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Reactivity of 5-hydroxy-5,6-dihydro-4*H*-pyrazines—easy and efficient access to ring-fused polycyclic diazinic systems

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ABSTRACT

An efficient synthesis of functionalized 1,4-diazinic hemiaminals starting from methyl-4*H*-1,4-oxazine-3-carboxylate moiety is reported. Given that various polycyclic heterocyclic frameworks could be easily obtained, this strategy may provide an efficient method to access a library of compounds based on privileged substructures that are of interest in drug discovery.

Identifying improved methods for heterocycles synthesis and, essentially, giving access to new heterocyclic scaffolds are of prime importance. Accordingly, a wide range of target-directed and diversity-oriented synthesis activities are devoted to the preparation of those frameworks.[1] In connection with our efforts to develop synthetic routes to nitrogen-containing heterocyclic derivatives and particularly six-membered ones, we intended to prepare 1,4-oxazine or 1,4-dihydropyrazine (Fig. 1), and various substituted derivatives of this kind.[2]

In some previous work, we reported an efficient method entailing a Michael/retro-Michael reaction which allowed the synthesis of original 1,4-diazine derivatives **2** (Scheme 1).[2g] In fact, starting from methyl-4*H*-1,4-oxazine-3-carboxylate **1**[2c] and in the presence of primary aliphatic amines, a range of original 1,4-diazinic hemiaminals **2** were easily isolated in fair to good yields.

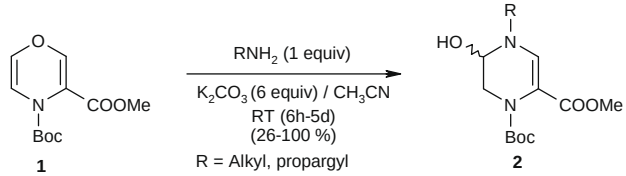
In this paper, we want to highlight the potential of our method as a synthesizing tool and to explore its scope by taking advantage of the potential alkyl iminium ion intermediate **A** (Scheme 2). The latter does constitute an enabling tool for intermolecular or intramolecular reactions that might afford efficient and versatile access to various substituted 1,4,5,6-tetrahydropyrazines **B** or **C**.

Herein, we describe an efficient strategy for the synthesis of functionalized 1,4-diazinic hemiaminals and its successful application to ease the construction of tri- or tetracyclic cores. Direct precursors or analogs of natural products could then be targeted, and in addition the method offers the potential advantage of directly introducing molecular diversity into molecules as a result of the original choice of the starting nucleophile.

The synthesis of the requisite precursors is illustrated in Table 1. Reaction onto α,β-unsaturated methyl ester **1** of primary amine bearing pendent aryl or heteroaryl substituents provided the original desired hemiaminals **2a–d** in fair to very good yields. As previously reported,[2g] the formation of the latter occurred via a Michael/retro-Michael reaction.

R_1, R_4 = aryl, heteroaryl, alkenyl, alkynyl, acyl, alkyl, hydroxyalkyl
R_2, R_3 = alkyl, allyl, hydroxyalkyl

Figure 1. Original 1,4-oxazine or dihydropyrazine derivatives.



Scheme 1. Access to diazinic hemiaminals **2**.[2g]

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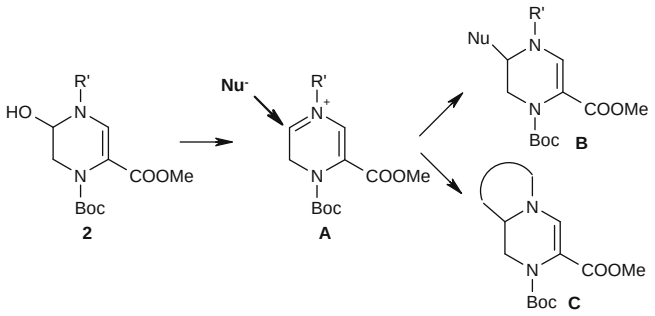


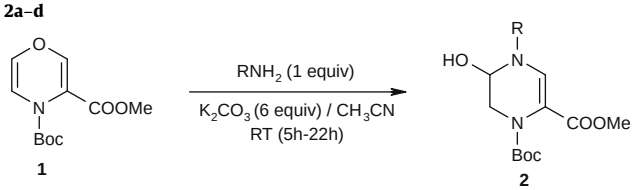
Scheme 2.

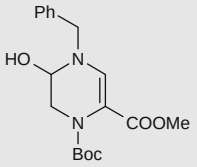
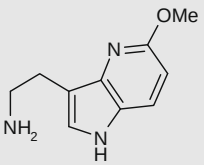
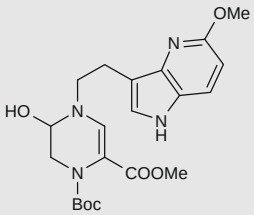
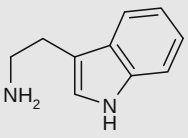
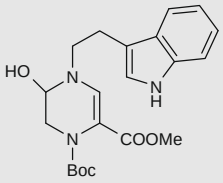
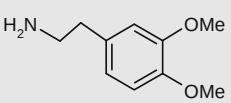
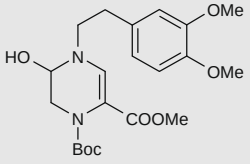
Having easy access to benzylic hemiaminal **2a**, we next examined the reactivity of the iminium ion intermediate (Scheme 2, **A**), generated under acidic conditions, toward nucleophilic addition[4] (Table 2). In the presence of $BF_3{\cdot}Et_2O$ at room temperature in dichloromethane, primary and secondary amines were successfully tested. Functionalized and stable diazinic derivatives **3a** and **3b** were thus isolated in good yields. By using TMSCN[2g] as a nucleophile, the attempted addition quickly occurred (Table 2, entry 3). However, in this case, concomitant removal of the Boc group was also observed to give unprotected unstable aminonitrile **3c** quantitatively isolated. Using this versatile intermediate and via the aminonitrile chemistry, a wide range of synthetic applications could be envisaged.[5]

Given these results, our intent, therefore, was turned to synthesize ring-fused aminal structures such as **4** in a one-pot procedure (Scheme 3). In fact, according to the above-described conditions and starting from unsaturated methyl ester **1**, 2-aminobenzylamine was selected. As first anticipated, the nucleophilic addition of the primary aliphatic amine function afforded the non-isolated hemiaminal intermediate. Then addition of $BF_3{\cdot}Et_2O$ into the crude mixture induced an intramolecular nucleophilic addition of the pendent primary aromatic amine functionality to the iminium ion intermediate. Thus, the ring-fused aminal derivative **4** was isolated in a one-pot procedure from oxazinic methyl ester **1** in high yield (78%). This strategy provides convenient access to a structural motif, which is present in many quinazoline alkaloids[6] (Fig. 2, i.e. fiscalin B[7]). It is worth noting that in each case, the newly formed diazinic derivative may be further decorated by subsequent nucleophilic addition onto the remaining unsaturated methyl ester function.

Next, we intended to examine the ability of hemiaminals **2b**, **2c,** and **2d** to undergo an intramolecular electrophilic cyclization reaction (Table 3). Accordingly, treatment of the azaindole derivative **2b** with trifluoroacetic acid in CH_2Cl_2 at room temperature for

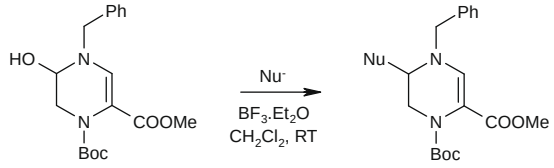
Table 1
Preparation of diazinic hemiaminal derivatives **2a**–**d**



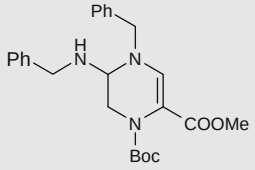
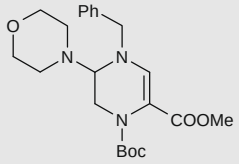
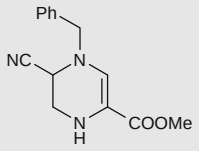
Entry	Reagents	Time (h)	Products[b] (yield %)
1	$PhCH_2NH_2$	22	 **2a** (100%)
2[a,c]		5	 **2b** (31%)
3		17	 **2c** (95%)
4		20	 **2d** (100%)

[a] Reaction performed at 80 °C.
[b] Isolated yield.
[c] See Ref. 3

Table 2
Nucleophilic addition on benzylic hemiaminal **2a**



2a **3**

Entry	Reagents	Time	Products[a] (yield %)
1	$PhCH_2NH_2$	24 h	 **3a** (80%)
2		26 h	 **3b** (61%)
3	TMSCN	30 min	 **3c**[2g] (100%)

[a] Isolated yield.

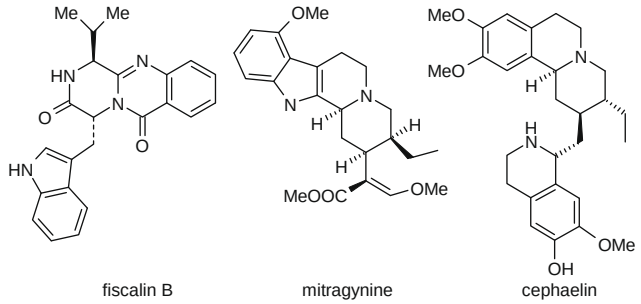
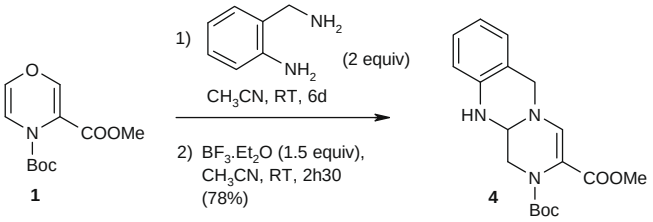


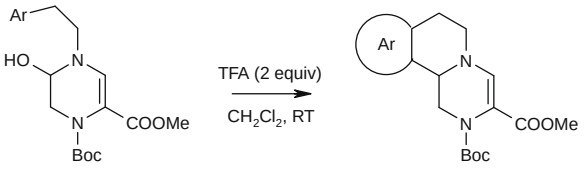
Figure 2. Structure of some representative alkaloids.



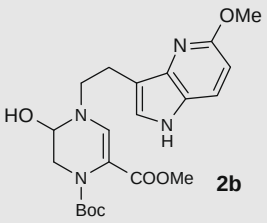
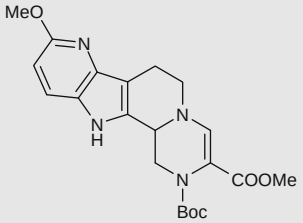
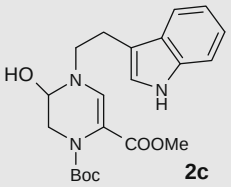
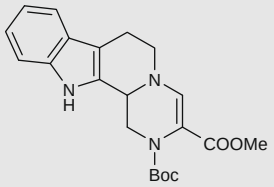
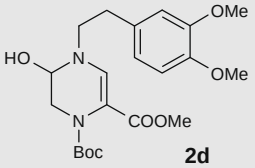
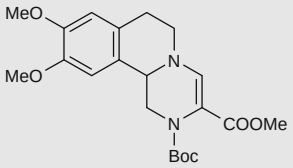
Scheme 3. One-pot access from **1** to ring-fused aminal diazinic derivative **4**.

2 h afforded the desired tetracyclic system **5a** in quantitative yield. Building on our novel efficient approach to diazinic hemiaminal ring system, rapid and efficient access to various analogs of indo-

Table 3
Intramolecular cyclization to hemiaminals **5a–c**



2 Ar = Aryl or Heteroaryl **3**

Entry	Reagents	Time (h)	Products[a] (yield %)
1	 **2b**	2	 **5a** (100%)
2[b]	 **2c**	17	 **5b** (78%)
3[b]	 **2d**	24	 **5c** (33%)

[a] Isolated yield.
[b] Addition of 1 equiv of pyridine.

lo[2,3-*a*]quinolizidine alkaloids[8] (Fig. 2, i.e., mitragynine[9]) could be envisioned.

When experimenting on tryptamine derivative **2c** (Table 3, entry 2), a concomitant cleavage of the Boc group was observed inducing the decomposition of the unstable intermediate enamine in acidic medium. So as to buffer the reaction medium as did the pyridinic nitrogen in **2b**, 1 equiv of pyridine was added. In this case, the desired tetracyclic indolyl derivative **5b** was recovered in 78% yield. An electrophilic cyclization also occurred when starting with dimethoxyphenyl derivative **2d**. The original tetracycle **5c**, isolated in moderate yield,[10] might allow an easy way to diazinic analogs of isoquinoline alkaloids (Fig. 2, i.e. cephaelin[11]).

To sum up, this method allowed an efficient transformation of one type of heterocycles, the 1,4-oxazine ring, into another, namely the 1,4-diazine system. As various polycyclic heterocyclic frameworks could be easily obtained, this strategy may efficiently provide access to a library of compounds based on privileged substructures that are of interest in drug discovery. The application of this methodology to the synthesis of more complex heterocyclic structures is currently under investigation in our laboratory and will be described in due course.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures and full spectroscopic data for all new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.03.152.

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