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Organocatalytic Modified Guareschi−Thorpe Type Regioselective Synthesis: A Unified Direct Access to 5,6,7,8-Tetrahydroquinolines and Other Alicyclic[*b*]-Fused Pyridines

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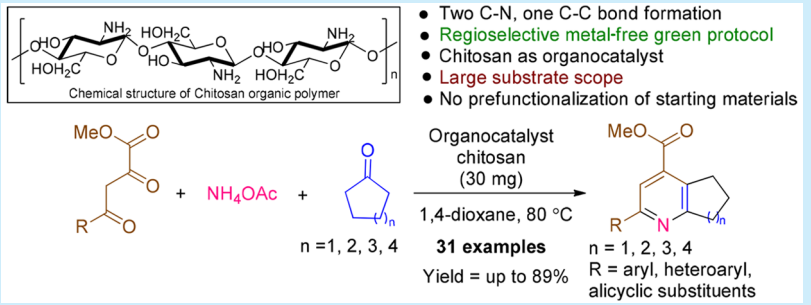
Supporting Information



ABSTRACT: An unprecedented organocatalytic, regioselective, modified Guareschi−Thorpe type protocol toward the modular synthesis of 5,6,7,8-tetrahydroquinolines **22a−g** and other alicyclic[*b*]-fused pyridines **23−28** via the identification of Chitosan as a heterogeneous catalyst is reported. This novel strategy is operationally simple and showed a wide range of functional group tolerance and substrate compatibility. The proposed mechanistic pathway involves an imine-enamine cascade approach for the synthesis of structurally diverse alicyclic[*b*]-fused pyridine heterocycles. The gram scale synthesis and identification of a new class of antifungal molecules **29−31** emphasize the practicality of this method.

Organocatalysis has received tremendous attention from synthetic chemists to catalyze transition-metal-free reactions to construct various natural products, pharmaceuticals, and organic materials during the past two decades because of its several advantages such as selectivity, safety, ease of handling, and economic perspectives.[1] Pyridine-nucleus-including substituted alicyclic[*b*]-fused pyridines, as a part or as a whole, constitute the core of a large family of natural products, bioactive pharmaceuticals, vitamins, alkaloids, chiral ligands, and functional materials[2,3] and are endowed with a wide range of biological activities[4] as shown by a few pharmaceutically privileged molecules **1a−e** (Figure 1).

Few methodologies for the synthesis of functionalized alicyclic[*b*]-fused pyridines have been reported via the construction of the pyridine ring either on alicyclic ring systems or via the construction of the alicyclic ring on the pyridine ring. While the latter route involves routine chemistry, the former route is quite challenging, as the construction of highly substituted pyridine is required to be built on the alicyclic ring. Almost a century ago, the Guareschi−Thorpe method was the landmark reaction for pyridine synthesis, which involves the condensation of the cyanoacetic ester with an acetoacetic ester in the presence of ammonia [Scheme 1A].[5] Since then, several methodologies have been reported in the literature to construct the alicyclic[*b*]-fused pyridines using cyclic ketones or its analogues.[6] Earlier, the synthesis of alicyclic[*b*]-fused pyridine was carried out via Pd-catalyzed oxidation of hydroxyenaminones followed by subsequent cyclization/aromatization [Scheme 1B(i)].[7a] Functionalized 5,6,7,8-tetrahydroquinoline i.e, a cyclohexane[*b*]-fused pyridine, was obtained in a lower yield when 2-methylcyclohexanone oxime was treated with diphenylacetylene in the presence of an iridium catalyst [Scheme 1B(ii)].[7b] The desired skeleton could also be constructed when cyclic/acyclic 1,3-dicarbonyl compounds react with activated *α*, *β*-unsaturated ketone in the presence of NH_4OAc using $K_5CoW_{12}O_{40}\cdot 3H_2O$ as the catalyst [Scheme 1B(iii)].[7c] A metal-free, MW-assisted four-component strategy using arylaldehydes, cyclohexanone,

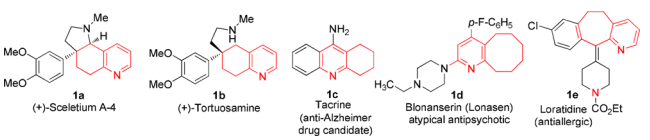


Figure 1. Few selected examples of pharmaceutically privileged molecules **1a−e** having functionalized alicyclic[*b*]-fused pyridines.

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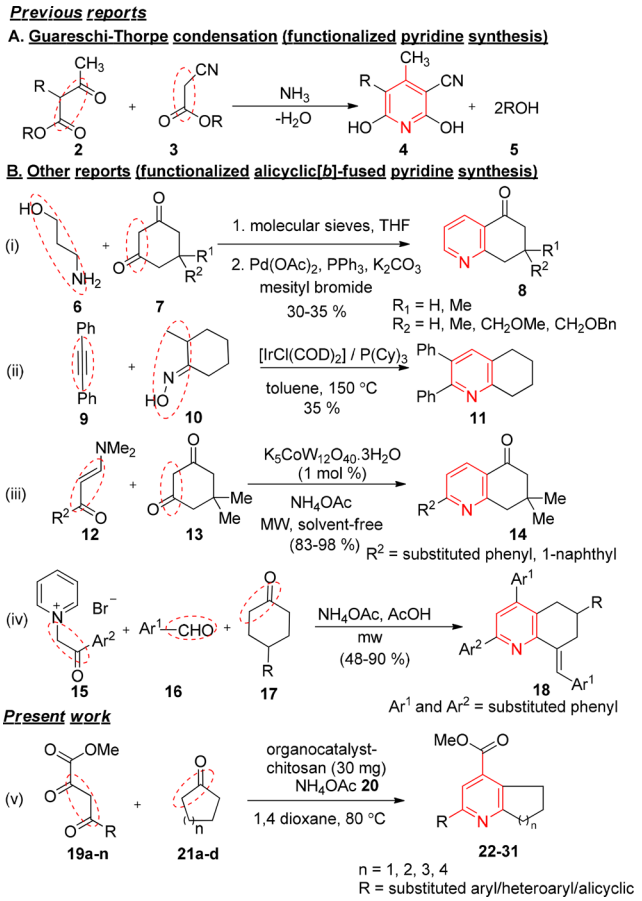
Scheme 1. Some Previous and Present Reports for the Synthesis of Alicyclic[*b*]-fused Pyridines

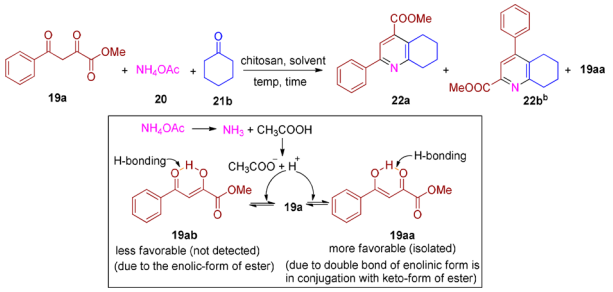


ammonium acetate, and *N*-phenacylpyridinium bromide as an activated ketone has also been utilized to construct alicyclic[*b*]-fused pyridines [Scheme 1B(iv)].[7d] However, all the previously reported protocols suffer from serious drawbacks, such as the use of expensive and toxic transition metal catalysts, harsh reaction conditions, multistep synthesis, activated carbonyl substrates, lower yields, and a limited substrate scope. Hence, the development of a more general, operationally simple, and environmentally benign method for the synthesis of alicyclic-[*b*]-fused pyridine motifs is highly desirable.

Herein, we report the identification of a commercially available chitosan as heterogeneous organocatalyst, which catalyzes an unprecedented, regioselective, three-component condensation reaction of an unactivated ketone, a diketo-ester and NH_4OAc in 1,4-dioxane as solvent at 80 °C which furnished alicyclic[*b*]-fused pyridines **22**−**31**, with a broad range of functional group tolerance and substrate compatibility [Scheme 1B(v)]. To the best of our knowledge, this is the first report of an organocatalyzed modified Guareschi−Thorpe type regioselective synthesis of 5,6,7,8-tetrahydroquinolines and other novel alicyclic[*b*]-fused pyridines.

To develop a modified Guareschi−Thorpe type condensation for the synthesis of alicyclic[*b*]-fused pyridines, we started our initial investigation on the model reaction using methyl 2,4-dioxo-4-phenylbutanoate **19a**, NH_4OAc **20**, and cyclohexanone **21b** as an unactivated ketone dissolved in EtOH, for the synthesis of methyl 2-phenyl-5,6,7,8-tetrahydroquinoline-4-carboxylate **22a** via screening of various catalysts (Table 1).

Table 1. Optimization Study: Identification of Catalyst[a]



s. no.	solvent	catalyst	mol (%)	temp (°C)	time (h)	yield of **22a**[c] (%)	yield of **19aa**[c] (%)
1	EtOH	–	–	80	4	trace[b]	92
2	EtOH	DBU	30	80	4	46	48
3	EtOH	DABCO	30	80	4	37	52
4	EtOH	Et_2NH	30	80	4	32	53
5	EtOH	L-proline	30	80	4	34	57
6	EtOH	piperidine	30	80	4	28	60
7	EtOH	DMAP	30	80	4	41	54
8	EtOH	Et_3N	30	80	4	21	68
9	EtOH	pyrolidine	30	80	4	48	44
10	EtOH	chitosan	30[d]	80	4	65	32

[a]Reaction conditions: **19a** (0.20 mmol), **20** (0.30 mmol), **21b** (0.30 mmol), and catalysts (mol %) were dissolved in EtOH and heated at 80 °C temperature under a N_2 atmosphere for 4 h. [b]Not isolated. [c]Isolated yield. [d]Performed with chitosan catalyst 60 mg (30 wt %, w.r.t. substrate **19a**).

As NH_3 was used as a nitrogen source as well as a base in Guareschi−Thorpe pyridine synthesis, we also planned to perform our reaction using NH_4OAc, which will provide a basic medium and also act as a nitrogen source. Unfortunately, it did not furnish the desired product **22a** (entry 1). Product **19a** exists in equilibrium with either **19aa** or **19ab** under the reaction medium. While **19aa**, the unreacted form of **19a**, was isolated in our reaction conditions, **19ab** was not detected at all. It prompted us to investigate this reaction using other various primary, *sec*- and *tert*-amines (Table 1; entries 2−9). A number of bases such as DBU, DABCO, Et_2NH, L-proline, Piperidine, DMAP, Et_3N, pyrrolidine, etc. were used in catalytic amounts (30 mol %) under reflux conditions in EtOH which furnished **22a** in 21−52% yields (Table 1, entries 2−9). Its other regioisomer, **22b**, was not detected at all. However, **19aa**, the unreacted form of **19a**, was isolated in 44−68% yields. The structures of **22a** and **19aa** were fully characterized by ESI-MS, ^1H NMR, ^{13}C NMR, FT-IR, and HRMS data. Furthermore, biopolymer chitosan has been well reported in literature which has been utilized as a heterogeneous catalyst in organic synthesis.[8] Therefore, we also carried out our model reaction using chitosan as a heterogeneous organocatalyst. Surprisingly, **22a** was obtained in 65% yield (Table 1, entry 10).

We further optimized the reaction efficacy by using chitosan in different solvents (Table 2, entries 1−8); consequently, 1,4-dioxane was found to be the best solvent which afforded **22a** in 70% yield (Table 2, entry 6). In contrast, the reaction did not furnish **22a** in H_2O (Table 2, entry 8).

Then, the effect of catalyst loading was studied on the model reaction (Table 2, entries 9−12). It was found that an increase in chitosan loading (80 mg) decreases the yield of **22a** (Table 2, entry 9). Contrary to this, a decrease in chitosan loading (40

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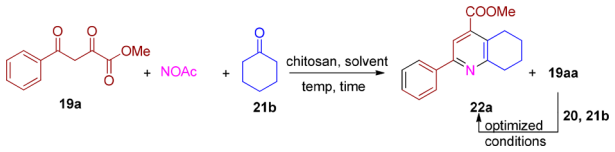
Table 2. Optimization Study: Screening of Reaction Parameters for the Synthesis of 22a[a]



s. no.	solvent	amount (mg)	temp (°C)	time (h)	yield[b] (%)
1	EtOH	60	80	4	65
2	$CHCl_3$	60	80	4	28
3	MeOH	60	80	4	63
4	DMF	60	80	4	52
5	DMSO	60	80	4	47
6	1,4-dioxane	60	80	4	70
7	toluene	60	80	4	20
8	H_2O	60	80	4	00
9	1,4-dioxane	80	80	4	56
10	1,4-dioxane	40	80	4	68
11	1,4-dioxane	30	80	4	77
12	1,4-dioxane	20	80	8	61
13	1,4-dioxane	30	80	8	80
14	**1,4-dioxane**	**30**	**80**	**10**	**87**
15	1,4-dioxane	30	100	12	81
16	1,4-dioxane	30	80	24	79

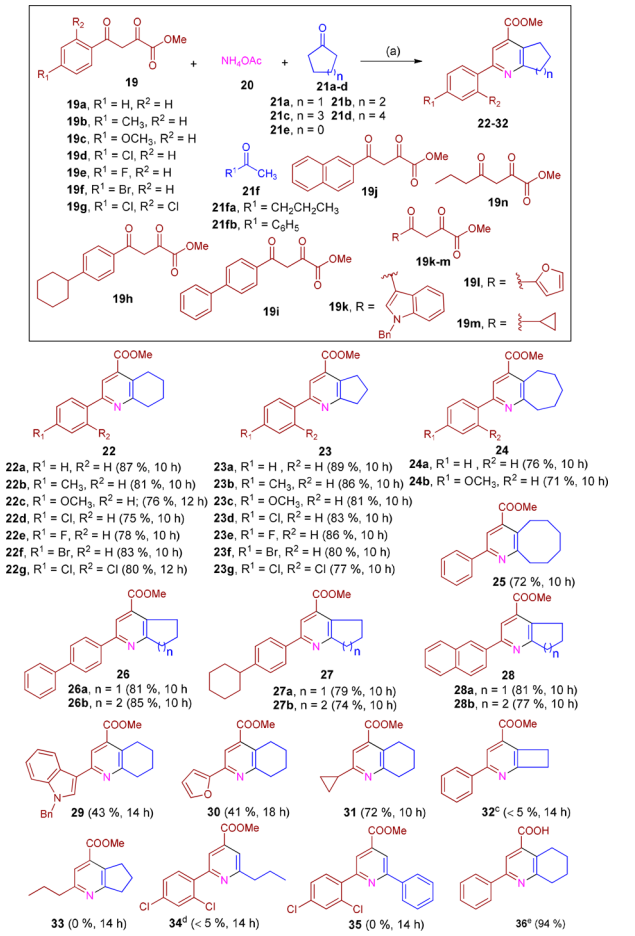
[a]Reaction conditions: **19a** (0.20 mmol), **20** (0.30 mmol), **21b** (0.30 mmol), and chitosan (as given amounts in table) were dissolved in solvents (as given in table) and heated at the given temperature under a N_2 atmosphere at given time. [b]Isolated yields after two steps. In the second step, the recovered intermediate **19aa** was again subjected to the same reaction conditions along with **20** and **21b**.

mg) increases the product yield to 68% (Table 2, entry 10). On further decreasing the chitosan loading to 30 mg, it was observed that a 30% catalyst loading was found to be the optimum condition for obtaining the product in 77% yield (Table 2, entry 11). A further decrease in chitosan loading does not have beneficial effects (Table 2, entry 12). Then, we studied the optimization of temperature and time (Table 2; entries 13−16); it was found that an 80 °C temperature and a 10 h time are optimal. Thus, overall, a catalyst loading of 30 mg of chitosan in a 1,4-dioxane solvent at 80 °C for 10 h was found to be the best reaction conditions for the synthesis of **22a** (Table 2, entry 14). The chitosan can be reused up to the fourth cycle with a minor decrease in yield indicating its catalytic efficiency (see Table 1 in the Supporting Information (SI)).

To explore the substrate scope and generality of the present method, various substituted aromatic/heteroaromatic/aliphatic diketo-esters **19a−n**, different cyclic (4/5/6/7/8-membered)/acyclic/aromatic carbonyl compounds **21a−f**, and **20** were subjected to the optimized reaction conditions which furnished the alicyclic[*b*]-fused pyridines **22−31** in up to 89% yields (Scheme 2). The present method proceeds smoothly for the synthesis of a variety of functionalized alicyclic[*b*]-fused pyridines. Initial observation showed that the different diketo-esters **19a−j** react with various cyclic ketones **21a−d** in the presence of NH_4OAc **20** under the optimized conditions to afford **22−28** in excellent yields. The seven- and eight-membered cyclic ketones, i.e. **21c−d**, furnished the corresponding alicyclic[*b*]-fused pyridine **24−25** in 71−76% yields.

Similarly, reaction of heteroaromatic/alicyclic diketoesters **19k−m** with cyclic ketones **21a−c** along with **20** under

Scheme 2. Substrate Scope[a,b]



[a]Reaction conditions: (a) **19a−n** (0.20 mmol), **20** (0.30 mmol), **21a−e** or **21fa−fb** (0.30 mmol), chitosan (30 mg, 15 wt % w.r.t. **19a−n**, respectively), 1,4-dioxane, 80 °C, N_2 atmosphere. [b]Isolated yields. [c]Not isolated. [d]Inseparable complex mixture. [e]For preparation of **36**, see section 1.2.5 in the SI.

optimized conditions furnished **29−31** in 41−72% yields. The generality of the reaction was also attempted using highly constrained cyclobutanone **21e** along with **19a** and **20**; unfortunately, **32** was formed in traces (<5%) but could not be isolated. It infers that the reaction proceeds smoothly with aromatic and alicyclic diketo esters **19a−j** and **19m**, with nonconstrained cyclic ketones **21a−d**. However, it proceeded slightly in low yields with heteroaromatic diketoesters **19k−m**. In contrast, the reaction did not furnished **33** with aliphatic diketoester **19n**. Also, **34** was not isolated when **21fa**, **19g**, and **20** were treated under the optimized reaction conditions, but the crude ^1H NMR spectra showed an inseparable complex mixture. Moreover, the reaction of **19g** with **21fb** and **20** did not furnish **35** due to the lower reactivity of **21fb** in comparison with cyclic ketones **21a−d**. Overall, the reaction proceeds smoothly with nonconstrained cyclic ketones as compared to constrained/acyclic ones. Aromatic diketoesters **19a−j** were found to be the most suitable substrate to generate a variety of 2-aryl substituted alicyclic [*b*]-fused pyridines (Scheme 2).

To illustrate the type of mechanism involved, control experiments were carried out under optimized reaction conditions in the presence of free-radical scavengers such as

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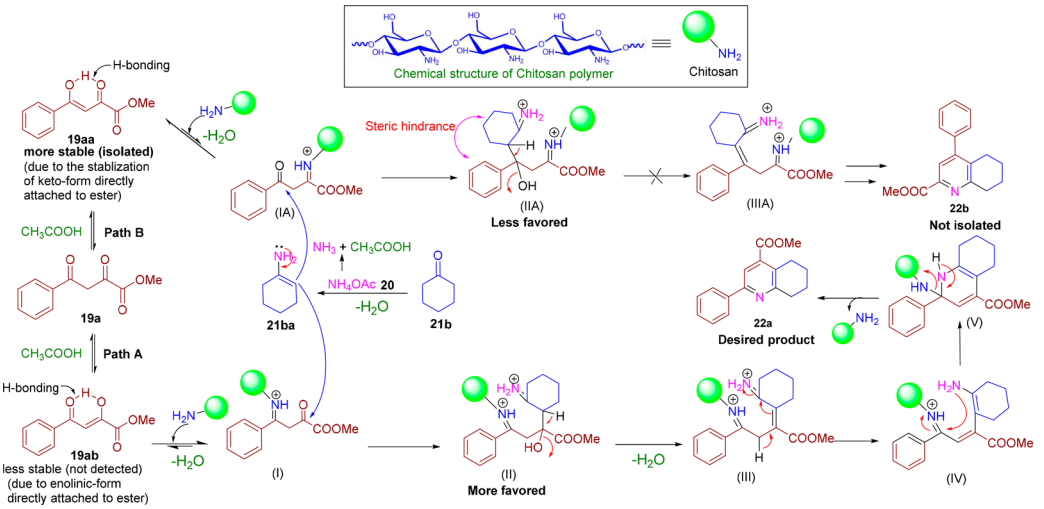

Figure 2. Plausible mechanism.

Tempo and BHT, which furnished **22a** in up to 84% and 79% yields, respectively. This indicates the involvement of an ionic mechanism rather than a free-radical mechanism (see SI; section 1.2.4).

Moreover, isonicotinic acid (regioisomer of vitamin B_3) and its analogues are present in a large number of natural products and drug candidates;[4a,9] the alicyclic[*b*]-fused isonicotinic acid derivative **36** was synthesized by the hydrolysis of compound **22a** using LiOH·H_2O (see SI; section 1.2.5). The versatility of the method was demonstrated by performing a gram scale synthesis of **22a**, which was obtained in 79% yield (see SI; section 4).

A plausible mechanism for the synthesis of **22a** involves imine-enamine cascade reactions (Figure 2). It is to be noted that **19a** exists in equilibrium with either more stable **19aa** (isolated) or less stable **19ab** (not detected) under an acidic medium of acetic acid generated from ammonium acetate. The reaction starts with the activation of compound **19aa** and **19ab** with chitosan via either path A or path B to generate iminium ion intermediate **I** or **IA**, respectively. Then, the leftover carbonyl group will be immediately attacked by enamine **21ba** (which is formed *in situ* from **21b** and NH_4OAc **20**) and forms more favorable intermediates **II** (less steric hindrance) preferentially over less favored **IIA** (due to steric hindrance between the cyclohexyl and phenyl moiety). Then, the sequence of reactions, i.e., removal of water, deprotonation of amines, abstraction of enolizable proton, and cyclization, furnished the desired product **22a** with the release of the catalyst (path A). On the other hand, **22b** was not isolated in our reaction. It is anticipated that steric hindrance between the cyclohexyl group and phenyl group destabilizes the formation of transition state **IIA** (path B). Therefore, this reaction occurs in a regioselective manner exclusively via path A (Figure 2).

Compounds **29**−**31** were assessed for their antifungal activity *in vitro* against *Aspergillus niger* and *Candida albicans* fungal strains.[10] The indole-based analogue **29** showed promising antifungal activity (MIC = 6.25 μg/mL) *in vitro* against the *Aspergillus niger* strain compared to Ketoconazole (MIC = 12.5 μg/mL; for details, see SI).

In conclusion, our study uncovered an unprecedented organocatalyst, regioselective, modified Guareschi−Thorpe type protocol for the modular synthesis of structurally diverse 5,6,7,8-tetrahydroquinolines **22a**−**g** and alicyclic[*b*]-fused pyridines **23**−**31**. With the operational simplicity, functional group compatibility, low catalyst loading, and reusability of the catalyst, the present methodology has substantially expanded the scope of fused pyridine derivatives accessible from readily available cyclic ketones and diketoesters as starting substrates. Also, the gram-scale synthesis and identification of new antifungal molecules (**29**−**31**) emphasize the practicality of this methodology. These findings disclosed a new synthetic route for the green synthesis of structurally diverse alicyclic[*b*]-fused pyridine heterocycles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02132.

Experimental details and characterization data, ^1H NMR and ^{13}C NMR spectra of all compounds **19aa**, **22**−**31**, and **36** (PDF)

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Notes

The authors declare no competing financial interest.

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