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COMMUNICATION

Self condensation of enamines mediated by acetylation. A novel approach to 1-(azol-5-yl)-(1*E*,3*Z*)-butadiene-4-*N*,*N*-dimethylamines†‡

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Novel self-condensation of 3-(azol-5-yl)-1,1-dimethylenamines has been found to form new C–C bonds leading to 2,4-(1,2,3-triazole-1,2,3-thiadiazole-3-phenylisothiazole)-(1*E*,3*Z*)-5-yl-butadiene-1-amines. The discovered reaction represents a new example of C–H functionalization in unsaturated systems and can serve an efficient synthetic approach to rational design of new 2,4-(diazole-5-yl)-dieneamines.

1,3-Dienes are, undoubtedly, an important class of compounds due to their applications in the preparation of dyes, UV screens, and drugs. They are key players in pericyclic and cyclocondensation processes and widely used for the synthesis of complex natural and unnatural products.[1] Therefore, the development of methods for the stereoselective synthesis of dienes has been an area of long-standing importance to chemists. Transition-metal-catalyzed sp^2–sp^2 cross-coupling reactions are extremely powerful tools for diene synthesis but they typically require the alkene geometry to be set in the form of a vinyl derivative prior to bond formation.[2] Several other methods are known in the literature to design dienes.[3]

Dieneamines due to their similarity to both enamines and dienes are prospective substrates for Diels–Alder reactions and other type cyclization processes.[4] Meantime the known methods for the synthesis of dieneamines are limited by reaction of acroleine with secondary amines,[4] 1,1-dimethyl-3-acetyleneamine with malononitrile,[5] enamines with β-trifluoroacetylvinyl ether[6] and 2-methyleneindolines with β-nitroenamines[7] catalyzed by cerium chloride. The first method led to a mixture of stereoisomers and others were not applicable for the preparation of a series of compounds. Therefore, the search for new stereoselective routes to dieneamines remains a synthetic challenge.

To the best of our knowledge, no explicit examples for the self-condensation of enamines are presented in the literature. Furthermore, no enamines with an azole ring at position 3 are described in the literature apart from our preliminary report[8] and patented reaction of isoxazole-3-1,1-dimethylenamine.[8] Because of the push–pull character of enamines[9] we proposed that their self-condensation could represent a simple, effective and universal method for the synthesis of dieneamines.

Our initial efforts were focused on the synthesis of enamines bearing 1,2,3-triazole moiety in position 3 of the molecule. 1,2,3-Triazoles are a very promising class of organic chemicals widely used in modern pharmacology, medicinal and materials chemistry, and other fields.[10] As a result, 1,2,3-triazole forming reactions have recently enjoyed much attention,[11] particularly those which based on the "click reaction" strategy.[12] On the other hand, the 1,2,3-triazoles containing either enamine or dieneamine fragments are not presented in the literature.

The starting enamines **3a–d** were prepared from 5-methyl-1,2,3-triazoles[13] **1a–d** by reaction with Brederek's reagent[14] **2** in a sealed tube at 100–110 °C. Enamines formation was shown to proceed in stereospecific manner to give the single reaction products (*E*)-5-(2-(dimethylamino)vinyl)-1,2,3-triazoles **3a–d** in high yields (Scheme 1). Their structure as *trans* isomer comes from the value of coupling constant (J = 13.2–13.6 Hz) for protons of ene fragment in ^{1}H NMR spectra (see ESI‡).

In order to obtain 1-aryl-1,2,3-triazoles bearing 3-oxobut-1-en-2-yl moiety **5** we studied the reaction of enamines **3a–d** with acetyl chloride at room temperature. To our surprise the formation of dieneamines **4a–d** were observed instead of expected ketones **5**. As a result, dimethyl 5,5′-((1*E*,3*Z*)-4-(dimethylamino)-buta-1,3-diene-1,3-diyl)bis(1-aryl-1*H*-1,2,3-triazole-4-carboxylates) **4a–d** were isolated in 60–84% yields as the only products. The rate of the reaction is shown to depend on the concentration of acetyl chloride. The increase of its concentration leads to the increase of both the rate of the reaction and yields of the formed dienes **4a–d**. The replacement of acetyl chloride by acetic acid in reaction of enamine **3d** caused drastic decrease the yield of dieneamine **4d** and formation of tar-like products containing according mass-spectra the product of hydrolysis of dieneamine,

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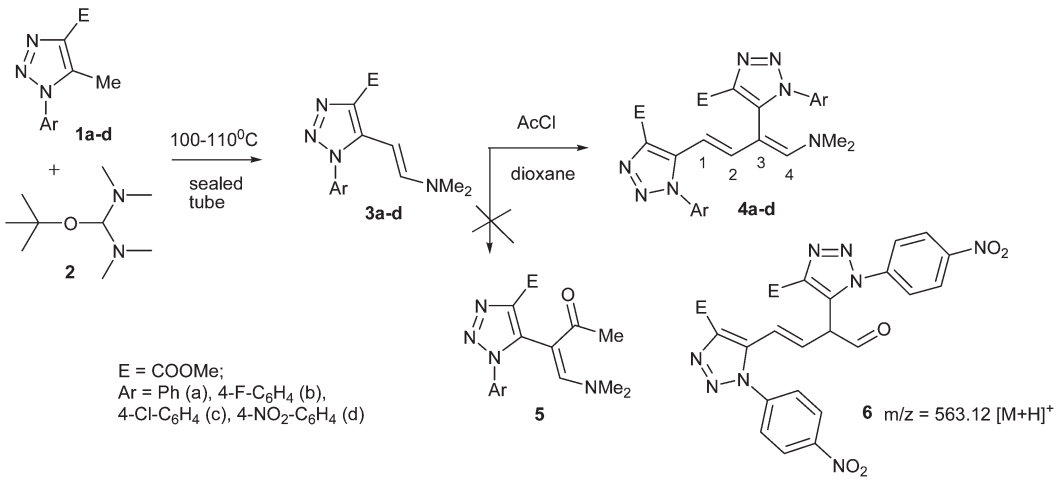
‡Electronic supplementary information (ESI) available: Experimental protocols are placed to Supporting materials. CCDC 867109 for compound **4a**. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob25331c



Scheme 1 Synthesis of enamines **3a–d** and dienes **4a–d**.

aldehyde **6**. All attempts to isolate pure compound **6** failed because of its instability.

The structures of dieneamines **4a–d** were completely confirmed by the combination of ^{1}H and ^{13}C NMR spectroscopy, mass-spectrometry and X-ray analysis. The presence of diene fragment in compounds **4a–d** was confirmed by the 2D HMBC and HMQC NMR experiments where cross-peaks were registered between four ethylene type carbons C_1–C_4 and three hydrogens atoms H_1, H_2, H_4: atom H_1 has cross-peaks with C_1, C_2 and C_3; H_2 – with C_1, C_2, C_3 and C_4; H_4 – with C_4, C_3 and C_2 (see ESI‡). The connections of the diene system with triazole rings was confirmed by cross-peaks between H_1 with both $C_{5'}$ and $C_{4'}$ and H_4 with $C_{5''}$ and $C_{4''}$. All the signals in the ^{1}H and ^{13}C NMR spectra of adducts **4** were assigned on the basis of 2D HSQC and HMBC experiments.

Considering the isomerization in butadienes, dieneamines **4a–d** are proposed to exist in the form of eight isomers (see ESI‡). It is worth noting that data from both NMR spectroscopy and TLC confirm the existence of compounds **4a–d** in the form of a single isomer.

The coupling constants for protons of $C_1H{=}C_2H$ double bonds are 15–16 Hz that is in accordance with *trans* configuration of $C_1{=}C_2$ bond and allowed one ruled out from consideration the four isomers bearing this fragment with the *cis* configuration of protons. The proton decoupled ^{13}C NMR spectra of compound **4d** were recorded and the spin–spin coupling constants $^{3}J_{C_{5'}-H_2} = 2.0$ Hz, $^{3}J_{C_{4'}-H_1} = 3.0$ Hz, $^{3}J_{C_4-H_2} = 7.2$ Hz and $^{3}J_{C_{5''}-H_4} = 7.2$ Hz were found. These data are in agreement with *trans*-E-*cis* form of prepared compounds. Consequently, the dimethylamino group and triazole ring are in *cis*-position. Configuration of prepared compounds as *trans*-E-*cis* isomers were also confirmed by NOESY experiments with dieneamine **4c** (Fig. 1) where the interaction of $C_{(4)}$–H with both $C_{(2)}$–H and protons of $(CH_3)_2N$ group were registered as cross-peaks of low intensity. The structure of dieneamines **4a–d** was unambiguously confirmed by X-ray analysis (Fig. 2) for crystal of dieneamine **4a**.

The analyzed crystal was found to be an adduct of two independent molecules of compound **4a**.

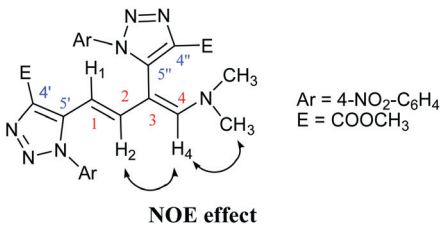


Fig. 1 NOE interaction of hydrogen atoms in butadiene–amine fragment.

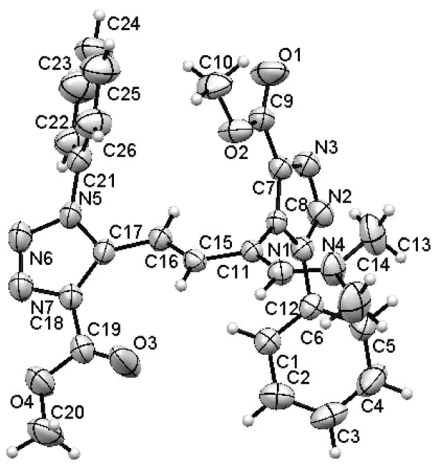


Fig. 2 Structure of **4a** in thermal ellipsoids of 50% probability.

Fig. 2 shows the molecular structure of one independent unit (molecule A) of compound **4a** determined by X-ray crystallography. The second unit (molecule B) has in general analogous configuration (see ESI‡). Butadienedimethylamino chains of molecules are planar with maximal deviations of its atoms from least-squares planes C(11)C(12)C(13)C(14)C(15)C(16)N(4) in molecule A equal 0.088 Å (for C(11)).

To expand the scope we involved 3-(1,2,3-thiadiazole)-1,1-dimethylaminoenamine **8** in the reaction. Enamine **8** was

prepared similar to compounds **3a–d** from corresponding 5-methyl-1,2,3-thiadiazole **7**[15] by reaction with Bredereck's reagent. The enamine **8** was treated with acetyl chloride at room temperature for 24 h which afforded butadieneamine **9** in 80% yield (Scheme 2).

The structure of compound **9** was confirmed by ^{1}H and ^{13}C NMR spectroscopy and mass-spectrometry. The structure of prepared compound **9** as *trans*-E-*cis* isomer was confirmed by HMBC, HMQC and NOE experiment (see ESI‡). The proton decoupled ^{13}C NMR spectrum of compound **9** is also in agreement with *trans*-E-*cis* form of prepared dieneamine **9**.

The signals for dieneamine fragment in their NMR spectra are similar to those of 1,2,3-triazole derivatives **4** but shifted to downfield: signals of C_1H and C_4H for 1.2 and 0.7 ppm, respectively and signals of C_1–C_4 are shifted for 1–4 ppm. The both NMR data and bathochromic shift of the long wave band in UV spectrum of dieneamine **9** (Fig. 3) in comparison with **4a** signified a rather stronger conjugation in thiadiazoledieneamine **9** than in triazole **4a**. Bathochromic shifts of long wave absorption bands in UV spectra of dieneamines **4a** and **9** respectively for 39 and 100 nm are observed as compared with enamine **3a**. It can be explained by elongation of the conjugation chain in the dieneamines. The mechanism explaining the formation of dieneamines **4** and **9** as *cis*-E-*trans* isomers is presented in Scheme 3. First, acylation or protonation of enamine **A** afforded intermediate **B** containing quaternary nitrogen atom. The latter reacted with starting compound **A** *via* two step nucleophilic substitution (addition + elimination) mechanism to yield intermediate **D**. As a result sp^2 hybridization of C_2 was switched to sp^3 and new C–C bond was formed. We assumed that change of conformation **D** → **E** *via* rotation around new σ-bond was required for tautomerization (likely *via* 1,3-H-shift) to form intermediate **F**. Deprotonation of intermediate **F** accomplished this transformation and resulted in final product **G** that was found by AM1 calculations (see ESI‡) the most stable among eight possible isomers for compounds **4** and **9**.

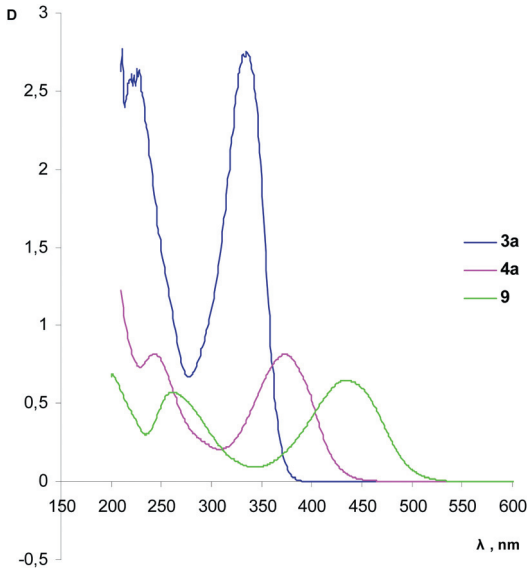
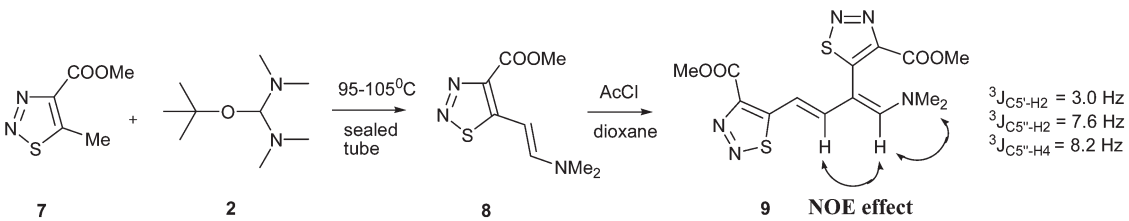
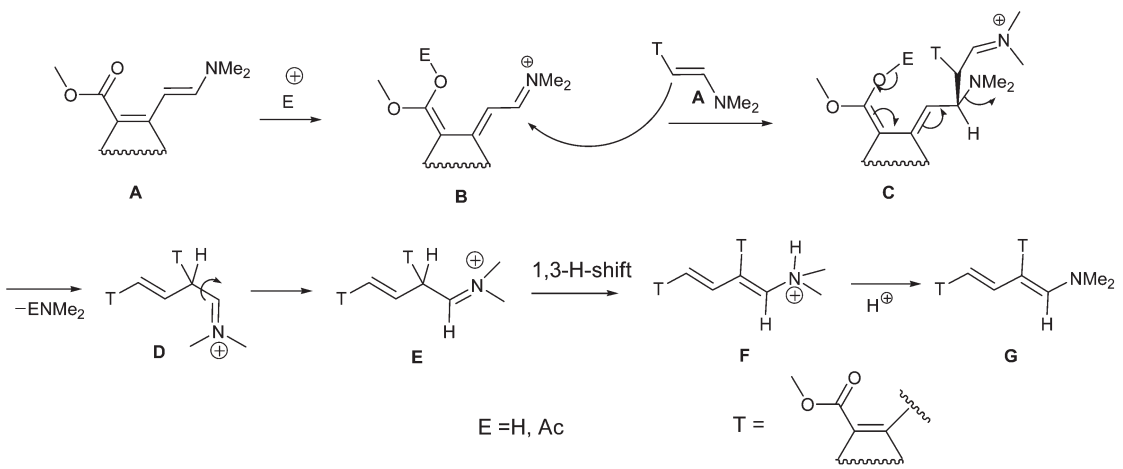


Fig. 3 UV spectra of enamine **3a** and dieneamines **4a** and **9**.



Scheme 2 The synthesis of enamine **8** and their reaction with acetyl chloride.



Scheme 3 Proposed mechanism for transformation of enamines **A** to dienes **G**.

Further development of this reaction, including studies on the reaction mechanism and scope, is being pursued and will be reported in due course.

Indeed, novel reaction of self-condensation for 3-(azol-5-yl)-1,1-dimethyleneamines has been found to afford 2,4-(1,2,3-triazole-1,2,3-thiadiazole-isothiazole)-(1*E*,3*Z*)-5-yl-butadiene-1-amines. The discovered reaction represents a new example of C–H functionalization in unsaturated systems and can serve an efficient synthetic approach to rational design of new 2,4-(diazole-5-yl)-dieneamines.

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