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Flexible Protocol for the Chemo- and Regioselective Building of Pyrroles and Pyrazoles by Reactions of Danishefsky's Dienes with 1,2-Diaza-1,3-butadienes

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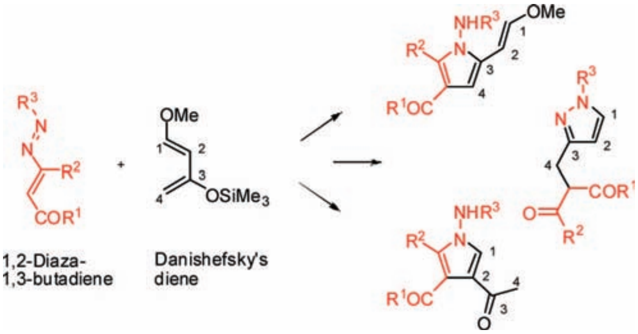
ABSTRACT



The versatility of the Mukaiyama−Michael-type addition/heterocyclization of Danishefsky's diene with 1,2-diaza-1,3-butadienes was applied to the synthesis of both 4*H*-1-aminopyrroles and 4,5*H*-pyrazoles. Thus, the same reagents furnished different types of highly functionalized azaheterocycles essentially depending on their structure: as a matter of fact, R^1 = COOR or CONR$_2$ differently affects the acidity of the proton at the adjacent carbon. An unexpected formation of 5*H*-1-aminopyrroles from the reactions carried out in water was also observed.

Nitrogen-containing heterocycles are the core structure in a large number of natural products as well as in many pharmacologically active compounds.[1] Due to the role of azaheterocycles in bio-organic chemistry, the search for new efficient methods for their synthesis represents an active field of interest.[2,3]

The use of an electron-rich diene, in *normal* and *hetero Diels−Alder cycloadditions*,[4,5] introduced by Danishefsky et al., offers a powerful tool in organic chemistry. Danishefsky's diene readily reacts with imines,[6] aldehydes,[7] alkenes/alkynes,[8] and even some electron-deficient aromatic rings[9] to afford the relevant hetero- and carbocyclic rings. Danishefsky's diene cycloadditions can be catalyzed by various Lewis acids, and asymmetric versions have also been developed.[6–10] Over the years, structural modifications of

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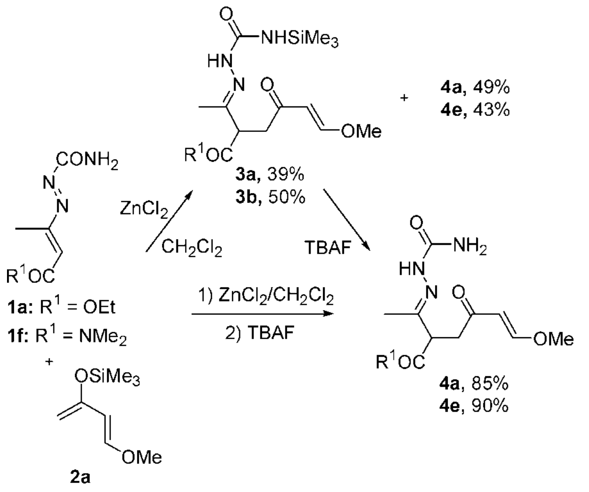
Danishefsky's electron-rich diene improved their reactivity and selectivity, as well as their acid and heat sensitivity.[11]

On the other hand, 1,2-diaza-1,3-butadienes[12] are highly versatile reagents that proved to be useful intermediates in the syntheses of several five- and six-membered azaheterocycles.[13] The high reactivity of these compounds, related to the electrophilicity of the terminal carbon atom (C-4) of the heterodiene system, has been shown to allow the 1,4-addition (Michael-type) of a variety of carbon and heteronucleophiles.[14,15] In such a framework, some of our recent efforts have been addressed in the development of new reactions able to give carbon–carbon bond formation via the Mukaiyama version of the Michael reaction of silyl enol ethers.[16] Thus, we have reported a facile approach to pyrrole and indole ring skeletons, by Lewis acid ($ZnCl_2$)-catalyzed Mukaiyama–Michael addition/heterocyclization of enolsilyl derivatives on 1,2-diaza-1,3-butadienes,[15] in which the Lewis acid catalysis represents an alternative to the alkali enolate method.

With the aim of extending this approach to reactions of other (silyloxy)alkene nucleophiles, we investigated the addition of 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (Danishefsky's diene, **2a**), 1-methoxy-2-methyl-3-trimethylsilyloxy-1,3-pentadiene (**2b**), and 1-dimethylamino-3-*tert*-butyldimethylsilyloxy-1,3-butadiene (Rawal's diene, **2c**) on some 1,2-diaza-1,3-butadienes (**1a**–**i**).

First, we examined the 1,4-addition of **2a** on 1,2-diaza-1,3-butadienes **1a**,**f** in the presence of a catalytic amount of $ZnCl_2$ in CH_2Cl_2 at room temperature.[15a] After the disappearance of the starting 1,2-diaza-1,3-butadienes, the checking of the crude mixtures by TLC revealed the presence of two products as major components, easily separated by flash chromatography and identified as the silylated (**3a**,**b**) and the desilylated (**4a**,**e**) hydrazonic 1,4-adducts, respectively. However, the above crude reaction mixtures by treatment with tetrabutylamonium fluoride (TBAF) directly gave **4a**,**e** (Scheme 1). All attempts to isolate Diels–Alder products failed suggesting that this reaction involves a Mukaiyama–Michael reaction and not a Diels–Alder-type process.[17,18]

Scheme 1. $ZnCl_2$-Catalyzed Mukaiyama–Michael-Type Addition of Danishefsky's Diene **2a** on 1,2-Diaza-1,3-butadienes **1a**,**f**



Encouraged by these preliminary results, we enlarged the scope of the previous reaction to a series of 1,2-diaza-1,3-butadienes **1a**–**i** first testing the reactivity with the Danishefsky's diene **2a**. Thus, the Mukaiyama–Michael derivatives **4a**–**h** were obtained in good to excellent yields (Scheme 2).

Interestingly, the 1,4-adducts **4a**–**d**, bearing the ester group ($R^1 = OR$) in the α-position to the C=N moiety, with TFA in THF furnished the relevant 4*H*-1-aminopyrroles **5a**–**d** in excellent yields via intramolecular ring closure (Scheme 2).[15] It is noteworthy that the more reactive tosyl

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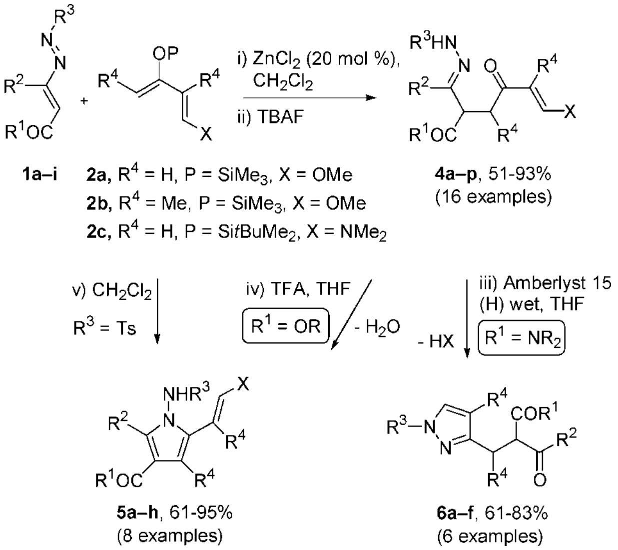
1,2-diaza-1,3-butadiene **1e** ($R^3 = Ts$) directly furnished the 4*H*-1-aminopyrrole **5e** in 61% yield without $ZnCl_2$ and/or TBAF catalysis (Scheme 2).

Scheme 2. $ZnCl_2$-Catalyzed Mukaiyama−Michael-Type Addition of 3-Siloxy-1,3-dienes **2a**−**c** on 1,2-Diaza-1,3-butadienes **1a**−**i**. Synthesis of 1-Aminopyrroles **5a**−**h** and pyrazoles **6a**−**f**

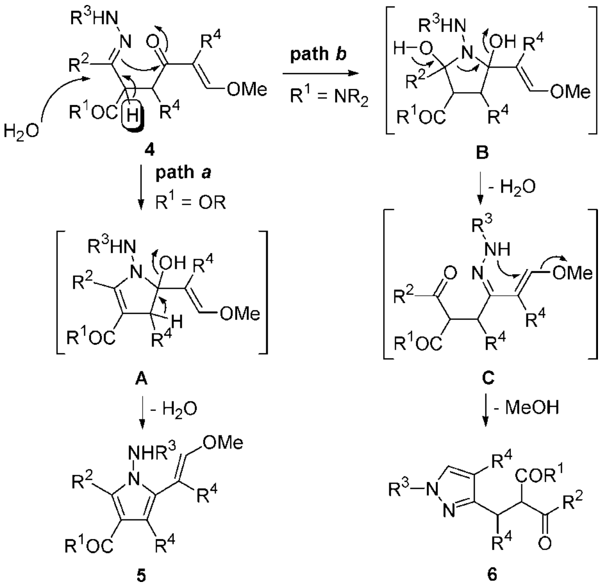


In contrast, the 1,4-adducts **4e**−**h**, containing the amide group ($R^1 = NR_2$) instead of the ester group ($R^1 = OR$), did not give the relevant 4*H*-1-aminopyrroles staying unchanged by treatment with TFA. This occurrence could be related to the expected lower acidity of the protons in the α-position to the C═N moiety of the hydrazonic adduct intermediates when the amide group replaces the ester one. Surprisingly, the treatment of the 1,4-adducts **4e**−**h** in THF with wet Amberlyst 15(H) gave the unexpected 4,5*H*-pyrazoles **6a**−**d** (Scheme 2) deriving from an "apparent" rearrangement of the azoalkene skeleton. A similar heterocyclization process has never been observed in our 30-year experience in the field of 1,2-diaza-1,3-butadienes. An X-ray diffraction study of **6a** unequivocally confirmed its structure.

The formation of **6** can be ascribed to a nucleophilic attack of a water molecule at the hydrazonic function of **4** followed by intramolecular cyclization (promoted from wet Amberlyst 15(H)) of the nitrogen on the carbonyl group to give a cyclic aminohemiacetal intermediate (**B**).

By ring opening, **B** collapses into the α,*β*-unsaturated hydrazone (**C**), furnishing an internal transfer of the hydrazone moiety. In turn, **C** aromatizes into the pyrazole **6** via an intramolecular Michael addition with loss of methanol molecule (path b, Scheme 3). However, the same 1,4-adduct **4** could furnish the 1-aminopyrrole **5** by intramolecular nucleophilic attack of the hydrazonic nitrogen (via prototropism CH/NH) at the carbonyl group producing the intermediate **A** followed by loss of water molecule (path a, Scheme 3). The alternative mechanisms of the heterocyclizations depend on a balance of the acidity of the proton in the α-position to the amide/ester (COR^1) moiety of the hydrazonic 1,4-adduct **4** and could occur via the common intermediate **B**.

Scheme 3. Mechanisms for the Formation of 1-Aminopyrrole **5** and Pyrazole **6**



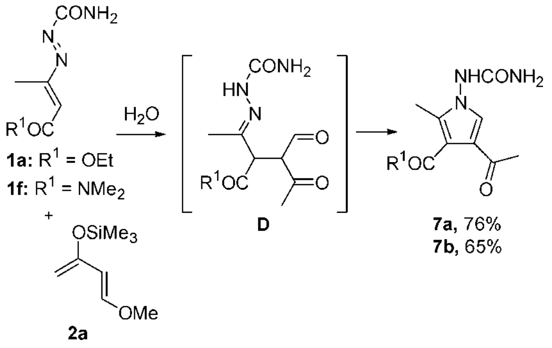
On the basis of these preliminary results, the scope of the reaction was extensively explored by using 1-methoxy-2-methyl-3-trimethylsilyloxy-1,3-pentadiene **2b**[11a] and 1-dimethylamino-3-*tert*-butyldimethylsilyloxy-1,3-butadiene **2c** (Rawal's diene).[11b–d] Both of these 3-siloxy-1,3-dienes proved effective reagents for the Mukaiyama−Michael addition on 1,2-diaza-1,3-butadienes (Scheme 2). In fact, the Danishefsky's type diene **2b** ($X = OMe$, $R^4 = Me$) reacted with 1,2-diaza-1,3-butadienes **1a**−**c**,**g**,**i** to give the 1,4-adduct intermediates **4i**−**m**, which, in turn, gave rise to different heterocyclization processes leading to 1-aminopyrroles **5f**−**h** or pyrazoles **6e**,**f** in excellent yields. Rawal's diene **2c** ($X = NMe_2$, $R^4 = H$), known to be substantially more reactive than Danishefsky's **2a** ($X = OMe$, $R^4 = H$),[11b] afforded the 1,4-adducts **4n**−**p** without Lewis acid ($ZnCl_2$) catalysis. Unfortunately, under the same heterocyclization reaction conditions, 1-aminopyrroles (**5**) and pyrazoles (**6**) were not observed, but only degradation products together with some unreacted starting materials were recovered. This particular behavior could be related to the electronic effect of the dimethylamino group in **2**. The NMe_2 group increases the nucleophilicity of **2c**, and then facilitates the formation of **4n**−**p**, but at the same time lowers the electrophilic character of the carbonylic carbon preventing both the heterocyclization processes.

It can be noted that the carbons of the reagents participate in a different way in the heterocyclization processes. In the transformations of **1a**−**i** and **2a**,**b** into **5a**−**h**, two carbons of the pyrrole ring of **5a**−**h** derive from C-3 and C-4 of the

Danishefsky's dienes **2a**,**b**, while the remaining carbons and nitrogens come from the 1,2-diaza-1,3-butadienes **1a**−**i**. On the other hand, in the transformation of **1a**−**i** and **2a**,**b** into **6a**−**f**, three carbons of the pyrazole ring derive from C-1, C-2, and C-3 of the Danishefsky's dienes **2a**,**b**, while the remaining two nitrogens come from the 1,2-diaza-1,3-butadienes **1a**−**i**.

Very interestingly, a different and unexpected behavior was observed when Danisheftsky's diene **2a** reacted with 1,2-diaza-1,3-butadienes **1a**,**f** in water and in the absence of Lewis acids. In fact, 5*H*-1-aminopyrroles **7a**,**b**, different from 4*H*-1-aminopyrroles **5a**−**h** obtained via the Mukaiyama−Michael-type addition/heterocyclization, were formed in good yields (Scheme 4). These results agree with the fact that the Danisheftsky's diene **2a** is a synthetic equivalent of 3-oxobutanal, likely because the hydrolytic process **2a** participates in the Michael addition as a masked 3-oxobutanal (**D**). Then, the following intramolecular nucleophilic attack of hydrazonic nitrogen at the highly reactive aldehydic carbonyl group produces 5*H*-aminopyrroles **7a**,**b**. These results are supported by spectroscopic evidence and are in agreement with some of our previous findings.[19]

Scheme 4. Water-Mediated Addition/Heterocyclization Reactions of Danishefsky's Diene **2a** on 1,2-Diaza-1,3-butadienes **1a**,**f**. Synthesis of 5*H*-Aminopyrroles **7a**,**b**



In the transformations of **1a**,**f** into **7a**,**b**, two carbons of the pyrrole ring of **7a**,**b** derive from C-1 and C-2 of the Danishefsky's diene **2a**, while the remaining carbons and nitrogens come from the 1,2-diaza-1,3-butadienes **1a**,**f**.

For example, different carbons of diene **2a** participate in the formation of 4*H*-1-aminopyrroles **5a**−**h** or that of 5*H*-1-aminopyrroles **7a**,**b**. Taken together, our result show that the study of Mukaiyama−Michael-type addition/heterocyclization sequence has given further examples of its synthetic utility and versatility, as a function of the experimental conditions used. In fact, we found that conditions able to furnish both 4*H*-1-aminopyrroles (**5**) and 4,5*H*-pyrazoles (**6**). Moreover, the unexpected formation of 5*H*-1-aminopyrroles (**7**) from 1,2-diaza-1,3-butadienes and Danishefsky's diene in water without Lewis acids catalysis further explains their reactivity. All azaheterocycles synthesized are highly functionalized and, therefore, can be further modified. The advantage of use the 1,2-diaza-1,3-butadienes as a building blocks in the modeling of azaheterocycles is the accessibility of the starting materials and the simplicity of the experimental procedures.

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Supporting Information Available: Experimental procedures, table of products, and full characterization for all compounds. X-ray crystallographic data (CIF) and ORTEP drawing of compound **6a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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