

# Reaction of aromatic amines and ethyl acetoacetate promoted by zeolite HSZ-360. Phosgene-free synthesis of symmetric diphenylureas

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Reaction of aromatic amines **1** with ethyl acetoacetate **2** in the presence of the commercially available acid zeolite HSZ-360 gives symmetric diphenylureas **3** in good yields and excellent selectivities.

Zeolites and other solid acids have opened new perspectives in synthetic organic chemistry not only in terms of yield and selectivity, but also concerning the work-up and the effluent pollution.<sup>1</sup> The use of both solid acids and non-toxic reagents leads to a substantial reduction in cost and environmental impact of the production processes.<sup>2</sup> Here we report preliminary results of our study concerning the synthesis of symmetric diphenylureas (DPUs) from aromatic amines and ethyl acetoacetate under solid acid catalysis.

Substituted ureas have received considerable attention due to their wide range of applications, e.g. for use as antidiabetic and tranquillizing drugs, antioxidants in gasoline, corrosion inhibitors and herbicides.<sup>3</sup> The conventional methods reported for the urea synthesis are essentially based on phosgene and isocyanates,<sup>4</sup> phosgene substitutes,<sup>5</sup> carbonates and carbamates<sup>6</sup> or carboxylic acid derivatives.<sup>7</sup> However, phosgene and isocyanates are toxic and expensive to handle and the above methods are often difficult to apply. There is, thus, a continuing interest in the catalytic synthesis of ureas *via* phosgene-free reactions. Our strategy, utilizing ethyl acetoacetate as carboxylating agent in place of phosgene and solid acids as catalysts represents an efficient, innovative and environmentally safe method for the synthesis of DPUs.

The reaction of aromatic amines **1** with ethyl acetoacetate **2** has been described in the literature to produce ethyl  $\beta$ -aryl-

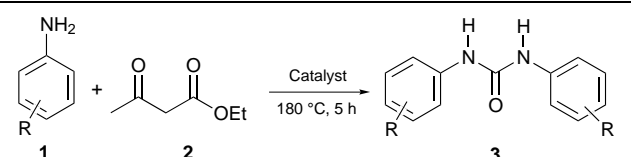
aminocrotonates or acetoacetoanilides,<sup>8</sup> depending on the temperature. We found that DPUs could be obtained as the sole reaction products by heating the same mixture in the presence of different solid acids (Table 1).

The reaction of *p*-anisidine, selected as the model substrate, with **2** in the presence of zeolite HSZ-360<sup>9</sup> in *o*-dichlorobenzene at 180 °C for 5 h gave *N,N'*-bis(4-methoxyphenyl)urea which was isolated in 60% yield and 93% selectivity (entry g). Zeolite HSZ-330,<sup>10</sup> with higher acidity and comparable surface area, was less effective (entry f). The use of two montmorillonites, K10 and KSF,<sup>11</sup> gave the product with lower yield and similar, high selectivity independent of surface area and acidity (entries d and e).

The acidity of the catalyst is likely to play an important role in the activation of **2**. Note that the present system seems to require an optimum acidity level with respect to both strength and nature of the individual Brønsted and Lewis sites. Indeed, the more active zeolite HSZ-360 has a lower concentration of acid sites than HSZ-330, but the individual sites are more strongly acidic.<sup>9,10</sup> Moreover the use of typical hard Brønsted and Lewis acids such as TsOH, ZnCl<sub>2</sub> and AlCl<sub>3</sub> results in the production of untractable mixtures of compounds (entries a, b and c).

The best result was achieved by carrying out the reaction with zeolite HSZ-360 under solventless conditions (76% yield, 95% selectivity) (entry h). This result is of particular interest since *o*-dichlorobenzene is on the 'black list' of the environmentally incompatible solvents.<sup>12</sup> In the control experiment with no zeolite catalyst only *p*-methoxyacetoacetanilide was recovered as reported above.<sup>8</sup> The general applicability of the present

Table 1 Formation of DPUs in the presence of different solid acid catalysts



Entry	R	Catalyst	Surface area/ m <sup>2</sup> g <sup>-1</sup>	Surface acidity/ mequiv. H <sup>+</sup> g <sup>-1</sup>	Solvent	Yield (%)	Selectivity (%)
a	4-OCH <sub>3</sub>	TsOH			1,2-Cl <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	a	—
b	4-OCH <sub>3</sub>	ZnCl <sub>2</sub>			1,2-Cl <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	a	—
c	4-OCH <sub>3</sub>	AlCl <sub>3</sub>			1,2-Cl <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	a	—
d	4-OCH <sub>3</sub>	KSF	15 ± 10	0.85 ± 0.03	1,2-Cl <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	43	92
e	4-OCH <sub>3</sub>	K10	200 ± 10	0.70 ± 0.03	1,2-Cl <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	45	90
f	4-OCH <sub>3</sub>	HSZ-330	460 ± 10	1.39 ± 0.03	1,2-Cl <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	52	94
g	4-OCH <sub>3</sub>	HSZ-360	500 ± 10	0.51 ± 0.03	1,2-Cl <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	60	93
h	4-OCH <sub>3</sub>	HSZ-360	500 ± 10	0.51 ± 0.03	None	76	95
i	H	HSZ-360	500 ± 10	0.51 ± 0.03	None	66	95
j	3-CH <sub>3</sub>	HSZ-360	500 ± 10	0.51 ± 0.03	None	77	93
k	4-CH <sub>3</sub>	HSZ-360	500 ± 10	0.51 ± 0.03	None	73	94
l	4-Cl	HSZ-360	500 ± 10	0.51 ± 0.03	None	58	96

<sup>a</sup> Untractable mixture of compounds.

DPU synthesis was demonstrated by extending the reaction to different aromatic amines **1** and recovering the products **3** with good yields and excellent selectivities (entries h–l).

A representative procedure for the preparation of DPUs is as follows: a flask containing a mixture of the selected aromatic amine **1** (10 mmol) and zeolite HSZ-360 (0.5 g) was placed in a hot oil bath (180 °C) and **2** (0.8 g, 0.8 ml, 6 mmol) was added dropwise during 1 min. The mixture was efficiently stirred at the same temperature for 5 h.<sup>13</sup> After cooling to room temp. the slurry was washed with boiling MeOH containing 5% water (2 × 100 ml). After filtration the product was recovered from the solution by addition of more water and cooling.<sup>14</sup> Alternatively, hot DMSO could be successfully utilized under the same conditions.

The formation of compounds **3** could be attributed to the initial production of acetoacetanilides and their subsequent reaction with a second molecule of aromatic amine to give DPUs and acetone. This hypothesis was in part confirmed by quantitative production of diphenylurea by heating a 1:1 mixture of acetoacetanilide and aniline in the presence of zeolite HSZ-360. We then estimated the catalyst activity on reuse. Our results confirmed that the activity of HSZ-360 recovered by filtration, washed with acetone and reactivated by heating at 500 °C for 8 h was the same for 5 runs.

In conclusion the above reported method of utilizing **2** as carboxylating agent, zeolite HSZ-360 as solid catalyst and avoiding the use of any solvent, represents an innovative phosgene-free route for the selective synthesis of symmetric diphenylureas.

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- 9 Zeolite HSZ-360 is a commercial (Tosoh Corp.) acid faujasitic-type catalyst with 13.9 SiO<sub>2</sub>–Al<sub>2</sub>O<sub>3</sub> molar ratio, pore size 7.4 Å, surface area 500 ± 10 m<sup>2</sup> g<sup>-1</sup> (determined in our laboratory by the BET method: S. Brunauer, P. H. Emmett and E. Teller, *J. Am. Chem. Soc.*, 1938, **60**, 309), acidity 0.51 mequiv. H<sup>+</sup> g<sup>-1</sup> [determined in our laboratory by temperature programmed desorption of ammonia gas (NH<sub>3</sub>-TPD): P. Berteau and B. Delmon, *Catal. Today*, 1989, **5**, 121] and with the following chemical composition (wt% dry basis): SiO<sub>2</sub> 89.0, Al<sub>2</sub>O<sub>3</sub> 10.9, Na<sub>2</sub>O 0.06.
- 10 Zeolite HSZ-330 is a commercial (Tosoh Corp.) acid faujasitic-type catalyst with 5.9 SiO<sub>2</sub>–Al<sub>2</sub>O<sub>3</sub> molar ratio, pore size 7.4 Å, surface area 460 ± 10 m<sup>2</sup> g<sup>-1</sup> (determined in our laboratory by the BET method), acidity 1.59 mequiv. H<sup>+</sup> g<sup>-1</sup> [determined in our laboratory by temperature programmed desorption of ammonia gas (NH<sub>3</sub>-TPD)] and with the following chemical composition (wt% dry basis): SiO<sub>2</sub> 86.1, Al<sub>2</sub>O<sub>3</sub> 13.7, Na<sub>2</sub>O 0.19.
- 11 KSF is a commercial (Fluka) montmorillonite with surface area 15 ± 10 m<sup>2</sup> g<sup>-1</sup>, acidity 0.85 mequiv. H<sup>+</sup> g<sup>-1</sup> [determined in our laboratory by temperature programmed desorption of ammonia gas (NH<sub>3</sub>-TPD)] and with the following chemical composition (average value): SiO<sub>2</sub> (54.0%), Al<sub>2</sub>O<sub>3</sub> (17.0%), Fe<sub>2</sub>O<sub>3</sub> (5.2%), CaO (1.5%), MgO (2.5%), Na<sub>2</sub>O (0.4%), K<sub>2</sub>O (1.5%); K10 is a commercial (Fluka) montmorillonite with surface area 200 ± 10 m<sup>2</sup> g<sup>-1</sup>, acidity 0.70 mequiv. H<sup>+</sup> g<sup>-1</sup> [determined in our laboratory by temperature programmed desorption of ammonia gas (NH<sub>3</sub>-TPD)] and with the following chemical composition (average value): SiO<sub>2</sub> (73.0%), Al<sub>2</sub>O<sub>3</sub> (14.0%), Fe<sub>2</sub>O<sub>3</sub> (2.7%), CaO (0.2%), MgO (1.1%), Na<sub>2</sub>O (0.6%), K<sub>2</sub>O (1.9%).
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- 13 By carrying out the reaction for longer times the same value of yield (~70%) was observed.
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