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Stereoselective Tandem Ring Opening of Imidazoles with Electron-Deficient Acetylenes and Water: Synthesis of Functionalized (*Z*,*Z*)-1,4-Diaza-2,5-dienes

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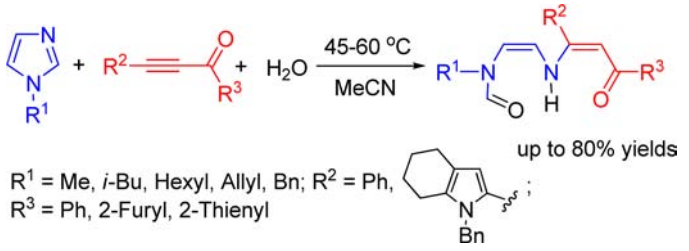
ABSTRACT



1-Substituted imidazoles undergo exceptionally facile stereoselective ring opening under the influence of electron-deficient acetylenes and water (equimolar ratio of the reactants) in MeCN at 45−60 °C without any catalysts to afford functionalized (*Z*,*Z*)-1,4-diaza-2,5-dienes, (*Z*,*Z*)-propenylaminoethenylformamides, in up to 80% yields. The reaction is rationalized to proceed in a tandem manner via zwitterionic vinyl carbanions formed by nucleophilic addition of imidazole to the triple bond. The carbanionic center is then quenched with water followed by the rearrangement of the intermediate 2-hydroxy-3-alkenylimidazolines.

Diazadienes and -trienes, particularly cyclic ones (pyridazines, pyrimidines, pyrazines and their dihydro derivatives), find enormous application in organic, bioorganic, and medicinal chemistry.[1] Their syntheses and modifications are well established and keep being developed.[2,3] Less studied and, respectively their syntheses much less elaborated, are their open-chained congeners. Meanwhile, they also attract great interest, especially isomerically pure and functionalized ones, as important ligands and synthetic building blocks.[4,5]

Most of the known diazadienes contain the C=N bonds and, hence, are actually the Schiff base type compounds.

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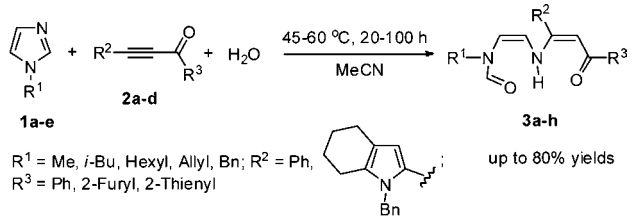
Diazadienes with both C=C bonds have been unknown until now, although their *N*-adjusent double bonds and *N* functionalities warrant rich reactivity.

Here we report our serendipitous finding that 1-substituted imidazoles **1a**–**e** under the influence of disubstituted electron-deficient acetylenes **2a**–**d** in the presence of water in MeCN without a catalyst (the **1**/**2**/water molar ratio = 1:1:1) undergo exceptionally easy (45–60 °C) ring opening to afford functionalized (*Z*,*Z*)-1,4-diaza-2,5-dienes **3a**–**h** in yields of up to 80% (Table 1).

Table 1. Synthesis of Functionalized (*Z*,*Z*)-1,4-Diaza-2,5-dienes **3** from 1-Substituted Imidazoles **1**, Electron-Deficient Acetylenes **2**, and Water



imidazole **1a-e**	acetylene **2a-d**	time (h)	diazadienes **3a-h**	yield (%)
1a	**2a**	20[a]	**3a**	66
1b	**2a**	47[a]	**3b**	50
1c	**2a**	36[a]	**3c**	64
1d	**2a**	50[a]	**3d**	60
1e	**2a**	75[a]	**3e**	68
1a	**2b**	23[b]	**3f**	66
1a	**2c**	30[b]	**3g**	80
1a	**2d**	100[c]	**3h**	15

[a] The temperature of reaction mixture was 45–50 °C. [b] The temperature of reaction mixture was 50–55 °C. [c] The temperature of reaction mixture was 55–60 °C.

The three-component reaction (Table 1) is strictly stereoselective: both alkenyl moieties are of the *Z*-configuration. In no case were the corresponding *E*-isomers detectable (^{1}H NMR) in the crude product even in trace amounts.

The yields of 1,4-diaza-2,5-dienes **3a**–**h** generally range 60–80%, sharply dropping (15%) when benzoylacetylene **2d** with 1-benzyltetrahydroindolyl substituent was employed, obviously due to its steric encumbrance. In this case, both acetylene **2d** and imidazole **1a** were mostly recovered, even after heating (55–60 °C) for 100 h. Also, the steric hindrance may explain the moderate yield (50%) in the reaction with 1-isobutylimidazole **1b**.

Noteworthy, monosubstituted (terminal) electron-deficient acetylenes almost do not give the 1,4-diaza-2,5-dienes just as minor products under the same conditions, for instance with benzoylacetylene, only about 5% of the expected 1,4-diaza-2,5-diene has been detected (^{1}H NMR) in the reaction mixture. In this case, the major isolated product (20% yield) was the trimer of benzoylacetylene, 1,3,5-tribenzoylbenzene (mp 113–115 °C, lit. mp 122 °C[6]), the other product being an oligomer of the approximate composition **1a**/benzoylacetylene/water = 1:3:5. Therefore, the main direction of this three-component reaction is the imidazole catalyzed oligomerization and hydration of the starting acetylene.

The isolated 1,4-diaza-2,5-dienes **3** are colored (dark-yellow, brown) oils (except the product **3h**, a dark-yellow powder) soluble in conventional organic solvents. Their structures have been supported by NMR (^{1}H, ^{13}C, ^{15}N) spectroscopy using 2D techniques (COSY, NOESY, HMBC, HSQC) and IR spectroscopy.

In the ^{1}H NMR spectra of adducts **3a**–**h**, singlets of H-6 protons are observed at 5.82–6.31 ppm and those of N*H* protons at 12.36–13.15 ppm. In the ^{13}C NMR spectra, the C=O group appears at 178.4–189.9, and the C=O group of formamide moiety is present at 161.3–162.9 ppm.

Configurational assignment of the synthesized 1,4-diaza-2,5-dienes **3** was carried out on the basis of 2D NOESY data. The cross-peaks between the H-2 and H-3 signals as well as those between the H-6 and *ortho*-protons of the phenyl ring suggest that all structures exist in the *Z*,*Z*-form (Figure 1).

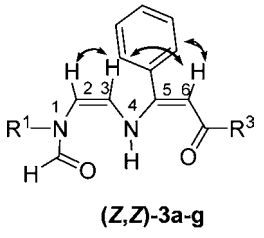


Figure 1. Cross-peaks in the 2D NOESY spectra of compounds **3a**–**g**.

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Besides, the rotation around the C−N amide bond has been recognized[7] to have a restricted character. Hence, a mixture of the *syn*- and *anti*-rotamers (ratio ~1:1) is observed in the ^{1}H and ^{13}C NMR spectra. Assignment of the rotamers in compounds **3** was performed using the 2D NOESY experiment. The cross-peak between the formyl and methyl group proton resonances is revealed in the *syn*-rotamer while the cross-peaks between the formyl proton, on the one hand, and the H-2 proton and N−H group proton, on the other hand, are present in the *anti*-rotamer (Figure 2).

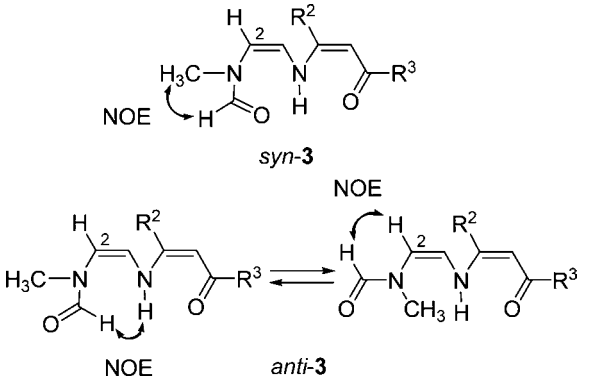
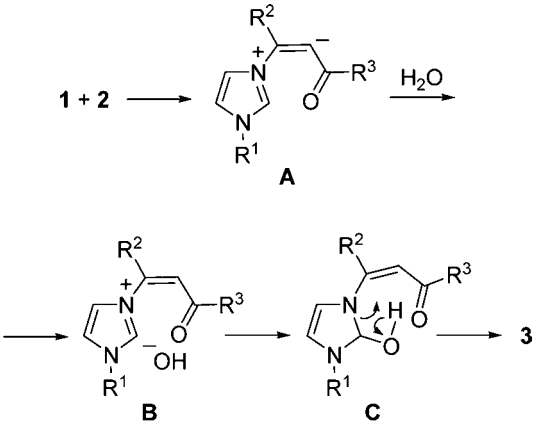


Figure 2. Cross-peaks in the 2D NOESY spectra of *syn*- and *anti*-rotamers **3**.

In the IR spectra, both of the carbonyl functions and double bonds at 1667−1683 cm^{-1} are observed as broad absorption bands.

The synthesis of 1,4-diaza-2,5-dienes, thus found, is assumed to be a three-component tandem reaction trigged by the nucleophilic attack of 1-substituted imidazole **1** at the triple bond of acetylene **2** (Scheme 1). The carbanionic center of the zwitterion **A** is quenched by the proton of water to form *N*-alkenylammonium hydroxide **B**. The nonionic form of the latter, 2-hydroxy-3-alkenylimidazoline **C**, rearranges to the final product **3** with cleavage of the imidazole ring. A somewhat

Scheme 1. Tentative Scheme of the 1,4-Diaza-2,5-diene **3** Formation from Imidazoles **1**, Electron-Deficient Acetylenes **2**, and Water



similar intermediate was postulated for the Bamberger imidazole cleavage[8a,b] under the influence of such robust electrophiles as acid chlorides[8a,b] and pyrocarbonates.[8c,d]

The stereochemistry of the reaction corresponds to the proposed mechanism. Indeed, the *Z*-configuration of the acylalkenyl moiety is in keeping with the *trans*-mode of the classic nucleophilic addition to acetylenes[9] leading to the adduct of the *Z*-configuration. The other alkenyl moiety possesses a *Z*-configuration due to its origination from the imidazole ring cleavage at the C(2)−N(3) bond.

The reaction that was revealed and conceptually the original synthesis of almost unknown 1,4-diaza-2,5-dienes based on this reaction are the results of our systematic studies[10] of the synthetic strategy using zwitterionic vinyl carbaniones, the adducts of neutral nucleophiles to acetylene, as versatile building blocks in organic synthesis.

In conclusion, stereoselective tandem ring opening of 1-substituted imidazoles with disubstituted electron-deficient acetylenes and water under mild conditions to give functionalized 1,4-diaza-2,5-dienes in modest to good yields has been unveiled. The previously unknown (*Z*,*Z*)-diazadienes bearing the formyl and acyl functions, thus synthesized, represent a promising family of building blocks for organic synthesis. The results obtained contribute to the basic chemistry of both imidazoles and acetylenes.

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Supporting Information Available. Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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