

Reaction of Aliphatic Amines with Acetoacetanilide in the Presence of Zeolite Catalyst. Solvent-Free Synthesis of Symmetric *N,N*-Dialkylureas

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Introduction

Use of clean heterogeneous catalysts such as clays and zeolites in organic synthesis has received considerable attention in the past few years, mainly due to the minimum production of byproducts and pollutant materials.¹

In fact, the possibility of performing efficient chemical transformations with reusable catalysts avoiding toxic reagents, large amount of solvents, and expensive purification methods represents a fundamental target of the modern organic synthesis.²

As a part of our program aimed at developing new, selective, and preparatively useful methodologies based on the use of heterogeneous catalysts as promoters for fine chemicals preparation,³ we have recently reported the synthesis of symmetric *N,N*-diphenylureas from aromatic amines and ethyl acetoacetate promoted by zeolite HSZ-360.⁴

By considering the mechanism of this reaction, we found it reasonable that the aromatic amine **1** first reacts with ethyl acetoacetate **2**, giving acetoacetanilide **3** which, in the presence of zeolite catalyst, is converted into *N,N*-diphenylurea **4** and acetone through nucleophilic attack by a second molecule of aromatic amine (Scheme 1).

On these grounds we attempted the preparation of unsymmetrical *N,N*-disubstituted ureas by reaction of acetoacetanilide with different aromatic amines under conditions similar to those employed for the synthesis of symmetrical ones. However, the process seemed to have a major drawback: the formation of all three possible diphenylureas in almost equimolecular amount. On the other hand, use of aliphatic amines resulted in the production of mixtures of *N*-phenyl-*N*-alkyl- and *N,N*-dialkylureas as the latter compounds the main reaction products.

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Scheme 1

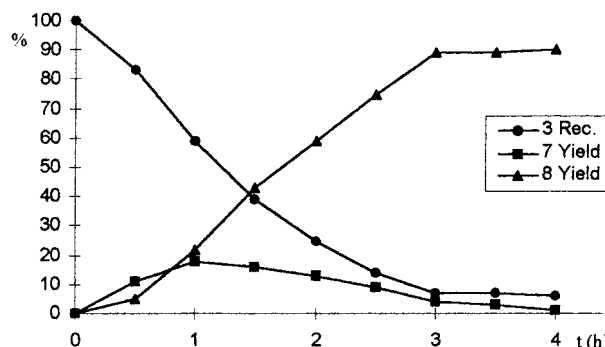
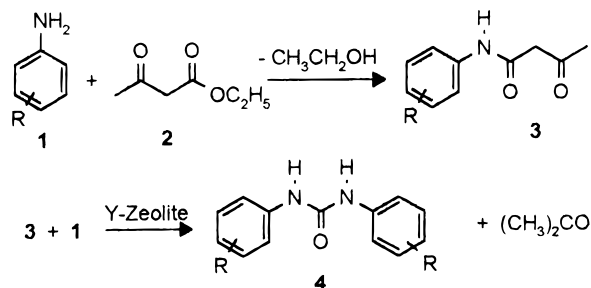


Figure 1. 1. Reactivity of acetoacetanilide **3** with benzylamine **5a** over dealuminated Y-zeolite HSZ-360 as a function of time.

Here we report results of our studies on the above-described reaction that allowed us to find a simple and safe methodology for the synthesis of symmetrical *N,N*-dialkylureas.

Substituted ureas are an industrially important class of compounds displaying a wide range of applications, e.g., use as herbicides, antioxidants in gasoline, corrosion inhibitors, and drugs.⁵ As most of the applied methods for the preparation of these compounds are essentially based on phosgene and isocyanates,⁶ there is a continuing interest in their catalytic synthesis via phosgene-free reactions.

Results and Discussion

To find out which pathway was operating in the process, the model reaction between acetoacetanilide **3** (0.01 mol) and benzylamine **5a** (0.04 mol) in 1,2-dichlorobenzene (5 mL) at 180 °C and in the presence of 0.5 g of zeolite HSZ-360 (surface acidity⁷ 0.51 mequiv of H^+ /g, $\text{SiO}_2/\text{Al}_2\text{O}_3$ molar ratio 13.9) was analyzed as function of time.⁸ It is evident from Figure 1 that acetoacetanilide **3** (Scheme 2, Y = NHPh) was converted into *N,N*-dibenzylurea **8a** via the unsymmetrical *N*-phenyl-*N*-benzylurea **7a** as the latter was detected in appreciable amounts at an intermediate stage. The concentration of **7a** raised the maximum value (20%) after 1 h, and then,

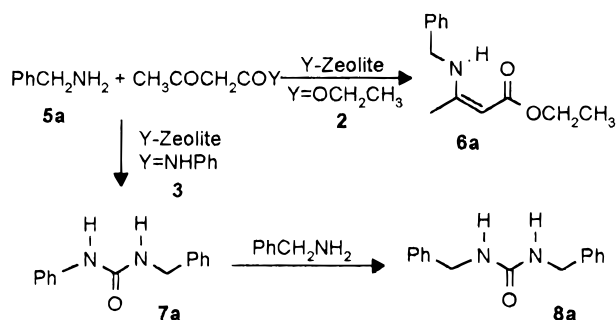
(5) Vishnyakova, T. P.; Golubeva, I. A.; Glebova, E. V. *Russ. Chem. Rev. (Engl. Transl.)* **1985**, *54*, 249.

(6) (a) March, J. *Advanced Organic Chemistry*; John Wiley & Sons: New York, 1985; p 370. (b) Knölker, H.-J.; Braxmeier, T.; Schlechtingen, G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2497.

(7) Determined in our laboratory by temperature-programmed desorption of ammonia gas (NH_3 -TPD): Berteau, P.; Delmon, B. *Catal. Today* **1989**, *5*, 121.

(8) Product analyses were carried out by HPLC.

Scheme 2



it gradually decreased down to disappearance after 3 h. In the meantime, the amount of product **8a** gradually increased to a maximum yield of 89% (95% selectivity).

From these results, it can be concluded that production of *N,N*-dibenzylurea **8a** involves prior formation of the *N*-phenyl-*N*-benzylurea **7a** through displacement of acetone. Intermediate **7a** further reacts with excess benzylamine, giving product **8a** with displacement of aniline. In a comparison experiment, *N*-phenyl-*N*-benzylurea **7a** was reacted with benzylamine **5a** under similar reaction conditions, affording product **8a** in 95% yield. Byproduct, due to the competitive attack on the keto group, was detected only in traces in the present reaction.

This result is of primary importance since the direct reaction of ethyl acetoacetate **2** (Scheme 2, Y = OCH₂CH₃) with benzylamine **5a** failed to produce *N,N*-dibenzylurea **8a** contrary to what has been previously observed with aromatic amines;⁴ in fact, in this case, the nucleophilic attack of the nitrogen mainly occurs on the keto group leading to the production of β -benzylaminocrotonic acid ethyl ester **6a** as reported previously in the literature.⁹

Concerning the effect of the solvent, a quite similar good result was obtained by carrying out the reaction in decalin in place of the more hazardous 1,2-dichlorobenzene. However, the best result (95% yield, 97% selectivity) was achieved by performing the process under solventless conditions.

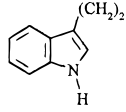
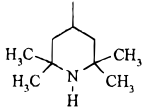
Use of typical Lewis acids such as ZnCl₂ and AlCl₃ resulted in the production of a complex mixture of compounds, and a comparative experiment with no catalyst gave the product **8a** in 35% yield. These observations argue in favor of the conclusion that the present reaction is particularly facilitated by acid zeolites. However, according to the general statement that the terms acidity and activity are not interchangeable in zeolite catalysis,¹⁰ we found that the catalyst performance is not directly related to the overall surface acidity. In fact, use of the zeolite HSZ-330 with surface area and pore dimensions similar to those of HSZ-360 but showing higher overall acidity (surface acidity 1.39 mequiv of H⁺/g, SiO₂/Al₂O₃ molar ratio 5.9) afforded the product **8a** in 65% yield and 95% selectivity. The different reactivity observed could be explained in terms of higher individual acidity¹¹ of the active sites of zeolite HSZ-360¹² with respect to those of zeolite HSZ-330.¹³

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(11) The characterization of the acidity of both catalyst by NH₃-TPD and FTIR pyridine absorption methods suggests that the acidity of zeolite HSZ-330 is mainly ascribable to Brønsted sites; on the contrary, Lewis sites are the most numerous in the zeolite HSZ-360.

Table 1. Synthesis of Various *N,N*-Dialkylureas

Entry	Alkyl group	8 Yield (%)	8 Select. (%)
a	PhCH ₂	95	97
b	C ₆ H ₁₁	85	95
c	C ₈ H ₁₇	82	93
d	C ₉ H ₁₉	80	94
e	C ₁₀ H ₂₁	85	95
f	(<i>R</i>)-Ph(CH ₃)CH	75	97
g	PhCH ₂ CH ₂	78	93
h		65	96
i		70	97

Then we faced the problem of the catalyst recycling. In the model reaction with benzylamine, zeolite, simply recovered by filtration, washed with hot methanol, and heated overnight at 500 °C was reused four times without significant loss of efficiency.

The scope of this procedure was expanded to the synthesis of different *N,N*-dialkylureas **8**. Synthetic results from Table 1 reveal that yield and selectivity are satisfactory or excellent. Most satisfying was the observation that even acid labile starting materials (entry h) and chiral amines (entry f) were converted into the corresponding symmetrical ureas with high selectivity and with complete retention of the optical activity. Of particular interest is the synthesis of compound **8i**, an industrial product patented as stabilizer for synthetic polymers.¹⁴ All isolated products were fully characterized by ¹H NMR and IR spectroscopy and MS spectrometry. The mass recovery and purity of these dialkylureas was good to excellent in view of the simplicity of our isolation procedure (see Experimental Section).

Unfortunately, attempts to extend the application to secondary amines (e.g., dibutylamine) resulted in the production of almost equimolecular mixtures of both symmetrical tetrasubstituted (**9**) and unsymmetrical trisubstituted (**10**) ureas.

In conclusion, we have developed a new, efficient, zeolite-catalyzed, and solvent-free synthesis of sym-

(12) HSZ-360 is a commercial (Tosoh Corp.) HY zeolite with pore size 7.4 Å, crystal dimension < 0.5 μm, surface area 500 ± 10 m²/g, and the following chemical composition (wt % dry basis): SiO₂ 89.0, Al₂O₃ 10.9, Na₂O 0.06.

(13) HSZ-330 is a commercial (Tosoh Corp.) HY zeolite with pore size 7.4 Å, crystal dimension < 0.5 μm, surface area 460 ± 10 m²/g, and the following chemical composition (wt % dry basis): SiO₂ 77.7, Al₂O₃ 22.2, Na₂O 0.2.

(14) Brandt, S.; Wolf, E. Ger. Offen. 1976, 2,640,409.

metrical *N,N*-dialkylureas from readily available acetoacetanilide and primary aliphatic amines. In every case, good yield and excellent selectivity has been achieved. Finally the catalyst could be easily removed from the reaction mixture and reused several times without loss of efficiency.

Experimental Section

General. Melting points are uncorrected. ¹H NMR spectra were recorded at 300 MHz. Mass spectra were obtained in EI mode at 70 eV. TLC analyses were performed on Merck 60 PF₂₅₄ silica gel plates using mixtures of hexane–ethyl acetate (5–25%). All the reagents were of commercial quality from freshly opened containers. Zeolites HSZ-360 and HSZ-330 (Tosoh Corp.) were utilized without previous thermal or chemical treatment.

Synthesis of *N,N*-Dialkylureas 8. General Procedure. To a solution of the selected aliphatic amine (20 mmol) and zeolite HSZ-360 (0.5 g) at 180 °C was added portionwise the acetoacetanilide (5 mmol, 0.9 g). After 3 h the reaction mixture was cooled to room temperature, hot methanol (50 mL) was added, and the catalyst was removed by filtration and washed with hot methanol (50 mL). After cooling to room temperature, the *N,N*-dialkylurea was precipitated by adding distilled water (150 mL). The product was isolated by Buchner filtration and recrystallized from methanol.

***N,N*-Dibenzylurea (8a):** pale brown solid, mp 167–168 °C (lit.¹⁵ mp 168 °C).

***N,N*-Dicyclohexylurea (8b):** pale yellow solid, mp 235–237.5 °C (lit.¹⁶ mp 237–238 °C).

***N,N*-Dioctylurea (8c):** white solid, mp 89–90 °C (lit.¹⁵ mp 90 °C).

***N,N*-Dinonylurea (8d):** white solid, mp 101–102.5 °C (lit.¹⁵ mp 101 °C).

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***N,N*-Didecylurea (8e):** white solid, mp 93.5–95 °C (lit.¹⁷ mp 94–95 °C).

(*R,R*)-*N,N*-Bis[α -methylbenzyl]urea (8f): pale yellow solid, mp 202–204.5 °C (lit.¹⁸ mp 204.5–206 °C).

***N,N*-Diphenethylurea (8g):** yellow solid, mp 139.5–141 °C (lit.¹⁹ mp 140–1 °C).

***N,N*-Bis[2(1*H*-indol-3-yl)ethyl]urea (8h):** pale brown solid, mp 136–138 °C.²⁰

***N,N*-Bis[3,3,5,5-tetramethyl-4-piperidyl]urea (8i):** white solid, mp 225–228 °C.¹⁴

***N,N,N,N*-Tetrabutylurea (9):** pale yellow oil, bp 117.5–118.5 °C/0.5 mmHg (lit.²¹ bp 119 °C/0.5 mmHg).

***N,N*-Dibutyl-*N*-phenylurea (10):** white solid, mp 82–83 °C (lit.²² mp 82.7–83 °C).

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