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Boric acid catalyzed Ugi three-component reaction in aqueous media†

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Atul Kumar,* Deepti Saxena and Maneesh Kumar Gupta

$B(OH)_3$ catalyzed Ugi three-component reaction for the synthesis of 2-arylamino-2-phenylacetamide has been developed using aldehydes, amines, and isocyanides in water. The synthesized 2-arylamino-2-phenylacetamides were efficiently converted into α-amino acid *via* acidic hydrolysis.

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Introduction

Over the past decades, multi-component reactions (MCRs) have demonstrated their ability and efficiency in the generation of chemical diversity.[1] MCRs are useful for the expedient creation of chemical libraries of drug-like compounds and optimization in drug discovery programmes.[2] In addition the advantages of multicomponent reactions are high atom-economy, selectivity, structural multiplicity and simple procedure. The Ugi four-component reaction (Ugi4-CR) is a powerful synthetic method for the synthesis of various novel nitrogen containing biologically active molecules.

Recently, List and Pan have done a fascinating modification in Ugi-4CR by converting it into Ugi-3CR (ABC type MCRs) for the synthesis of 2-arylamino-2-phenylacetamide by using phenyl phosphinic acid.[3] Shaabani *et al.* also reported cellulose-SO_3H as a biodegradable solid acid catalyzed Ugi three-component reaction.[4] However, it involved prolonged reaction time and non-green solvent (Scheme 1). Therefore, it is desirable to develop a green and eco-friendly protocol for the preparation of 2-arylamino-2-phenylacetamide.

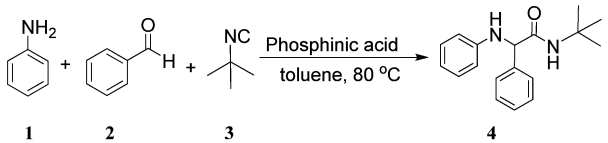
Nowadays, there has been increasing interest in development of green synthetic pathways and processes.[5] This technique led to a growing interest in the field of organic synthesis in water.[6] In relation to this, significant efforts have been dedicated to develop organic reactions in water with many inherent advantages over reactions in conventional organic solvents. Therefore, development of an Ugi three-component reaction operated in water will be of great practical value.

Phenylacetamide and α-amino acid scaffolds display a wide range of biological activities (Fig. 1). Etidocain is used for treatment of neuronal voltage-gated sodium channels (NVSC)[7] and NPPG is a class of CRF (corticotropin releasing factor) antagonists in neuropsychiatric disorders.[8–10] Enalapril and Quinapril are potent inhibitors of angiotensin-converting enzyme (ACE)[11] and are widely used in clinics (Fig. 1).

Inspired from these, we focused our efforts towards the development of green synthesis of multi-component reactions (MCRs)[12] to synthesize various biologically important scaffolds. Herein, we wish to report the first boric acid catalyzed Ugi three-component reaction in water for the synthesis of 2-arylamino-2-phenylacetamide **4** (Scheme 2). The synthesized 2-arylamino-2-phenylacetamides were conveniently hydrolyzed to afford biologically important α-amino acids **5**.

Results and Discussion

Initially, we intended to find an efficient catalyst for the synthesis of a tandem one-step Ugi three-component reaction from aniline **1**, benzaldehyde **2** and *tert*-butylisocyanide **3** (Table 1) as a model reaction. At the outset we explored the three-component reaction catalyzed by several metal Lewis acids such as $Zn(OTf)_2$, $Fe(OTf)_3$, and $Cu(OTf)_2$, but these Lewis acids proved to be ineffective promoters (Table 1, entries 1, 2 and 3). We further optimized the reaction with other metal Lewis acids *e.g.* $In(OTf)_3$, $Bi(OTf)_3$ and CuBr (Table 1, entries 4, 5 and 6) but the desired product was obtained in poor yield. Employing this stepwise catalyst screening procedure, we have also tried the reaction with $TiCl_4$ and $NiCl_4$ but the stable product was isolated from the reaction with lower yield (Table 1, entries 7 and 8). These experiments were carried out at constant 5 mol% amount of catalyst, over reaction times



Scheme 1 Ugi three-component reaction.

Medicinal and Process Chemistry Division, Central Drug Research Institute, CSIR, Lucknow, India. E-mail: dratulsax@gmail.com; Fax: +91-522-26234051; Tel: +91-522-2612411

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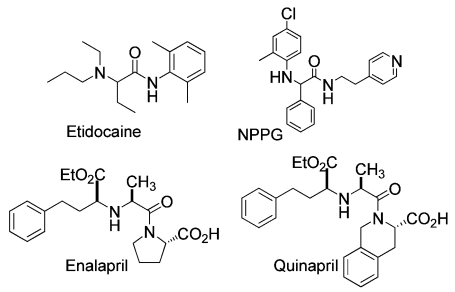
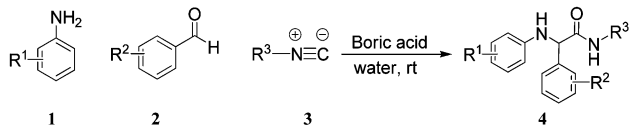


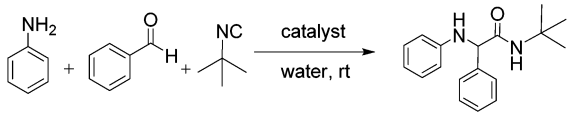
Fig. 1 Biologically active compounds containing amide and amino acid skeleton.



Scheme 2 Boric acid catalyzed Ugi three-component reaction for the synthesis of 2-arylamino-2-phenylacetamide **4**.

ranging from 3 to 8 h and the desired product was not obtained in good yield (Table 1, entries 1–8). After screening these catalysts we go with 5 mol% of boric acid as a catalyst but we obtain a moderate yield (Table 1, entry 9). Next we tried the reaction with 10 mol% boric acid and the best result was observed within 1 h (Table 1, entry 10). Boric acid is a homogenous and useful catalyst for a number of synthetic transformations for example, aza-Michael addition,[13] thia-Michael addition,[14] and Biginelli reaction.[15]

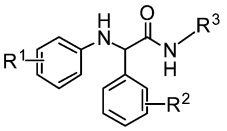
Table 1 Effect of catalysts for synthesis of 2-arylamino-2-phenylacetamide **4**[a]



Entry	Catalyst	Time (h)	Yield (%)[d]
1	$Zn(OTf)_2$	3	25
2	$Fe(OTf)_3$	4	30
3	$Cu(OTf)_2$	3	20
4	$In(OTf)_3$	6	35
5	$Bi(OTf)_3$	6	38
6	CuBr	7	39
7	$TiCl_4$	8	30
8	$NiCl_4$	6	26
9	$B(OH)_3$[b]	3.5	52
10	$B(OH)_3$[c]	1	90

[a] Reaction conditions: aniline (1 mmol), benzaldehyde (1 mmol), *tert*-butylisocyanide, (1 mmol), and catalyst (10 mol%) in water (5 mL) at rt. [b] 5 mol% boric acid. [c] 10 mol% boric acid. [d] Isolated yield.

Table 2 Boric acid catalyzed synthesis of 2-amino-2-phenylacetamide **4** derivatives in water[a]



Entry	R^1	R^2	R^3	Prod.	Time (min)	Yield (%)[b]
1	H	H	*t*BuNC	**4a**	60 min	90
2	4-OMe	4-Cl	*c*HexNC	**4b**	55 min	80
3	4-OMe	4-Cl	*t*BuNC	**4c**	55 min	78
4	2,4-diMe	H	*c*HexNC	**4d**	60 min	82
5	4-Cl	4-Cl	*t*BuNC	**4e**	50 min	81
6	4-Cl	H	*t*BuNC	**4f**	60 min	80
7	4-OMe	4-Br	*t*BuNC	**4g**	50 min	75
8	3-OMe	4-Cl	*c*HexNC	**4h**	60 min	80
9	4-OMe	H	*c*HexNC	**4i**	45 min	83
10	2,4-diMe	4-Cl	*t*BuNC	**4j**	45 min	80
11	H	3,5-OMe	*t*BuNC	**4k**	60 min	77
12	H	3,5-OMe	*c*HexNC	**4l**	55 min	75
13	3-OMe	4-Br	*t*BuNC	**4m**	60 min	81
14	4-OMe	4-F	*t*BuNC	**4n**	60 min	79
15	H	4-Br	*t*BuNC	**4o**	60 min	75

[a] Reaction conditions : aniline (1 mmol), aldehyde (1 mmol), isocyanide (1 mmol), and 10 mol% boric acid in water (5 mL) at r.t. for a given time. [b] Isolated yield.

It was observed that the loading of catalyst (5 to 10 mol%) plays an important role in the reaction and 10 mol% of boric acid was found to be sufficient to obtain the desired product **4a** in good to excellent yield (Table 2, entries 1–15).

In order to study the solvent effect on the reaction of aniline benzaldehyde, and *tert*-butylisocyanide catalyzed by boric acid, we performed the reaction in different solvents. First we choose polar protic solvents like EtOH, MeOH and *iso*-propanol the desired product was obtained in lower yield **4a** (Table 3, entries 1, 2 and 3). A similar attempt using non-polar solvents like CH_2Cl_2 and toluene under the same conditions again gave **4a** with poor yield (Table 3, entries 4 and 5). We further carried out this experiment in CH_3CN, DMF and DMSO at room temperature and isolated the product in moderate

Table 3 Effect of solvents for the synthesis of 2-amino-2-phenylacetamide[a]

Entry	Solvent	Time/(h)	Yield (%)[b]
1	EtOH	3	22
2	MeOH	4	25
3	*iso*-Propanol	3	30
4	CH_2Cl_2	6	20
5	Toluene	8	28
6	CH_3CN	5	41
7	DMF	6	45
8	DMSO	5	50
9	H_2O	1	90

[a] Reaction conditions: aniline (1 mmol), benzaldehyde (1 mmol), and *tert*-butylisocyanide (1 mmol) with 10 mol% boric acid at r.t. for a given time. [b] Isolated yield.

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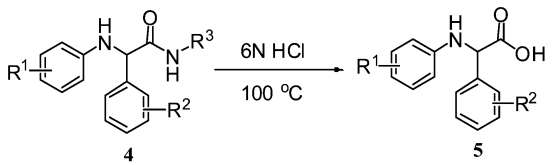

Scheme 3 Synthesis of *N*-substituted α-amino acid **5**.

yield (Table 3, entries 6, 7 and 8). By keeping the vital aspect of water in mind we tried the reaction in the same and obtained the best result (Table 3, entry 9). From the above discussion it is clear that the picking of water with boric acid was the right choice, because boric acid is a fine catalyst and plays a very essential catalytic role in organic reactions.[16] The result of solvents effect with boric acid are shown in Table 3.

Under these optimized reaction conditions a number of 2-arylamino-2-phenylacetamide derivatives were synthesized using various aromatic anilines, aldehydes and isocyanides. The results of this study are summarized in Table 2.

The structures of the desired products **4** were fully characterized by spectroscopic technique like mass spectroscopy, ^{1}H NMR, ^{13}C NMR, and elemental analysis. Searching for the utility of **4** we further converted it into *N*-substituted α-amino acid **5** derivatives *via* acidic hydrolysis, accomplished by heating in 6N HCl at 100 °C (Scheme 3). The results are summarized in Table 4, ESI.†

Conclusion

In conclusion, we have developed first aqueous strategy for an Ugi three-component reaction for the synthesis of 2-arylamino-2-phenylacetamide from aniline, aldehyde and isocyanide by using boric acid as a catalyst. *N*-substituted α-amino acids can be also synthesized from 2-arylamino-2-phenylacetamide derivatives *via* acidic hydrolysis. The advantage of this improved methodology is to construct the chemical library of phenylacetamide and α-amino acid derivatives.

Experimental

General experimental procedure for synthesis of compounds (4)

In a typical experiment, the aniline (1 mmol), aldehyde (1 mmol), isocyanide (1 mmol), and boric acid (10 mol%) were taken in 5 mL water. The reaction mixture was vigorously stirred at room temperature, until the completion of the reaction (monitored by thin layer chromatography). After completion the reaction mixture was extracted with ethyl acetate. The organic layer was dried over sodium sulphate and concentrated under vacuum to give the crude product. The crude product was purified by column chromatography (silica gel, 100–200 mesh) to afford the corresponding product **4**.

General experimental procedure for synthesis of compounds (5)

In a 25 mL round-bottom flask, 2-arylamino-2-phenylacetamide **4** (1 mmol) in 6N HCl (10 mL) was stirred at 100 °C. The reaction mixture was cooled at room temperature then extracted with ethyl acetate. The organic layer was dried over sodium sulphate to obtain the crude product, which was purified by column chromatography (silica gel, 100–200 mesh) to afford the corresponding product **5**.

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