## Communications

## Synthetic Methods

## Multicomponent Reactions for the Synthesis of Complex Piperidine Scaffolds\*\*

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The structures of small natural molecules have been optimized by evolution and are therefore tailored to interact with natural macromolecules to induce a biological response.<sup>[1]</sup> They represent an invaluable resource in the discovery process of new therapeutic agents. Since the natural product is usually not endowed with the biological properties desired for a chemotherapeutic agent, a series of skeletal and stereochemical analogues have to be generated by using synthesis. A promising strategy (diverted total synthesis, DTS)<sup>[1g]</sup> involves the production of a set of advanced intermediate scaffolds by using a multicomponent reaction (MCR)<sup>[2]</sup> and subsequent transformations to additionally increase the molecular complexity and diversity. Polysubstituted piperidines are common subunits in natural alkaloids and many biologically relevant molecules, representing attractive scaffolds for the production of natural product analogues having interesting biological profiles. To the best of our knowledge there are only a few MCRs for the construction of structurally and stereochemically diverse polysubstituted piperidine derivatives.<sup>[3]</sup> Some years ago we reported a new synthesis of polysubstituted piperidines by using the Diels-Alder reactions of 3-trialkylsilyloxy-2-azadienes with electron-poor olefins (Scheme 1).<sup>[4]</sup> These dienes were prepared from the reaction of acid chlorides with Ntrialkylsilylimines derived from non-enolizable aldehydes.<sup>[5]</sup> The drawback of the method resulted from the thermal instability of the azadienes, which are very reactive towards electrophilic reagents and either cyclize<sup>[6]</sup> or decompose upon distillation. This instability resulted in severe limitations of the type of functional groups that could be introduced into the cycloadducts.

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**Scheme 1.** Sequence of five reactions leading to piperidone scaffolds. TMS = trimethylsilyl, X = alkoxy, amide.

We envisioned the synthesis of the diene and the cycloaddition reaction in a single operation.<sup>[7]</sup> This four-component process<sup>[2b]</sup> involving the combination of readily available reactants (aldehyde, equivalent of ammonia, acyl chloride, and dienophile) should allow the incorporation of high levels of skeletal, functional, and stereochemical diversity in the piperidone products (Table 1).

To establish the experimental conditions of this MCR we first prepared piperidone 1a (Table 1, entry 1), which we had previously<sup>[4b]</sup> synthesized by reacting the purified 2-azadiene with trans-methyl crotonate. The sequential addition of benzaldehyde, LiHMDS, and propionyl chloride in the presence of triethylamine in toluene generated the intermediate azadiene in situ. Then the cycloaddition, with moderately active dienophiles like trans-methyl crotonate, proceeded in refluxing toluene for a few hours, after which the triethylamine hydrochloride had to be filtered off to avoid competitive decomposition of the basic azadiene. Therefore, petroleum ether was first added to the precipitate triethylamine hydrochloride and then the filtrate was treated with trans-methyl crotonate and heated to reflux, and then the addition of methanol gave piperidone 1a. This simple procedure gave a much better yield (75%) than the earlier method using a purified azadiene (33% yield).<sup>[4b]</sup> When the MCR involved a more reactive dienophile (Table 1, entries 5 and 6), the reaction was conducted in one pot without the addition of petroleum ether and filtration of the triethylamine salt.

There are interesting aspects to this one-pot four-component piperidone synthesis (Table 1). The scope of the method was considerably expanded by making possible the introduction of functional groups or substituents which would have prevented the isolation and purification of the corresponding 2-azadienes. A variety of functional groups were tolerated at C4 (Table 1, entries 4–6) and C5 (Table 1, entries 5 and 6).



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**Table 1:** Four-component synthesis of piperidone scaffolds involving an intermolecular Diels–Alder reaction.





[a] Only the major product is shown. [b] Combined yields of *exo* and *endo* products. [c] Ratios determined by <sup>1</sup>H NMR analysis based on the crude products. [d] Component **B** was LiHMDS in all cases. [e] The reaction was run at room temperature. HMDS = hexamethyldisilazide, X = alkoxy, amide.

The presence of an *ortho*-functionalized phenyl group (e.g., a nitro group, Table 1, entry 2) or a reactive heterocycle (e.g., an indole ring, Table 1, entry 3) at C2 permitted the construction of an additional ring. In contrast alkyl groups at C2 were not accessible because the MCR failed using an aldehyde having an  $\alpha$ -hydrogen atom. This limitation could be overcome by the introduction of an (E)-2-alkyl-cinnamyl

was extremely fast and could be conducted in one pot. The scope of the reaction sequence was very broad, allowing the preparation of diversely functionalized piperidine rings fused to a five- or six-membered ring. As expected, the absolute configurations of the diene and dienophile substituents were maintained in the products. Two NMR features permitted the establishment of the *endo* or *exo* configurations of the

substituent which was readily transformed into a ketone by ozonolysis (Scheme 2). This additionally increases the power of the method for the construction of complex heterocyclic molecular skeleton as shown by the formation of the tetracyclic molecule **3** when the MCR is used in combination with three additional steps.

The MCR also allowed the creation of four stereogenic centers with the same stereochemical dichotomy that had been observed<sup>[4]</sup> for related reactions involving pure 2-azadienes: cyclic dienophiles yielded endo adducts (Table 1, entries 6 and Scheme 2, product 1g) whereas acyclic dienophiles gave exo adducts (Table 1, entries 1-4) as major stereoisomers. However, when the diene carried a large substituent at C5, the major isomer resulted from an exo addition even with a cyclic dienophile (Table 1, entry 5). In all cases the configurations of both the diene and dienophile were retained in the adducts.

The four-component reaction was applied to the preparation of the spirolactam 6 in 50% yield by reacting aldehyde 4, LiHMDS, acetyl chloride, and dienophile 5 (Scheme 3). By using a subsequent mesylation of the alcohol and intramolecular alkylation of the spirolactam nitrogen atom, the molecular complexity of the product increased; pentacyclic compound 7 (81% for 2 steps), which is an advanced intermediate for the diverted synthesis of analogues of aspidosperma alkaloids,<sup>[8]</sup> was isolated.

Connecting the carboxylic acid chloride component to the dienophile<sup>[9]</sup> resulted in two rings by virtue of an intramolecular Diels– Alder reaction of the in situ generated azadienes (Table 2). In all cases the cycloaddition reaction

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Scheme 2. Sequential MCR/ozonolysis/aromatization/condensation.



**Scheme 3.** Synthesis of an advanced intermediate for diverted synthesis of aspidosperma alkaloid analogues. TBS = *tert*-butyldimethylsilyl, TS = 4-methyltoluenesulfonyl, TBAF = *n*-tetrabutylammonium fluoride, Ms = methanesulfonyl.

products: 1) the NMR chemical shifts of the vicinal protons at C2 and C3, which are shielded in the *exo* isomers, and 2) the coupling constant between these protons, which are larger for the *exo* products. The structural and stereochemical assignments were confirmed by X-ray diffraction analyses of products **1h** and **1k**.<sup>[10]</sup>

The stereochemical outcome of the cycloaddition step varied with the nature of the aldehyde. Combining *o*-nitrobenzaldehyde or *N*-tosyl-2-indole aldehyde with a *trans*-unsaturated ethyl ester led to a high *endo* selectivity (Table 2, entries 1–3) and a *trans* fusion of the two rings. In contrast, the combination of 2-chlorocinnamaldehyde with a *trans*-unsaturated ester (Table 2, entries 4 and 5) gave the *exo* adduct as the major isomer and a *cis* fusion of the two rings. Given the limited number of cases, it would be premature to propose a rational for these stereochemical differences. However, the results are quite promising in terms of the possible incorporation of stereochemical diversity into the products **1**. Entry l of Table 2 shows that the MCR could be applied to the synthesis of an advanced scaffold for producing analogues of dendrobatid alkaloid 251F.<sup>[11]</sup>





[a] Only the major product is shown. [b] Combined yields of *exo* and *endo* products. [c] Ratios determined by <sup>1</sup>H NMR analysis based on the crude products. [d] Component **B** was LiHMDS in all cases. X = alkoxy.

In summary, we have demonstrated that the MCR for making piperidine scaffolds is considerably expanded in scope compared to the earlier method involving the isolation of 2azadienes. Attractive features of this MCR are its versatility, convenience (it uses simple and often commercially available material), and efficiency in creating skeletal, functional, and stereochemical complexity in a single operation. A wide range of piperidine scaffolds can be prepared having a substitution pattern controlled by the selection of the reactants. A variety of functionalities are tolerated, making possible additional transformations into diverse mono-and polycyclic piperidine derivatives. The stereochemical course of the reaction can be controlled by an appropriate choice in the dienophile component (cyclic or acyclic, *cis* or *trans*) giving opportunities for stereochemical diversity. The scope of the MCR was expanded by linking the dienophile to the acid chloride, thereby yielding piperidones fused to a five- and sixmembered ring with *endo* or *exo* selectivity, which apparently depends on the nature of the groups at C2. At present no multicomponent reaction leading to piperidine derivatives offers such a high level of functional, structural, and stereochemical diversity. We are optimistic that this highly flexible and robust methodology will provide quick and easy access to complex molecular structures which are of therapeutic interest.

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