u>$_2$, ^3J 8.0 Гц), 4.47 d (4H, -O-C<u>H</u>$_2$-NH, ^3J 8.0 Гц), 6.96 br. s (2H, N<u>H</u>). ^{13}C NMR spectrum, δ, ppm: 15.39 (<u>C</u>H$_3$), 62.31 (O<u>C</u>H$_2$), 70.63 (HN-<u>C</u>H$_2$-O-), 157.78 (<u>C</u>(O)).

***N,N′*-bis(methoxymethyl)thiourea (2a)**. Yield 91%, resinous substance. ^{1}H NMR spectrum, δ, ppm: 3.17 br. s (6H, OCH$_3$), 4.84 br. s (4H, HNCH$_2$O), 8.35 br. s (2H, NH). Mass spectrum, *m*/*z* (*I*rel, %): 203.110 [*M* + K]$^+$.

Aminomethylation of amines with N,N′-bis(alcoxymethyl)(thio)urea 1a,b(2a). Metod A. 10 Mmol of **1a**(**1b** or **2a**), 0.5 mmol of $Sm(NO_3)_3 \cdot 6H_2O$ or $CuCl_2 \cdot 2H_2O$, 10 mmol of amine and 5 mL of alcohol were stirred for 8 h at 70 °C. Compounds **3a–f**, **4a–d** and **5a–c** were isolated from the reaction mixture using column chromatography on SiO_2.

Aminomethylation of amines N,N′-bis(alkoxymethyl)(thio)ureas 1a,b(2a,b) obtained *in situ*. Metod B. 3 Mmol (thio)urea, 6 mmol paraformaldehyde, 0.5 mmol $Sm(NO_3)_3 \cdot 6H_2O$ and 30 mmol alcohol were stirred for 2 h at 70 °C. Then 10 mmol of amine was added to the reaction mass and then stirred for another 6 h at 70 °C. Compounds **3a–f**, **4a–d**, and **5a–c** were isolated from the reaction mixture by column chromatography on SiO_2.

Aminomethylation of aminebenzamides with formaldehyde and (thio)urea. Metod C. 10 mmol of aminobenzamide, 1 mmol of $NiCl_2 \cdot 6H_2O$ or $Sm(NO_3)_3 \cdot 6H_2O$, 10 mmol of (thio)urea and 20 mmol of formaldehyde (37% aqueous solution) were stirred for 8 h at 70 °C. Compounds **5a–c** and **6 – 8** were isolated from the reaction mixture using column chromatography.

5-Cyclohexyl-(1,3,5-triazinan)-2-one (3a). Yield 52% (metod A), 64% (metod B), crystals, mp 205–207 °C ([4]).

5-tert-Butyl-(1,3,5-triazinan)-2-one (3b). Yield 45% (metod A), 52% (metod B), crystals, mp 181–183 °C ([4]).

5-Hydroxyethyl-(1,3,5-triazinan)-2-one (3c). Yield 36% (metod A), 43% (metod B), crystals, mp 174–176 °C ([4]).

5-Cyclohexyl-(1,3,5-triazinan)-2-thione (3d). Yield 54% (metod A), 67% (metod B), crystals, mp 173–175 °C ([4]).

5-tert-Butyl-(1,3,5-triazinan)-2-thione (3e). Yield 49% (metod A), 53% (metod B), crystals, mp 170–172 °C ([4]).

5-Hydroxyethyl-(1,3,5-triazinan)-2-thione (3f). Yield 38% (metod A), 41% (metod B), crystals, mp 161–163 °C ([4]).

2-[({[(Methoxymethyl)carbamoyl]amino}methyl) amino] benzamide (4a). Yield Yield 65% (metod B), resinous substance. Mass spectrum, *m*/*z* (*I*rel, %): 275.122 $[M+Na]^+$ ([20]).

3-[({[(Methoxymethyl)carbamoyl]amino}methyl)- amino] benzamide (4b). Yield 69% (metod B), light brown substance, mp 145–150 °C. ([20]). Mass spectrum, *m*/*z* (*I*rel, %): 275.1361 $[M+Na]^+$.

3-[({[(Ethoxymethyl)carbamoyl]amino}methyl)- amino] benzamide (4c) Yield 58% (metod B), light brown substance, mp 204–208 °C. ([20]) Mass spectrum, *m*/*z* (*I*rel, %): 289.1271 $[M+Na]^+$.

4-{[({[(Ethoxymethyl)amino]carbonyl}amino)methyl]amino}benzamide (4d). Yield 52% (metod B), white substance, mp 141–144 °C. ([20]). Mass spectrum, *m*/*z* (*I*rel, %): 289.1268 $[M+Na]^+$.

4-Thioxo-2,3,4,5,6,7-hexahydro-1,3,5,7-benzotetraazecin-8(1*H*)-one (5a). Yield 59% (metod B), 21% (metod C), cream colored amorphous powder, mp 44–48 °C ([6]).

5-Thioxo-2,4,6,8-tetraazabicyclo [8.3.1]tetradeca-1(14),10,12-trien-9-one (5b). Yield 61% (metod B), 22% (metod C), cream colored amorphous powder, mp 68–72 °C ([6]).

5-Thioxo-2,4,6,8-tetraazabicyclo[8.2.2]tetradeca-1(12),10,13-trien-9-one (5c). Yield 47% (metod B), 14% (metod C), cream colored amorphous powder, mp 65–70 °C ([6]).

3-({[(Aminocarbonyl)amino]methyl}amino)benzamide (6): Yield 25% (metod C), light brown substance, mp 90–94 °C. ^{1}H NMR spectrum, δ, ppm: 4.46–4.49 m (2H, HNC$\underline{H}_2$NH), 5.52 br. s (2H, NH_2), 6.30 and 6.65 br. s (2H, NH), 6.81 br. s (1H, CH), 7.06–7.20 m (3H, CH), 7.35 and 7.78 br. s (2H, NH_2). ^{13}C NMR spectrum, δ, ppm: 48.78 (HN$\underline{C}H_2$NH), 112.14, 116.36, 116.99, 129.36 (CH), 135.45 [$\underline{C}(CONH_2)$], 146.39 [$\underline{C}(NHCH_2)$], 158.09 [HN(C=O)NH], 169.00 (C=O). Mass spectrum, *m*/*z* (*I*rel, %): 231.116 [*M* + Na]$^+$.

4,4′-[Carbamido-*N*,*N*′-bis(methylamino)]di-benzamide (7). Yield 18% (metod C), mp 61–64 °C ([20]).

2-({[2-(Aminocarbonyl)phenyl]amino}methylamino)benzamide (8). Yield 41% (metod C), white amorphous substance, mp 158–162 °C ([6]).

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