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Construction of Nitrogen-Fused Tetrahydroquinolines via a Domino Reaction

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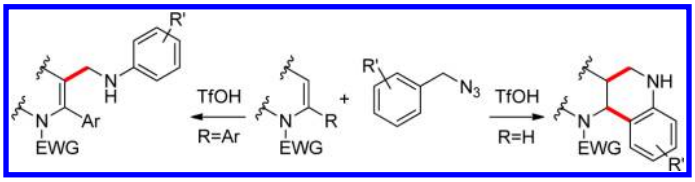
ABSTRACT



An efficient domino approach for the diastereoselective synthesis of polyfunctionalized nitrogen-fused tetrahydroquinoline frameworks under mild conditions has been developed. The scope and limitation of this transformation were investigated by using a range of readily accessible enamides and benzyl azides. This method is also applicable to the formation of 2,3-functionalized enamides.

One of the main challenges in modern organic synthesis is to develop highly selective methodologies giving efficient and rapid access to motifs frequently found in "privileged structures".[1] In light of these facts, diversity-oriented synthesis (DOS) has emerged over the past decade for the preparation of new compound libraries in order to increase their molecular diversity.[2] This tool is now recognized for its ability to find new leads for potential medicinal applications and also to highlight interactions between small molecules and macromolecules during the biological process. Thus, the development of either new convenient, diversified, or step-economical approaches can be introduced by domino reactions.[3]

Polycyclic nitrogen-containing compounds are among the most ubiquitous heterocycles in nature, especially nitrogen-fused tetrahydroquinolines,[4] which were recently referred to as privileged structures in drug discovery because of their wide spectrum of potential biological activities.[5] As an example, this framework is present in the natural products martinelline acid or (+)-martinelline[6] (Figure 1). The latter have attracted considerable attention because they are the first naturally occurring nonpeptide bradykinin B1 and B2 receptor antagonists and the first naturally occurring hexahydropyrrolo[3,2-*c*]quinoline tricycles.

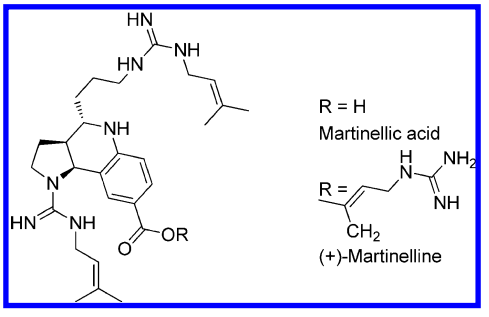


Figure 1. Alkaloids containing nitrogen-fused tetrahydroquinoline structural fragments.

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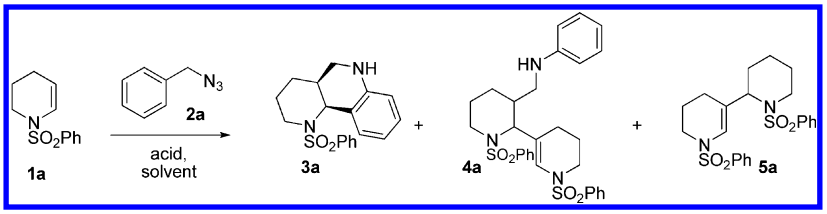
Table 1. Optimization of the Domino Reaction onto Enamide **1a** in the Presence of Benzyl Azide **2a**



entry	equiv of **2a**	acid (equiv)	solvent	time[a] (h)	yield **3a**[b] (%)	yield **4a**[b] (%)	yield **5a**[b] (%)
1	1.1	TfOH (1.2)	toluene	2	48	18	0
2	1.1	TfOH (1.2)	toluene	0.25	14		11
3	1.1	TfOH (1.2)	toluene	5	15		0
4	1.1	TfOH (0.2)	toluene	5	12		24
5	3	TfOH (3.1)	toluene	2	0		0
6	0.8	TfOH (0.85)	toluene	2	11		22
7	1.1	TfOH (1.5)	toluene	2	7		trace
8[c]	1.1	TfOH (1.2)	toluene	2	trace		trace
9[d]	1.1	TfOH (1.2)	toluene	2	0	0	59
10	1.1	$BF_3 \cdot Et_2O$ (1.2)	toluene	2	0		0
11	1.1	$AlCl_3$ (1.2)	toluene	2	trace		trace
12	1.1	TfOH (1.2)	CH_2Cl_2	7	trace		trace

[a] Reaction time after complete reaction between benzyl azide and acid ($c \approx 0.2$ mol·L^{-1}). [b] Yield of pure product after purification by column chromatography. [c] Reaction mixture: $c \approx 0.067$ mol·L^{-1}. [d] Reaction was carried out at −78 °C before slowly increasing the temperature up to 20 °C.

In our quest to generate libraries for biological screening,[7] we focused our attention on the construction of nitrogen-fused tetrahydroquinoline cores via a domino reaction starting from benzyl azides and easily accessible enamides. Azides are involved in a wide array of reactions especially for the construction of new carbon−nitrogen bonds; they have received much attention in recent years.[8] Among these studies, Aubé and co-workers underlined an unprecedented reactivity of benzyl azides under acidic conditions.[9] They reported the acid-promoted rearrangement of alkyl azides providing iminium intermediates which could be trapped by carbonyl compounds in a variant of the Mannich reaction. Recently, Zhai's group described the construction of a range of tetrahydro-5*H*-indolo[3,2-*c*]quinolines via a benzyl azide-to-iminium rearrangement followed by two sequential Pictet−Spengler reactions.[10] Consequently, we decided to study this alkyl azide-to-iminium rearangement in presence of enamide for the direct construction of original nitrogen-fused tetrahydroquinoline scaffolds.

Initially, we examined the reaction with benzyl azide **2a** (1.1 equiv) in the presence of triflic acid (1.2 equiv) in toluene at 0 °C for 15 min (Table 1, entry 1). After complete disappearance of the starting material, enamide **1a** (1 equiv) was added to the solution before stirring at room temperature for 2 h. The reaction afforded the desired pyrido-fused tetrahydroquinoline **3a** (48% yield) and the byproduct **4a** (18% yield). The stereochemistry *cis* in **3a** was clearly determined by relevant ^{1}H NOE NMR experiments.[11] However, the stereochemistry of **4a** could not be confirmed. Mechanistically, the presence of **3a** and **4a** derivatives could be explained as depicted in Scheme 1. Upon protonation, benzyl azide **2a** afforded intermediate species which underwent rearrangement to form an iminium ion with concomitant loss of molecular nitrogen.[9] The latter was trapped by nucleophilic addition of enamide **1a**, creating the first new carbon−carbon bond.[12] After subsequent cyclization onto the newly formed *N*-sulfonyliminium ion via a Pictet−Spengler reaction, the second carbon−carbon bond was performed, affording **3a** as a *cis* diastereoisomer. Alternatively, instead of the cyclization step and from the *N*-sulfonyliminium ion, a nucleophilic attack of a second enamide **1a** could occur, leading to derivative **4a**.

Different parameters were thus investigated (Table 1). Much lower yields were observed by modifying the reaction time (entries 2 and 3), the proportion of the different reactants (entries 4−7) or the dilution (entry 8), despite the

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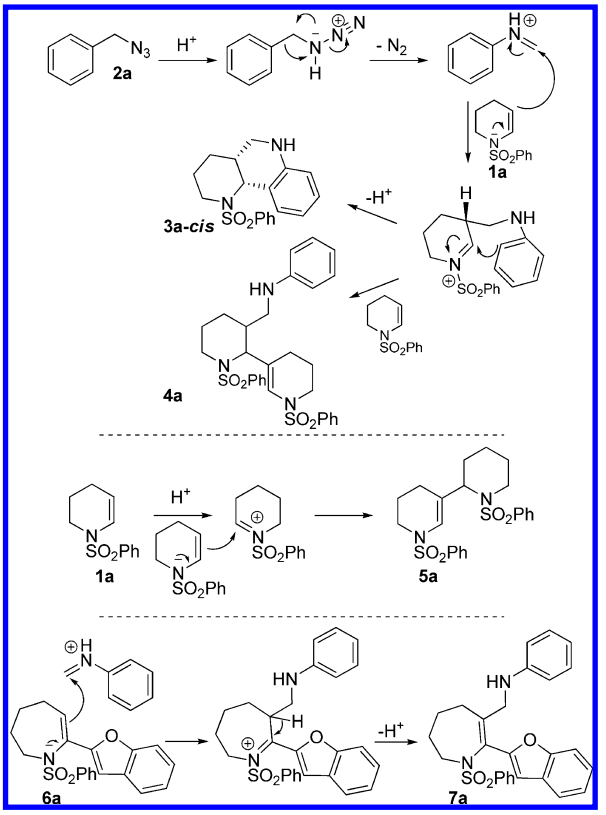
Scheme 1. Plausible Mechanism for the Formation of Products **3a**, **4a**, **5a**, and **7a**

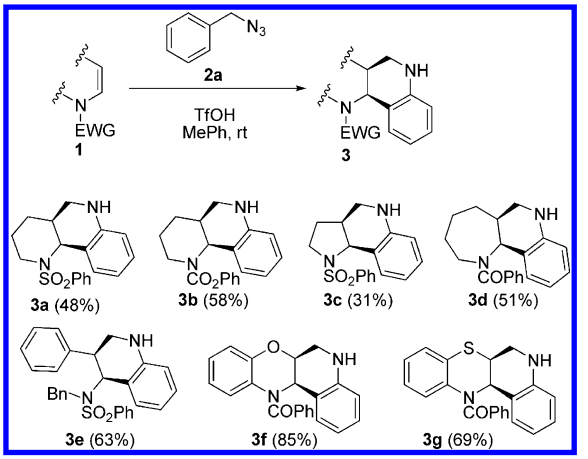


consumption of all starting materials after 5 min. A third product, **5a**, resulting from the conjugated addition of **1a** under acidic conditions, was also isolated (Scheme 1).

By carrying out the reaction first at −78 °C and by slowly increasing to room temperature, only **5a** was isolated in 59% yield (entry 9). No beneficial effect was observed by changing the nature of the acidic source (entries 10 and 11) or the solvent (entry 12). The use of triflic acid seems to be crucial for the process.

Having established the optimal conditions, we next examined the scope of this domino reaction. As shown in Scheme 2, five-, six-, and seven-membered cyclic enamides were investigated. It should be noted that the nature of the electron-withdrawing *N*-protecting group on the starting enamide depends only on its synthetic availability. Starting first from the cyclic enamides **1a**–**d**, the domino reaction led in moderate yields to the following corresponding tricyclic scaffolds: hexahydrobenzo[*h*][1,6]naphthyridines **3a** or **3b**, hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline **3c**, and octahydro-1*H*-azepino[3,2-*c*]quinolin **3d**.[4] It should be mentioned that for each experiment, traces of byproduct **4** or **5** (Scheme 1) were observed but not isolated. Acyclic enamide was found to give the expected tetrahydroquinoline core **3e** in good yield. The *cis* relationship of the two newly generated tertiary carbon centers was confirmed by NMR experiments.[11] Notably, excellent yields up to 85% of fused tetrahydroquinolines **3f** and **3g** were obtained starting from the corresponding antiaromatic

Scheme 2. Scope of the Domino Reaction by Varying Enamides **1**[a,b]



[a] Reaction conditions: **1** (1 equiv), **2** (1.1 equiv), and TfOH (1.2 equiv) for 2 h at rt. [b] Yields of pure product after purification by column chromatography.

benzoxazinic or benzothiazinic enamides, which clearly indicates that more electron-rich enamides favored this process. A total *cis* diastereoselectivity was also observed.[11]

Diversification was introduced by carrying out this domino reaction with a range of benzyl azides **2** in the presence of benzoxazinic enamide **1g** (Scheme 3). Screening with electron-neutral, -rich, and -poor benzyl azides was examined in order to obtain the original heterocycles **3g**–**o**, not yet described in the literature. Pleasingly, it appears that a wide range of benzyl azides were suitable partners for this reaction; as expected, better yields were obtained with activating groups. Low yield (**3k**, 23%) was obtained with a *p*-nitro-substituted benzyl azide, which led to unstable iminium species. Interestingly, when the reaction was carried out with a *meta*-substituted benzyl azide, only the more congested regioisomer **3l** was isolated in 71% yield without any trace of the sterically less congested one. A similar and total regioselectivity was observed starting from 2-(azidomethyl)-naphthalene leading to the formation of a single regioisomer, the pentacycle **3n** isolated in 63% yield. It is also worthy of note that the reaction was successful with a secondary benzyl azide; the fused tetrahydroquinolines **3o** was indeed furnished, albeit with low yield (32%).[13] As previously described in the literature,[14] the *endo*-**3o** derivative was isolated as a single diastereoisomer.

In addition, we also focused on exploring C2-substituted enamides **6** (Scheme 4). Starting from the 2-benzofuran derivative **6a**, we obtained the 2,3-difunctionalized enamide **7a** in quantitative yield. No trace of the previously described C2-cyclized derivative was found. This excellent

(13) The presence of a benzylic substituent retarded the reaction and decomposition occurred prior to the complete consumption of the starting material.

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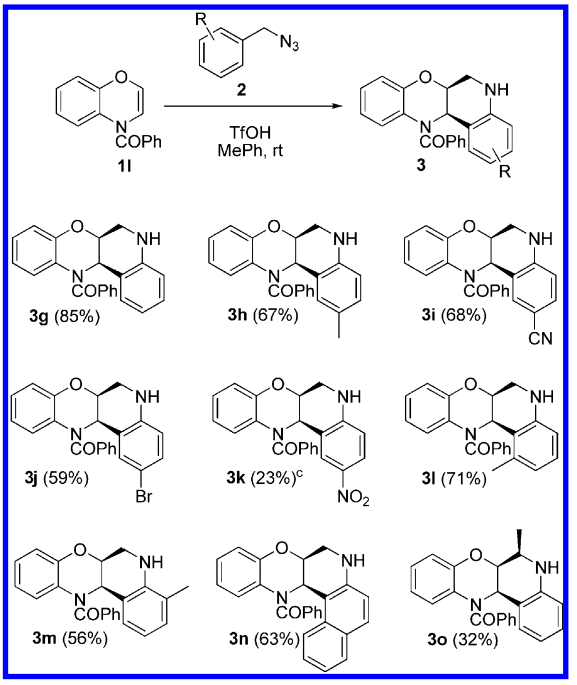
Scheme 3. Scope of the Domino Reaction with Varying Benzyl Azides **2**[a,b]

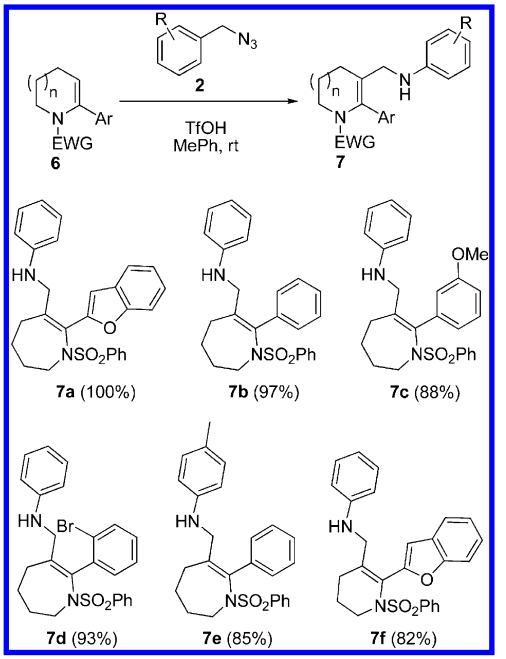


[a] Reaction conditions: **1** (1 equiv), **2** (1.1 equiv), and TfOH (1.2 equiv) for 2−4 h. [b] Yield of pure product after purification by column chromatography. [c] TfOH (2.4 equiv) was used.

result led us to consider other enamides **6** bearing different aromatic groups at the C2 position. A series of difunctionalized enamides **7a**−**f** were thus synthesized with very good to high yields. This transformation, consisting in the acidic promoted rearrangement of benzyl azide followed by the nucleophilic addition of enamide onto the iminium ion intermediate, gives the opportunity to further functionalize the newly synthesized disubstituted enamides, thereby enhancing its synthetic value.

In conclusion, we have developed a simple one-pot strategy to prepare various and eventually novel nitrogen-fused tetrahydroquinoline scaffolds via a domino reaction. Strikingly, this original reactivity was carried out under mild conditions starting from readily available enamides and

Scheme 4. Scope of the Reaction with Varying C2-Functionalized Enamides **6**[a,b]



[a] Reaction conditions: **1** (1 equiv), **2** (1.1 equiv), and TfOH (1.2 equiv) for 2−4 h. [b] Yield of pure product after purification by column chromatography.

benzyl azides. In addition, 2,3-difunctionalized enamides bearing a β-aminomethyl side chain were also easily obtained. Further studies both on the potential scope and synthetic applications of this attractive reaction, including acyclic enamides, are in progress in our laboratory.

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Supporting Information Available. Full characterization details including ^{1}H and ^{13}C NMR, IR, MS, and HRMS. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.