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Diastereoselective Synthesis of Tetracyclic Tetrahydroquinoline Derivative Enabled by Multicomponent Reaction of Isocyanide, Allenoate, and 2-Aminochalcone

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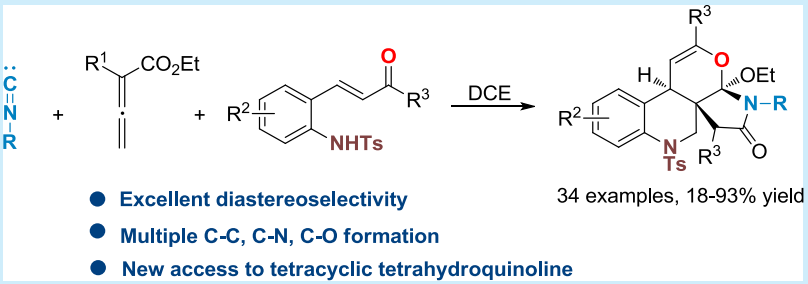
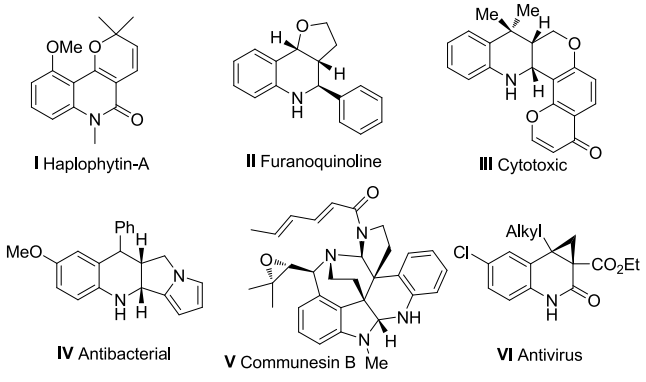


ABSTRACT: We report here a multicomponent protocol to assemble several polycyclic dihydropyran-fused tetrahydroquinoline structures with excellent diastereoselectivity. This procedure employs simple feedstocks to accomplish a series of diverse structures, which is difficult to attain by traditional sequences.

Tetrahydroquinolines belong to a privileged class of nitrogen-containing scaffolds usually found in natural products, and they possess many biological activities.[1] For example, haplophytin-A (I), which is a tricyclic hemiterpenoid alkaloid, is isolated from a methanol extract of *Haplophyllum acutifolium* (Scheme 1).[2a] Furanoquinoline II exhibits impressive antitubercular activity.[2b] Tetrahydroquinoline derivatives III and IV also shows in vitro cytotoxicity and antibacterial activity, respectively.[2c,d] In addition, cyclopropane-fused tetrahydroquinolines are found to behave as potent HIV-1 inhibitors with the aid of cyclopropane and ester moiety.[2e] As a consequence, new methods to access functionalized tetrahydroquinolines have attracted considerable interest from chemists and pharmacologists.[3,4] As such, reactions including aza-Diels–Alder reactions, hydrogenation, and sequential cycloaddition, as well as metal-catalyzed arylation processes, have been well-documented.[5−7] A careful literature screening reveals that 2-aminochalcone and its derivatives are useful synthons to create many types of tetrahydroquinolines and other related N-containing heterocycles.[8] Thus, the Hui group has developed a NHC-catalyzed synthesis from readily available 2-aminochalcones and 2-bromoenals. This method enables the generation of three consecutive stereogenic centers through double Michael addition and lactonization processes.[9a] The Zhu group has demonstrated that the combination of *ortho*-amino cinnamate, aldehyde, and α-isocyano acetamide provided a successful example to approach structurally unusual bridged tetrahydroquinoline (Scheme 2, eq 1).[9b] On the other hand, phosphine-catalyzed annulation involving electron-deficient allenoate has also been widely investigated.[10,11] In such cases, Guo and co-workers have reported that 2-tosylaminochalcones could react with allenoates to synthesize disubstituted indolines (Scheme 2, eq 2).[12a] Interestingly, a modification by Kwon with 2-amidobenzaldehydes as substrate

Scheme 1. Examples of Biologically Active Tetrahydroquinoline Scaffolds



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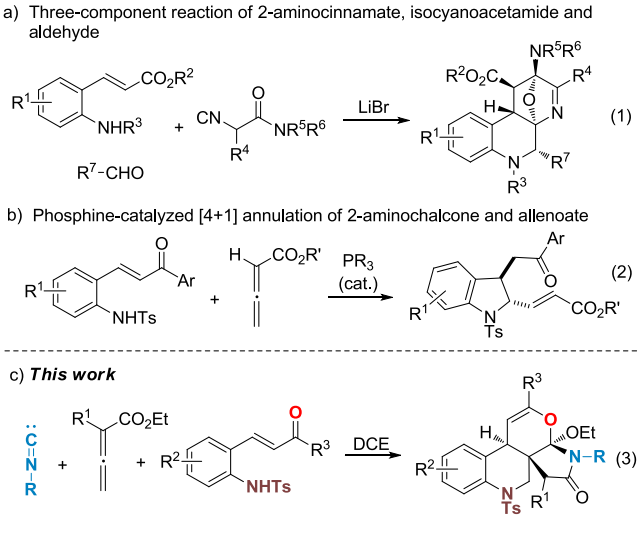
Scheme 2. Previous Reports and Our Design



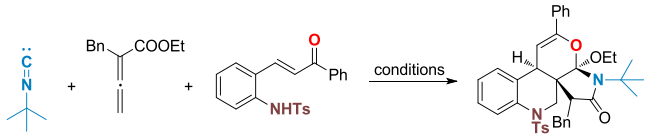
has been utilized to produce 1,2-dihydroquinoline.[12b] Although many successful approaches toward tetrahydroquinolines synthesis exist, stereoselective synthesis of such species with structural diversity remains underexploited.

Isocyanides as fundamental building blocks offer a straightforward pathway for the occurrence of a wide range of reactions.[13] In particular, multicomponent reactions incorporating isocyanides are believed to maximize synthetic efficiency and increase structural complexity, which substantially expands their application prospect in organic synthesis, as well as drug discovery endeavor.[14,15] Regardingly, our group is engrossed in introducing the isocyanide reactivity to engage new transformations.[16] As a continuation, we expected that a multicomponent strategy incorporating isocyanide, 2-aminochalcone, and allenoate (Scheme 2, eq 3) might furnish complementary access aiming to the diastereoselective construction of polycyclic tetrahydroquinoline.

At the outset of our investigation, *tert*-butyl isocyanide (**1a**) was used as the model substrate to react with partners allene (**2a**) and 2-aminochalcone (**3a**). Upon treating this mixture in toluene at 80 °C, we observed an annulation adduct **4a** (13% yield) (Table 1, entry 1). Then, we screened the influence of solvent, temperature, and substrate ratio to improve the reaction performance. Among the solvents tested, dioxane, dimethylformamide (DMF), and acetane (MeCN) could enhance **4a**, while tetrahydrofuran (THF) and dimethylsulfoxide (DMSO) only produced poor results (Table 1, entries 2−6). An elevated yield of **4a** (33% yield) was isolated when DCE was used as the solvent (Table 1, entry 7). Next, we found that the reaction temperature had a strong impact on present conversion. For instance, slightly increased temperature seemed to be favorable (Table 1, entry 11). In sharp contrast, heating the mixture at other temperatures, such as 60, 70, 100, and 120 °C, simply resulted in negative outcomes (Table 1, entries 9−13), respectively. In addition, attempts to improve the reaction performance also relied on the appropriate ratio between substrates. Pleasingly, the employment of excess amount of substrates **1a** and **2a** dramatically increased adduct **4a** (Table 1, entries 14−17) and the ratio 3:2:1 brought the highest yield.

After the optimal reaction conditions were identified, we then surveyed the substrate scope of different isocyanides **1** (Scheme 3). Aliphatic isocyanides **1** having linear chain

Table 1. Reaction Optimization[a]



entry	solvent	temperature (°C)	ratio (1:2:3)	yield[b,c] (%)
1	toluene	80	1:1:1	13
2	dioxane	80	1:1:1	16
3	THF	80	1:1:1	trace
4	DMSO	80	1:1:1	trace
5	DMF	80	1:1:1	20
6	MeCN	80	1:1:1	25
7	DCE	80	1:1:1	33
8[d]	DCE	80	1:1:1	15
9	DCE	60	1:1:1	trace
10	DCE	70	1:1:1	15
11	DCE	90	1:1:1	37
12	DCE	100	1:1:1	31
13	DCE	120	1:1:1	17
14	DCE	90	1:2:1	39
15	DCE	90	1:1:2	36
16	DCE	90	2:1:1	41
17	DCE	90	2:2:1	66
18	DCE	90	3:2:1	73
19	DCE	90	2.5:2:1	69

[a]Unless specified otherwise, all reactions were performed with *tert*-butyl isocyanide **1a** (0.1 mmol), ethyl 2-benzylbuta-2,3-dienoate **2a** (0.1 mmol), and 2-aminochalcone **3a** (0.1 mmol) in 3 mL of solvent in a sealed tube, 12 h. [b]Yields after silica gel chromatography. [c]In all cases, d.r. > 20:1. [d]Reaction time is 8 h.

including both *n*-butyl isocyanide and benzyl isocyanide were found to be particularly good reaction components (**4b** and **4c**). Reaction with ethyl 2-isocyanoacetate also worked well for the developed annulation (**4d**). In particular, sterically hindered isocyanides such as 1,1,3,3-tetramethylbutyl, cyclohexyl, and admantyl isocyanides also served as efficient reaction couplers (**4e**−**4g**). We also defined the configuration of compound **4a** using the single crystal analysis (CCDC 2054200). Then, aromatic isocyanides were evaluated under standard conditions. Accordingly, the dihydropyran-fused tetrahydroquinoline derivatives **4h**−**4l** were prepared smoothly when isocyanides having *para*- and *meta*-position substitution were utilized. Unfortunately, the experiments also suggested that aromatic isocyanides bearing substituents at the *ortho*-position were unable to give the corresponding product.

We also employed various substituted allenoates **2** to undergo this conversion and these substrates were effectively converted to the desired products **5a**−**5i** (Scheme 4). Similarly, α-methyl substituted allenoate underwent the present transformation to deliver product **5j**. Nevertheless, the scope of this method could not be extended to unsubstituted allenoate, which remained intact when subjected to standard conditions. Absolute configuration of compound **5k** was also defined (CCDC 2054194).

The feasibility of a variety of 2-aminochalcones **3** under the standard conditions were subsequently examined. In this regard, these reactions were insensitive to differently substituted TsNH-tethered chalcones **3** with substituent R^2 at C5, C4, or C3 on the aniline moiety. As shown in Scheme 5,

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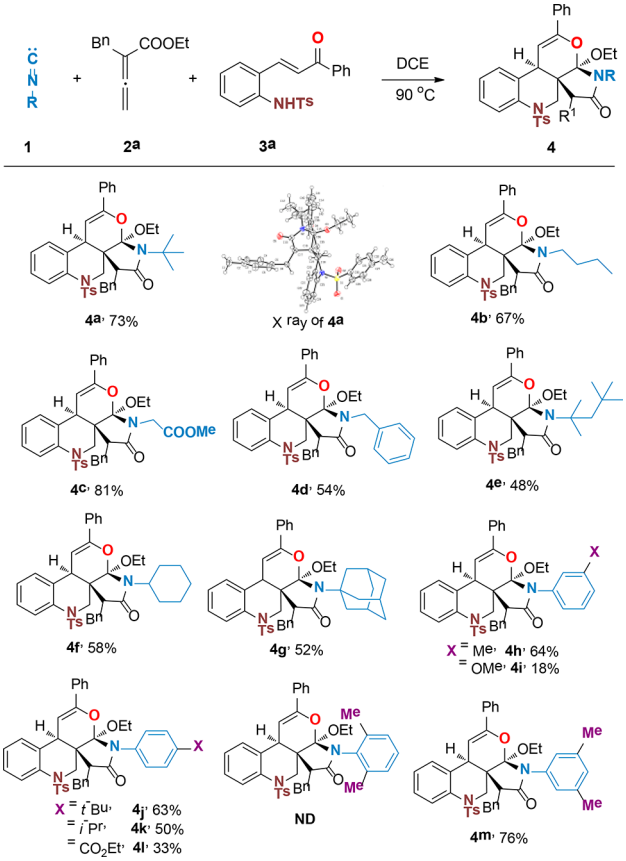
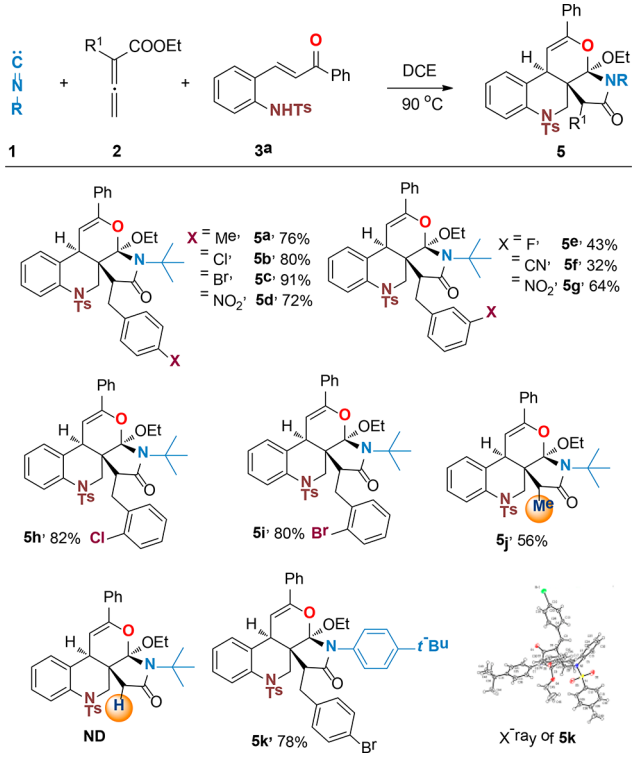
Scheme 3. Scope of the Reaction, with Respect to the Isocyanide 1[a−c]



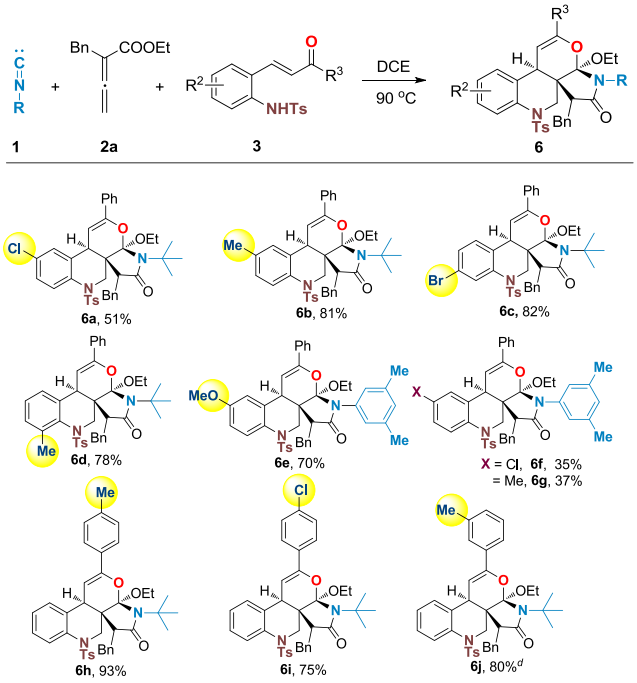
[a]Reaction condition A: 0.3 mmol of isocyanide **1**, 0.2 mmol ethyl 2-benzylbuta-2,3-dienoate **2a**, and 0.1 mmol 2-aminochalcone **3a** in DCE (3 mL) in sealed tube, 90 °C, 12 h. [b]Yields of product after silica gel chromatography. [c]d.r. > 20:1.

Scheme 4. Scope of the Reaction with Respect to the Allenoate 2[a−c]



[a]Reaction condition A. [b]Yields of product after silica gel chromatography. [c]d.r. > 20:1.

Scheme 5. Scope of the Reaction, with Respect to the 2-Aminochalcone 3.[a−c]



[a]Reaction conditionA. [b]Yields of product after silica gel chromatography. [c]d.r. > 20:1. [d]d.r.= 2.5:1.

many substituents including chloro, methyl, bromo, and methoxyl groups on the aromatic ring were compatible (**6a**−**6g**). Next, varying the substituent R^3 on another aromatic ring of 2-aminochalcone **3** was conducted. In such cases, compound **6h** was isolated in excellent yield (93%) when substrate **3** having *para*-methyl substitution on the R^3 group was used. Notably, the above-mentioned experimental results also showed that electronic properties and substitution on the aromatic ring had no influence on the diastereoselectivities, which was exemplified by the high diasteromeric ratio (dr) value (>20:1) in all cases.

To probe more insight into this multicomponent protocol, several control experiments were subsequently performed (see the Supporting Information for details). In this light, 2-aminocinnamaldehyde **7a** having an aldehyde group experienced the standard conditions to produce corresponding product **8a**. Unfortunately, no reaction occurred when 2-aminocinnamate **9a** was used. These results suggested that this annulation might necessitate the presence of a strongly electron-deficient group bearing the alkenyl group. In addition, a scale-up reaction was also conducted.

Following previous reports and the obtained experimental data, an explanation of present conversion is detailed (Scheme 6). The first step involves a previously described generation of active zwitterionic intermediate **A** ↔ **B**[10,11,16b] through interaction of isocyanide **1** and allenoate **2**. This resonance stabilized intermediate experiences proton transfer with **3a** to afford compound **C** and **D**. Subsequent Michael addition

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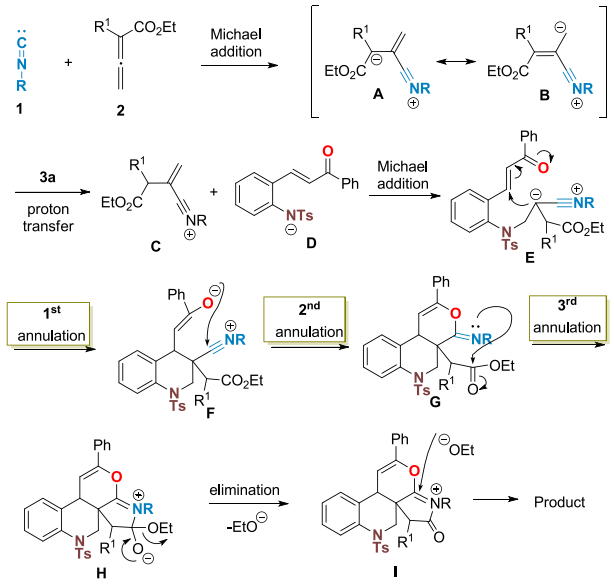
Scheme 6. Proposed Mechanism



generates key intermediate **E**. Next, sequential annulation essentially produces intermediate **H**.[16b,17] After that, the elimination and nucleophilic addition occurs to yield the final product.

In summary, an arduous diastereoselective synthesis of polycyclic tetrahydroquinoline derivative has been achieved through multicomponent methods using readily available starting materials. Mechanistically, the formation of resultant [6.6.5]-fused rings involves sequential Michael addition, triple intramolecular cyclization, proton transfer, and elimination processes. This method is also distinguished by operational simplicity, increased molecular complexity, and structural diversity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00912.

Experimental procedures, characterization data, and ^{1}H NMR and ^{13}C NMR spectra for new compounds (PDF)

Accession Codes

CCDC 2054200 and 2054194 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge viawww.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: + 44 1223 336033.

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Notes

The authors declare no competing financial interest.

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