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Efficient catalyst-free Domino approach for the synthesis of novel 2-benzazepine derivatives in water

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ABSTRACT

A novel one-pot eco-friendly protocol for the synthesis of 2-benzazepine derivatives in water has been developed. 4-Chloro-3-formyl coumarin reacts with benzyl amines under catalyst-free conditions in aqueous medium to afford substituted 5-(2′-hydroxyaryl)-4-amido-2-benzazepines in excellent yields.

Azepines are prevalent motifs in several natural products possessing diverse biological properties.[1] Benzazepine is a fused *N*-heterocyclic moiety present as a key structural fragment in various biologically active molecules[2] and naturally occurring alkaloids, such as aphanorphine, lennoxamine, and cephalotaxine, which are known to have anxiolytic action.[3] The structural complexity and biological importance of benzazepines prompted intense research by organic chemists to develop novel methodologies for their synthesis. Although considerable amount of work has been carried out on 1- and 3-benzazepines,[4–13] there are very few reports for the synthesis of 2-benzazepines.[14] The classical synthesis of 2-benzazepines apply Bischler–Napieralski[15] cyclization or the Friedel–Crafts acylation reaction. Gschwend reported the synthesis of 1-phenyl-2-benzazepin-5-ones using acid-catalyzed cyclization of substituted benzophenones,[16] while Eugene J. Trybulski et al. reported the synthesis using substituted aminobenzophenones.[17] However, most of the above-mentioned methods utilize expensive organic solvents and catalysts which employ multi-step synthetic methodologies.

Recently, there has been enormous emphasis on the green and sustainable chemistry, where high importance has been given for the development of novel and eco-friendly methodologies which can reduce or eliminate the use and generation of hazardous industrial wastes.[18] Water being the most inexpensive and non-hazardous natural source has contributed generously in addressing most of the above-described problems and in the course of time has turned out as an inevitable alternative to many volatile organic solvents in several synthetic methodologies.[19] A major breakthrough in this direction was first demonstrated by Breslow and Rideout who reported Diels–Alder reactions in water.[20] Recently, Yao and co-workers have described an elegant method for the synthesis of indolyl(nitro)chromans with very high diastereoselectivities under catalyst-free aqueous conditions.[21] Also, several reports have been documented in recent years where water has been employed as a preferred solvent for the synthesis of numerous elusive nitrogen-containing heterocyclic molecules.[22] Hence, it would be of considerable interest to demonstrate the synthesis of these imperative heterocyclic frameworks using green technology platforms. In quest to identify a general approach to highly functionalized benzazepines under mild conditions from readily available starting materials, we have envisaged a versatile *scaffold hopping* methodology starting from 4-chloro-3-formyl coumarin to achieve required disubstituted benzazepines **3a–k**.[23]

4-Chloro-3-formyl coumarin when reacted with 2 equiv of *p*-methyl benzyl amine in water yields a white precipitate of benzazepine **3a** in 3 h with 83% yield. The process did not require any work-up procedures and the product was obtained as white precipitate in pure form from the reaction mixture which was isolated by simple filtration. This is a straightforward and high yielding one-step protocol for the generation of substituted 5-(2′-hydroxyaryl)-

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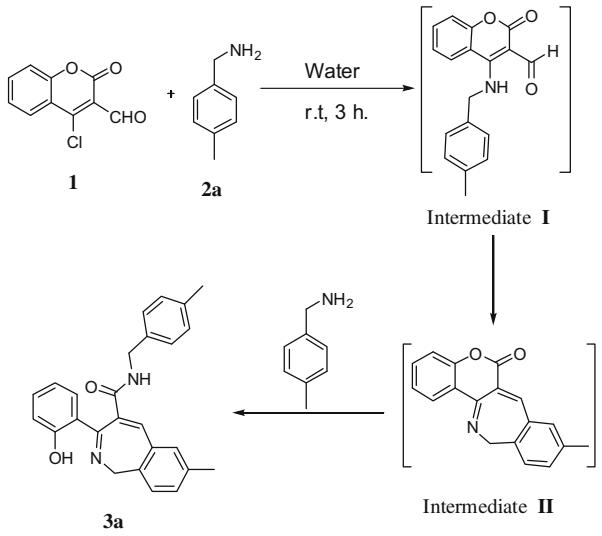
4-amido-2-benzazepines and to the best of our knowledge a first report for the synthesis of 2-benzazepines in water. To validate our choice of water as a solvent and the effect of other organic solvents on the reaction, we have screened various solvents for optimization of the method. As shown in Table 1 (entries 1–6), the reaction was comparatively slower in non polar solvents such as dichloromethane and chloroform than the polar solvents such as acetonitrile, methanol, ethanol, and water. Water was found to be the best solvent from our observations which could afford excellent yield of the product in short reaction times (Table 1, entry 1). As shown in Scheme 1, the reaction was presumed to go through substitution of chloro group in coumarin by benzyl amine giving rise to an intermediate **I**, followed by a cyclization to afford intermediate **II**. The final step of the reaction involves second molecule of benzyl amine which participates in a ring opening of the coumarin followed by subsequent amidation resulting in benzazepine **3a** in one-pot.

To confirm the proposed mechanism, an attempt was made to isolate intermediates **I** and **II** (Scheme 1), and experiments were conducted in water with 1 equiv of *p*-methyl benzyl amine and 4-chloro-3-formyl coumarin. Intermediate **I** was obtained as a white precipitate after 20 min of stirring the reaction mixture at room temperature and on further continuation of the reaction for 90 min, cyclized intermediate **II** was obtained. Both the intermediates were isolated in separate experiments and were characterized completely to support the proposed mechanism (see Supplementary data). While ring opening of coumarins has been previously described,[24] the typical procedures employed strong bases such as lithium aluminum hydride and sodium hydroxide leading to harsh reaction conditions.

However, we could accomplish the required ring opening in the present protocol under very mild reaction conditions under catalyst-free conditions along with the in situ formation of an amide bond. With the above-mentioned optimized conditions in hand, further experiments were conducted to expand the utility of the reaction and substrate scope with a series of benzyl amines (**2a–k**). As illustrated in Table 1, *p*-methyl benzyl amine reacts with 4-chloro-3-formyl coumarin to afford the benzazepine product **3a** in good yield (Table 1, entry 1). Similarly, other electron-rich benzyl amines having *p*-OMe, *o*-Me, and *m*-Me substitutions react in 3–5 h and the corresponding products were isolated in good yields (Table 1, entries 7, 11, and 12). Unsubstituted benzyl amine and benzyl amines having various chloro and fluoro substitutions also react smoothly to afford the corresponding benzazepine products in 3 h with 80–92% yields (Table 1, entries 8–10, 13, and 16). Disubstituted benzyl amines such as 3,4-dimethoxy and 2,3-difluoro benzyl amines also react well under the reaction conditions to afford the corresponding benazepine derivatives in 4 and 6 h, respectively (Table 1, entries 14 and 15).

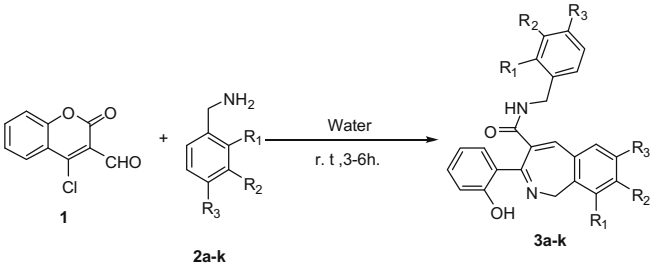


Scheme 1. Proposed reaction mechanism for the synthesis of 2-benzazepine **3a**.

In general, the reaction has a wide applicability to a variety of benzyl amine substrates affording their corresponding products in good to excellent yields. In hope of further broadening the scope of the reaction and with the aim to achieve higher diversity, a mixed substrate combination was also attempted. To explore the above-mentioned possibility a reaction was performed with equimolar amounts of 4-chloro-3-formyl coumarin, *p*-methyl benzyl amine, and *o*-chlorobenzyl amine in one-pot. To 4-chloro-3-formyl coumarin in water, *p*-methyl benzyl amine and *o*-chlorobenzyl amine were added sequentially to generate benzazepine **4** (Scheme 2) with higher diversity as a single product.

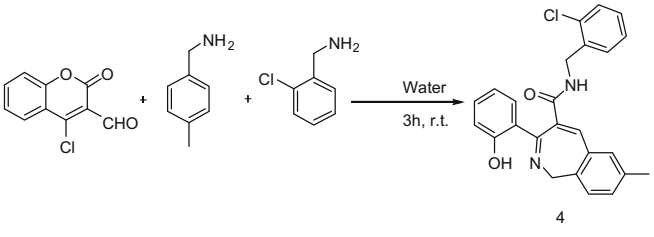
In summary, we have developed a novel and efficient route for the synthesis of 4,5-disubstituted-2-benzazepine scaffolds from readily available 4-chloro-3-formyl coumarin and benzyl amines in water. Moreover, the synthesis does not involve complicated work-up procedures and avoids the use of expensive organic solvents making the protocol highly attractive for greener technologies.

Table 1
Synthesis of 2-benzazepines **3a–k**



Entry	**2a–k**	Product[a]	Solvent	Time (h)	Yields[b] (%)
1	$R_1 = R_2 = H$, $R_3 = CH_3$	**3a**	H_2O	3	83
2	$R_1 = R_2 = H$, $R_3 = CH_3$	**3a**	CH_3OH	5	75
3	$R_1 = R_2 = H$, $R_3 = CH_3$	**3a**	C_2H_5OH	6	76
4	$R_1 = R_2 = H$, $R_3 = CH_3$	**3a**	CH_3CN	4	77
5	$R_1 = R_2 = H$, $R_3 = CH_3$	**3a**	CH_2Cl_2	10	25
6	$R_1 = R_2 = H$, $R_3 = CH_3$	**3a**	$CHCl_3$	10	35
7	$R_1 = R_2 = H$, $R_3 = OCH_3$	**3b**	H_2O	5	81
8	$R_1 = R_2 = H$, $R_3 = Cl$	**3c**	H_2O	3	89
9	$R_1 = R_2 = H$, $R_3 = F$	**3d**	H_2O	3	82
10	$R_1 = R_3 = H$, $R_2 = Cl$	**3e**	H_2O	3	90
11	$R_1 = CH_3$, $R_2 = R_3 = H$	**3f**	H_2O	5	84
12	$R_1 = R_3 = H$, $R_2 = CH_3$	**3g**	H_2O	3	82
13	$R_1 = R_2 = R_3 = H$	**3h**	H_2O	3	80
14	$R_1 = H$, $R_2 = R_3 = OCH_3$	**3i**	H_2O	6	85
15	$R_1 = R_2 = F$, $R_3 = H$	**3j**	H_2O	4	90
16	$R_1 = Cl$, $R_2 = R_3 = H$	**3k**	H_2O	3	92

[a] All the products were characterized by IR, NMR, and mass spectroscopy.
[b] Isolated yields after column chromatography.



Scheme 2. Synthesis of 2-benzazepine **4** by sequential method.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.04.020.

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23. *General synthetic procedure for 2-benzazepines* **3a**–**k**: A mixture of 4-chloro-3-formyl coumarin 1 (1.0 mmol) and substituted benzyl amines **2a**–**k** (2.0 mmol) was stirred in water (15 mL) at room temperature for 3–6 h as indicated in Table 1. After completion of the reaction, the solid products (**3a**–**k**) were filtered and washed with methanol.
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