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Multicomponent Synthesis of Tetrahydroisoquinolines

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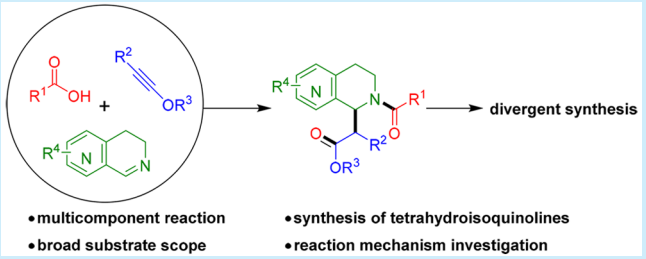
Supporting Information

ABSTRACT: A multicomponent synthesis of tetrahydroisoquinolines from carboxylic acids, alkynyl ethers, and dihydroisoquinolines is described. This process features readily available starting materials, simple experimental procedures for achievement of molecule complexity, and structural diversity. The preliminary control experiment and crossover reaction provide important insight into the reaction mechanism. The formed tetrahydroisoquinolines could be transformed to an array of compounds.



Multicomponent reactions (MCRs) are defined as a process that employs three or more starting materials in a one-pot reaction to form a single product that contains essentially all of the reactants.[1] Due to the simple experimental procedures and one-pot character, the MCRs have become excellent tools for rapid formation of small molecules with the achievement of brevity and diversity. In the past decades, several MCRs have been well developed and widely used in natural product synthesis and drug discovery.[2] For example, the Ugi four-component reaction has been a powerful and efficient method for accessing α-amino amides both in academia and industry.[3] Therefore, the development of MCRs for construction of biological interesting molecules continues to attract considerable attention for their obvious atom- and step-economy.

Tetrahydroisoquinolines (THIQs) are privileged structural motifs often occurring in natural products and pharmaceuticals (Figure 1).[4] Thus, much effort has been devoted to the synthesis of THIQs,[5] and the traditional methods include Bischler−Napieralski cyclization/reduction and Pictet−Spengler reaction.[6] Li and co-workers proposed a cross-dehydrogenative coupling (CDC) strategy for direct functionalization of THIQs.[7] Recently, the CDC method for THIQs synthesis has been well applied with visible-light catalysis by Wu, Xiao, Jiang, and Yu.[8] Notably, the asymmetric CDC functionalization of THIQs has been developed by Liu.[9] Meanwhile, Zhang, Mashima, Zhou, Zhao, and many other groups have, respectively, developed the enantioselective synthesis of THIQs via hydrogenation and kinetic resolution.[10] Alternatively, the hydrogen-transfer-mediated reaction has also been explored for preparation THIQs.[11] Very recently, Clayden and co-workers disclosed an elegant synthesis of 1-aryl THIQs via an acid-mediated ring contraction from cyclic ureas.[12] Interestingly, Zhu, Martin, Ma, and Sun proved that the MCRs could deliver THIQs via Ugi reaction, cyclization and aza-Diels−Alder reaction.[13] Despite these advances, the general and straightforward synthetic method toward THIQs and facile derivatization is in high demand.

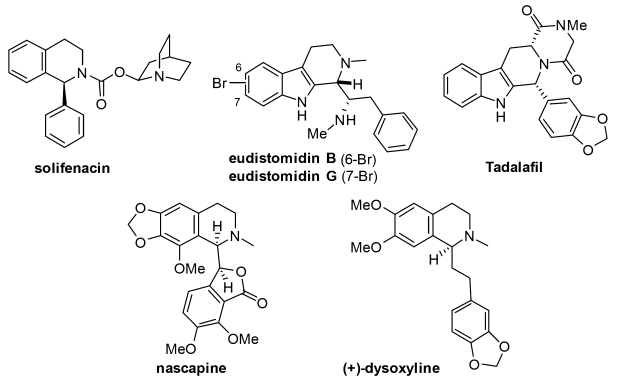


Figure 1. Representative biologically interesting tetrahydroisoquinolines.

Electron-rich alkynes such as ynamines, ynamides, alkynyl ethers, and alkynyl thioethers have been widely used as versatile tools in organic synthesis, especially in heterocycle synthesis.[14] Previously, we established a ynamide-involving Ugi-type four-component synthesis of β-amino amides, and the scope is limited to anilines and aryl aldehydes.[15] As a continuation of our efforts in MCRs and heterocycle synthesis,[16] we are interested in the MCRs development toward THIQs and their application in divergent synthesis. Herein, we report a multicomponent synthesis of THIQs from carboxylic acids, alkynyl ethers and dihydroisoquinolines; this protocol offers ample opportunities for derivatization to access an array of compounds (Scheme 1).

We commenced our study by investigating benzoic acid **1a**, ynamide **2a**, and dihydroisoquinoline **3a**. Initially, we carried out the reaction by mixing **1a** and **2a** in DCM at room

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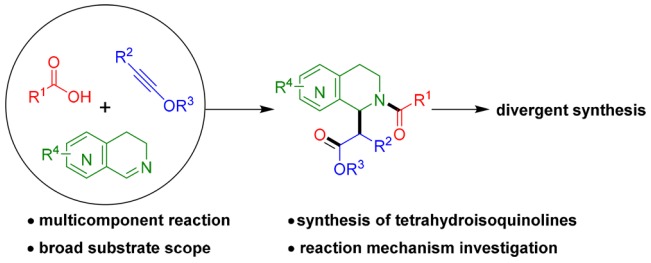
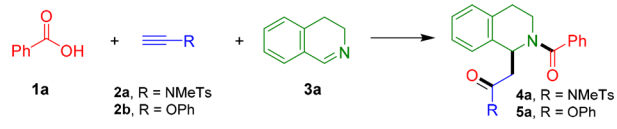
Scheme 1. Multicomponent Synthesis of Tetrahydroisoquinolines



temperature under argon to give the α-acyloxy enamide intermediate and then added **3a** and catalytic $BF_3{\cdot}Et_2O$ as additive to trap the intermediate, but the desired tetrahydroisoquinoline product **4a** was not formed (Table 1, entry 1).

Table 1. Reaction Optimization[a]



entry	alkyne	additive[b]	temp (°C)	solvent	yield[c] (%)
1	**2a**	$BF_3{\cdot}Et_2O$	rt	DCM	0
2	**2a**	$BF_3{\cdot}Et_2O$	80	DCE	0
3	**2b**	$BF_3{\cdot}Et_2O$	rt	DCM	trace
4	**2b**	Ag_2O	rt	DCM	trace
5	**2b**	Ag_2O	80	DCE	73
6	**2b**	$Ag_2O/BF_3{\cdot}Et_2O$	rt	DCM	0
7	**2b**	$Ag_2O/BF_3{\cdot}Et_2O$	80	DCE	55
8	**2b**	$Ag_2O/Cu(OTf)_2$	80	DCE	71
9	**2b**	$Ag_2O/Sc(OTf)_3$	80	DCE	69
10	**2b**	Ag_2O	80	toluene	67
11	**2b**	Ag_2O	80	THF	66
12	**2b**	Ag_2O	80	DMF	48
13	**2b**	Ag_2O	80	dioxane	81
14	**2b**	Ag_2O	100	dioxane	84 (80[d])
15	**2a**	Ag_2O	100	dioxane	27

[a]Reaction conditions: **1a** (0.25 mmol), **2** (0.3 mmol), and additive were added to solvent (2 mL) and stirred for 5 h, then **3a** (0.25 mmol) was added and kept for 3 h. [b]Ag_2O (5 mol %), Lewis acid (5 mol %). [c]Yield refers to isolated product. [d]5 mmol scale.

Raising the temperature to 80 °C in DCE also did not give the product (entry 2). At this stage, we hypothesized that the alkynyl ether could be used to replace ynamide to serve as a C2 building block because the alkoxyl group showed different electronic properties with ynamide which might lead to new reactivity.[17] Next, the alkynyl ether **2b** was subjected to the reaction, and various parameters were tested. $BF_3{\cdot}Et_2O$ was employed as additive, and the reaction did not yield the desired THIQ **5a**, due to the failure of α-acyloxy enol ester intermediate formation (entry 3). Inspired by the fact that Ag_2O could facilitate the formation of α-acyloxy enol esters from carboxylic acid and ethynyl ether, we attempted the reaction with 5 mol % of Ag_2O at room temperature and failed to observe the formation of product (entry 4). To our delight, when the reaction was conducted at 80 °C, the THIQ product **5a** was isolated in 73% yield (entry 5). The product was characterized by standard analysis, and the structure was confirmed by X-ray analysis. This encouraged us to further optimize the reaction. The combination of Ag_2O with Lewis acids such as $BF_3{\cdot}Et_2O$, $Cu(OTf)_2$, and $Sc(OTf)_3$ was found to be inferior, and the product was formed in decreased yields (entries 6–9). Next, a survey of solvent showed that toluene and THF were effective to give comparable yields (entries 10 and 11), while DMF was not optimal and the yield dropped significantly (entry 12). Gratifyingly, when the reaction was conducted in dioxane, the THIQ **5a** could be generated in good yields (entries 13 and 14). On the other hand, when ynamide **2a** was subjected to this condition, **4a** could be formed in 27% yield (entry 15).

With the optimized reaction conditions in hand, we next set out to explore the substrate scope (Figure 2). Various

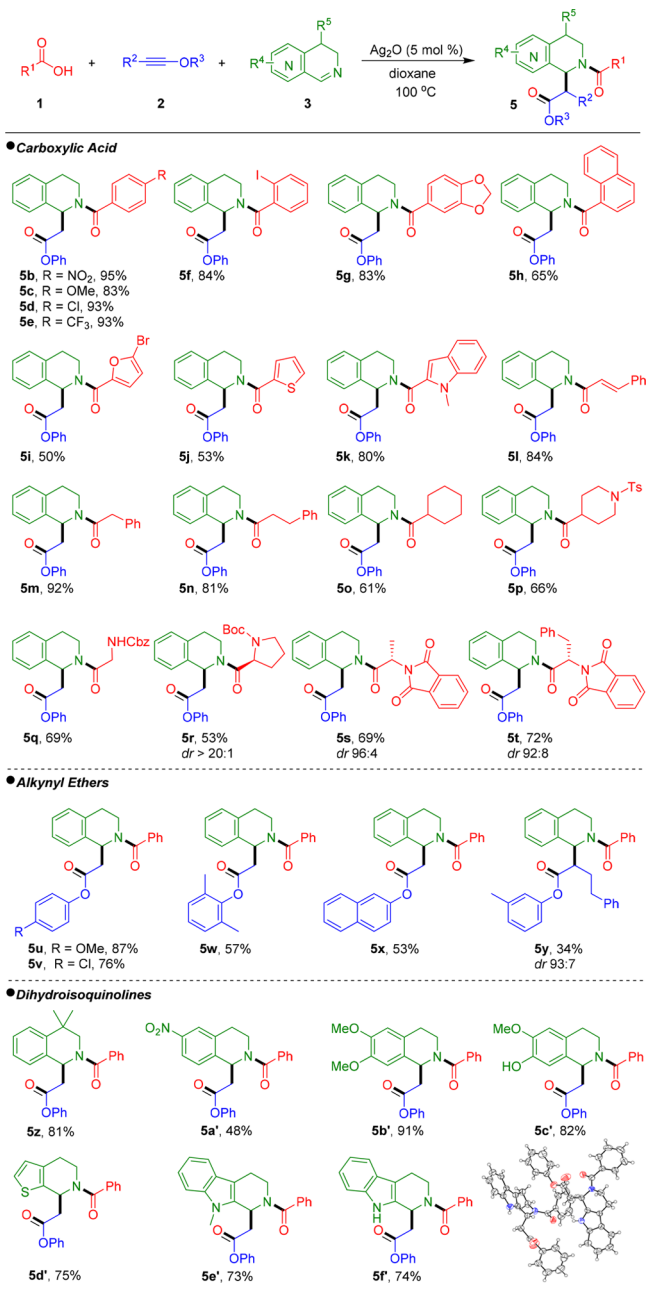


Figure 2. Substrate scope. Reaction conditions: **1** (0.25 mmol), **2** (0.3 mmol), and additive (5 mol %) were added to solvent (2 mL) and stirred for 5 h, then **3** (0.25 mmol) was added and kept for 3 h. Yield refers to isolated product.

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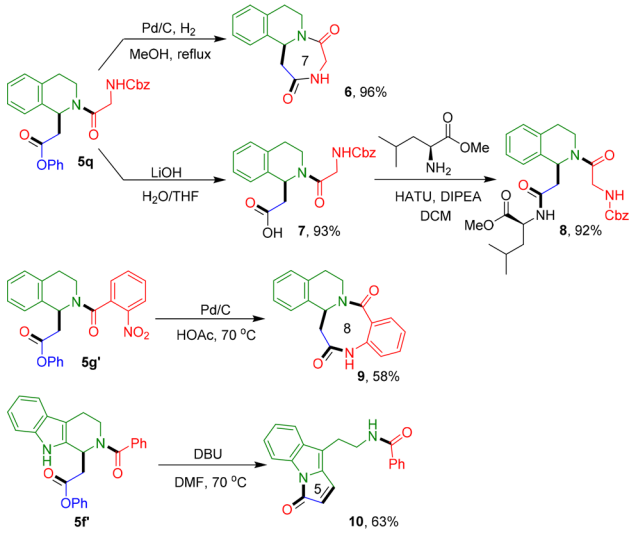
substituted benzoic acids proceeded well in the process to deliver products in good to excellent yields, and valuable groups such as nitro, methoxy, chloro, trifluoromethyl, and iodo were tolerated (**5b**–**g**). Moreover, 1-naphthyl carboxylic acid, unsaturated cinnamic acid, and heteroaromatic carboxylic acids containing furan, thiophene, and indole participated well in the MCRs to deliver the corresponding THIQs (**5h**–**l**). Alkyl carboxylic acids, including phenylacetic acid, 3-phenylpropiolic acid, cyclohexanecarboxylic acid, and piperidine-4-carboxylic acid, were found to be suitable (**5m**–**p**). Notably, when N-protected amino acids such as glycine, L-proline, L-alanine, and L-phenylalanine were subjected to this process, the reaction furnished the THIQs in good yields in up to 92:8 dr (**5q**–**t**). Furthermore, diverse alkynyl ethers were also tested and found applicable (**5u**–**y**). When the internal alkynyl ether (**2f**) was used, the THIQ product (**5y**) was formed with high diastereoselectivity (dr 93:7), albeit in 34% yield. On the other hand, a variety of dihydroisoquinolines were tested in this process. Many substitutions such as nitro, methoxy, hydroxyl, thiophene, and indole ring were well tolerated in this process (**5z**–**f′**). In addition, the structure of **5f′** was confirmed by X-ray analysis. Given the importance of THIQs in natural products and medicinal chemistry, this method provided a simple and efficient access to these molecules with the achievement of sufficient structural diversity.

To demonstrate the synthetic utility, a diversification was carried out to deliver an array of compounds with the core structure of THIQ (Scheme 2). For example, hydrogenation of

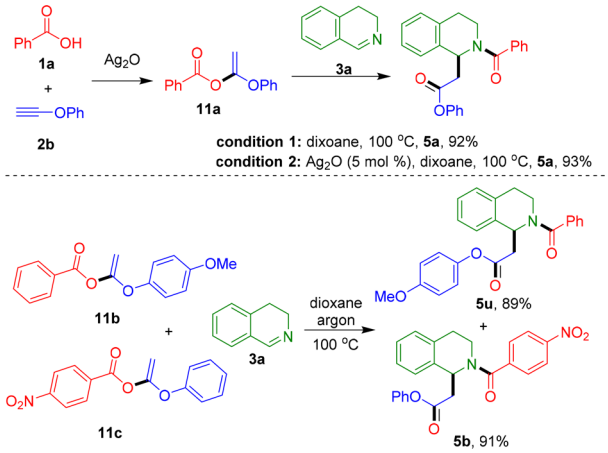
Scheme 2. Diversification of Tetrahydroisoquinolines



5q removed the Cbz-protecting group with concomitant lactamization to furnish the tricyclic 1,4-diazepane-2,5-dione **6** in excellent yield, and this compound is a type of antitumor UCB13-UEV enzyme inhibitor.[18] On the other hand, hydrolysis of **5q** to **7** and further coupling with L-leucine methyl ester gave the peptidomimetic **8** in 92% yield. Additionally, hydrogenation/lactamization of **5g′** delivered the eight-membered heterocycle **9**. For the indole-containing THIQ **5f′**, a fragmentation/cyclization cascade occurred to give 3*H*-pyrrolo[1,2-*a*]indol-3-one **10** upon treatment with DBU.

To gain insights into the reaction mechanism, control reactions were conducted (Scheme 3). Benzoic acid **1a** was coupled with **2a** in the presence of Ag_2O to deliver

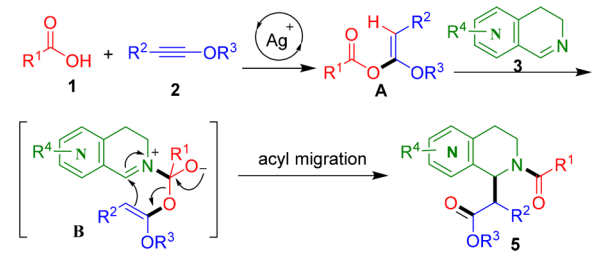
Scheme 3. Control Experiment and Crossover Reaction



intermediate **11a**. Either with or without Ag_2O, **11a** coupled with **3a** to give the THIQ **5a** in comparable yield, indicating that Ag_2O was not essential in this step. Meanwhile, a crossover reaction was also conducted. When the prepared *α*-acyloxy enol esters **11b** and **11c** were subjected to the reaction with dihydroisoquinoline **3a** in dioxane at 100 °C, only **5b** and **5u** were exclusively detected.

On the basis of these results and the literature,[19] a plausible reaction mechanism for this multicomponent reaction was proposed in Scheme 4. Initially, carboxylic acids **1** couple with

Scheme 4. Proposed Reaction Mechanism



the alkynyl ether **2** to give the *α*-acyloxy enol ester **A**. Addition of dihydroisoquinoline **3** to **A** forms the species **B**, which undergoes intramolecular rearrangement to produce the THIQ **5**. Thus, this multicomponent reaction process is different than the previous multicomponent synthesis of *β*-amino amides. In this process, the *α*-acyloxy enol ester intermediate **A** is reactive toward nucleophilic addition by the electron-rich dihydroisoquinoline **3**. With respect to ynamide, the *α*-acyloxy enamide intermediate generated from carboxylic acid and ynamide was less reactive toward addition by dihydroisoquinoline, no matter whether Lewis acid is added or not.

In summary, a multicomponent synthesis of tetrahydroisoquinolines has been developed. In this reaction, the alkynyl ether serves as a C2 building block to enable the rapid assembly with carboxylic acid and dihydroisoquinoline to furnish the privileged tetrahydroisoquinoline with structural diversity. Moreover, control experiments and crossover reactions were conducted to elucidate a plausible reaction mechanism. The formed tetrahydroisoquinolines are transformed into an array of useful compounds.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01159.

Full experimental procedures, characterization data, and NMR spectra data (PDF)

Accession Codes

CCDC 1810979 and 1829219 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.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, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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