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Diversity-Oriented Synthesis of Polycyclic Diazinic Scaffolds

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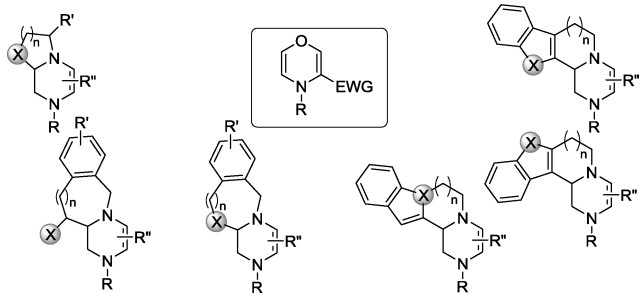
ABSTRACT



An efficient and versatile synthesis of a polycyclic diazinic system starting from oxazine has been developed using a two-step Michael/retro Michael and cyclization sequence. The substrates were synthesized with good to high yields giving rapid access to molecular diversity.

The continuing demand to synthesize new and original collections of small molecules with useful therapeutic properties[1] and also to understand the mechanisms that control biological processes[2] has required the development of fast and easy synthetic methods. In this context, diversity-oriented synthesis (DOS) continues to be an essential area to generate libraries of molecules by varying functional groups, building blocks, stereochemistry, and molecular frameworks to obtain molecular diversity.[3] By controlling all of these parameters, the total synthesis of natural products can be envisaged to find potential new leads for drug discovery. Considerable research has been carried out in recent years to develop new and efficient methods to increase the scaffold diversity present in compound libraries. Privileged heterocyclic structures are attractive for drug discovery because of the high hit rates and the pharmacological profiles of their derivatives relative to those of other ring systems. Polycyclic diazinic systems are omnipresent in various alkaloids (i.e., saframycin, naphthyridinomycin, quinocarcin, etc.) that exhibit a wide array of biological activities, including antitumor[4] and antiparkinsonian properties.[5] Accordingly, these polycyclic diazinic structures are also attractive targets for the synthesis of pharmaceutical agents.[6] As part of our ongoing research program toward the development of efficient methodologies to generate biologically relevant molecules, we recently reported an efficient Michael/retro-Michael sequence that allows the synthesis of a range of diazinic frameworks.[7,8] Accordingly, the prepared pivotal hemiaminal **2** was easily transformed via a nucleophilic addition into various polycyclic diazinic derivatives (Figure 1). Although the structures of compounds **I** and **IV**–**VII** derived from **2** are mostly known,[4−6] little else is known

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regarding the biological activity of compounds having the analogue substructures **II** or **III**. Therefore, the present article is devoted to the investigations in our laboratory on a further expansion of our initial discovery that provides ready access to various privileged structures containing a diazinic framework.

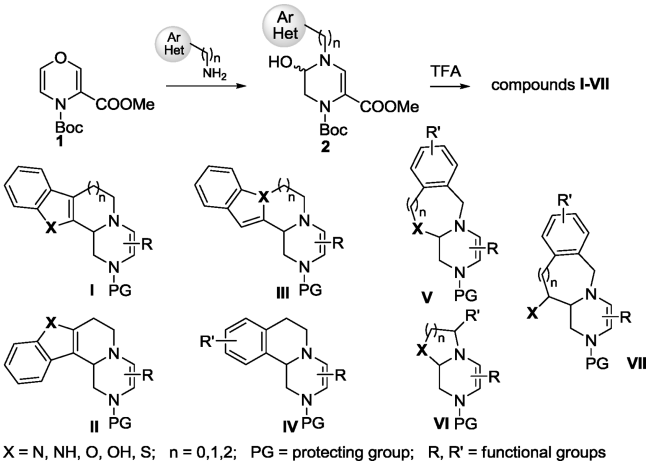
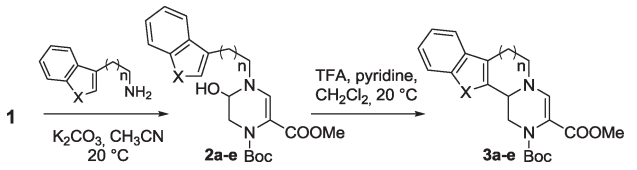


Figure 1. Diversity-oriented strategy.

We chose the methyl4*H*-1,4-oxazine-3-carboxylate **1**[7,8] as the common input for this Michael/retro-Michael sequence (Figure 1) as it allows the preparation of various 1,4-diazinic systems depending on the choice of the starting nucleophilic amine. To this end, the reactivity of various primary amines such as heteroaromatic-3-alkylamines, heteroaromatic-2-alkylamines, ω- functionalized alkylamines, aromatic alkylamines and 2-functionalized benzylamines was investigated. The amines were prepared according to the literature or according to the reported experimental procedure. Consequently, when the obtained key intermediate **2** was treated with acid, the potential iminium ion intermediate could be trapped by a range of nucleophiles to afford various polycyclic diazinic cores (for instance, derivatives **I**–**VII** in Figure 1).[9] The dihydropyrazine scaffold obtained could then be easily further functionalized.[10] To simplify the following discussion, for each primary amine studied, the Michael/retro-Michael sequence and the cyclization step will be addressed concomitantly.

Primarily, we wanted to explore access to heterocyclic analogues of quinolizidine derivatives **I, II** or **III** containing different heteroatoms (Figure 1, X = O, S, N) at various positions with respect to the diazinic core. In the light of previously reported results,[8] we thus first explored

Table 1. Reaction with Varying Heteroaromatic-3-alkylamines



entry	n	X	addition step yield[a] (%)	cyclization step yield[a] (%)
1	0	NH	**2a** (84)	**3a** (0)
2	1	NH	**2b** (95)	**3b** (78)
3	2	NH	**2c** (80)	**3c** (11)
4	1	O	**2d** (74)	**3d** (82)
5	1	S	**2e** (74)	**3e** (46)

[a] Yield of pure product after purification by column chromatography.

the Michael/retro-Michael sequence with heteroaromatic 3-alkylamines containing either a nitrogen, an oxygen or a sulfur atom (Table 1). Sequential treatment of **1** with tryptamine (1 equiv) and with TFA (2 equiv) in the presence of pyridine (1 equiv) provided in two steps, the desired adduct **2b** in 95% yield and then the cyclized product **3b** in 78% yield (entry 2). The presence of pyridine, in the cyclization step, was required to buffer the reaction medium and to avoid the concomitant Boc group cleavage which will lead otherwise to a rapid decomposition of the unstable enamine intermediate. Indole-3-alkylamines bearing different sizes of chains were also investigated. Although the Michael/retro-Michael sequence afforded in each case the desired hemiaminal intermediate (respectively **2a** or **2c**) in good yields (entries 1 and 3), poor yields were unfortunately obtained for the cyclization step (product **3a** or **3c**). It is noticeable that at room temperature, this step was slow to form five- or seven-membered rings, and competing substrate decomposition was observed prior to the complete consumption of the starting material. By applying harsher reaction conditions, using a large excess of TFA, and/or by removing pyridine and/or by varying the time or the temperature of the reaction, decomposition was favored in all cases. Otherwise, the change of heteroatom in the starting heteroaromatic-2-alkylamine[11] afforded a molecular framework embodied in **3d** or **3e** not described yet in the literature. In this case, disappointing results were obtained for the cyclization step even in the favorable case of the six-membered ring. The benzothiophene derivative **3e** was isolated with a poor yield of only 46% (entry 5) due probably to its lesser reactivity in electrophilic aromatic substitution compared to benzofuran **3d** (entry 4) or indole derivative **3b** (entry 2).[12] As before, harsh acidic conditions were not helpful.

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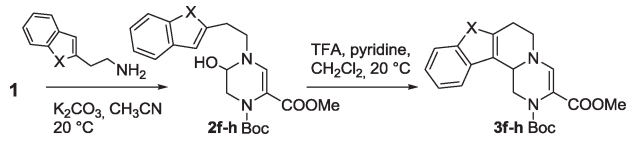
(12) Gotta, M. F.; Mayr, H. *J. Org. Chem.* **1998**, *63*, 9769–9775.

Table 2. Reaction with Varying Heteroaromatic-2-ethylamines

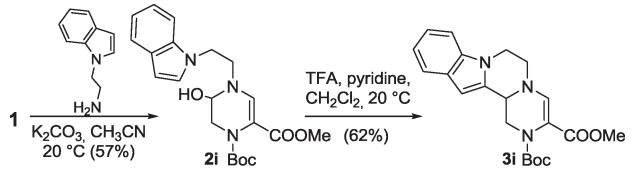


entry	X	addition step yield[a] (%)	cyclization step yield[a] (%)
1	NH	**2f** (62)	**3f** (92)
2	O	**2g** (67)	**3g** (79)
3	S	**2h** (74)	**3h** (74)

[a] Yield of pure product after purification by column chromatography.

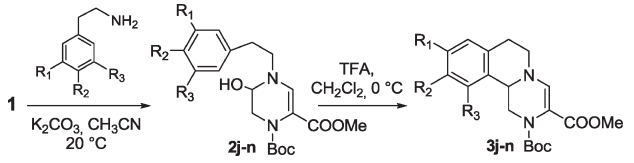
It should be pointed out at this stage that the advantage of our methodology lies in the fact that different hits can be targeted by introducing various functionalities on the substituents borne by the starting primary amine in order to obtain derivatives that exhibit potentially favorable biological properties. To further expand the scope of the reaction, modification of the heterocyclic primary amines containing the alkylamino group branched in position 2[13] was therefore tested (Table 2). Satisfying yields were obtained with the nitrogen (entry 1), the oxygen (entry 2) or the sulfur derivatives (entry 3) affording after the cyclization step respectively the tetracycles **3f**,[14] **3g**, or **3h**. It is important to mention that, to the best of our knowledge, **3g** and **3h** constitute two original and unpublished tetracyclic compounds. The biological relevance of compound such as **3f** arises from the observation that derivatives with identical frameworks exhibit central nervous system activities.[15] When the ethylamino side chain is attached directly to the indole nitrogen atom, the above-mentioned Michael/retro-Michael sequence afforded the hemiaminal precursor **2i** which upon acid-catalyzed cyclization led in satisfactory yields to an original and unpublished tetracyclic scaffold **3i**, a triaza-benzo[*a*]fluorene skeleton (Scheme 1).

Scheme 1. Reaction with 2-(1*H*-Indol-1-yl)ethanamine



Diversification was also introduced by carrying out reactions with primary amines bearing different aryl substituents (Table 3). In all cases, the Michael/retro-Michael sequence gave satisfactory yields up to 100%. However, for the cyclization step, the use of 2 equivalents of TFA in the presence of 1 equivalent of pyridine afforded first the desired 3,4-dimethoxyphenyl derivatives **3j** in only 33% yield. The removal of the pyridine decreased the yield to 0%, because of the Boc group cleavage. Finally, the use of 12 equivalents of TFA at 0 °C for only one minute allowed us to isolate the desired compound **3j** in 90% yield (entry 1).

Table 3. Reaction with Varying Aromatic Alkyl Amines



entry	R_1	R_2	R_3	addition step yield[a] (%)	cyclization step yield[a] (%)
1	OMe	OMe	H	**2j** (100)	**3j** (90)
2	OMe	OMe	OMe	**2k** (65)	**3k** (96)
3	OMe	H	H	**2l** (84)	**3l** (93)
4	H	F	H	**2m** (93)	**3m** (0)
5	H	H	H	**2n** (95)	**3n** (0)

[a] Yield of pure product after purification by column chromatography.

Then, as expected, derivatives **3j**–**l** bearing electron-donating aryl groups were isolated in good yields, giving access to high potential target molecules (entries 1–3).[6] However it should be noted that the intermediate **2m** bearing a deactivating substituent, a fluorine atom, on the *para*-position of the aryl group did not make it possible to isolate the corresponding cyclized derivative **3m** (entry 4), as for derivative **2n** bearing no substituent (entry 5). We can also point out that no regioisomer was observed by NMR analysis for compounds **3j** and **3l**. With these results in hand, we next explored the cyclization step with different functionalized benzylamines bearing an alkylamino or alkylhydroxy side chain in ortho position (Table 4). With a derivative bearing two primary amine functionalities, a one-pot Michael/retro-Michael/cyclization sequence was accomplished in high yields affording, without purification of the intermediate **2o**–**p**, the triaza-derivative **3o** or **3p** (entries 1–2) whose framework is present in many quinazoline alkaloids or analogues.[16]

Starting from an amino alcohol substrate, oxygenated analogues were isolated in two steps with good yield giving the original products **3q** or **3r**, not described yet in the literature (entries 3–4). In both series, the six-membered ring was unsurprisingly favored compared to the five-membered ring. In addition, we also focused on exploring ω- functionalized alkylamines in order to obtain the ergotamine central skeleton or analogues (Table 5).[17]

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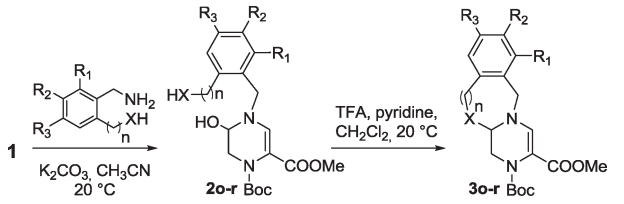
Table 4. Reaction with Varying 2-Functionalized Benzylamines



entry	X	R_1	R_2	R_3	addition step yield[a] (%)	cyclization step yield[a] (%)
1	NH	H	H	H	**2o** (–)[b]	**3o** (76)
2	NH	H	H	H	**2p** (–)[b]	**3p** (86)
3	O	H	H	OMe	**2q** (87)	**3q** (89)
4	O	OMe	OMe	OMe	**2r** (73)	**3r** (93)

[a] Yield of pure product after purification by column chromatography. [b] Directly used in the next step without further purification.

The five- and the six- membered oxygenated rings readily delivered the desired products **3s** and **3t** (entries 1–2). Introducing a substituent alpha to the primary amine function by using L-Alaninol dramatically decreased the yield of the Michael/retro-Michael sequence (only 28% yields) (entry 3). Attempts were made to increase this yield by modifying certain parameters (solvent, temperature and base), however without any success. As with hindered alkylamines the nucleophilic addition is slow, decomposition occurred prior to the complete consumption of the starting material. However, for the cyclization step, the desired bicyclic derivative **3u** was isolated as a single trans diastereoisomer (determined by 2D Noesy NMR) thanks to the chiral pool. Moreover, the one-pot Michael addition/cyclization was carried out with ethylenediamine in moderate yield (entry 4).

The last challenge was the construction of the pyrazino-[1,2-*b*]isoquinoline core which is present in many essential natural alkaloids[4] (Scheme 2). Synthesis of the intermediate **4** was performed following the previously described sequence. Using TMSCN and $BF_3.Et_2O$ at −78 °C then allowed the conversion of the hemiaminal **4** to the aminonitrile **5** in good yield. Reduction of the nitrile with Red-Al,[18] followed by treatment of the resulting aldehyde with TFA[19] gave the desired cyclized product **6** in moderate yield over two steps.

In conclusion, we have described an elegant method for the efficient synthesis of natural product-like molecules containing a diazinic framework, a privileged structure, by using a diversity-oriented synthesis (DOS) approach.

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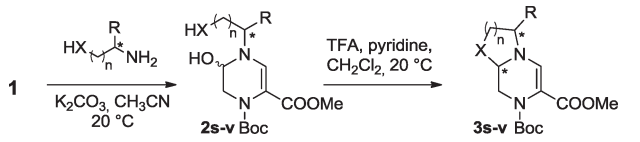
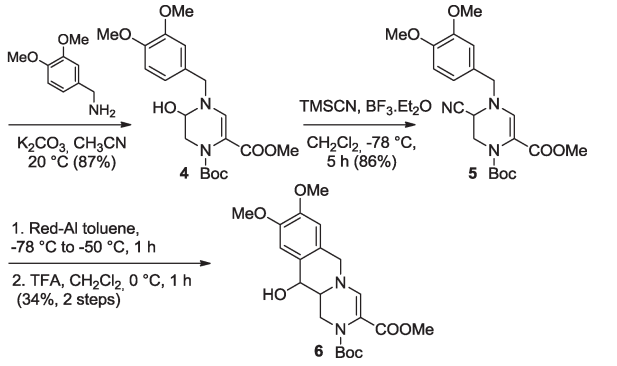
Table 5. Reaction with Varying ω-Functionalized Alkylamines



entry	*n*	R	X	addition step yield[a] (%)	cyclization step yield[a] (%)
1	1	H	O	**2s** (79)	**3s** (83)
2	2	H	O	**2t** (96)	**3t** (88)
3	1	Me	O	**2u** (28) 48:52	**3u** (78) trans
4	1	H	NH	**2v** (–)[b]	**3v** (53)

[a] Yield of pure product after purification by column chromatography. [b] Directly used in the next step without further purification.

Scheme 2. Synthesis of a Pyrazino[1,2-*b*]isoquinoline Core



Performing the Michael/retro Michael and cyclization sequence on the 1,4-oxazine skeleton allowed us, by changing the nature of the starting nucleophile, to create molecules with alternative scaffolds. Diversity could also be introduced through Michael acceptors. The polycyclic diazinic skeletons obtained may be further functionalized to generate small compound libraries for submission to pharmacological studies. Further development of this methodology is currently in progress in our laboratory.

Acknowledgment. We thank Gérard Coudert, Professor Emeritus of the University of Orleans, for fruitful discussions.

Supporting Information Available. Full characterization details including ^1H 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.