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Atom economy
One-pot Multicomponent reaction

ABSTRACT

A novel series of functionalized 13*H*-benzo[*f*]chromeno[4,3-*b*][1,7]naphthyridines and 1,3-diphenylbenzo[*f*][1,7]naphthyridines have been synthesized by an efficient regioselective one-pot multicomponent synthesis through intra and intermolecular imino Diels-Alder reaction. In this method, we have achieved complete regioselectivity and atom economy with polysubstituted core motifs in moderate to good yields. The proposed mechanism of this reaction has also discussed.

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Introduction

In cancer chemotherapy, topoisomerase I has been identified as most important target by many researchers following to the discovery of plant alkaloid *camptothecin* and its analogues in 1966.[1] The camptothecins such as topotecan,[2a,b] irinotecan[2c] and belotecan[2d] were only chemical class of TopI inhibitors approved for clinical use, albeit *camptothecin* efficiency and applications have been hindered by many factors.[2] In that process many synthetic analogues such as indenoquinolines have emerged as alternatives for camptothecin (Scheme 1).[3] In the continuous and extensive research efforts by many researchers result the modification of A, B, and D rings of the indenoisoquinoline (Scheme 1), in particular the 5-membered C-ring of the indenoisoquinoline system was replaced by six-membered nitrogen heterocyclic rings, ensued the dibenzo[*c*,*h*][1,6]naphthyridines (Scheme 1) with potent *in vitro* anticancer activity and topoisomerase I inhibition.[4] As we know among all heterocyclic systems, naphthyridine and its derivatives have attracted increasing attention due to its pharmacophore with broad spectrum of potent biological aspects (Fig 1).[5] Although for the construction of the subjected core motifs require multistep methods.[4b, 6]

Recently, Michel *et al*.,[6a] designed a multistep protocol for the development of new benzo[*b*]chromeno[6,5-*g*][1,8]naphthyridin-7-ones and benzo[*b*]chromeno[7,6-*g*][1,8]-naphthyridin-6-ones as anticancer agents. Chen, W-L *et al*.,[6b] also synthesized the

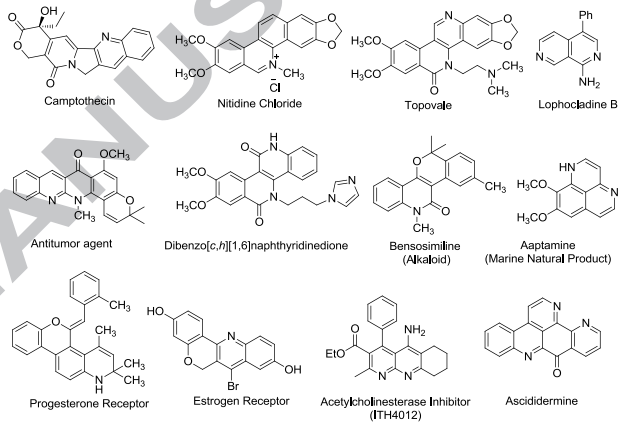


Figure 1. Representative examples of biologically important naphthyridines

benzo[*f*][1,7]naphthyridines as one of their substrates by hydride- induced anionic cyclization. Over the years, our group actively engaged in the development of novel classes of heterocyclic systems with potential biological applications.[7] As a result in this report, we wish to describe an efficient regioselective one-pot synthetic method for novel series of 13*H*-benzo[*f*]chromeno[4,3-*b*][1,7]naphthyridines and 1,3-diphenylbenzo[*f*][1,7]naphthyridines by hetero Diels-Alder reaction with internal and external acetylenic dienophiles under mild reaction conditions. Hetero Diels-Alder (HDA) reactions are one of the most mainstays of heterocycles, natural and non-natural product synthesis.[8] Among HDAs, imino Diels-Alder

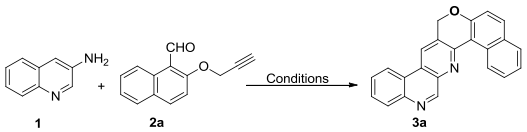
Scheme 1. Representation of research objective

reactions provide a useful platform for the insertion of nitrogen or oxygen atoms in the ring structures result the construction of biologically and pharmaceutically functionalized heterocycles with regio-, diastereo- and enantio-selectivity.[9]

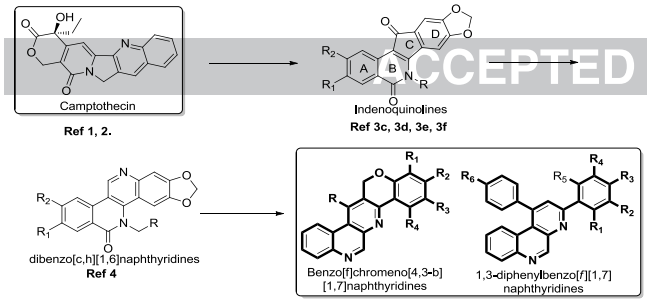
Results and discussions

Our study was instigated with the optimization of reaction condition for the construction of novel 13*H*-benzo[*f*]chromeno[4,3-*b*][1,7]naphthyridines (For full optimization table 1 see in supporting information). In an initial experiment, we treated 3-aminoquinoline **1**, and **2a** with 20 mol% $BF_3.Et_2O$ in CH_3CN solvent at reflux temperature which was failed to afford desired product (entry 1, Table 1). We also tested different Lewis acid catalysts in DCM and CH_3CN

Table 1. Optimization of reaction conditions



No	Catalyst	Solvent	Temp(^{o}C)	Time (h)	Yield (%)[a]
1	$BF_3.Et_2O$ (20 mol%)	MeCN	Reflux	24	N.R
2	CF_3COOH (20 mol%)	MeCN	Reflux	24	N.R
3	CuI (20 mol%)	MeCN	Reflux	48	N.R
4	$Sc(OTf)_3$ (20 mol%)	MeCN	Reflux	24	N.R
5	$InBr_3$ (20 mol%)	MeCN	Reflux	24	N.R

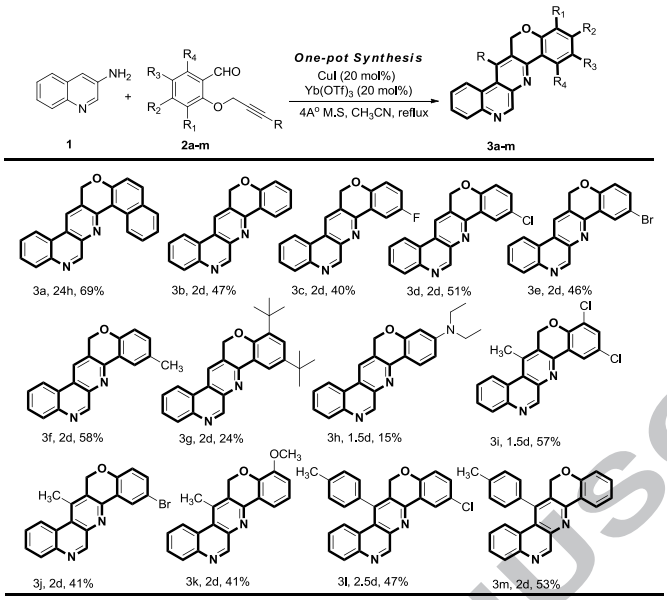


6	SnF_2 (0.2 eq.)	DCM	RT	48	N.R
7	I_2 (0.2 eq.)	DCM	Reflux	24	N.R
8	CuI (10 mol%) /$BF_3.Et_2O$ (20 mol%)	MeCN	Reflux	24	N.R
9	CuI (10 mol%)/$InBr_3$ (10 mol%)/4A^o M.S	MeCN	Reflux	24	10
10	CuI (10 mol%)/$Yb(OTf)_3$ (10 mol%) /4A^o M.S	MeCN	Reflux	24	42
11	**CuI (20 mol%)/$Yb(OTf)_3$ (20 mol%) /4A^o M.S**	**MeCN**	**Reflux**	**24**	**69**[b]
12	CuI (20 mol%)/$Sc(OTf)_3$ (20 mol%) /4A^o M.S	MeCN	Reflux	48	38
13	CuI (20 mol%)/$La(OTf)_3$ (20 mol%) /4A^o M.S	MeCN	Reflux	48	51
14	CuI (20 mol%)/$Yb(OTf)_3$ (20 mol%)	Toluene	Reflux	48	47[c]
15	CuI (20 mol%)/$Yb(OTf)_3$ (20 mol%)	DCM	Reflux	48	20[c]
16	CuI (20 mol%)/$Yb(OTf)_3$ (20 mol%)	1,4-dioxane	Reflux	48	17[c]
17	CuI (20 mol%)/$Yb(OTf)_3$ (20 mol%)	DCE	Reflux	48	22[c]
18	CuI (20 mol%)/$Yb(OTf)_3$ (20 mol%)	DMF	110	48	N.R[d]

[a]Refers to column purified products and yields were calculated relative to **2a**. [b]Reaction conditions: **1** (0.693 mmol; 1.0 equiv), **2a** (0.346 mmol; 0.5 equiv), 5-10 mL of solvents used in all entries except entries 15-18, where 1.0 mL of Ionic liquids were used; M.S = Molecular Sieves. [c]NMR Yield (TCE as internal standard; TCE = 1,1,2,2-Tetrachloroethane) Optimized reaction conditions shown in bold. [d]N.R = No Reaction.

solvents, which have been proven in a catalytic amount to activate imines in cycloaddition reactions[10] but were, failed to provide the desired product (entries 3-7). As Bota *et al*[11a] and Corey *et al*[11b] introduced copper in Diels-Alder reactions; we also attempted copper use in our screening conditions as shown in table 1. Interestingly, in the combination of CuI, $InBr_3$ and 4A^o Molecular sieves in CH_3CN solvent provided the desired product in 10% yield (entry 9, Table 1). This one-pot reaction condition prompted us to investigate further the reaction in various Lewis acid catalysts and solvents. As anticipated by altering the Lewis acid to $Yb(OTf)_3$ (10 mol%) provided the desired product in 42% yield (entry 10, Table 1). Gratifyingly, when we attempted 20 mol% CuI, 20 mol% $Yb(OTf)_3$, in CH_3CN solvent at reflux temperature with 4A^o Molecular sieves as additive in one-pot provided the desired intramolecular Imino Diels-Alder product in good yield (69%, entry 11, Table 1). In ^{1}H NMR spectrum of **3a**, two singlets at δ 9.64 ppm, 8.65 ppm and unexpected doublet at δ 9.65 ppm were observed and following careful analysis of COSY spectrum (Supporting Information), we identified the cyclization occurred through the fourth position of 3-aminoquinoline ring rather than second position. We also tried with different copper salts but CuI found to be the best choice. To improve the yield, we examined different solvents such as Toluene, DCM, DMF, DMSO, Dioxane, and DCE including ionic liquids with different transition metal triflates (See Table 1in supporting information). Nevertheless, the yield of the desired product was not improved. However, we preferred $Yb(OTf)_3$ for further optimization since it owns some advantages such as eco-friendly nature, inexpensive, nontoxic and it has also been used as a catalyst in many organic transformations.[12] After the different screening results, the optimized one-pot reaction condition found to involve 20 mol% CuI, 20 mol% $Yb(OTf)_3$, 0.5 equiv. of 4A^o Molecular sieves in 5-10 mL of CH_3CN at reflux temperature afford the desired intramolecular Imino Diels-Alder product. Having the reaction condition in hand, the substrate scope of this reaction with different *O*-propargyl salicylaldehydes (**2a-m**) in one-pot were successfully employed with 3-aminoquinoline through an intra-

Table 2. Substrate scope for intramolecular one-pot [4+2] cycloaddition reaction[e]

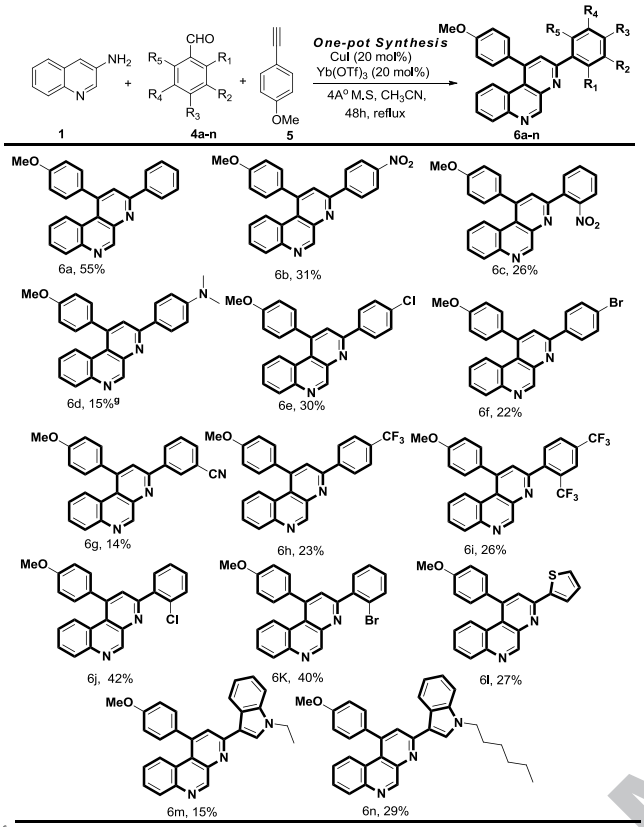


[e]Reaction conditions: **1** (0.693 mmol; 1.0 equiv), **2a-m** (0.5 equiv), 20 mol% CuI, 20 mol% $Yb(OTf)_3$, 4A^o Molecular Sieves (0.5 equiv.), 5-10 mL of CH_3CN at reflux temperature

molecular imino Diels-Alder reaction to produce the corresponding 13*H*-benzo[*f*]chromeno[4,3-*b*][1,7]naphthyridines (**3a-m**) as shown in table 2.

The literature reports disclosed the naphthyridine[4, 5] and chroman[13] core motifs independently exhibit most significant medicinal values and also found in numerous natural products as well as in therapeutics. This intramolecular imino Diels-Alder reaction could provide a value route to the fusion of these core motifs resulting the 13*H*-benzo[*f*]chromeno[4,3-*b*][1,7]naphthyridines (**3a-m**). Various substitution patterns at R_1, R_2, R_3, R_4 as well as R were well tolerated in the reaction condition (Table 2). When we introduced R = Aryl, Methyl substitutions (internal alkynes) slightly improved the yields of the reaction. This Imino Diels-alder reaction impartially affects by the electron donating groups at R_2 position (**3h**) and bulky groups at R_1, R_3 positions (**3g**). Overall, this intramolecular imino Diels-Alder reaction provided moderate to good yields of **3a-m** as shown in Table 2. Having optimized catalyst system in hand, next we turned our attention towards multicomponent intermolecular imino Diels-Alder reaction by varying aromatic and hetero aromatic aldehydes with external acetylenic dienophiles provided 1,3-diphenylbenzo[*f*][1,7]naphthyridines (**6a-n**) as shown in Table 3.

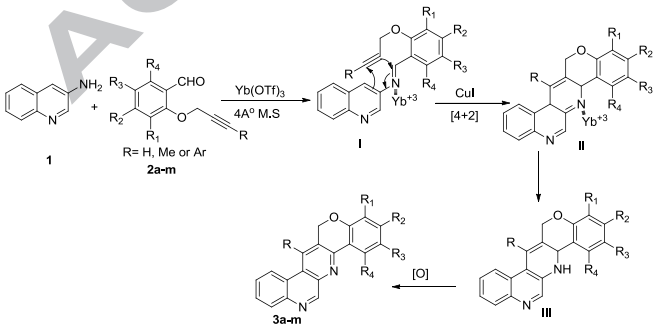
Table 3. Substrate scope for intermolecular one-pot [4+2] cycloaddition reaction[f]



[f]Reaction conditions: **1** (0.693 mmol; 1.0 equiv), **4a-k** (0.4 equiv), **5** (0.8 equiv.) 20 mol% CuI, 20 mol% $Yb(OTf)_3$, 4A° Molecular Sieves (0.5 equiv.), 5-10 mL of CH_3CN at reflux temperature. [g]**6d** reaction yield ~70% but isolated yield 15%.

In this intermolecular imino Diels-Alder reaction condition found to involve 1.0 equiv of 3-aminoquinoline, 0.4 equiv. of aromatic or heteroaromatic aldehydes (**4a-k**), 0.8 equiv. of **5**, 20 mol% CuI, 20 mol% $Yb(OTf)_3$, 0.5 equiv. of 4A° Molecular sieves in 5-10 mL of CH_3CN at reflux temperature afforded the 1,3-diphenylbenzo[*f*][1,7]naphthyridines (**6a-n**) in moderate yields. In the substrate scope expansion, we tried different substitution pattern at R_1, R_2, R_3, R_4 and R_5 positions; when we tried, any electron withdrawing groups at R_2, R_3 position of aldehydes greatly influence the yield of products (**6g**, **6h**, **6i**). However, electron-donating group at R_3 position provided relatively good reaction yield but in the case of **6d**, which is, not stable enough to isolate. When we attempted heteroaromatic aldehydes (**6l**, **6m**, **6n**) in this reaction, observed complete imine formation but subsequent to [4+2] cycloaddition reaction provided low yields which is due to steric hindrance between bulky substituted imine and electron rich phenyl acetylenic dienophile. Based on the literature reports,[14] we have depicted the plausible reaction mechanism of CuI/$Yb(OTf)_3$ catalyzed intramolecular Imino Diels-Alder reaction in Scheme 2.

To explain the mechanism, in the first step the imine (**I**) formed from 3-aminoquinoline (**1**) and *O*-propargylated salicylaldehydes (**2a-m**) in presence of $Yb(OTf)_3$ and then which is involved in [4+2] cycloaddition reaction in presence of CuI produces **II** and it isomerizes to **III** which is further oxidized by



Scheme 2. Plausible mechanism for the synthesis of **3a-m**.

air to afford the final aromatized 13*H*-benzo[*f*]chromeno[4,3-*b*][1,7]naphthyridines (**3a-m**).

In conclusion, we have developed a simple and efficient one-pot method for the synthesis of novel functionalized 13*H*-benzo[*f*]chromeno[4,3-*b*][1,7]naphthyridines (**3a-m**) and 1,3-diphenylbenzo[*f*][1,7]naphthyridines (**6a-n**) in moderate to good

yields. In this method, we have achieved complete regioselctivity in both intramolecular and intermolecular cyclizations by using $CuI/Yb(OTf)_3$ catalyst system in CH_3CN solvent at reflux temperature. This method has the advantages of easy availability, flexibility of starting materials, and it is one of the best examples for an atom-economy and one-pot multicomponent reaction. The synthesized derivatives also exhibiting most significant biological activities and their related studies under progress, which will be reported shortly.

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Supplementary Material

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office.

Highlights:

- One-pot multi-component synthetic methodology for novel scaffolds was developed.
- It is an atom-economy reaction affording poly-substituted napthyridine core motifs.
- This imino diels-alder reaction allows broad substrate scope.
- We have achieved complete regioselectivity with inexpensive catalytic system.
- Unusual plausible reaction mechanism has also been discussed.

Graphical Abstract

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A facile one-pot regioselective synthesis of functionalized novel benzo[*f*]chromeno[4,3-*b*][1,7]naphthyridines and benzo[*f*] [1,7]naphthyridines *via* an Imino Diels-Alder reaction

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