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Self-condensation of β-(isoxazol-5-yl) enamines under treatment with acetyl chloride and acids. Synthesis of novel 1,3-diisoxazolyl-1,3-dieneamines and 1,3,5-triisoxazolyl benzenes

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ABSTRACT

Two directions for self-condensation of β-(isoxazol-5-yl) enamines under treatment with either acetyl chloride or acids were found leading to new 1,3-diisoxazolyl-1,3-dieneamines and 1,3,5-triisoxazolyl benzenes. The effect of solvent, acid, temperature and the reaction time on the ratio of reaction products were investigated. Trans-*E*-cis configuration of prepared 1,3-diisoxazolyl-1,3-dieneamines was unambiguously confirmed by 2D NMR spectra and X-ray analysis. A new mechanism of 1,3-diisoxazolyl-1,3-dieneamines formation was proposed.

1. Introduction

Dieneamines due to their similarity to both enamines and dienes are prospective substrates for cycloaddition reactions and other type cyclization processes.[1–4] They are also known to be used in the strategy for HOMO activation via amine organo-catalysis of asymmetric Diels–Alder reaction.[5] Therefore reactions of dieneamines could find wide application in modification of natural compounds and interesting intermediates in drug discovery. The known methods for the synthesis of dieneamines are not numerous and include reactions of acroleine with secondary amines,[1–4] 1,1-dimethyl-3-acetyleneamine with malononitrile,[6] enamines with β-trifluoroacetylvinyl ether,[7] and 2-methyleneindolines with β-nitroenamines[8] catalyzed by cerium chloride. Because they have some limitations and are not applicable for the synthesis of large series of compounds, the search of new stereoselective routes to dieneamines remains a synthetic challenge. Quite recently, we have found a new approach to 1,3-diazolyl dieneamines in 1,2,3-triazol-5-yl and thiadiazol-5-yl series based on the novel self-condensation of β-azolyl enamines mediated by acetylation.[9] The scope and limitations of this method are not known. Also it is not clear whether the other compounds can catalyze the process of the formation of 1,3-dieneamines from β-enamines.

The isoxazole ring is an important pharmacophore in modern drug discovery. Isoxazoles are known to show anticancer,[10,11] antibacterial,[12] antiplatelet activity,[13] activity on human β-adrenergic receptors,[14] analgesic and antimicrobial activity,[15] miscellaneous activity,[16,17] anti-inflammatory, and immunomodulatory activity.[18]

Therefore our initial efforts to expand the scope of the self-condensation of dieneamines were focused on the synthesis of 1,3-dieneamines bearing isoxazole rings at positions 2 and 4 of the molecule. Data on the ability of sulfonyl chlorides, hydrochloric and *p*-toluene sulfonic acid, and BF_3 to mediate self-condensation of dieneamines are also reported.

2. Results and discussion

The starting enamines **2a**–**i** were prepared from alkyl 5-methyl-3-arylisoxazole-4-carboxylates **1a**–**i** by the reaction with dimethyl formamide dimethyl acetal (DMF–DMA) in the presence of *N*-methylimidazole at 80 °C.[18–20] Enamines formation was shown to

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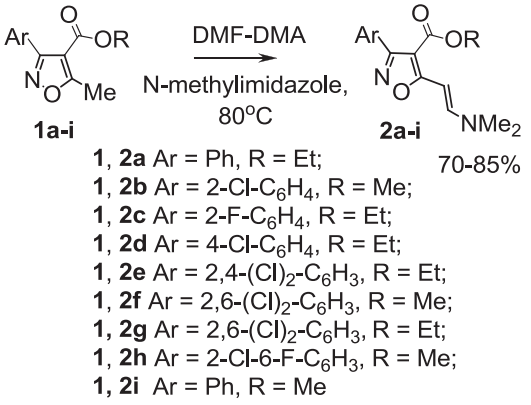
proceed in stereospecific manner to give the single reaction products (*E*)-alkyl-3-(2-aryl)-5-(2-(dimethylamino)vinyl)isoxazole-4-carboxylates **2a**–**i** in high yields (Scheme 1). Their assigned structure as the trans-isomers is deduced from the coupling constant (J=12.0–16.0 Hz) for protons of ene fragment in ^{1}H NMR spectra (see Experimental section and Supplementary data).



Scheme 1. Synthesis of enamines **2a**–**i**.

The prepared isoxazolyl enamines **2a**–**h** were examined for ability to undergo self-condensation reaction in the presence of acetyl chloride in anhydrous 1,4-dioxane in the conditions found earlier for the syntheses of 1,2,3-triazolyl and 1,2,3-thiadiazolyl dieneamines.[9] To our delight the novel diethyl 5,5′-((1*E*,3*Z*)-4-(dimethylamino)buta-1,3-diene-1,3-diyl)bis(3-phenylisoxazole-4-carboxylate) **3a** was stereoselectively produced in 80% isolated yield (Table 1, entry 1). In contrast to results found for **2a**, self-condensation of enamine **2b** underwent via two directions to form the mixture of dieneamine **3b** and the new product of the reaction, 1,3,5-triisoxazolyl benzene **4b** in 1:1 ratio in 79% total yield (Table 1, entry 2). The ratio of the compounds **3** and **4** depends on both nature of aryl and on the temperature used. Generally the increase of temperature leads to increase of the yield of trisubstituted benzenes **4**. Remarkably, that 2,6-dichloroaryl derivative **2e** afforded the single product **3e** both at room temperature and at 50 °C while 2-chloro-6-fluoro derivative **2h** furnished diene **3h** at room temperature and compound **4h** as a single product at 50 °C and long period of the reaction (Table 1, entry 8). It looks like dieneamines **3** are kinetic and benzenes of type **4** are thermodynamic products of the reaction.

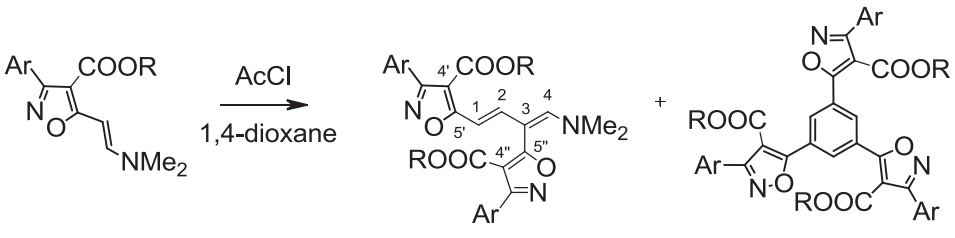
The structures of dieneamines **3a**–**h** were confirmed by the combination of ^{1}H and ^{13}C NMR spectroscopy, mass-spectrometry, and X-ray analysis. The NMR spectra for products **3a**–**h** demonstrate that all of the compounds belong to the same structural type. Thus, the ^{1}H NMR spectra contain doublets of the C^1–H protons at 6.30–6.43 ppm, singlets of the C^4–H protons at 6.95–7.03 ppm, doublets of C^2–H protons at 7.50–7.70 ppm, broad singlets of the protons of $N(CH_3)_2$ groups at 2.74–2.95 ppm, and signals of the protons of alkoxycarbonile groups and aromatic rings in the corresponding areas. The presence of a diene fragment in compounds **3a**–**h** was confirmed by the 2D HMBC and HSQC NMR experiments for products **3f** and **3h** 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 Supplementary data). The connections of the diene system with the isoxazole rings are confirmed by cross-peaks between H^1 with both $C^{5'}$ and $C^{4'}$ and H^4 with $C^{5''}$ and $C^{4''}$ also. The coupling constants for protons of C^1H=C^2H double bonds are 15.2–16.0 Hz that is in accordance with trans-configuration of C^1=C^2 bond and allowed one to rule out from consideration the four isomers bearing this fragment with the cis configuration of protons.

The ^{13}C NMR spectra contain signals of C^3 at 93.6–94.0 ppm, C^1 at 102.2–102.4 ppm, C^2 at 141.7–142.0 ppm, C=O at 161.0–162.0 ppm and this is in agreement with literature data for these groups in similar compounds.[9] Signals of carbon atoms in ^{13}C NMR spectra for $N(CH_3)_2$ groups of compounds **3** were not decoupled but revealed from HSQC spectra.

The configuration of the prepared compounds as trans-*E*-cis isomers was also confirmed by NOESY experiments with dieneamine **3f** where the interaction of C^4–H with both C^2–H and protons of $(CH_3)_2N$ group were registered as cross-peaks (see Supplementary data). The structure of dieneamines **3a**–**h** is further supported by X-ray analysis (Fig. 1) for the crystal of dieneamine **3e**.

According to the X-ray data, compound **3e** is crystallized in centrosymmetric space group. The molecule is non-planar (Fig. 1), it has an *S*-trans-configuration of its diene moiety, a planar configuration of its enamine moiety and is characterized by disordering

Table 1
Self-condensation of enamines **2a**–**h** to dienes **3a**–**h** and benzenes **4a**–**e**,**h** under action of acetyl chloride



Entry	Enamine	Diene **3**[a], yield	Benzene **4**[a], yield
1	**2a**	**3a**, Ar=Ph, R=Et, 80%	**4a**, Ar=Ph, R=Et, 16%[b]
2	**2b**	**3b**, Ar=2-Cl–C_6H_4, R=Me, 40%	**4b**, Ar=2-Cl–C_6H_4, R=Me, 39%
3	**2c**	**3c**, Ar=2-F–C_6H_4, R=Et, 30%	**4c**, Ar=2-F–C_6H_4, R=Et, 9%
4	**2d**	**3d**, Ar=4-Cl–C_6H_4, R=Et, 54%	**4d**, Ar=4-Cl–C_6H_4, R=Et, 35%
5	**2e**	**3e**, Ar=2,4-$(Cl)_2$–C_6H_3, R=Et, 64%	**4e**, Ar=2,4-$(Cl)_2$–C_6H_4, R=Et, 12%
6	**2f**	**3f**, Ar=2,6-$(Cl)_2$–C_6H_3, R=Me, 61%, (96%[b])	The product was not formed
7	**2g**	**3g**, Ar=2,6-$(Cl)_2$–C_6H_3, R=Et, 81%	The product was not formed
8	**2h**	**3h**, Ar=2-Cl–6-F–C_6H_3, R=Me, 80%	**4h**[b], Ar=2-Cl–6-F–C_6H_3, R=Me, 55%

[a] Reactions were carried out with 1.0 mmol of enamines **2** and 3.0 mmol of acetyl chloride in anhydrous 1,4-dioxane (4 mL) at room temperature for 20–22 h.
[b] The reaction was carried out at 50 °C for 8 h (**3f**), 25 h (**4a**), and 9 days (**4h**).

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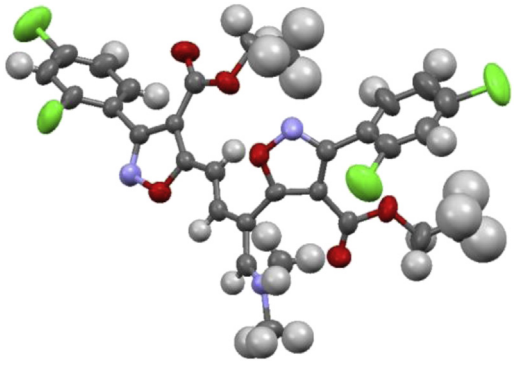

Fig. 1. X-ray structure of compound **3e**.

of *m*-dichlorophenyl in positions **2** with a coefficient of occupancy 0.93/0.07. Molecular packing is formed without any shortened intermolecular contacts (see Supplementary data).

The structures of the 1,3,5-triisoxazolyl benzenes **4** were deduced from their ^{1}H and ^{13}C NMR and mass spectra. Further confirmation of the structure of **4** came from the analysis of single-crystal X-ray data of **4h** (Fig. 2). The ^{1}H NMR spectra of benzenes **4a**–**e**,**h**,**i** revealed three kinds of protons: three protons singlet in the range of 8.74–8.98 ppm corresponding to three protons at 2,4,6-positions of the benzene ring, multiplets at 7.20–7.70 ppm belonging to aromatic protons of aryls at position 3 of isoxazole rings, and signals of protons corresponding alkoxy groups in upfield. The ^{13}C NMR spectra of benzenes **4a**–**e**,**h**,**i** show signals of carbon atoms of aromatic rings at 109.8–163.6 ppm including two types of signals of carbons of symmetrically substituted benzene ring, carbons atoms of alkoxy groups at 13.6–61.8 (OCH_2CH_3) ppm and 52.4–52.8 (OCH_3) ppm, and characteristic signals of the C=O the carbons atoms at 170.3–170.6 ppm.

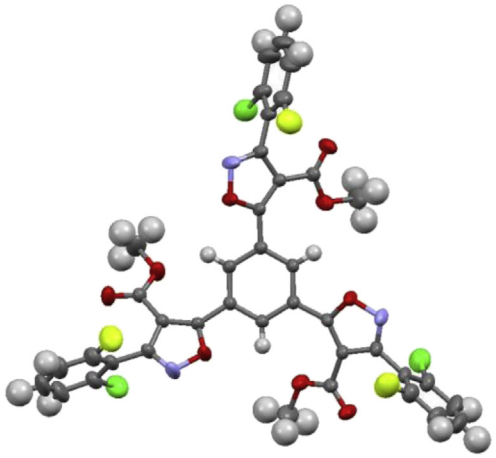

Fig. 2. X-ray structure of compound **4h**.

In contrast to dieneamines **3f**,**g**, which were prepared in high yields from enamines **2f**,**g**, all our attempts to prepare benzenes **4f**,**g** failed (Table 1, entries 6 and 7).

According to the X-ray diffraction data the compound **4h** is crystallized in centrosymmetric space group. Molecule of the compound **4h** is placed in partial position on threefold axis (Fig. 2). Cl- and F-substituents of arene fragment are disordered in two positions with coefficients of occupancy 0.75/0.25. Bond distances and angles are typical for these compounds. The molecular packing has disordered solvent voids included in the refinement by SQUEEZE procedure of program PLATON.[21]

The most closely related published work to this was reported by Elnagdi[22] and Elgharmy,[23] in their synthesis of 1,3,5-triaroyl benzenes by the condensation of enaminones (3-(dimethylamino)-1-phenylprop-2-en-1-one) in acetic acid. Interestingly, one of the mechanisms proposed by Elgharmy includes the formation of intermediate 1,3-dibenzoyl dieneamines, which were neither isolated nor spectroscopy identified.

In contrast, dieneamines **3** were found to be rather stable products. We have involved **3b** in reaction with enamines **2b** in the presence of acetyl chloride to form compound **4b** in 60% yield (Scheme 2).

Monitoring of the transformation of various enamines **2** at 50 °C by TLC has shown the initial fast formation of dieneamines **3** followed by a slow formation of compounds **4** and disappearance of **2**. Both of these experiments are in a good agreement with [4+2] cycloaddition mechanism of the reaction.

It should be specially noted the method found here for the synthesis of trisubstituted benzenes **4** can be used in supramolecular chemistry for the preparation of dendrimers.[24–27] To find optimal conditions for the syntheses of amino dienes **3** and 1,3,5-trisubstituted benzenes **4** we have studied the ratio of products **3a** to **4a** formed from enamine **2a** depending on the nature of the solvent, catalyst, temperature and time of the reaction (see the full report in Table 1 of the Supplementary data). Tosyl chloride and thionyl chloride were found inactive. On the contrary, hydrochloric and *p*-toluene sulfonic acids (PTSA), and trifluoroborane (BF_3) were shown to mediate self-condensation of enamines **2a**. Albeit, the use of 2 equiv of PTSA led to formation of benzene **4a** in low yield accompanied by tar-like impurities. On the other hand the use of 2.2 equiv of HCl led to **3a** in 70% yield along to 10% of benzene **4a**. Reaction of enamine **2i** with 1.2 equiv of BF_3 methyl etherate at 70 °C afforded benzene **4i** in 80% yield.

The use of acetyl chloride is the most effective for the synthesis of both dieneamine **3a** and benzene **4a**. The best results for the synthesis of dieneamine **3a** were obtained in anhydrous 1,4-dioxane in the presence of 3 equiv of acetyl chloride. Benzene **4a** was obtained in highest yield either with the use of 3 equiv of acetyl chloride in anhydrous 1,4-dioxane or in neat acetyl chloride. Replacement of 1,4-dioxane by other solvents and increase of the temperature led to decrease of the yield for compounds **3**, **4** due to the formation of the tar-like products.

To expand the reaction of self-condensation to enamines of isothiazole series we treated (*E*)-5-(2-(dimethylamino)vinyl)-3-phenylisothiazole-4-carbonitrile **5a**[28] with acetyl chloride at 50–55°C for 16 h. In contrast to the self-condensation of β-isoxazolyl enamines the reaction of β-isothiazolyl enamine **5a** led to a mixture of a several compounds that after separation by column chromatography and further double crystallization afforded butadieneamine **6** in 25% yield (Scheme 3). Furthermore, reaction of (*E*)-5-(2-(dimethylamino)vinyl)-3-phenylisothiazole-4-carbonitrile **5b** with acetyl chloride gave a complex mixture of inseparable compounds.

The structure of compound **6** was confirmed by ^{1}H and ^{13}C NMR spectroscopy, mass-spectrometry, and X-ray analysis.

The signals for dieneamine fragment in their ^{13}C NMR spectra are similar to those of isoxazole derivatives **3** but shifted up-field: signals for C^1–H and C^2–H by 0.05 and 0.48 ppm, respectively, and signal of C^4–H is shifted down-field by 0.04 ppm. The coupling constants for protons of $C^1H{=}C^2H$ double bonds are 15.6 Hz that is in accordance with trans-configuration of $C^1{=}C^2$ bond.

Final confirmation of the structure of **6** came from the analysis of single-crystal X-ray data of **6**.

According to the X-ray data, compound **9** is crystallized in centrosymmetric space group. A general view of the molecule and numeration of atoms is presented in Fig. 3.

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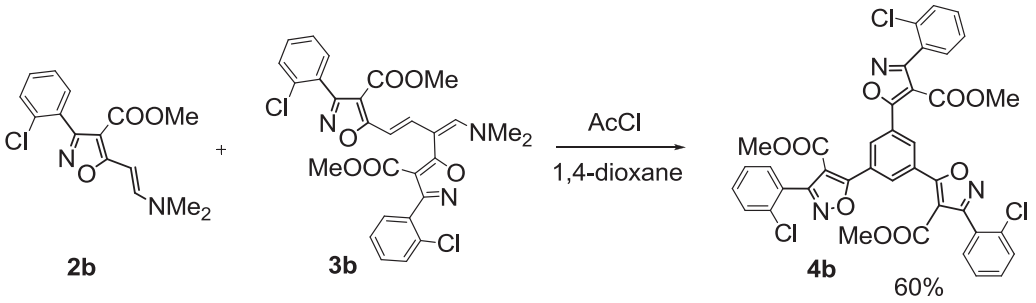
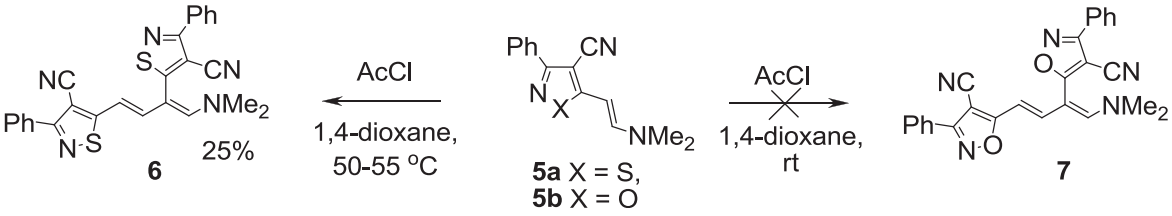


Scheme 2. [4+2] Cycloaddition of enamine **2b** to dieneamine **3b** leading to benzene **4b**.



Scheme 3. Transformation of enamines **5a**,**b** under action of acetyl chloride.

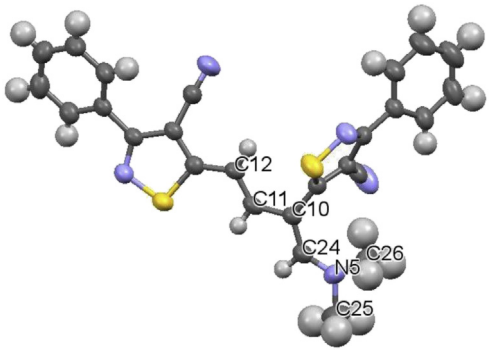
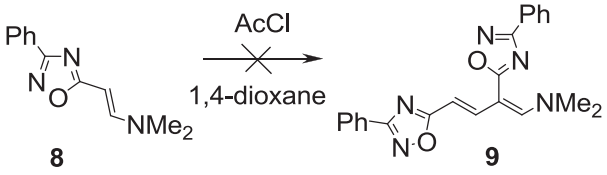


Fig. 3. View of molecule **6** according to X-ray data.



Scheme 4. Failed attempt for the preparation of dieneamine **9**.

Bonds distances and angles are typical for this class of compound. In particular, length of sp^2-sp^2 bond in *S*-trans-diene system C(10)C(11) 1.436(3) Å is typical for conjugated system. Dimethyl amine moiety has strong conjugation with diene system and exists in planar geometry: deviation of N(5) atom from plane C(24)C(25)C(26) is 0.062 Å. Angle between plane of diene system and thiazole ring at C(10) in compound is 73.3°, while for thiazole in compound at C(12) it is 9.5°. However, no significant distinction in the bond distance and the angle between similar moieties are observed, suggesting that conjugation of the thiazole at C(12) atom also is not significant. The molecular packing has no any specific intermolecular contacts or stereometry.

All our attempts to prepare 2,4-di-(oxazole-5-yl)dienamine **9** by self-condensations of enamine **8** using the optimal conditions found for the synthesis of dienamines **3** failed (Scheme 4). Starting 1,2,4-oxadiazol-5-yl-ethenamine **8** was recovered from the reaction mixture only.

Obviously the presence of a carbonyl group in the γ-position relative to *tert*-amine is required for the self-condensation into dieneamines to proceed. The fact that the self-condensation of enamines is mediated, not only with acetyl chloride (described earlier[9]) but with acids and Lewis acids as well expands our knowledge of this process and of mechanism of the reaction (Scheme 5). Therefore we assume the first step of the reaction to involve the interaction of lone pair of electrons of carbonyl oxygen atom with electrophilic specie **E** no matter whether it is acetyl cation, proton from a mineral acid or a Lewis acid. Further interaction of cationic specie **C** derived from enamine **2A** with intact enamine **2A** leads to formation of a new σ-bond to afford specie **D** bearing a positive charge at another nitrogen atom. The latter can undergo an elimination of dimethyl amine that is favored by the presence of an acid/acetyl chloride, in medium. Most probably this step is rate-limiting one of the overall process. It is believed that elimination of dimethyl amine is also enhanced by formation of a long π-conjugated system in specie **E**. The elimination of E^+ can automatically occur to form the final product **3** (Scheme 5). We have proved that dieneamines **3** are intermediates in the synthesis of benzenes **4** from enamines **2** (see above). In their turn reactions of dieneamines **3** with enamines **2** can undergo via two different mechanisms to furnish first either cyclohexenes **F** (by [4+2] cycloaddition) or trienes **G** (similar to formation of dieneamines **3** from enamines). Elimination of two molecules of dimethyl amine from cyclohexene **F** can finalize the transformation of dienes **3** to benzenes **4**. Alternatively, trienes **G** can afford benzenes **4** by elimination of dimethyl amine via two-step process involving 1,6-electrocyclic reaction.

3. Conclusions

The unusual reactivity of β-azolyl enamines in respect to acetyl chloride, hydrochloric, and *p*-toluene sulfonic acid and trifluoroboran methyl etherate is described. β-Azolyl enamines when treated with these reagents undergo self-condensation to form either single 1,3-diazolyl dieneamines and 1,3,5-triazolyl benzenes

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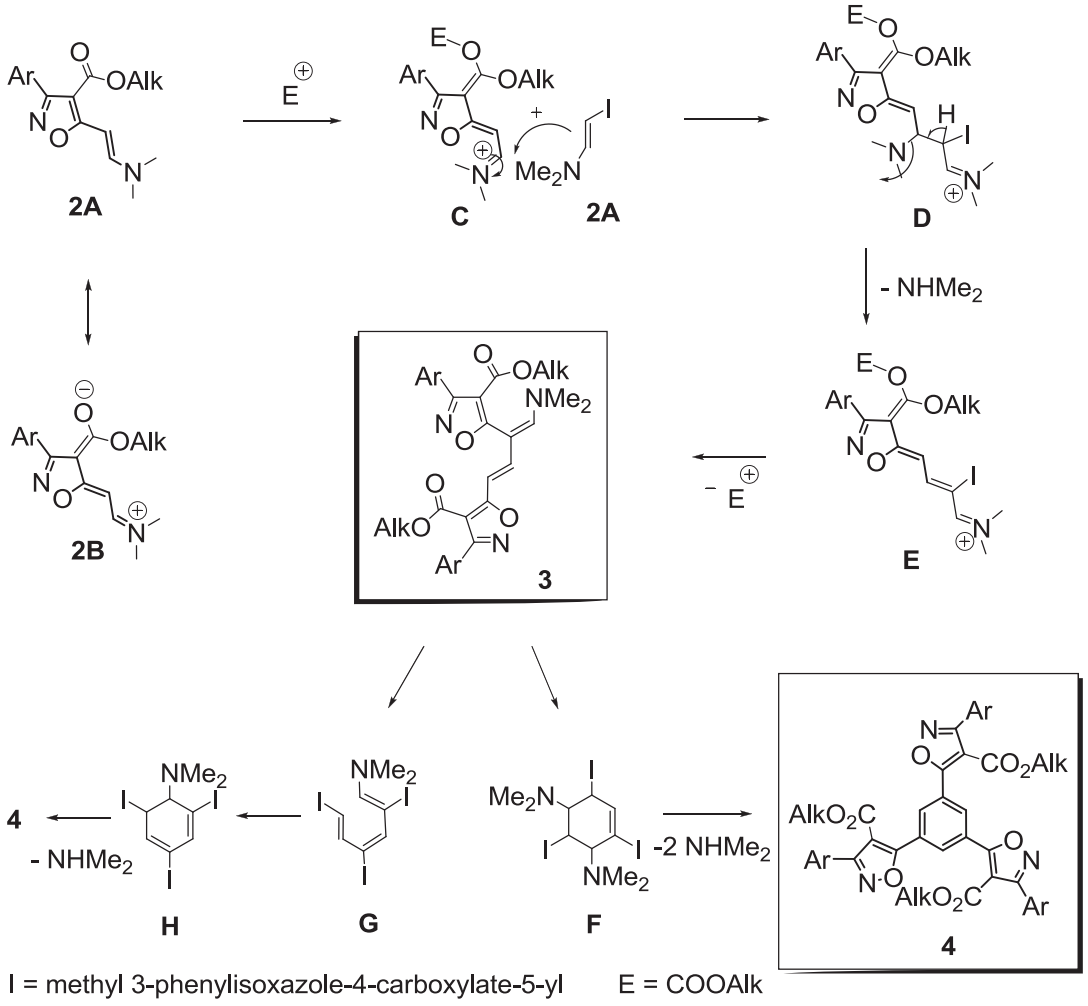

Scheme 5. Plausible mechanisms for the formation of dieneamine **3** and benzenes **4**.

or their mixtures depending on the both nature of azole ring and conditions of the reaction.

4. Experimental section

4.1. General

^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance II spectrometer in $CDCl_3$ or DMSO-d_6 (400 and 100 MHz, respectively) using Me_4Si as an internal standard. Mass spectrometric data (MS) were obtained on Bruker Daltonics MicrOTOF-Q II with an electrospray ionization source (ESI-MS). UV spectra were recorded with a Perkin–Elmer Lambda 50 UV/VIS spectrometer. Microanalyses were performed on Perkin–Elmer Series II CHNS/O 2400 elemental analyzer. Single-crystal X-ray diffraction analysis was performed at 295(2) K on an Xcalibur 3 diffractometer equipped with a CCD detector (ω-scanning at 1° step and 20-s exposure per frame, crystal-detector distance 50 mm, Mo Kα-irradiation). The progress of the reactions and the purity of the compounds were monitored by TLC on TLC Silica gel $60F_{245}$ Aluminum sheets (Merck KGaA).

4.2. General procedure for the preparation of enamines 2a–i, 5b

The mixture of DMF–DMA (3.0 equiv), *N*-methylimidazole (3.0 equiv), and corresponding alkyl 5-methyl-3-arylisoxazole-4-carboxylates **1a**–**h** or 5-methyl-3-phenylisoxazole-4-carbonitrile (1.0 equiv, 1.0–10.0 mmol) was heated for 6 h at 80 °C. The reaction mixture was concentrated in vacuo to dryness, and the residue was purified by flash chromatography over silica gel (60–120) using EtOAc/hexane (1:2) as eluent to give the enamines **2a**–**i**, **5b** in 70–85% yield.[19,28]

Enamines **2a**,**h** synthesized by this method have identical analytical characteristics with the products described earlier.[18,20]

*4.2.1. (E)-Methyl 3-(2-chlorophenyl)-5-(2-(dimethylamino)vinyl)isoxazole-4-carboxylate (**2b**).* Light yellow solid, yield 80%, mp 149–151 °C; R_f=0.47 (EtOAc/hexane 1:1); ^{1}H NMR ($CDCl_3$): δ 3.01 (6H, br s, $N(Me)_2$), 3.60 (3H, s, COOMe), 5.71 (1H, d, *J* 13.6 Hz, CH=), 7.30–7.45 (4H, m, Ar–H), 7.53 (1H, d, *J* 13.6 Hz, =CH); UV (^{i}PrOH) λ, nm (log ε) 345 (4.57); ^{13}C NMR ($CDCl_3$): δ 50.9, 82.3, 100.6, 126.3, 129.2, 129.7, 130.2, 130.8, 134.1, 148.4, 160.9, 163.2, 171.7; ESI-MS: *m*/*z*=307.08 $[M+H]^+$; Anal. Calcd (%) for $C_{15}H_{15}ClN_2O_3$: C, 58.73; H, 4.93; N, 9.13. Found: C, 58.64; H, 4.54; N, 9.09.

*4.2.2. (E)-Ethyl 3-(2-fluorophenyl)-5-(2-(dimethylamino)vinyl)isoxazole-4-carboxylate (**2c**).* Yellow solid, yield 80%; mp 53–55 °C; R_f=0.40 (EtOAc/hexane 1:1); ^{1}H NMR ($CDCl_3$): δ 1.06 (3H, t, *J* 7.0 Hz, OCH_2CH_3), 3.00 (6H, br s, $N(Me)_2$), 4.10 (2H, q, *J* 7.0 Hz, OCH_2CH_3), 5.73 (1H, d, *J* 16.0 Hz, CH=), 7.11 (1H, t, *J* 8.0 Hz, Ar–H), 7.19 (1H, t, *J* 8.0 Hz, Ar–H), 7.39–7.47 (2H, m, Ar–H), 7.51 (1H, d, *J* 16.0 Hz, CH=); ^{13}C NMR ($CDCl_3$): δ 13.9, 59.8, 82.4, 100.8, 115.4 (d, $J_{C,F}$

21.0 Hz), 118.7 (d, $J_{C,F}$ 16.0 Hz), 123.7 (d, $J_{C,F}$ 3.0 Hz), 131.0 (d, $J_{C,F}$ 3.0 Hz), 131.1 (d, $J_{C,F}$ 8.0 Hz), 148.4, 158.2, 160.7 (d, $J_{C,F}$ 249.0 Hz), 163.0, 175.0; UV (^{i}PrOH) λ, nm (log ε) 345 (4.60); ESI-MS: m/z=305.12 $[M+H]^+$; Anal. Calcd (%) for $C_{16}H_{17}FN_2O_3$: C, 63.15; H, 5.63; N, 9.21. Found: C, 63.54; H, 5.47; N, 9.16.

*4.2.3. (E)-Ethyl 3-(4-chlorophenyl)-5-(2-(dimethylamino)vinyl)isoxazole-4-carboxylate (**2d**).* Yellow solid, yield 70%, mp 65–68 °C; R_f=0.41 (EtOAc/hexane 1:1); ^{1}H NMR ($CDCl_3$): δ 1.18 (3H, t, J 7.0 Hz, OCH_2CH_3), 3.01 (6H, br s, $N(Me)_2$), 4.17 (2H, q, J 7.0 Hz, OCH_2CH_3), 5.73 (1H, d, J 13.2 Hz, CH=), 7.40 (2H, d, J 8.1 Hz, Ar–H), 7.57 (2H, d, J 8.1 Hz, Ar–H), 7.63 (1H, d, J 13.2 Hz, =CH); ^{13}C NMR ($CDCl_3$): δ 14.0, 59.0, 82.4, 99.3, 127.9, 128.3, 130.9, 135.1, 148.2, 161.7, 162.8, 175.4; UV (^{i}PrOH) λ, nm (log ε) 346 (4.65); ESI-MS: m/z=321.09 $[M+H]^+$; Anal. Calcd (%) for $C_{16}H_{17}ClN_2O_3$: C, 59.91; H, 5.34; N, 8.73. Found: C, 59.53; H, 5.21; N, 8.62.

*4.2.4. (E)-Ethyl 3-(2,4-dichlorophenyl)-5-(2-(dimethylamino)vinyl)isoxazole-4-carboxylate (**2e**).* Yellow solid, yield 70%, mp 80–82 °C; R_f=0.38 (EtOAc/hexane 1:1); ^{1}H NMR ($CDCl_3$): δ 1.04 (3H, t, J 7.0 Hz, OCH_2CH_3), 3.02 (6H, br s, $N(Me)_2$), 4.08 (2H, q, J 7.0 Hz, OCH_2CH_3), 5.73 (1H, d, J 13.2 Hz, CH=), 7.29–7.32 (2H, m, Ar–H), 7.47 (1H, s, Ar–H), 7.53 (1H, d, J 13.2 Hz, =CH); ^{13}C NMR ($CDCl_3$): δ 13.9, 59.9, 82.3, 100.7, 126.7, 128.7, 129.1, 131.7, 135.2, 135.6, 148.5, 160.1, 162.6, 174.9; UV (^{i}PrOH) λ, nm (log ε) 346 (4.58); ESI-MS: m/z=355.05 $[M+H]^+$; Anal. Calcd (%) for $C_{16}H_{16}Cl_2N_2O_3$: C, 54.10; H, 4.54; N, 7.89. Found: C, 54.19; H, 4.50; N, 7.78.

*4.2.5. (E)-Methyl 3-(2,6-dichlorophenyl)-5-(2-(dimethylamino)vinyl) isoxazole-4-carboxylate (**2f**).* Yellow solid, yield 80%, mp 157–160 °C; R_f=0.38 (EtOAc/hexane 1:1); ^{1}H NMR ($CDCl_3$): δ 3.02 (6H, br s, $N(Me)_2$), 3.60 (3H, s, COOMe), 5.73 (1H, d, J 13.2 Hz, CH=), 7.28–7.31 (1H, m, Ar–H), 7.36–7.38 (2H, m, Ar–H), 7.56 (1H, d, J=13.2 Hz, =CH); ^{13}C NMR ($CDCl_3$): δ 51.0, 82.3, 100.1, 127.6, 129.4, 130.5, 135.3, 148.6, 158.6, 162.8, 174.9; UV (^{i}PrOH) λ, nm (log ε) 346 (3.99); ESI-MS: m/z=341.04 $[M+H]^+$; Anal. Calcd (%) for $C_{15}H_{14}Cl_2N_2O_3$: C, 52.80; H, 4.14; N, 8.21. Found: C, 53.39; H, 4.01; N, 8.68.

*4.2.6. (E)-Ethyl 3-(2,6-dichlorophenyl)-5-(2-(dimethylamino)vinyl) isoxazole-4-carboxylate (**2g**).* Yellow solid, yield 77%, mp 95–97 °C; R_f=0.38 (EtOAc/hexane 1:1); ^{1}H NMR ($CDCl_3$): δ 0.95 (3H, t, J 7.2 Hz, OCH_2CH_3), 3.02 (6H, br s, $N(Me)_2$), 4.03 (2H, q, J 7.2 Hz, OCH_2CH_3), 5.76 (1H, d, J 13.2 Hz, CH=), 7.28–7.30 (1H, m, Ar–H), 7.37 (2H, d, J 8.4 Hz, Ar–H), 7.57 (1H, d, J 13.2 Hz, =CH); UV (^{i}PrOH) λ, nm (log ε) 346 (4.38); ESI-MS: m/z=355.05 $[M+H]^+$; Anal. Calcd (%) for $C_{16}H_{16}Cl_2N_2O_3$: C, 54.10; H, 4.54; N, 7.89. Found: C, 54.37; H, 4.47; N, 7.96.

*4.2.7. (E)-Methyl 5-(2-(dimethylamino)vinyl)-3-phenylisoxazole-4-carboxylate (**2i**).* Yellow solid, yield 70%, mp 85–87; R_f=0.55 (EtOAc/hexane 1:1); ^{1}H NMR ($CDCl_3$): δ 3.01 (6H, br s, $N(Me)_2$), 3.68 (3H, s, COOMe), 5.73 (1H, d, J 12.0 Hz, CH=), 7.38–7.43 (3H, m, Ar–H), 7.50 (1H, d, J 12.0 Hz, =CH), 7.57–7.59 (2H, m, Ar–H); ^{13}C NMR ($CDCl_3$): δ 50.8, 82.5, 99.3, 127.7, 129.1, 129.3, 129.6, 148.3, 162.6, 163.5, 175.3; UV (^{i}PrOH) λ, nm (log ε) 346 (4.55); ESI-MS: m/z=273.12 $[M+H]^+$; Anal. Calcd (%) for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.27; H, 5.99; N, 10.20.

*4.2.8. (E)-5-(2-(Dimethylamino)vinyl)-3-phenylisoxazole-4-carbonitrile (**5b**).* Yellow solid, yield 83%, mp 136–138 °C; R_f=0.39 (EtOAc/hexane 1:1); ^{1}H NMR ($CDCl_3$): δ 3.02 (6H, br s, $N(Me)_2$), 5.16 (1H, d, J 12.0 Hz, CH=), 7.47–7.53 (4H, m, H–Ar+CH=), 7.92–7.93 (2H, m, H–Ar); ^{13}C NMR ($CDCl_3$): δ 78.5, 80.1, 114.6, 127.2, 127.4, 129.0, 130.6, 148.5, 160.8, 177.9; UV (^{i}PrOH) λ, nm (log ε) 342 (4.95); ESI-MS: m/z=239.11 $[M+H]^+$; Anal. Calcd (%) for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76. Found: C, 75.70; H, 5.99; N, 11.70.

4.3. General procedure for the preparation of dienamines 3a,f,g,h

To a solution of the corresponding enamine **2** (1.0 mmol, 1.0 equiv) in anhydrous 1,4-dioxane (4 mL) was added acetyl chloride (3.0 mmol, 3.0 equiv) and the reaction mixture was stirred at room temperature for 20–22 h. The resulting mixture was evaporated under reduced pressure to dryness and residue was purified by column chromatography over silica gel (60–120) using EtOAc/hexane (1:2) as eluent to give the products **3** as yellow solids.

*4.3.1. Diethyl 5,5′-((1E,3Z)-4-(dimethylamino)buta-1,3-diene-1,3-diyl)bis(3-phenylisoxazole-4-carboxylate) (**3a**).* Yield 80%; mp 121–123 °C; R_f=0.35 (EtOAc/hexane 1:1); ^{1}H NMR ($CDCl_3$): δ 1.12 (6H, m, $2OCH_2CH_3$), 2.91 (6H, br s, $N(CH_3)_2$), 4.17 (4H, dd, J 6.6 Hz, $2OCH_2CH_3$), 6.33 (1H, d, J 15.6 Hz, C^1–H), 6.95 (1H, s, C^4–H), 7.41–7.62 (10H, m, Ar–H), 7.70 (1H, d, J 15.6 Hz, C^2–H); ^{13}C NMR ($CDCl_3$): δ 13.7, 13.8, 60.7, 61.8, 94.4, 102.3, 127.9, 128.3, 128.9, 129.1, 129.3, 129.5, 130.0, 141.3, 151.1, 162.6, 162.7, 163.1, 171.9, 172.9; UV (^{i}PrOH): λ, nm (log ε)=392 (4.60); ESI-MS: m/z 528.21 $[M+H]^+$; Anal. Calcd (%) for $C_{30}H_{29}N_3O_6$: C, 68.30; H, 5.54; N, 7.96. Found: C, 68.51, H, 5.32; N, 7.84.

*4.3.2. Dimethyl 5,5′-((1E,3Z)-4-(dimethylamino)buta-1,3-diene-1,3-diyl)bis(3-(2,6-dichlorophenyl)isoxazole-4-carboxylate) (**3f**).* Yield 61%; mp 251–253 °C; R_f=0.40 (EtOAc/hexane 1:1); ^{1}H NMR ($CDCl_3$): δ 2.74 (6H, br s, $N(CH_3)_2$), 3.61 (3H, s, OCH_3), 3.64 (3H, s, OCH_3), 6.32 (1H, d, J 15.2 Hz, C^1–H), 7.01 (1H, s, C^4–H), 7.28–7.45 (6H, m, Ar–H), 7.50 (1H, d, J 15.2 Hz, C^2–H); ^{13}C NMR ($CDCl_3$): δ 51.6, 52.01, 94.04, 102.4, 112.6, 127.8, 128.0, 128.2, 128.7, 130.9, 131.2, 135.4, 135.5, 141.7, 151.5, 159.2, 159.5, 161.0, 161.9, 172.1, 172.6; UV (^{i}PrOH): λ, nm (log ε)=392 (4.48); ESI-MS: m/z 636.02 $[M+H]^+$; Anal. Calcd (%) for $C_{28}H_{21}Cl_4N_3O_6$: C, 52.77; H, 3.32; N, 6.59. Found: C, 52.53; H, 3.44; N, 6.52.

*4.3.3. Diethyl 5,5′-((1E,3Z)-4-(dimethylamino)buta-1,3-diene-1,3-diyl)bis(3-(2,6-dichlorophenyl)isoxazole-4-carboxylate) (**3g**).* Yield 81%; mp 192–195 °C; R_f=0.37 (EtOAc/hexane 1:1); ^{1}H NMR ($CDCl_3$): δ 0.96 (3H, t, J 7.2 Hz, OCH_2CH_3), 1.02 (3H, t, J 7.2 Hz, OCH_2CH_3), 2.93 (6H, br s, $N(CH_3)_2$), 4.03–4.10 (4H, m, $2OCH_2CH_3$), 6.43 (1H, d, J 15.2 Hz, C^1–H), 7.03 (1H, s, C^4–H), 7.29–7.44 (6H, m, Ar–H), 7.52 (1H, d, J 15.2 Hz, C^2–H); ^{13}C NMR ($CDCl_3$): δ 13.5, 13.8, 42.9, 60.1, 60.6, 93.8, 102.3, 112.3, 127.6, 127.7, 128.5, 129.0, 130.6, 131.0, 135.5, 141.6, 151.5, 159.0, 159.1, 160.3, 161.2, 172.0, 172.7; UV (^{i}PrOH) λ, nm (log ε) 391 (4.57); ESI-MS: m/z 664.04 $[M+H]^+$; Anal. Calcd (%) for $C_{28}H_{21}Cl_4N_3O_6$: C, 54.16; H, 3.79; N, 6.32; Found: C, 54.31; H, 3.55; N, 6.26.

*4.3.4. Dimethyl 5,5′-((1E,3Z)-4-(dimethylamino)buta-1,3-diene-1,3-diyl)bis(3-(2-chloro-6-fluorophenyl)isoxazole-4-carboxylate) (**3h**).* Yield 80%; mp 219–220 °C, R_f=0.36 (EtOAc/hexane 1:1); ^{1}H NMR (DMSO-d_6): δ 2.95 (6H, br s, $N(CH_3)_2$), 3.53 (3H, s, OCH_3), 3.60 (3H, s, OCH_3), 6.10 (1H, d, J 15.6 Hz, C^1–H); 7.26 (1H, t, J 8.4 Hz, Ar–H), 7.34 (1H, t, J 8.4 Hz, Ar–H), 7.44 (1H, s, C^4–H), 7.45 (1H, d, J 15.6 Hz, C^2–H), 7.51–7.64 (4H, m, Ar–H); ^{13}C NMR ($CDCl_3$): δ 42.9, 51.3, 51.9, 93.9, 102.3, 104.8 (d, $J_{C,F}$ 2.4 Hz), 114.0 (d, $J_{C,F}$ 21.0 Hz), 114.2 (d, $J_{C,F}$ 21.0 Hz), 118.0 (d, $J_{C,F}$ 19.0 Hz), 125.1 (d, $J_{C,F}$ 3.3 Hz), 125.2 (d, $J_{C,F}$ 3.3 Hz), 131.2 (d, $J_{C,F}$ 9.3 Hz), 131.6 (d, $J_{C,F}$ 9.3 Hz), 135.1 (d, $J_{C,F}$ 4.0 Hz), 135.2 (d, $J_{C,F}$ 4.0 Hz), 141.4, 151.3, 156.0, 156.2, 160.7 (d, $J_{C,F}$ 251.8 Hz),161.8 (d, $J_{C,F}$ 251.8 Hz), 161.8, 172.3; UV (^{i}PrOH): λ, nm (log ε)=392 (4.62); ESI-MS: m/z 604.08 $(M+H)^+$; Anal. Calcd (%) for

$C_{28}H_{21}Cl_2F_2N_3O_6$: C, 55.64; H, 3.50; N, 6.95. Found: C, 55.48; H, 3.41; N, 6.89.

4.4. General procedure for the preparation of dienes 3b–e and benzenes 4b–e

To a solution of corresponding enamine **2** (1.0 mmol, 1.0 equiv) in anhydrous 1,4-dioxane (4 mL) was added acetyl chloride (3.0 mmol, 3.0 equiv) and the reaction mixture was stirred at room temperature for 20–22 h. The resulting mixture was evaporated under reduced pressure to dryness and residue was purified by column chromatography over silica gel (60–120) using EtOAc/hexane (1:2) as eluent to give the dienes **3b**–**e** as major product (R_f 0.15–0.20) and benzenes **4b**–**e** as minor products (R_f 0.45–0.54).

*4.4.1. Dimethyl 5,5′-(4-(dimethylamino)buta-1,3-diene-1,3-diyl) bis(3-(2-chlorophenyl)isoxazole-4-carboxylate) (**3b**).* Yield 40%; mp 160–161 °C; R_f=0.30 (EtOAc/hexane 1:1); ^{1}H NMR ($CDCl_3$): δ 2.94 (6H, s, $N(CH_3)_2$), 3.61 (3H, s, OCH_3), 3.64 (3H, s, OCH_3), 6.32 (1H, d, J 15.6 Hz, C^1–H), 7.02 (1H, s, C^4–H), 7.31–7.50 (8H, m, Ar–H), 7.55 (1H, d, J 15.6 Hz, C^2–H); ^{13}C NMR ($CDCl_3$): δ 51.4, 52.0, 94.0, 102.2, 126.6, 126.9, 129.2, 129.5, 129.6, 130.7, 131.0, 131.1, 134.0, 134.2, 141.7, 151.5, 161.3, 161.4, 161.7, 162.3, 172.1, 172.5; UV (^{i}PrOH): λ, nm (log ε)=392 (4.64); ESI-MS: m/z 568.10 $(M+H)^+$; Anal. Calcd (%) for $C_{28}H_{23}Cl_2N_3O_6$: C, 59.17; H, 4.08; N, 7.39. Found: 59.28; H, 4.00; N, 7.44.

*4.4.2. Trimethyl 5,5′,5″-(benzene-1,3,5-triyl)tris(3-(2-chlorophenyl) isoxazole-4-carboxylate) (**4b**).* Yellow solid; yield 39%; mp 155–158 °C; R_f=0.56 (EtOAc/hexane 1:1); ^{1}H NMR ($CDCl_3$): δ 3.72 (9H, s, OCH_3), 7.40–7.57 (12H, m, Ar–H), 8.96 (3H, s, Ar–H); ^{13}C NMR ($CDCl_3$): δ 52.4, 110.6, 127.0, 127.9, 128.3, 129.7, 131.3, 132.2, 134.0, 161.8, 162.0, 170.4; UV (^{i}PrOH): λ, nm (log ε)=272 (4.71); ESI-MS: m/z 784.06 $(M+H)^+$; Anal. Calcd (%) for $C_{39}H_{24}Cl_3N_3O_9$: C, 59.67; H, 3.08; N, 5.35. Found: C, 59.74; H, 3.03; N, 5.30.

Compound **4b** can be prepared also by the cycloaddition of dieneamine **3b** to enamine **2b**. A solution of enamine **2b** (0.016 g, 0.053 mmol, 1.0 equiv), dieneamine **3b** (0.03 g, 0.053 mmol, 1.0 equiv), acetyl chloride (0.011 mL, 0.16 mmol, 3.0 equiv) in anhydrous benzene (2 mL) was stirred at room temperature for 5 days. The resulting mixture was evaporated under reduced pressure to dryness and the residue was purified by flash column chromatography over silica gel (60–120) using EtOAc/hexane (1:3) as eluent to give benzene **4b** in 60% (0.024 g) yield.

*4.4.3. Diethyl 5,5′-(4-(dimethylamino)buta-1,3-diene-1,3-diyl)bis(3-(2-fluorophenyl)isoxazole-4-carboxylate) (**3c**).* Yield 30%; mp 167–169 °C; R_f=0.36 (EtOAc/hexane 1:1); ^{1}H NMR ($CDCl_3$): δ 1.08 (6H, m, $2OCH_2CH_3$), 2.92 (6H, br s, $N(CH_3)_2$), 4.08–4.17 (4H, m, $2OCH_2CH_3$), 6.35 (1H, d, J 16.0 Hz, C^1–H), 7.00 (1H, s, C^4–H), 7.10–7.22 (4H, m, Ar–H), 7.41–7.63 (5H, m, H–Ar+C^2–H); ^{13}C NMR ($CDCl_3$): δ 13.8, 13.9, 43.0, 60.4, 61.0, 93.9, 102.3, 108.5, 115.5 (d, $J_{C,F}$ 21.0 Hz), 115.6 (d, $J_{C,F}$ 22.0 Hz), 117.9 (d, $J_{C,F}$ 18.0 Hz), 123.9 (d, $J_{C,F}$ 3.5 Hz), 130.9 (d, $J_{C,F}$ 21.8 Hz), 131.2 (d, $J_{C,F}$ 8.2 Hz), 131.5 (d, $J_{C,F}$ 8.2 Hz), 141.7, 151.6, 158.4, 158.8, 160.5 (d, $J_{C,F}$ 250.0 Hz), 160.6 (d, $J_{C,F}$ 250.0 Hz), 161.9, 172.5; UV (^{i}PrOH): λ, nm (log ε)=392 (4.57); ESI-MS: m/z 664.19 $[M+H]^+$; Anal. Calcd (%) for $C_{30}H_{27}F_2N_3O_6$: C, 63.94; H, 4.83; N, 7.46. Found: 64.10; H, 4.89; N, 7.42.

*4.4.4. Triethyl 5,5′,5″-(benzene-1,3,5-triyl)tris(3-(2-fluorophenyl)isoxazole-4-carboxylate) (**4c**).* Yellow solid; yield 9%; mp 125–127 °C; R_f=0.60 (EtOAc/hexane 1:1); ^{1}H NMR ($CDCl_3$): δ 1.06 (9H, t, J 7.2 Hz, $3OCH_2CH_3$), 4.23 (6H, q, J 7.2 Hz, $3OCH_2CH_3$), 7.20 (3H, t, J 8.6 Hz, Ar–H), 7.30 (3H, t, J 8.0 Hz, Ar–H), 7.49–7.55 (3H, m, Ar–H), 7.64 (3H, t, J 8.7 Hz, Ar–H), 8.93 (3H, s, H–Ar); ^{13}C NMR ($CDCl_3$): δ 13.6, 61.6, 110.7, 115.7, 117.2 (d, $J_{C,F}$ 14.5 Hz), 124.4 (d, $J_{C,F}$ 3.4 Hz), 127.8, 131.0 (d, $J_{C,F}$ 2.4 Hz), 132.1 (d, $J_{C,F}$ 4.2 Hz), 132.2, 159.4, 161.4, 160.5 (d, $J_{C,F}$ 250.0 Hz), 170.3; UV (^{i}PrOH): λ, nm (log ε)=272 (4.54); ESI-MS: m/z 778.19 $[M+H]^+$; Anal. Calcd (%) for $C_{42}H_{30}F_3N_3O_9$: C, 64.86; H, 3.89; N, 5.40. Found: C, 64.94; H, 3.84; N, 5.42.

*4.4.5. Diethyl 5,5′-(4-(dimethylamino)buta-1,3-diene-1,3-diyl)bis(3-(4-chlorophenyl)isoxazole-4-carboxylate) (**3d**).* Yield 54%, mp 128–130 °C; R_f=0.40 (EtOAc/hexane 1:1); ^{1}H NMR ($CDCl_3$): δ 1.11 (3H, t, J 7.2 Hz, OCH_2CH_3), 1.17 (3H, t, J 7.2 Hz, OCH_2CH_3), 2.92 (6H, br s, $N(CH_3)_2$), 4.12 (2H, q, J 7.2 Hz, OCH_2CH_3), 4.21 (2H, q, J 7.2 Hz, OCH_2CH_3), 6.30 (1H, d, J 15.6 Hz, C^1–H), 6.96 (1H, s, C^4–H), 7.38–7.46 (5H, m, Ar–H+C^2–H), 7.57 (2H, d, J 8.4 Hz, Ar–H), 7.68 (2H, d, J 8.0 Hz, Ar–H); ^{13}C NMR ($CDCl_3$): δ 13.9, 60.4, 61.1, 94.5, 99.8, 111.5, 126.8, 127.4, 128.1, 128.5, 130.4, 130.7, 135.8, 136.2, 151.4, 161.4, 161.7, 162.0, 162.3, 172.4, 173.0; UV (^{i}PrOH): λ, nm (log ε)=392 (4.57); ESI-MS: m/z 596.13 $[M+H]^+$; Anal. Calcd (%) for $C_{30}H_{27}Cl_2N_3O_6$: C, 60.41; H, 4.56; N, 7.04. Found: 60.50; H, 4.61; N, 7.00.

*4.4.6. Triethyl 5,5′,5″-(benzene-1,3,5-triyl)tris(3-(4-chlorophenyl) isoxazole-4-carboxylate) (**4d**).* Yellow solid; yield 35%; mp 130–131 °C, R_f=0.56 (EtOAc/hexane 1:1); ^{1}H NMR ($CDCl_3$): δ 1.15 (9H, t, J 7.2 Hz, $3OCH_2CH_3$), 4.27 (6H, q, J 7.2 Hz, $3OCH_2CH_3$), 7.48 (6H, d, J 8.4 Hz, Ar–H), 7.64 (6H, d, J 8.4 Hz, Ar–H), 8.74 (3H, s, H–Ar); ^{13}C NMR ($CDCl_3$): δ 13.7, 61.8, 109.6, 126.7, 127.9, 128.6, 130.5, 131.5, 136.4, 161.5, 162.5, 170.5; UV (^{i}PrOH): λ, nm (log ε)=267 (4.76); ESI-MS: m/z 826.10 $[M+H]^+$; Anal. Calcd (%) for $C_{42}H_{30}Cl_3N_3O_9$: C, 60.99; H, 3.66; N, 5.08. Found: C, 60.91; H, 3.58; N, 5.02.

*4.4.7. Diethyl 5,5′-(4-(dimethylamino)buta-1,3-diene-1,3-diyl)bis(3-(2,4-dichlorophenyl)isoxazole-4-carboxylate) (**3e**).* Yield 64%, mp 152–155 °C; R_f=0.42 (EtOAc/hexane 1:1); ^{1}H NMR ($CDCl_3$): δ 1.02–1.09 (6H, m, $2OCH_2CH_3$), 2.94 (6H, br s, $N(CH_3)_2$), 4.06–4.14 (4H, m, $2OCH_2CH_3$), 6.36 (1H, d, J 15.2 Hz, C^1–H), 7.03 (1H, s, C^4–H), 7. 33 (2H, s, Ar–H), 7.36–7.52 (5H, m, Ar–H+C^2–H); ^{13}C NMR ($CDCl_3$): δ 13.7, 13.8, 60.3, 60.9, 93.6, 102.3, 126.8, 127.2, 129.2, 129.3, 131.7, 134.8, 135.0, 135.9, 136.4, 141.6, 141.7, 151.7, 160.4, 160.5, 161.6, 172.5; UV (^{i}PrOH): λ, nm (log ε)=393 (4.61); ESI-MS: m/z 664.05 $[M+H]^+$; Anal. Calcd (%) for $C_{30}H_{25}Cl_4N_3O_6$: C, 54.16; H, 3.79; N, 6.32. Found: C, 54.30; H, 3.91; N, 6.26.

*4.4.8. Triethyl 5,5′,5″-(benzene-1,3,5-triyl)tris(3-(2,4-dichlorophenyl) isoxazole-4-carboxylate) (**4e**).* Light yellow; yield 12%; mp 190–192 °C; R_f=0.58 (EtOAc/hexane 1:1); ^{1}H NMR ($CDCl_3$): δ 1.06 (9H, t, J 7.1 Hz, $3OCH_2CH_3$), 4.19 (6H, q, J 7.1 Hz, $3OCH_2CH_3$), 7.40 (1H, d, J 7.1 Hz, Ar–H), 7.42 (2H, d, J 7.1 Hz, Ar–H), 7.46 (2H, s, Ar–H), 7.48 (1H, s, Ar–H), 7.55 (3H, d, J 7.1 Hz, Ar–H), 8.98 (3H, s, Ar–H); ^{13}C NMR ($CDCl_3$): δ 13.7, 61.7, 110.8, 127.3, 127.4, 127.8, 129.6, 132.0, 132.4, 135.0, 136.8, 161.0, 161.5, 170.6; UV (^{i}PrOH): λ, nm (log ε)=273 (4.77); ESI-MS: m/z 927.99 $[M+H]^+$; Anal. Calcd (%) for $C_{42}H_{27}Cl_6N_3O_9$: C, 54.22; H, 2.93; N, 4.52. Found: C, 54.63; H, 2.99; N, 4.31.

4.5. General procedure for the preparation of benzene 4a in different solvents

To a solution of enamine **2a** (0.7 mmol, 1.0 equiv) in the correspondent solvent (4 mL) (see Table 1 in the Supplementary data), acetyl chloride (2.1 mmol, 3.0 equiv) was added and the reaction mixture was stirred at room temperature until the starting enamine **2a** and intermediate diene **3a** disappeared according to TLC analysis (from 20 h to 22 days). The resulting mixture was evaporated under reduced pressure to dryness and the residue was purified by column chromatography over silica gel (60–120) using EtOAc/hexane (1:2) as eluent to give benzene **4a** in 36–65% yield.

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*4.5.1. Triethyl 5,5′,5″-(benzene-1,3,5-triyl)tris(3-phenylisoxazole-4-carboxylate) (**4a**).* Colorless solid; mp 128–130 °C; R_f=0.67 (EtOAc/hexane 1:1); ^{1}H NMR ($CDCl_3$): δ 1.12 (9H, t, *J* 7.2 Hz, 3OCH$_2$*CH*$_3$), 4.26 (6H, q, *J* 7.2 Hz, 3O*CH*$_2$CH$_3$), 7.49–7.51 (9H, m, Ar–H), 7.67–7.70 (6H, m, Ar–H), 8.76 (3H, s, Ar–H); ^{13}C NMR ($CDCl_3$): δ 13.8, 61.8, 109.8, 128.1, 128.4, 128.4, 129.3, 130.2, 131.5, 161.9, 163.6, 170.3; UV (^{i}PrOH): λ, nm (log ε)=270 (4.79); ESI-MS: *m*/*z* 724.22 [M+H]$^+$; Anal. Calcd (%) for $C_{42}H_{33}N_3O_9$: C, 69.70; H, 4.60; N, 5.81. Found: C, 69.93; H, 4.71; N, 5.75.

4.6. Trimethyl 5,5′,5″-(benzene-1,3,5-triyl)tris(3-(2-chloro-6-fluorophenyl)isoxazole-4-carboxylate) (4h)

A solution of enamine **2h** (0.162 g, 0.5 mmol, 1.0 equiv) and acetyl chloride (0.236 g, 3.0 mmol, 6.0 equiv) in anhydrous 1,4-dioxane (4 mL) was kept at 50 °C for 9 days. After that the volatiles were evaporated, the residue was treated with boiling water. The residue was extracted with several portions of boiling heptane to get free of tars and the extract was concentrated. The solid thus formed was purified by column chromatography on silica gel, eluent EtOAc/heptanes (1:2) to give benzene **4h**. Colorless solid; yield 55% (0.077 g); mp 181–183 °C; R_f=0.58 (EtOAc/hexane 1:1); ^{1}H NMR ($CDCl_3$): δ 3.73 (9H, s, OCH_3), 7.17 (3H, td, *J* 8.5 Hz, 1.0 Hz, Ar–H), 7.33–7.39 (3H, m, Ar–H), 7.45 (3H, td, *J* 8.2, 5.9 Hz, Ar–H) 8.98 (3H, s, Ar–H); ^{13}C NMR (DMSO-d_6): δ 52.8, 110.7, 115.2 (d, $J_{C,F}$ 21.6 Hz), 116.7 (d, $^2J_{C,F}$ 18.3 Hz), 126.1, 127.3, 133.1, 133.6 (d, $J_{C,F}$ 9.6 Hz), 134.3 (d, $J_{C,F}$ 3.7 Hz), 156.7, 160.6 (d, $J_{C,F}$ 251.8 Hz), 160.8, 171.1; ^{19}F NMR (376 MHz, $CDCl_3$): δ −109.54 (s, 1F); ESI-MS, *m*/*z* 838.03 [M+H]$^+$; Anal. Calcd (%) for $C_{39}H_{21}Cl_3F_3N_3O_9$: C, 55.83; H, 2.52; N, 5.01. Found: C, 55.71; H, 2.27; N, 5.07.

4.7. Trimethyl 5,5′,5″-(benzene-1,3,5-triyl)tris(3-phenylisoxazole-4-carboxylate) (4i)

The solution of enamine **2i** (0.3 g, 1.1 mmol, 1.0 equiv) and $BF_3{\cdot}O(CH_3)_2$ (60% solution) (0.2 mL, 1.3 mmol, 1.18 equiv) in anhydrous 1,4-dioxane (2 mL) was stirred at 60–70 °C for 12 h until TLC does not show the presence of starting enamine and intermediate dieneamine in the reaction mixture. The reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (60–120) using EtOAc/hexane (1:3) as eluent to give product **4i**. Colorless solid; yield 80% (0.20 g); mp 152–155 °C; R_f=0.64 (EtOAc/hexane 1:1); ^{1}H NMR ($CDCl_3$): δ 3.80 (9H, s, OCH_3), 7.47–7.55 (9H, m, Ar–H), 7.68–7.70 (6H, m, Ar–H), 8.72 (3H, s, Ar–H); ^{13}C NMR ($CDCl_3$): 52.6, 109.5, 128.2, 128.3, 128.6, 129.1, 130.3, 131.3, 162.4, 163.4, 170.3; ESI-MS, *m*/*z* 682.17 [M+H]$^+$; Anal. Calcd (%) for $C_{39}H_{27}N_3O_9$: C, 68.72; H, 3.99; N, 6.16. Found: C, 68.81; H, 3.92; N, 6.09.

4.8. 5,5′-((1*E*,3*Z*)-4-(Dimethylamino)buta-1,3-diene-1,3-diyl) bis(3-phenylisothiazole-4-carbonitrile) (6)

To a solution of enamine **5a** (0.18 g, 0.705 mmol) in anhydrous 1,4-dioxane (3 mL) was added acetyl chloride (0.11 mL, 1.55 mmol) and the reaction mixture was stirred at 50–55°C for 16 h. The dark yellow precipitate obtained was filtered off, washed with ether, and dried. The product was purified through silica gel column chromatography by eluting with EtOAc/hexane (1:2) and further double recrystallization with EtOAc/hexane to give the diene **6**. Yellow solid; yield 25% (0.041 g); mp 208–210 °C; R_f=0.37 (EtOAc/hexane 1:1); ^{1}H NMR ($CDCl_3$): δ 2.97 (6H, br s, N(CH_3)$_2$), 6.28 (1H, d, *J* 15.2 Hz, C^1–H), 6.99 (1H, s, C^4–H), 7.22 (1H, d, *J* 15.2 Hz, C^2–H), 7.47–7.56 (10H, m, Ar–H); ^{13}C NMR ($CDCl_3$): δ 45.0, 94.2, 105.9, 108.1, 114.2, 115.4, 127.8, 127.9, 128.9, 129.1, 130.3, 130.7, 132.9, 133.3, 141.4, 150.0, 167.4, 167.9, 173.9, 175.7; UV (^{i}PrOH): λ, nm (log ε)=252 (6.10), ESI-MS: *m*/*z* 466.11 [M+H]$^+$; Anal. Calcd (%) for $C_{26}H_{19}N_5S_2$: C, 67.07; H, 4.11; N, 15.04, S, 13.77. Found: C, 67.01; H, 4.15; N, 15.00, S, 13.69.

4.9. X-ray diffraction study

*4.9.1. X-ray diffraction study of **3e**.* X-ray intensity data were collected with a Xcalibur S diffractometer using standard procedure (λ(Mo K$_\alpha$)=0.71069 Å radiation, *T*=295(2) K, ω-scanning with step 1°). Absorption correction was not applied (μ=0.426 mm^{-1}). On angles 2.65<θ<26.37° 14,453 reflections were collected, 6122 (R_{int}=0.0579) independent reflections, 2340 reflections with $I>2\sigma(I)$. Completeness to θ=26.37° 95.5%. Unit cell parameters were refined using all collected spots after the integration process. Crystal is triclinic, space group *P*−1, *a*=6.7961(8) Å, *b*=13.1361(14) Å, *c*=17.9928(10) Å, α=82.653(7)°, β=80.199(7)°, γ=83.538(9)°, *V*=1563.1(3) Å^3. For compound $C_{30}H_{25}Cl_4N_3O_6$, *Z*=2, ρ (calcd)=1.414 g/cm^3. SHELXTL program[28] was used for solution and refinement of structure. Structure was refined in anisotropic approximation for non-hydrogen atoms, hydrogen atoms were placed in calculated positions and refined in isotropic approximation in 'riding' model. The details of the refinement and the final *R* indices: R_1 [$I>2\sigma(I)$]=0.0471, R_1 (all data)=0.1567, wR_2 [$I>2\sigma(I)$]=0.0759, wR_2 (all data)=0.0851, *S*=1.005. Largest diffraction peak and hole 0.274 and −0.400 ē/Å^3.

*4.9.2. X-ray diffraction study of **4h**.* Single-crystal X-ray diffraction analysis was performed at 295(2) K on an Xcalibur 3 diffractometer equipped with a CCD detector (ω-scanning at 1° step and 20-s exposure per frame, crystal-detector distance 50 mm, Mo Kα-irradiation). Colorless prismatic crystals of **4h** belong to the trigonal system, space group *R*−3. Unit cell parameters: *a*=*b*=16.7694(4) Å, *c*=24.3406(9) Å, α=β=90°, γ=120°, *V*=5927.8(3) Å^3, ρ (calcd)=1.410 g/cm^3, μ=0.304 mm^{-1}, *Z*=6. To collect and edit the experimental data and refine the unit cell parameters, we used the CrysAlis CCD program.[29] At 3.49<θ<28.30° 13,293 reflections were collected, 3251 independent reflections (R_{int}=0.0175), 2209 reflections with $I>2\sigma(I)$. The experiment completeness at θ<28.30° was 99.2%. The structure was solved and refined using the SHELX program package.[29] The refinement was carried out by the full matrix least-squares method by F^2 with all non-hydrogen atoms taken in the anisotropic approximation. The hydrogen atoms were placed in calculated positions and included in refinement in the 'rider' model in the isotropic approximation with dependent thermal parameters. Final parameters of refinement: R_1=0.0492, wR_2=0.1560 (for reflections with $I>2\sigma(I)$), R_1=0.0667, wR_2=0.1646 (for all data), *S*=1.017. Largest diffraction peak and hole 0.407 and −0.295 ēÅ^{-3}.

*4.9.3. X-ray diffraction study of **6**.* Single-crystal X-ray diffraction analysis was performed at 295(2) K on an Xcalibur 3 diffractometer equipped with a CCD detector (ω-scanning at 1° step and 20-s exposure per frame, crystal-detector distance 50 mm, Mo Kα-irradiation). Orange plates of crystals belong to monoclinic system, space group $P2_1/c$. Unit cell parameters: *a*=19.9068(9) Å, *b*=7.4737(3) Å, *c*=15.8609(7) Å, α=γ=90°, β=96.935(4)°. *V*=2342.48(18) Å^3, ρ (calcd)=1.320 g/cm^3, μ=0.252 mm^{-1}, *Z*=4. To collect and edit the experimental data and refine the unit cell parameters, we used the CrysAlis CCD program.[30] At 2.90<θ<28.29° 11,166 reflections were collected, 5626 independent reflections (R_{int}=0.0341), 2294 reflections with $I>2\sigma(I)$. The experiment completeness at θ<26.00° was 98.0%. The structure was solved and refined using the SHELX program package.[29] The refinement was carried out by the full matrix least-squares method by F^2 with all non-hydrogen atoms taken in the anisotropic approximation. The hydrogen atoms were placed in calculated positions and included in refinement in the 'rider' model in the isotropic approximation

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with dependent thermal parameters. Final parameters of refinement: R_1=0.0376, wR_2=0.0721 (for reflections with $I>2\sigma(I)$), R_1=0.1049, wR_2=0.0757 (for all data), S=1.001. Largest diffraction peak and hole 0.243 and −0.175 ēÅ^{-3}.

Deposition numbers for compounds **3e** (CCDC 978581), **4h** (CCDC 978580), and **6** (CCDC 978582) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2014.04.015. These data include MOL files and InChiKeys of the most important compounds described in this article.

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