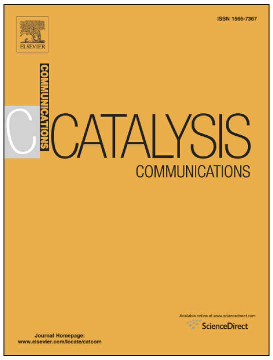

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Three-component synthesis of amidomethylarenes and -heteroarenes over Hβ zeolite under solvent-free conditions

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ABSTRACT

A highly efficient and eco-friendly protocol has been described for the synthesis of amidomethylarenes and -heteroarenes via one-pot three-component coupling reaction of amides, aldehydes and (hetero)arenes over a heterogeneous catalyst (Hβ zeolite) in solvent-free conditions. The scope and limitations of this catalytic process are demonstrated with various amides and arenes and the corresponding amidoalkylated arene products were obtained in moderate to excellent yields. The preliminary mechanistic insight (control experiments) suggest that bisamide and/or N-(hydroxymethyl)benzamide are probable intermediates in this reaction. Moreover, the catalyst can be reused without any significant loss of the catalytic activity and only water is produced as by-product.

Keywords: Amides, Arenes, Multicomponent reactions, Heterogeneous catalysis, Zeolites.

1. Introduction

In recent years, multicomponent reactions (MCRs) are becoming a powerful synthetic approach [1-3] to generate compounds with structural complexity and diversity in a single step, with improved atom and time economy, simplicity and a lower number of reactions and purification steps [4,5]. In particularly, coupling of aldehydes, alkynes and amides (A^3-coupling) is one of the best examples of such a process and this alteration has received much attention [6,7]. Amidoalkylated arenes and heteroarenes obtained from A^3-coupling reactions are synthetically versatile and key intermediates for the preparation of many biologically active nitrogen compounds and biological active molecules [8], such as luotonin A [9], an alkaloid, or the antiretroviral Raltegravir [10]. Hence, the synthesis of α-substituted amide derivatives has attracted great interest to synthetic chemists. Among a variety of methods for the synthesis of functionalized α-substituted amides, three-component aza-Friedal-type amidoalkylations with *in situ* generated acylimines or acyliminium ions is one of the most straightforward and atom-economic approach to access a variety of corresponding α-substituted amides [11-15]. Especially, the *in situ* generation of reactive imine derivatives from an aldehyde and an amide embodies an atom-economical [16] synthesis of amidoalkylated (hetero)arenes due to the fact that water is only side product and these reactions could meet the requirements of modern sustainable organic synthesis [17]. However, most of these methods experience one or more disadvantages, such as the use of stoichiometric amounts of Lewis or Brønsted acids [18-20] and the substrate scope is strictly limited to the indole and naphthol [21-23]. Recently, $Bi(OTf)_3$-catalyzed three-component reaction between amides, formaldehyde and arenes was reported by George Manolikakes et al. and Jaratjaroonphong et al. [24-26]. However, the recovery and reuse of catalyst and the need of organic solvent as the reaction medium are the main drawbacks associated with this system. Therefore, the development of a solvent-free and eco-friendly heterogeneous catalytic method for the synthesis of amidomethylarenes and -heteroarenes from amides, formaldehyde and arenes is highly desirable.

Solvent-free synthesis is an important part of green chemistry because of need to eliminate the use of toxic organic solvents, which are the cause for the majority of waste and pollution generated by chemical processes. Furthermore, there are distinct advantages of these solvent-free protocols, such as reduction costs, less energy requirements, faster reaction rates and thus reduction in reactor size and capital investment [27-29]. Over the past decades, catalysis by zeolites and related materials has become an attractive research area in the fields of heterogeneous catalysis and green chemistry. As an important type of solid acid catalysts, zeolites have been extensively used for replacement of highly toxic and corrosive mineral acids or inorganic Lewis acids in the synthesis of fine chemicals [30, 31]. This is mainly due to the fact that zeolites have well defined porous structures with large amount of acid sites (both Bronsted and Lewis type) present on the inner surface of these zeolitic materials. One of the most important properties of zeolites is the great variety of topologies and pore architectures, together with the possibility to adjust their acidity (type, concentration and strength of acid sites) [32, 33]. Hence, the catalytic activity of zeolites could be tailored for special chemical transformations. Additionally, their eco-friendly nature, high surface area and adsorption capacity, chemical and thermal stability, make them ideal materials for heterogeneous catalysis. In a continuation of our efforts toward the development of novel and eco-friendly synthetic procedures using zeolites

[34], we herein report a new, efficient and environmentally friendly catalytic method for the synthesis of amidomethylarenes and -heteroarenes from amides, formaldehyde and (hetero)arenes over Hβ zeolite under solvent-free conditions**.**

2. Results and discussion

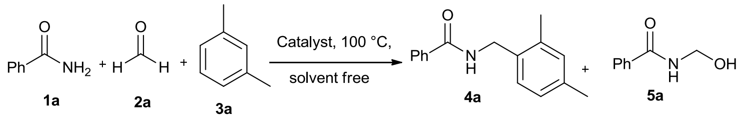
2.1. Catalyst screening

In the initial investigation, the reaction between benzamide (**1a**), aqueous formaldehyde (**2a**) and *m*-xylene (**3a**) was chosen as a model system to optimize the different parameters of the reaction. The reaction was performed with various zeolites, HMCM-41, montmorillonate K10, SiO_2, SiO_2-Al_2O_3, HCl, H_2SO_4 and *L*-proline at 100 °C in a sealed tube for 10 h to find out the best catalyst (Table 1, entries 1-12). Among the catalysts screened, Hβ zeolite displayed a higher catalytic activity and gave **4a** product yield of 91% (Table 1, entry 5).

2.2. Optimization of reaction conditions

The influence of temperature was investigated, after found the best catalyst (Hβ zeolite) for this transformation. The reaction was remarkably accelerated by varying the reaction temperature from room temperature to 100 ^{o}C, and the yield was increased from 0 to 91% (Table 1, entries 5 and 14-16). The molar ratio of formaldehyde and arene had a significant influence on the product yield (Table 1, entries 5 and 17-20). The present reaction was also conducted with different amounts of catalyst. It was found that 100 mg of catalyst gave the best result (Table 1, entries 5 and 21-23). The product **4a** was not obtained in the absence of catalyst, thus confirming the

Table 1: Screening of reaction conditions for the synthesis of *N*-(2,4-dimethylbenzyl)benzamide.



Entry	Catalyst	Temperature (°C)	Yield (%)[a]	
			4a	**5a**
1	HY	100	20	35
2	NaY	100	-	62
3	HZSM-5(40)	100	49	-
4	H-mordenite	100	-	29
5[b]	Hβ	100	91	<3
6	HMCM-41	100	5	<5
7	Montmorillonate K10	100	-	36
8	SiO_2	100	6	-
9	SiO_2-Al_2O_3	100	9	-
10[b,c]	HCl	100	54	20
11[c]	H_2SO_4	100	44	21
12[c]	*L*-proline	100	-	-
13	Without catalyst	100	-	-
14	Hβ	RT	-	-
15	Hβ	60	38	-
16[b]	Hβ	80	68	-
17[d]	Hβ	100	34	5
18[b,e]	Hβ	100	80	10
19[b,f]	Hβ	100	51	18
20[b,g]	Hβ	100	92	<3
21[h]	Hβ	100	32	-
22[b,i]	Hβ	100	54	-
23[b,j]	Hβ	100	70	-

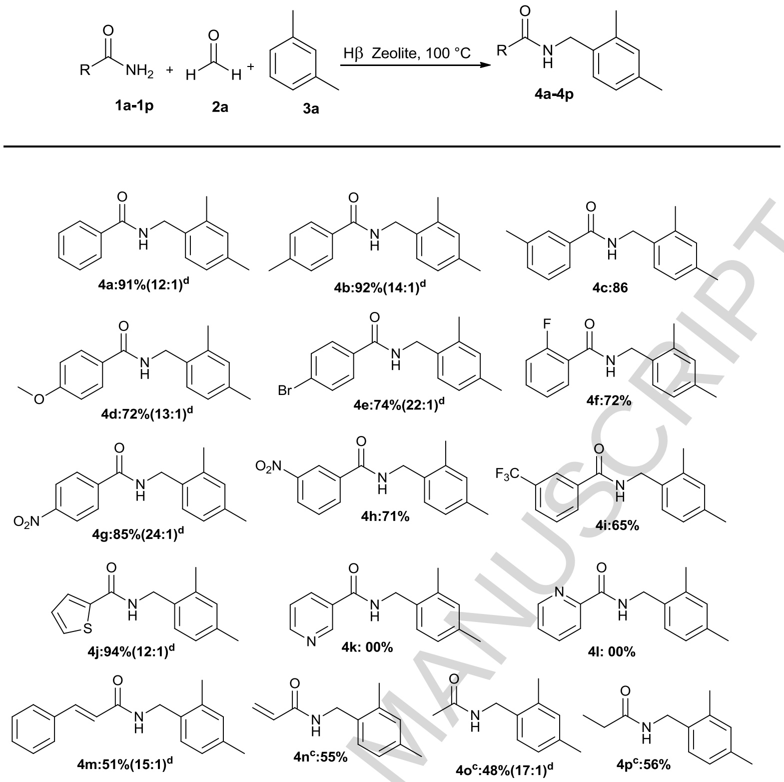
Reaction conditions: **1a** (1 mmol), aqueous formaldehyde (**2a**) (37%, 1.5 mmol), **3a** (2 mmol), catalyst (100 mg), 100 °C, 10 h, sealed tube. [a] Isolated yields. [b] Obtained as a 12:1 mixture of regioisomers. [c] 30 wt.% of catalyst. [d] **2a** (37%, 1 mmol). [e] **2a** (37%, 2 mmol). [f] **3a** (1 mmol). [g] **3a** (3 mmol). [h] Catalyst (25 mg). [i] Catalyst (50 mg). [j] Catalyst (75 mg).

catalyst role in the reaction (Table 1, entry 13). In all cases, the amidoalkylated product was obtained as a mixture of regioisomers (12:1 ortho/para -vs ortho/ortho-substitution). After extensive screening, we have observed that 1:1.5:2 molar ratio of benzamide, formaldehyde and *m*-xylene (1 mmol of benzamide, 1.5 mmol of aqueous formaldehyde and 2 mmol of *m*-xylene) at 100 ^{o}C over Hβ zeolite (100 mg) under solvent-free conditions are the optimum conditions to get the maximum yield of the desired product.

2.3. Variation of carboxamides

With the optimized conditions established, the generality of the Hβ zeolite-catalyzed approach was investigated with a variety of amides (Table 2). Surprisingly, all the carboxamides used in the reaction were reacted smoothly with formaldehyde and *m*-xylene to afford moderate to excellent yields of the corresponding amidomethylated arene products (Table 2). The reaction with various electron-donating groups present on

Table 2: Variation of carboxamides.[a]



[a] Reaction conditions: **1a-1p** (1 mmol), **2a** (37%, 1.5 mmol), **3a** (2 mmol), Hβ zeolite (100 mg), 100 °C, 10 h, sealed tube. [b] Isolated yields. [c] Temperature (80 °C). [d] Obtained as a mixture of regioisomers, ratio of regioisomers given in parentheses.

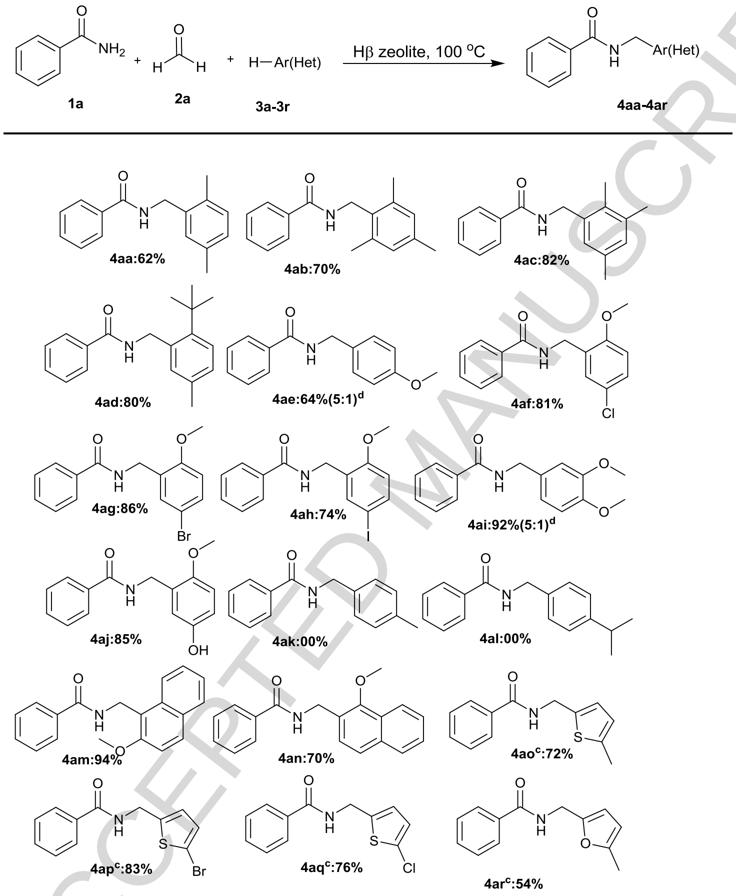
aromatic ring of benzamide furnished respective products in 72-92% yields (Table 2, **4a-4d**). Electron-withdrawing groups bearing benzamides also afforded the corresponding products in 65-85% yields (Table 2, **4g-4i**). Halogen substituted aromatic amides participated well in this reaction to afford the desired products in 74 and 72% yields, respectively (Table 2, **4e** and **4f**). In the case of heteroaryl amides, different results were observed. Thiophene-2-carboxamide proceeded smoothly and afforded the corresponding product in 94% yield (Table 2, **4j**), whereas nicotinamide and picolinamide did not react under the present reaction conditions even after a prolonged reaction time (Table 2, **4k** and **4l**). Notably, cinnamamide afforded the respective product in 51% yield (Table 2, **4m**). Further, the efficiency of this reaction was also investigated with aliphatic amides *i.e.*, acrylamide, acetamide and propanamide provided the corresponding products in 48-56% yields (Table 2, **4n**, **4o** and **4p**).

2.4. Variation of arenes and heteroarenes

Under similar reaction conditions, a variety of arenes were employed to further extend the scope of the Hβ zeolite, which is the promotion of the three-component coupling reaction (Table 3). The results show that both aromatic and heteroaromatic arenes (except electron-poor heteroarenes) underwent the multicomponent reaction smoothly to provide the corresponding amidomethylated arene products, in moderate to excellent yields, with high regioselectivity (Table 3, **4aa-4aj** and **4am-4ar**). Di- and tri-alkyl substituted arenes (*p*-xylene, mesitylene, 1,2,4-trimethylbenzene and 4-*tert*-butyltoluene) yielded the respective products in 62-82% yields (Table 3, **4aa-4ad**). Whereas mono alkyl substituted benzenes (toluene **3k** and cumene **3l)** were unsuccessful under similar reaction conditions due to the fact that the methyl and isopropyl (mono alkyl benzene) are less ring activating groups compared to other activating groups (Table

3). Anisole and substituted anisoles furnished the desired amidoalkylated products in 64-92% yields (Table 3, **4ae-4ai**). 4-Methoxyphenol also afforded the corresponding amidoalkylated product in 85% yield (Table 3, **4aj**). The electron-rich naphthalenes such as 2-methoxynaphthalene and 1-methoxynaphthalene were reacted smoothly and yielded the

Table 3: Variation of arenes and heteroarenes.[a]



[a] Reaction conditions: **1a** (1 mmol), **2a** (37%, 1.5 mmol), **3a-3r** (2 mmol), Hβ (100 mg), 100 °C, 10 h, sealed tube. [b] Isolated yields. [c] Temperature (80 °C). [d] Obtained as a mixture of regioisomers, ratio of regioisomers given in parentheses.

respective products in 94 and 70% yields (Table 3, **4am** and **4an**). In the case of heterocycle arenes, electron-rich heterocycles, such as different substituted thiophenes and 2-methyl furan, gave the corresponding amidomethylated arene products in 54-83% yields (Table 3, **4ao-4ar**). On the contrary, electron-deficient heteroaromatic arenes (2-methylpyridine, 3-methylpyridine and 3,6-dimethylpyridine) were unsuccessful under similar reaction conditions.

In heterogeneous catalysis, the recovery and reusability of the catalyst is an important feature for their industrial applications and environmental considerations. The catalyst (zeolite) was easily separated from the reaction mixture by simple filtration and the collected catalyst was calcined at 450 °C to use in the next cycle. The reusability of the catalyst was checked by the reaction of benzamide with formaldehyde and *m*-xylene under standard reaction conditions. The reused catalyst showed persistent activity even after the fifth reuse (see the ESI, Fig. S1). The powder XRD analysis of reused catalyst matched well with fresh catalyst, thus suggesting that the crystallinity of the reused catalyst is comparable to the original material (see the ESI, Fig. S2). There was no leaching of aluminium or silicon from zeolite (Hβ) which was confirmed by elemental analysis.

2.5. Temperature-programmed desorption of ammonia (NH_3-TPD)

Temperature-programmed desorption of ammonia (NH_3-TPD) was carried out to determine the amount and strength of acid sites present in the Hβ zeolite. The NH_3-TPD profile recorded is shown in Fig 1. Two desorption peaks are observed centered at 205 and 380 °C on the Hβ zeolite, corresponding to its weak (53.8%) and strong (46.2%) acidic sites, respectively. The total amount of acidity measured by NH_3-TPD for the Hβ zeolite was 1.16 mmol/g. These results reveal that the combination of weak and strong acidic sites are largely responsible for the high yields of the corresponding amidomethylarene and -heteroarene products (**4**) in this reaction.

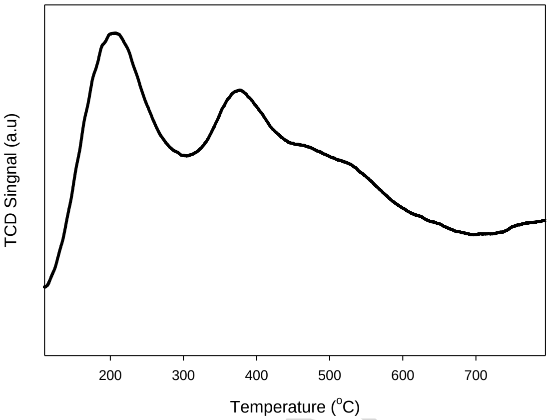


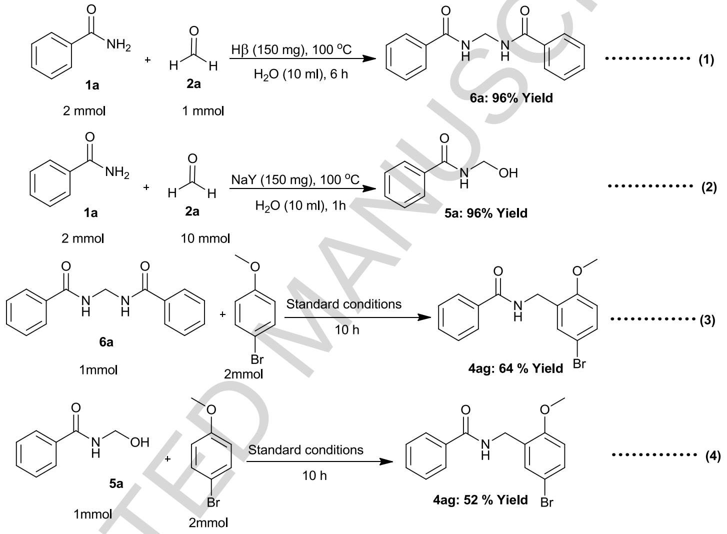
Fig. 1: NH_3-TPD profile recorded on Hβ zeolite.

2.6. Activity studies and FT-IR spectra of fresh, pyridine and 2,6-dimethylpyridine adsorbed Hβ zeolite

In order to know the nature of active sites for this reaction, we have performed two separate experiments. For this purpose, two bases were chosen as acid site blockers, such as pyridine and 2,6-dimethylpyridine. These bases were adsorbed on the Hβ zeolite separately. The surface poisoned samples were analyzed by FT-IR and used for the three-component coupling reaction of benzamide, formaldehyde and *m*-xylene (see ESI for further details). The results show that Bronsted acid sites are responsible for this reaction.

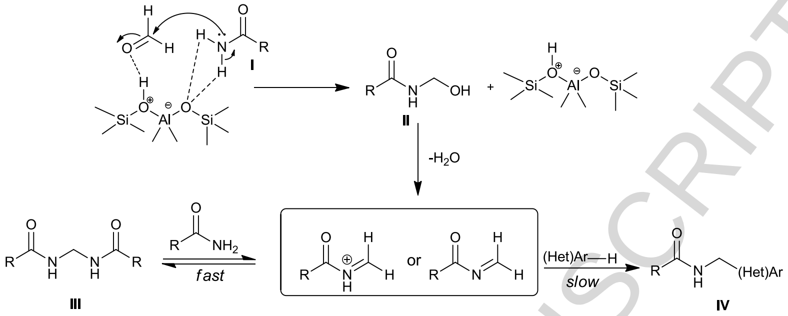
2.7. Control experiments

After evaluating the scope and limitations of this present catalytic system, we were interested in gaining insight into the reaction mechanism. In this context, a couple of experiments were carried out and these are presented in Scheme 1. During our initial screenings with Hβ zeolite, we could observe the formation of bisamide (**6a**) along with N-(hydroxymethyl)benzamide (**5a**), and these are the expecting intermediates which we prepared for both products using our previous report [Scheme 1, Eq. (1) and (2)] [35]. To find the intermediate for this transformation, we performed the reaction between bisamide and 4-bromoanisole in the presence of Hβ catalyst, where the expected amidoalkylated product in 64% yield was obtained [Scheme1, Eq. (3)]. The reaction of N-(hydroxymethyl)benzamide with 4-bromoanisole also gave the same product [Scheme 1, Eq. (4)].



Scheme 1: Control experiments.

Based on the above investigated results and literature reports [24, 25], a plausible reaction mechanism for the three-component amidoalkylation reaction over Hβ zeolite has been proposed as shown in Scheme 2. It is speculated that the reaction is initiated by the adsorption of formaldehyde on the acid sites of Hβ zeolite (Bronsted acid sites activates the carbonyl group of the formaldehyde and weak conjugate base (framework oxygen) activates the amine group of the amide), which subsequently reacts with amide (**I**) to provide the carbinolamide intermediate (**II**). After formation of the carbinolamide intermediate, two different paths were evaluated based on the above experimental reactions, either an elimination of water leads to the formation of a reactive acylimine or acyliminium species, or it further reacts with another amide in the presence of acidic sites of zeolite to give the bisamide (**III**), which can decompose to form the acylimine. In the presence of a suitable nucleophilic arene, the electrophilic acylimine can react in an aza-Friedel-Crafts reaction to afford the amidoalkylated product (**IV**).



Scheme 2: Proposed mechanism.

3. Conclusions

In summary, we have developed a simple and green protocol for the three-component synthesis of amidomethylarenes and -heteroarenes from readily available amides, formaldehyde and (hetero)arenes over Hβ zeolite under neat conditions. The noteworthy features of the present method are the use of non-hazardous and reusable catalyst, broad substrate scope, absence of solvent, higher yields of the desired products, high atom economy (only water as by-product), simple work-up procedure and mild reaction conditions, which make it an inexpensive and environmentally benign protocol. Moreover, the scope and limitations of this protocol are demonstrated with various amides and arenes.

Acknowledgements

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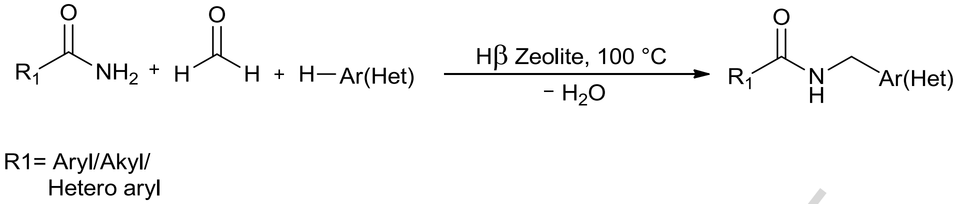

Graphical abstract

Highlights

- Hβ exhibits excellent activity towards the synthesis of amidomethylated arenes.
- This protocol was developed under solvent-free conditions
- The reaction was explored with variety of amides and (hetero)arenes
- The catalyst can be reused without significant loss in their catalytic activity.