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$BF_3{\cdot}Et_2O$ mediated one-step synthesis of *N*-substituted-1,2-dihydropyridines, indenopyridines and 5,6-dihydroisoquinolines†

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A simple and efficient one-pot synthesis of *N*-substituted-1,2-dihydropyridines, indenopyridines and 5,6-dihydroisoquinolines by a $BF_3{\cdot}Et_2O$ mediated novel methodology, from easily available α,β-unsaturated ketones/arylidene ketones, phenyl acetylenes and substituted nitriles, has been described. This novel annulation provides quick access to complex polycyclic frameworks with an excellent substrate scope.

As an important class of nitrogen-containing heterocycles, pyridines and isoquinolines represent ubiquitous structural motifs that occur in natural products and pharmaceutically active molecules.[1] In particular, fused pyridines and isoquinolines are of high pharmaceutical relevance.[2] For instance, dopamine receptor agonists like glaucine and apomorphine are clinically active drug candidates which are explored against bronchitis, inflammation, and Alzheimer's and Parkinson's disease respectively.[3] ARC 111 (Topovale) is presently under clinical trials as a topoisomerase I targeting antitumor drug (Fig. 1).[4] Harmaline and lavendamycin belong to fused-pyridine alkaloids which were investigated for central nervous system stimulation and antitumor and antibiotic effects, respectively.[5] Azafluorenone derivatives such as dielsine (Fig. 1), dielsinol, onychnine, dielsiquinone, *etc*. were employed as important building blocks in the synthesis of many bioactive natural products.[6] Therefore, novel synthetic pathways leading to the highly functionalized isoquinoline and pyridine derivatives continue to be the targets of extensive synthetic interest.

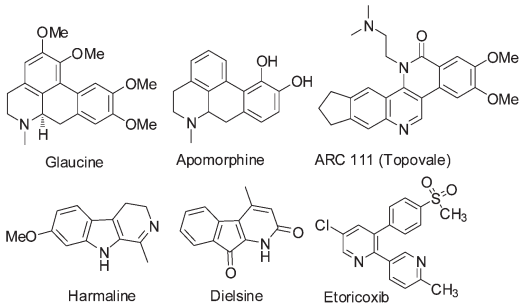

Fig. 1 Selected bioactives with isoquinoline and pyridine motifs.

Numerous synthetic methods have been reported for the preparation of functionalized pyridines and isoquinolines.[7] Most of these methods were reported with Lewis acid catalyzed tandem nucleophilic additions or cyclisation of *ortho*-alkynylaldimines. Carbophilic Lewis acids like $In(OTf)_3$, $AgNTf_2$, $Au(PPh)_3$ and AgOTf were used as catalysts in such methods.[8] Among these reactions, a selected few reports exist, utilizing *ortho*-alkynylaldehydes, amines and nucleophiles using Lewis acid catalysts.[9] Castillo *et al.* reported an aza-Diels–Alder reaction of benzyne with an imine to afford the corresponding dihydroisoquinoline.[10] In 2014, Enders *et al.* reported the asymmetric synthesis of tetrahydropyridines *via* an organocatalytic one-pot multicomponent domino reaction.[7a] Despite considerable advancement made in this field, the existing methods often require the use of expensive metal catalysts, ligands or starting materials that are not readily available and in some cases require multi-step procedures. Therefore, novel synthetic approaches to the functionalized pyridines and dihydroisoquinolines, with simple substrates, inexpensive catalysts, utilizing mild conditions are highly desirable.

In continuation of our efforts to develop new synthetic protocols for heterocyclic frameworks and valuable polycyclic building blocks,[11] herein, we report the $BF_3{\cdot}Et_2O$ mediated domino synthesis of *N*-substituted-1,2-dihydropyridines, indenopyridines and 5,6-dihydroisoquinolines from α,β-unsaturated

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†Electronic supplementary information (ESI) available: Experimental procedures, optimization table, ^1H and ^{13}C NMR spectra of all new compounds (PDF), X-ray crystal structure data for **3b** (CIF), X-ray crystal structure data for **7a** (CIF). CCDC 1452927 and 1452906. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c6ob02133f

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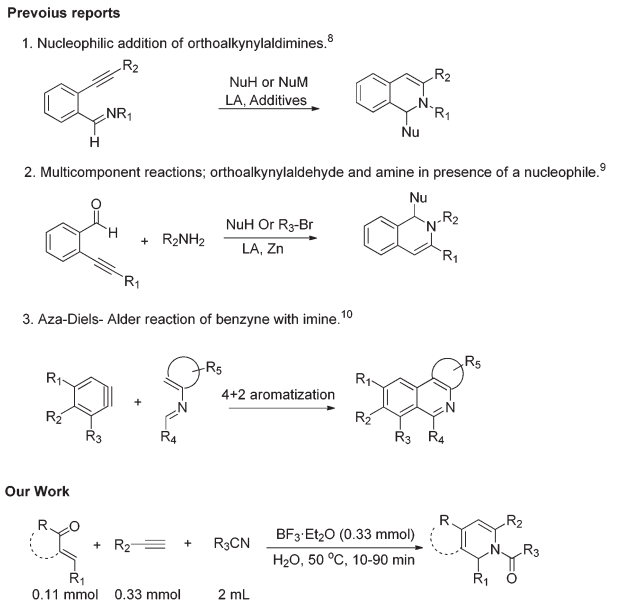
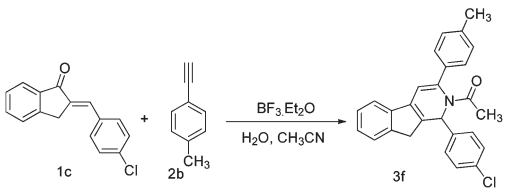
ketones/arylidene ketones, phenyl acetylenes and substituted nitriles in one-pot (Scheme 1).

At the outset, the model reaction of 2-(4-chlorobenzylidene)-2,3-dihydroindenone (**1c**) and 4-methyl phenylacetylene (**2b**) was conducted in the presence of $BF_3{\cdot}Et_2O$ (1.0 equiv.) in CH_3CN at room temperature (Table 1) in an effort to synthesize indenopyrans. The desired product was not observed, however, to our delight an unexpected product having the same R_f as **1c** was observed, and isolated to give the unexpected *N*-acetylated indenopyridine (**3f**) in trace amounts. Encouraged by this serendipitous result, we screened various reaction parameters to optimize the reaction conditions (see the ESI†). The effect of solvents was tested by using CH_3CN (2.0 equiv.) with toluene, THF, DMF, DCE, DCM, *etc*. However, none of them gave a desired product. We have also investigated the reaction using different Lewis acids like $Sc(OTf)_3$, $Zn(OTf)_3$, $Cu(OTf)_3$, and $La(OTf)_3$, and Brønsted acids like TFA, benzoic acid, and phenylboronic acid, but the reaction did not afford the expected product. Additives such as gold catalysts, I_2, CuI, *etc*. could not offer any significant improvement in the yields. Encouraging results were observed when the reaction was conducted at an elevated temperature of 50 °C, hence, 50 °C is found to be the optimized temperature for the reaction. Furthermore, we have observed that the product formation is suppressed when the reaction is conducted using molecular sieves, or under dry conditions, indicating the role of water in the reaction. Hence, in an effort to quantify the amount of water, the requirement of 2.0 equiv. of water for the desired product was also confirmed (see the ESI†). Attempts by varying the loading of $BF_3{\cdot}Et_2O$ and phenyl acetylene were made, and the results indicated that in the presence of 3.0 equiv. of $BF_3{\cdot}Et_2O$ and phenyl acetylene the reaction could furnish **3f** in 78% yield (Table 1, entry 7). Therefore, entry 7 is finalized as the optimized conditions for demonstrating the generality of the reaction.



Scheme 1 One-pot approach for *N*-substituted-1,2-dihydropyridines, indenopyridines and 5,6-dihydroisoquinolines.

Table 1 Optimization of substrates and catalyst[a]



Entry	**1c** (equiv.)	**2b** (equiv.)	$BF_3{\cdot}Et_2O$ (equiv.)	**3f**[b] (yield%)
1	1	1	1	20
2	1	2	1	32
3	1	3	1	42
4	1	3	0.3	14
5	1	3	0.5	22
6	1	3	2	51
7	1	3	3	78

[a] Unless otherwise specified, all of the reactions were carried out at 50 °C, **1c** (0.11 mmol), H_2O (0.22 mmol) in 2 mL of CH_3CN. [b] Isolated yield.

All the new compounds were characterized by various spectroscopic techniques like ^1H NMR, ^{13}C NMR, and HRMS analysis (see the ESI†) and finally the structures were unambiguously confirmed by single-crystal X-ray analysis (Fig. 2).[12] With the confirmation of new structures, we investigated the scope of the reaction using various substituted 2-arylidene-2,3-dihydroindenones and phenylacetylenes and the representative results are summarized in Scheme 2. Interestingly, furan, thiophene and naphthyl substituted arylidene ketones also afforded the annulated products in moderate yields (**3j–3q**).

To further demonstrate the versatility of this process, reactions between various substituted 2-arylidene-3,4-dihydronaphthalenone (**4**) and substituted phenyl acetylenes (**2**) in CH_3CN in the presence of $BF_3{\cdot}Et_2O$ have furnished fused *N*-acetylated 5,6-dihydroisoquinolines (**5**) (Scheme 3) in good to moderate yields. *N*-Acetylated 5,6-dihydroisoquinoline (**5k**) was obtained when the reaction was extended to 2-benzylidene cyclohexanone with phenylacetylene (**2a**) (Scheme 3). Subsequently, the uniqueness of the annulations was further examined by engaging α,β-unsaturated ketones (**6**) and phenylacetylenes (**2**) to afford 2,4,6-trisubstituted 1,2-dihydropyridines (Scheme 4). Gratifyingly, it was observed that the reaction proceeded efficiently with α,β-unsaturated ketones bearing electron donating or electron withdrawing substituents.

Fig. 2 Single-crystal X-ray structures for **3b** and **7a**.

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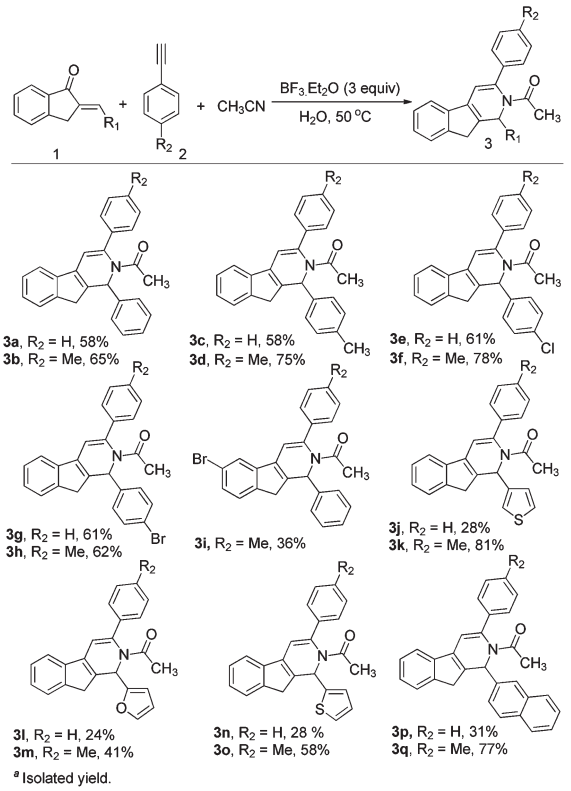
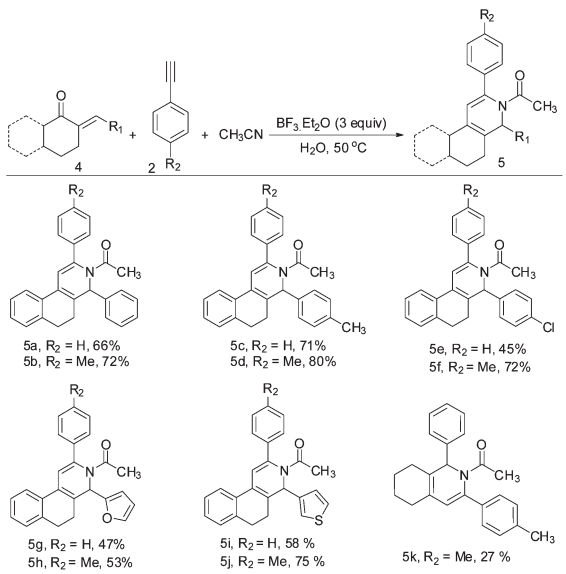
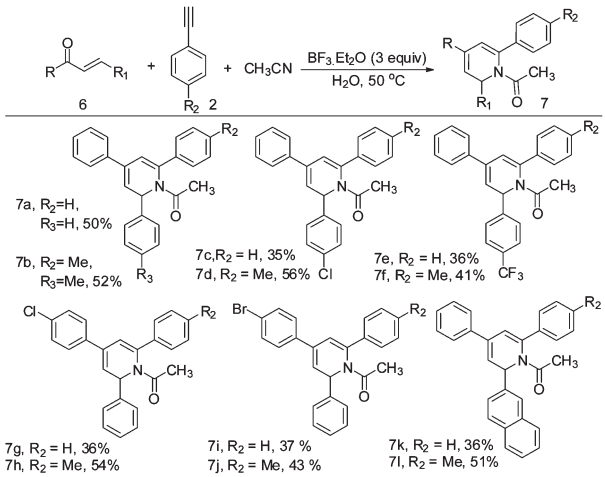


Scheme 2 Scope of the reaction for *N*-acetylated indenopyridines.[a]

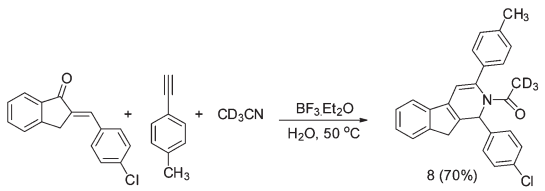


Scheme 3 One-pot access for *N*-acetylated dihydro-isoquinolines.

In order to confirm the role of acetonitrile in *N*-acetylation, the experiment was performed in CD_3CN. As expected, we were pleased to observe the deuterated *N*-acetylated indenopyridine in 70% yield (Scheme 5).



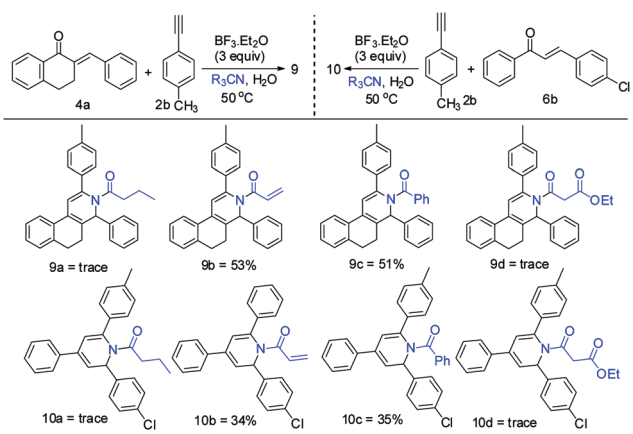
Scheme 4 One-pot approach for trisubstituted *N*-acetylated 1,2 dihydropyridines.



Scheme 5 Control experiment with CD_3CN.

In the light of successful *N*-acetylation of pyridines and isoquinolines, we envisioned the synthesis of their amido derivatives with various nitriles (Scheme 6). Interestingly, the reaction worked well with benzonitrile and acrylonitrile to yield the corresponding amido derivatives in good yield. Even though the expected products were formed, by-products dominated the reaction with butyronitrile and ethyl cyanoacetate.

Based on the aforementioned experimental results, a plausible mechanistic pathway is outlined in Scheme 7. Since $BF_3{\cdot}OEt_2$ is oxophilic, it coordinates to the carbonyl oxygen



Scheme 6 Scope of nitriles.

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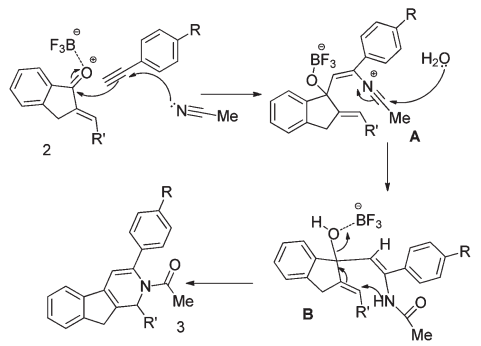
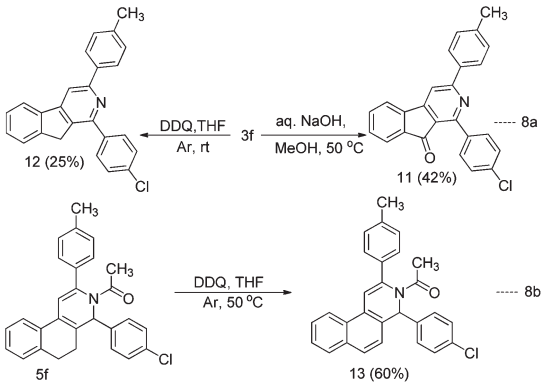


Scheme 7 Plausible mechanistic pathway.

making 1,2 addition of phenylacetylene to the arylidene ketones favourable, resulting in successive addition of acetonitrile to phenyl acetylene. Intermediate **B** is formed by the hydrolysis of the nitrile group on intermediate **A**, under acidic conditions. Subsequent intramolecular Michael addition or cyclization of amide nitrogen affords product **3**.

The synthetic utility of products **3** and **5** were also demonstrated by further diversification of some selected compounds (Scheme 8). An attempt towards the deacetylation of **3f** to the corresponding dihydroindenopyridine using NaOH in methanol resulted in the aromatization and oxidation of the methylene carbon to afford indenopyridinone **11** in a moderate yield (Scheme 8a).[13] However, oxidation of **3f** using DDQ afforded the corresponding indenopyridine **12** (Scheme 8a). In contrast, when **5f** was subjected to DDQ mediated oxidative conditions, the corresponding *N*-acetylated benzo[*f*]isoquinoline (**13**) was formed (Scheme 8b).

In conclusion, we have disclosed a novel strategy for the synthesis of functionalised *N*-substituted-1,2-dihydropyridines, indenopyridines, and 5,6-dihydroisoquinolines from readily available simple substrates. The synthetic utility of the products has led to azafluorenone derivatives. These potentially bioactive derivatives could be easily transformed into polycyclic building blocks that are difficult to access from traditional methods. The protocol offers mild conditions, short reaction time, and convenient one-pot operation, without dry solvents or an inert atmosphere. Further experiments based on other α,β-unsaturated ketones are in progress.



Scheme 8 Synthetic utility of products **3f** & **5f**.

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