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p-TsOH-promoted synthesis of (*E*)-6-phenyl-7-styryl-5,6-dihydrodibenzo[*b,h*][1,6]naphthyridines via cascade intramolecular aza-Michael addition/Friedlander condensation of 2'-aminochalcones in a SDS/H_2O system

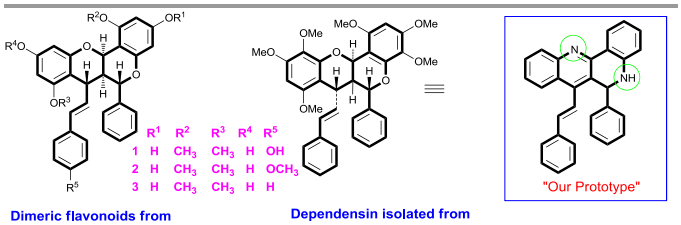
Makthala Ravi,[a‡] Parul Chauhan,[a‡] Shikha Singh,[a] Ruchir Kant [b] and Prem. P. Yadav*[a]

Brønsted acid-promoted cascade synthesis of novel (*E*)-6-phenyl-7-styryl-5,6-dihydrodibenzo[*b,h*][1,6]naphthyridines has been achieved via homodimerization of 2'-aminochalcones by employing sodium dodecylsulphate (SDS) as a surfactant in water. Besides water as environmentally benign reaction media, the reactions proceeds smoothly with high atom-economy under sequential one-pot protocol.

Bioactive natural products and natural product-inspired molecules have played a pivotal role in the drug discovery research.[1] The synthesis of natural and unnatural complex molecules generally involves a large number of synthetic steps using various hazardous organic solvents and reagents, apart from extraction and purification processes in each step. This leads to a large amount of waste that increases the overall cost. Designing cascade sequences to accomplish target-oriented syntheses of structurally complex natural products has remained a major challenge in the art of total synthesis.[2]

From the standpoint of green and sustainable approach, the development of synthetic processes for the construction of privileged scaffolds with high atom economy in water rather than organic solvents is eco-friendly and economical.[3] In addition, being an ideal green solvent, water can also accelerate organic reactions such as Michael additions, intramolecular cyclizations, rearrangements and nucleophilic substitutions due to its unique reactivity and selectivity at elevated temperature.[4] However, the use of aqueous reaction media is often limited due to the poor solubility of organic compounds in water. This can be overcome by the use of surfactants as solubilizing agents via a spontaneous aggregation in water to form a reactive micellar system having a hydrophobic core and hydrophilic corona.[5]

Dependensin, an antiplasmodial natural product isolated from *Uvaria dependens* and related antiparasitic dimeric flavonoids isolated from *Arrabidaea brachypoda* are densely functionalized fused benzopyranes bearing four stereocenters and one trans double bond (Scheme 1).[6] Additionally, 1,6-naphthyridines have been shown to be potent as HIV-1 integrase inhibitors,[7] anticancer[8] and antimalarial agents.[9] The extended benzenoid core of dibenzo[*b,h*][1,6]naphthyridine is also an important class of fluorophore and reported as DNA intercalating agents.[10] In view of the medicinal and fluorescent properties of 1,6-naphthyridines, the development of sustainable and green methodologies towards the synthesis of dibenzo[*b,h*][1,6]naphthyridines is highly desirable. Herein, for the first time, a new route for the synthesis of aza-analogues of dimeric flavonoids via Brønsted acid-promoted homodimerization of 2'-aminochalcones in an aqueous micellar (SDS/H_2O) system is reported.



Scheme 1 Dimeric flavonoids.

As a part of our ongoing efforts towards the development of ecofriendly methods for the synthesis of novel bioactive heterocycles,[11] we became interested in natural product inspired synthesis of (*E*)-6-phenyl-7-styryl-5,6-dihydrodibenzo[*b,h*][1,6]naphthyridines in a one-pot reaction under aqueous conditions. The reported method for the total synthesis of dependensin involved an acid-promoted ring opening of flavene to a stable benzyl carbocation, which upon further cyclization with another flavene molecule delivered the homodimerized compound (Scheme 2).[12] Based on the above analysis and literature reports for the cascade synthesis of

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† Electronic Supplementary Information (ESI) available: Experimental procedures, compound characterization, X-ray crystal structure data and ORTEP drawing for **4i** and **2s**; copies of NMR spectra of all the final compounds. For ESI and crystallographic data in CIF see DOI: 10.1039/b000000x/
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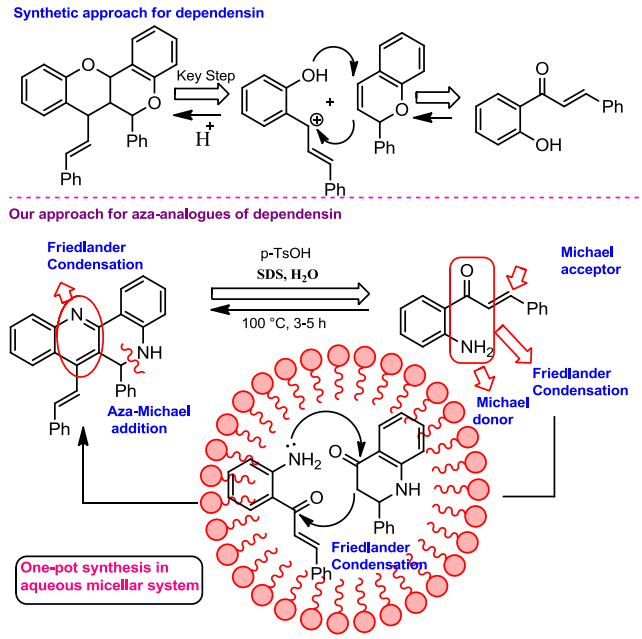
dibenzo[*b,h*][1,6]naphthyridines from a 2'-amino-substituted carbonyl precursor,[10,13] we speculated that 2'-aminochalcones may undergo homodimerization via an intramolecular aza-Michael addition in the presence of an acid to give aza-flavanone, which may subsequently react with another 2'-aminochalcone under the same acidic conditions to finally deliver the homodimerized product.



Scheme 2 Key analysis for acid-promoted homodimerized molecules.

To test this hypothesis initially, the starting material 2'-aminochalcone was synthesized from 2'-aminoacetophenone and benzaldehyde in the presence of base in ethanol.[14] The hypothesis was actualized when 2'-aminochalcone **1a** was treated with 3 equiv. of *p*-toluenesulfonic acid (*p*-TsOH) in EtOH at 80 °C for 4h. The reaction proceeded well to yield 76% of homodimerized product **2a** and 20% of aza-flavanone **3a** (Table 1, entry 1). However, 1 equivalent of *p*-toluenesulfonic acid in EtOH at 80 °C delivered the desired product **2a** in 68% yield (Table 1, entry 2). Based on the compatibility of Bronsted acids with aqueous solutions and the feasibility of cyclization reaction in water[15], the reaction was attemped in aqueous medium with 3 equiv of *p*-TsOH at 100 °C for 4h, which afforded homodimerized product **2a** in 64% yield (Table 1, entry 3). Delighted with this result, the reaction was performed with 1 equiv of *p*-TsOH, which drastically reduced the yield of **2a** to 10% (Table 1, entry 4), which may be due to the poor solubility of the substrate. To overcome the solubility issue and the possibility of dehydration reactions in the presence of surfactants,[16] the reaction with 20 mol% of sodium dodecyl sulfate (SDS) and 1 equiv. of *p*-TsOH in water was performed at 100 °C for 4h. The reaction proceeded smoothly and afforded 78% of homodimerized product **2a** and 20% of aza-flavanone **3a** (Table 1, entry 5), Decreasing the amount of SDS to 10 mol% and *p*-TsOH to 0.5 equiv. reduced the yield to 55% and 42%, respectively (Table 1, entries 6 and 7). It is noteworthy that the product can be obtained as precipitated solid without any further work up, however, column chromatography was required to achieve analytical purity. Next, the experiment was carried out at room temperature and 60 °C; no product formation was observed under either of these conditions (Table 1, entries 8 and 9). Encouraged by these results, a variety of Brønsted acids and Lewis acids were screened based on their ability to promote the Friedlander condensation[17,18] (Table 1, entries 10-16). Among the tested acids TfOH and $InCl_3$ provided homodimerized product **2a** in 60% and 67% yields respectively (Table 1, entries 13 and 15). However, *p*-TsOH produced the best yield of **2a** (Table 1, entry 5). Also, various anionic, non-ionic and cationic surfactants (see the SI, Table 1, entries 17-21) such as SLS, PF-127, Tween 80, Triton-X100 and TBAI were screened with varying results.

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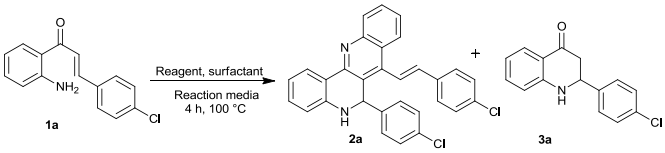
Table 1 Optimization of reaction conditions[a]



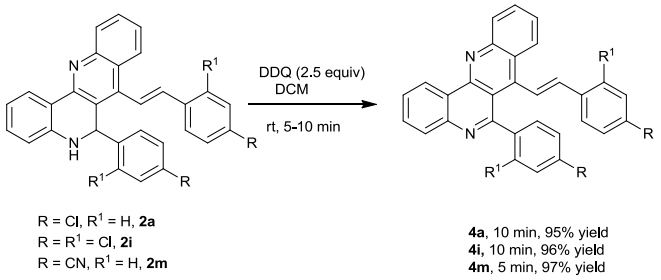
Entry	Reagent (equiv)	Surfactant SDS (20 mol%)	Reaction media	Yield[b] 2a	Yield[b] 3a
1[c]	*p*-TsOH (3)	-	Ethanol	76	20
2[c]	*p*-TsOH (1)	-	Ethanol	68	18
3	*p*-TsOH (3)	-	Water	64	24
4	*p*-TsOH (1)	-	Water	10	10
5	***p*-TsOH (1)**	**SDS**	**Water**	**78**	**20**
6[d]	*p*-TsOH (1)	SDS	Water	55	18
7	p-TsOH (0.5)	SDS	Water	42	24
8[e]	*p*-TsOH (1)	SDS	Water	-	15
9[f]	*p*-TsOH (1)	SDS	Water	-	17
10	TFA (1)	SDS	Water	20	30
11	AcOH (1)	SDS	Water	-	25
12	$MeSO_3H$ (1)	SDS	Water	52	35
13	TfOH (1)	SDS	Water	60	33
14	$FeCl_3$ (1)	SDS	Water	46	20
15	$InCl_3$ (1)	SDS	Water	67	25
16	I_2 (1)	SDS	Water	15	51

[a]Reaction conditions: **1a** (1.0 mmol), reagent (1.0 mmol), surfactant (20 mol%), reaction media (10 mL) at 100 °C. [b]Isolated yields, [c]At 80 °C, [d]10 mol% of SDS was used. [e]At room temperature. [f]At 60 °C.

Among the screened surfactants (see the SI, Table 1, entries 17 and 20), only SLS and Triton-X100 provided >70% yield of homodimerized product **2a** and other surfactants did not provide a satisfactory result in comparison to SDS (Table 1, entries 17-21 vs entry 5, see the supporting Information). Further solvent optimization with protic solvents such as methanol and isopropanol delivered the homodimerized product **2a** in 60% and 30% yields respectively (Table 1, entries 22 and 23, see the supporting Information), however, aprotic solvents such as acetonitrile and toluene were ineffective for homodimerization, but produced aza-flavanone 3a exclusively (Table 1, entries 24 and 25, see the supporting information).

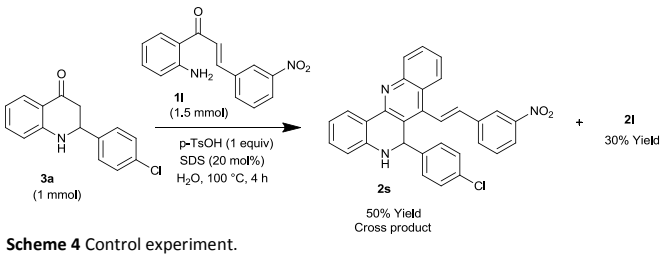
Using optimized reaction conditions, the scope and generality were further investigated. The reactions of 2'-aminochalcones bearing electron withdrawing groups such as chloro, bromo, fluoro, 2,4-dichloro, 3,4-dichloro, 2,5-dibromo, nitro and cyano, afforded the corresponding homodimerized products in moderate to good yields (Table 2, products **2a-2n**). 2'-Aminochalcones bearing electron donating groups such as methyl and methoxy on the phenyl ring and furyl substituted 2'-aminochalcone produced homodimerized products, albeit in low yields (Table 2, products **2p-2r**). The lower yields in cases with electron donating groups may result from a decrease in the electrophilicity at the carbonyl carbon, which is unfavourable for the Friedlander condensation.

The synthesized (*E*)-6-phenyl-7-styryl-5,6-dihydrodibenzo[*b,h*][1,6]naphthyridines were further oxidized to (*E*)-6-phenyl-7-styryldibenzo[*b,h*][1,6]naphthyridines in the presence of DDQ in DCM for 5-10 min at room temperature. The reaction proceeded smoothly and provided excellent yields of the corresponding oxidized products (Scheme 3). The structure of oxidized product **4i** was unambiguously confirmed by X-ray analysis (CCDC 1025096, see the SI).



Scheme 3 Oxidation of homodimerized compounds.

To prove that the exact mechanism involved aza-flavanone formation followed by Friedlander condensation, an experiment was conducted with aza-flavanone (**3a**) and 2'-aminochalcone **1l** under the optimized conditions. The reaction afforded desired Friedlander condensation product **2s** in 50% yield along with 30% of the homodimerized product **2l** (Scheme 4). The structure of **2s** was unambiguously confirmed by X-ray analysis (CCDC 1058218, see the SI).



Scheme 4 Control experiment.

Table 2 Scope of homodimerization of 2'-aminochalcones[a]

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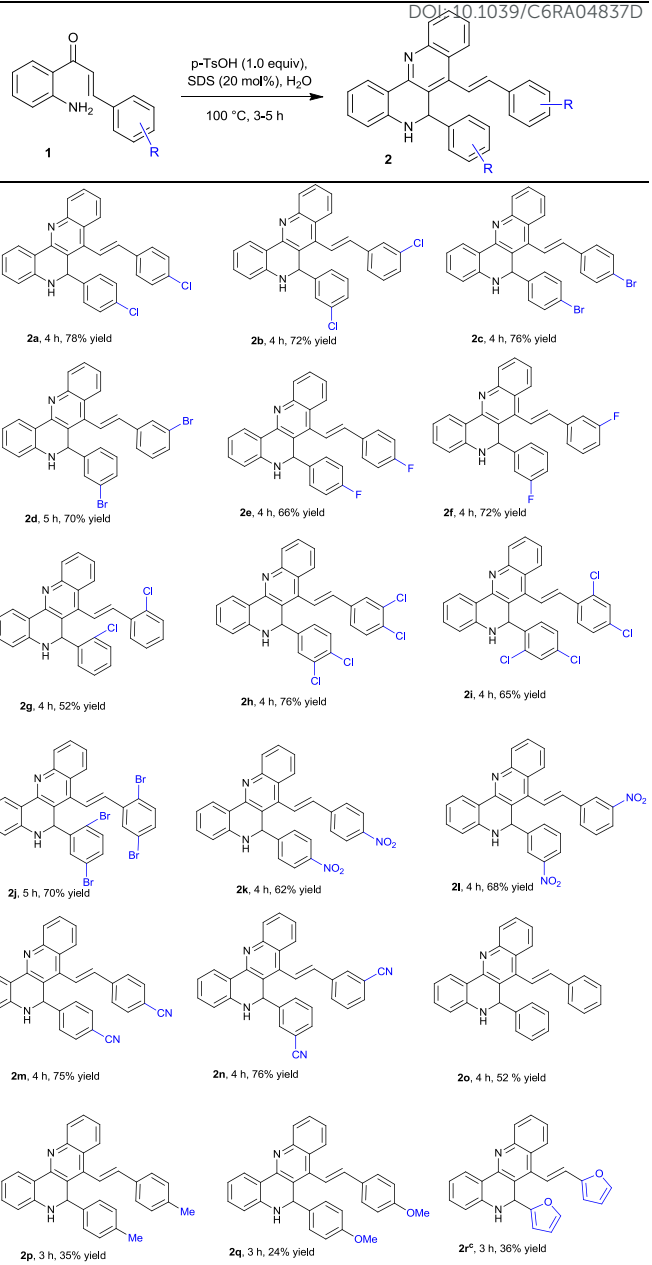
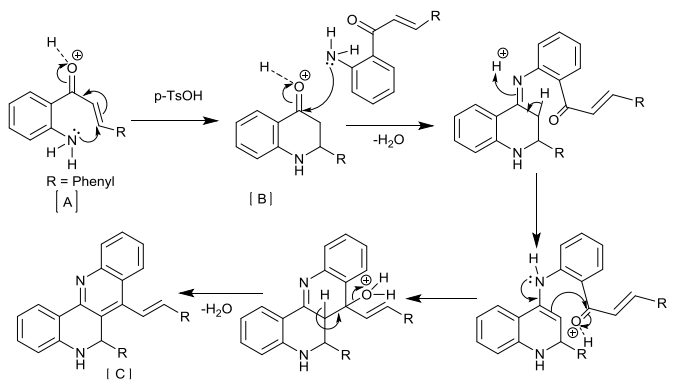


[a]Reaction conditions: **1** (1.0 mmol), *p*-TsOH (1.0 mmol), SDS (0.2 mmol), H_2O (10 mL) at 100 °C, time and isolated yields are given, [c] (*E*)-1-(2-aminophenyl)-3-(furan-2-yl)prop-2-en-1-one was used.

Based on our experimental results and literature reports,[17,18] we proposed a plausible mechanism for homodimerization as shown in (scheme 5). 2'-Aminochalcone [**A**] undergoes an intramolecular aza-Michael addition in the presence of acid to form aza-flavanone [**B**], which subsequently reacts with another molecule of 2'-aminochalcone in the presence of acid via a Friedlander condensation to afford homodimerized product [**C**].



Scheme 5 Plausible mechanism.

In conclusion, we have developed an efficient and straightforward methodology for the synthesis of (*E*)-6-phenyl-7-styryl-5,6-dihydrodibenzo[*b,h*][1,6]naphthyridines in aqueous media by using SDS as a surfactant with good yields. This methodology offered a sequential one-pot synthetic operation with high atom economy, under greener conditions, using water as the medium and no workup with organic solvent. Application of the present methodology towards exploration of unique cascade sequences is under progress.

Acknowledgements

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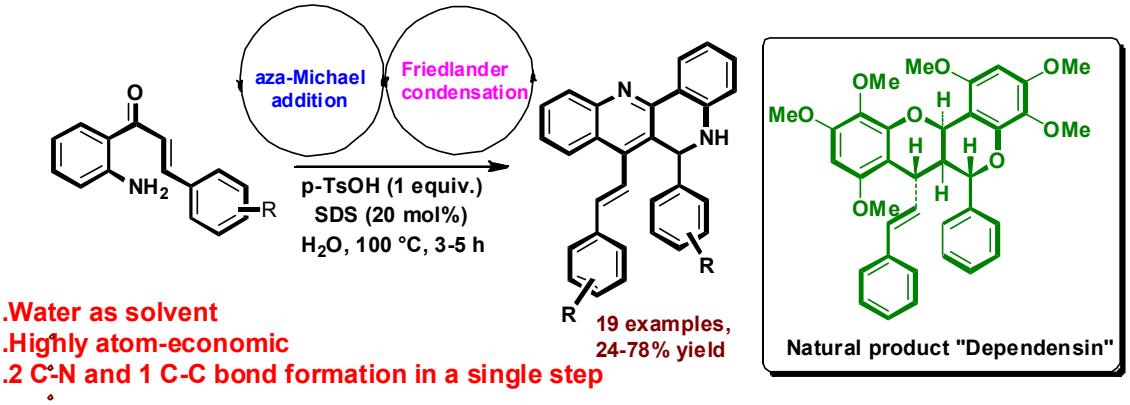

p-TsOH-promoted one-pot cascade synthesis of novel (*E*)-6-phenyl-7-styryl-5,6-dihydrodibenzo[*b,h*][1,6]naphthyridines via homodimerization of 2'-aminochalcones has been developed in a SDS/H_2O system.