



Short communication

A convenient and clean synthesis of methylenebisamides and carbinolamides over zeolites in aqueous media



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ABSTRACT

A simple, efficient and environmentally benign protocol for the synthesis of methylenebisamides and carbinolamides in high yields from aromatic amides and formaldehyde in the presence of heterogeneous catalysts (H β and NaY zeolites) using water as a solvent is demonstrated. Moreover, the catalyst is recyclable and can be reused without significant loss in its catalytic activity.

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The amide functionality is ubiquitous in nature and is found in many biologically active compounds, natural products, pharmaceuticals, polymers and peptides [1,2]. Particularly, bisamides are key fragments for the installation of *gem*-diaminoalkyl residues in retro-inverso pseudopeptide derivatives [3] by treating the respective amide with iodobenzene bistrifluoroacetate [4] and also adaptable intermediates in the synthesis of biologically active compounds [5], *N*-(α -alkoxybenzyl) benzamides [6] and peptidomimetic compounds [7]. *N*, *N'*-Methylenebisamides are usually prepared by the reaction of formaldehyde with corresponding amides or nitriles using different catalysts including triflic acid [8], sulfuric acid [9,10] and SBSSANPs [11]. Other approaches employing hexamethylenetetramine [12] and activated sulfoxides [13–15] have also been reported. Nevertheless, most of the existing methods suffer from one or more major drawbacks such as, inadequate yields, harsh reaction conditions, tedious purification procedures and use of toxic and/or corrosive materials.

Carbinolamides are apparently a simple combination of an amide and aldehyde, and they have been found as key intermediates in the generation of biologically active α -amidated peptide hormones [16, 17]. Moreover, this functionality plays a critical role in the activity of

commonly used antibiotic i.e., bicycomycin [18,19]. Carbinolamides are generally prepared by *N*-hydroxy methylation of benzamides with formaldehyde using Al₂O₃ [20] and K₂CO₃/Solvent [21–23].

Catalysts based on zeolites possess major importance both in petroleum and fine chemical industries [24,25]. This is mainly due to the fact that zeolites have uniform channel size, unique molecular shape selectivity, strong acidity and good thermal/hydrothermal stability. The BEA-type of zeolite consists of an intergrowth of two or more polymorphs comprised of a three dimensional system of 12-membered ring channels [26]. Zeolite beta has pore diameters of 0.76 \times 0.64 nm and 0.55 \times 0.55 nm. The BEA framework topology attracts much attention because of the large available micro-pore volume, large-pore channel system and the presence of active sites in different concentrations that are useful in a number of acid-catalyzed reactions [27,28]. NaY zeolite is a synthetic zeolite: it has a faujasite structure and is amphoteric [29] in nature. Its intrinsic pore structure containing framework oxygen is responsible for the basic active sites, which effectively activate polar reactant molecules [30].

Recently, from an economical and environmental point of view, the use of water as solvent has attracted much interest because of its natural advantages such as inexpensive, non-flammable, abundantly available solvent and non-toxic [31]. In continuation of our efforts toward the development of novel and eco-friendly synthetic protocols using zeolites [32–34] herein, we report a simple, efficient and environmentally benign approach for the synthesis of *N,N'*-methylenebisamides and

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carbinolamides using zeolites in aqueous media. However, to the best of our knowledge, hitherto there have been no reports for the synthesis of *N,N'*-methylenebisamides and carbinolamides using zeolites in aqueous media.

Initially, we investigated the reaction of benzamide (2 mmol) (1a) with formaldehyde (1 mmol) as a model system to optimize the different parameters of the reaction (Table 1). In order to choose the best catalyst first, the reaction was carried out over various zeolites, MCM-41 and montmorillonite K10 in water at 100 °C for 12 h and the results are summarized in Table 1. Among the catalysts examined, H β zeolite has exhibited the best catalytic activity due to its higher acidity and large pore size, which furnished the corresponding methylenebisbenzamide in excellent yield (Table 1, entry 8). Under the similar reaction conditions, HY, H-mordenite and HZSM-5 (40) provided the corresponding methylenebisbenzamides in <40% yield, along with substantial amounts of the *N*-(hydroxymethyl)benzamides (<40% yield) (Table 1, entries 1, 3 and 7). MCM-41 and montmorillonite K10 produced the *N*-(hydroxymethyl)benzamide as a major product (<40%) (Table 1, entries 4 and 5), along with small amounts of the respective methylenebisbenzamide (<10%). Whereas, NaY has given selectively *N*-(hydroxymethyl)benzamide product in 46% yield (Table 1, entry 2).

Once H β catalyst was found as the best catalyst for the formation of *N,N'*-methylenebisbenzamide, further we have studied the effect of mole ratio of benzamide to formaldehyde from 2:1 to 2:2 under the similar reaction conditions and it did not have any significant effect on the product yield (Table 1, entries 9 and 10). The present reaction was also conducted with different amounts of catalyst and it was found that both 150 mg and 200 mg of catalyst gave the best results within 6 h (Table 1, entries 12 and 13). Next, the reaction was carried out over H β with different Si/Al ratios and observed that there was no considerable effect on the product yield (Table 1, entries 14 and 15). In the absence of catalyst desired product (*N,N'*-methylenebisbenzamide) was not observed, but *N*-(hydroxymethyl)benzamide obtained in 29% yield. As can be seen from the above obtained results, the optimized reaction conditions to

get the highest yield for this reaction are 2:1 mole ratio of benzamide to formaldehyde in water (10 ml) at reflux temperature (100 °C) over H β catalyst (150 mg).

To explore the scope of the present system under the optimized conditions, a variety of aromatic amides reacted with formaldehyde in the presence of H β zeolite, afforded low to excellent yields of the corresponding *N,N'*-methylenebisamide products (Table 2). In order to determine the influence of substitution on the aromatic ring of benzamide with this reagent system, we have carried out the reaction with different substituted benzamides. Highly activating or moderately activating groups present on aromatic ring of benzamide gave excellent yields of the respective *N,N'*-methylenebisamides (Table 2, entries 2–6). Deactivating groups present on aromatic ring of benzamides also rendered high yields (in exception nitro substituted benzamide) (Table 2, entries 7–11). However, nitro substituted benzamide provided lower yields (Table 2, entries 12 and 13). Five-membered heteroaryl amide i.e. thiophene-2-carboxamide yielded the respective *N,N'*-methylenebisamide product with 90% yield (Table 2, entry 14). Cinnamamide also reacted smoothly and gave the corresponding *N,N'*-methylenebisamide in 87% yield (Table 2, entry 15).

Interestingly, *N*-(hydroxymethyl)benzamide product was obtained selectively when the reaction was performed in the presence of NaY zeolite. Stimulated by the affirmative preliminary results, we considered to develop a simple methodology for the synthesis of carbinolamides. Next, our efforts were focused on achieving the highest yield, then we investigated the reaction of benzamide (1a) (2 mmol) with different mole ratios of formaldehyde using NaY zeolite (100 mg) in water at 100 °C for 6 h (Table 3) and observed that 10 mmol of formaldehyde provided the highest yield (Table 3, entry 6). While increasing the amount of catalyst (150 mg) the yield of the desired product was increased from 86% to 96% and the reaction time was also reduced (Table 3, entry 7). In the absence of a catalyst yield the desired product was only 16% (Table 3, entry 8) and this observation clearly indicates the influence of the catalyst on the reaction. The above-presented results show that the optimized reaction conditions to get the highest yield for this reaction are 1:5 mole ratio of benzamide to formaldehyde in water (10 ml) at 100 °C over NaY zeolite (150 mg) (Table 1, entry 7).

Table 1
Optimization for synthesis of *N,N'*-methylenebisbenzamide.

| Entry | Catalyst | Yield (%) ^a | |
|-------|------------------------|------------------------|-----------------|
| | | 2a | 2b |
| 1 | HY | 28 | 35 |
| 2 | NaY | 46 | – |
| 3 | H-Mordenite | 34 | 24 |
| 4 | Montmorillonite K10 | 38 | 6 |
| 5 | HMCM-41 | 20 | 2 |
| 6 | HZSM-5 (300) | 32 | 16 |
| 7 | HZSM-5 (40) | 37 | 37 |
| 8 | H β (Si/Al = 19) | 4 | 94 |
| 9 | H β (Si/Al = 19) | 4 | 94 ^b |
| 10 | H β (Si/Al = 19) | 4 | 94 ^c |
| 11 | Absence of catalyst | 29 | – |
| 12 | H β (Si/Al = 19) | – | 96 ^d |
| 13 | H β (Si/Al = 19) | – | 96 ^e |
| 14 | H β (Si/Al = 15) | – | 96 ^d |
| 15 | H β (Si/Al = 20) | – | 94 ^d |

Reaction conditions: 1a (2 mmol), aqueous formaldehyde (37%, 1 mmol), catalyst (100 mg), H₂O (10 ml), 100 °C, 12 h.

^a Isolated yields.

^b Aqueous formaldehyde (37%, 1.5 mmol).

^c Aqueous formaldehyde (37%, 2 mmol).

^d H β (150 mg), 6 h.

^e H β (200 mg), 6 h.

Table 2
Synthesis of *N,N'*-methylenebisamides using H β zeolite.

| Entry | R | Yield ^a (%) |
|-------|---|------------------------|
| 1 | Ph | 96 ^b |
| 2 | 3-MeOC ₆ H ₄ | 83 |
| 3 | 4-MeOC ₆ H ₄ | 91 |
| 4 | 2-MeC ₆ H ₄ | 79 |
| 5 | 3-MeC ₆ H ₄ | 94 |
| 6 | 4-MeC ₆ H ₄ | 93 |
| 7 | 2-FC ₆ H ₄ | 94 |
| 8 | 2-ClC ₆ H ₄ | 93 |
| 9 | 4-BrC ₆ H ₄ | 90 |
| 10 | 3-CF ₃ C ₆ H ₄ | 82 |
| 11 | 4-CF ₃ C ₆ H ₄ | 96 |
| 12 | 3-NO ₂ C ₆ H ₄ | 23 |
| 13 | 4-NO ₂ C ₆ H ₄ | 10 |
| 14 | 2-C ₄ H ₃ S | 90 |
| 15 | PhCH = CH | 87 |

Reaction conditions: Amide (2 mmol), aqueous formaldehyde (37%, 1 mmol), H β zeolite (150 mg), H₂O (10 ml), 100 °C, 24 h.

^a Isolated yields.

^b 6 h.

Table 3
Optimization for synthesis of *N*-(hydroxymethyl)benzamide.

| Entry | HCHO (mmol) | Yield ^a (%) |
|-------|-------------|------------------------|
| 1 | 1 | 46 |
| 2 | 2 | 55 |
| 3 | 4 | 76 |
| 4 | 6 | 80 |
| 5 | 8 | 82 |
| 6 | 10 | 86 |
| 7 | 10 | 96 ^b |
| 8 | 10 | 16 ^c |

Reaction conditions: 1a (2 mmol), NaY (100 mg), H₂O (10 ml), 100 °C, 6 h.

^a Isolated yields.

^b NaY (150 mg), 1 h.

^c Absence of catalyst, 1 h.

Having optimized the reaction conditions, a variety of amides were allowed to react with formaldehyde to give the corresponding carbinolamides good to excellent yields (Table 4). Benzamides substituted with either activating (methyl, methoxy) (Table 4, entries 2–6) or deactivating groups (halide, nitro, trifluoromethyl) (Table 4, entries 7–13) underwent the reaction smoothly and furnished the corresponding carbinolamide products in excellent yields. However, a relatively longer reaction time (24 h) was required for nitro substituted benzamides (Table 4, entries 12 and 13) to provide excellent yields of the corresponding carbinolamides. Five-membered heteroaryl amide i.e. thiophene-2-carboxamide and cinnamamide were also shown to be effective under the similar reaction conditions (Table 4, entries 14 and 15).

The reusability of the catalysts was also been investigated and no significant loss in their catalytic activity was observed (see Supporting Information).

In summary, we have developed a simple, versatile and green protocol for the synthesis of *N,N'*-methylenebisamides and carbinolamides from aromatic amides and formaldehyde using zeolite (H β and NaY) as a catalyst in aqueous media. Prominent

Table 4
Synthesis of carbinolamides using NaY zeolite.

| Entry | R | Time (h) | Yield ^a (%) |
|-------|---|----------|------------------------|
| 1 | Ph | 1 | 96 |
| 2 | 3-MeOC ₆ H ₄ | 5 | 88 |
| 3 | 4-MeOC ₆ H ₄ | 5 | 89 |
| 4 | 2-MeC ₆ H ₄ | 3 | 90 |
| 5 | 3-MeC ₆ H ₄ | 3 | 81 |
| 6 | 4-MeC ₆ H ₄ | 3 | 95 |
| 7 | 2-FC ₆ H ₄ | 3 | 93 |
| 8 | 2-ClC ₆ H ₄ | 3 | 82 |
| 9 | 4-BrC ₆ H ₄ | 10 | 89 |
| 10 | 3-CF ₃ C ₆ H ₄ | 3 | 92 |
| 11 | 4-CF ₃ C ₆ H ₄ | 4 | 94 |
| 12 | 3-NO ₂ C ₆ H ₄ | 24 | 84 |
| 13 | 4-NO ₂ C ₆ H ₄ | 24 | 90 |
| 14 | 2-C ₄ H ₃ S | 10 | 72 |
| 15 | PhCH = CH | 3 | 77 |

Reaction conditions: Amide (2 mmol), aqueous formaldehyde (37%, 10 mmol), NaY (150 mg), H₂O (10 ml), 100 °C.

^a Isolated yields.

advantages obtainable by this method are broad substrate scope, water as solvent (green solvent), high atom economy (only water as by-product), use of non-hazardous and reusable catalysts, formation of cleaner products with high yields, mild reaction conditions, and easy set-up and work-up procedures, which make it an inexpensive and environmentally benign protocol.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.catcom.2014.12.006>.

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