

Reactivity of 3-substituted pyrazole-5-diazonium salts towards 3-azolyl enamines. Synthesis of novel 3-azolylpyrazolo[5,1-*c*][1,2,4]triazines

Daria L. Alexeeva,^a Elena V. Sadchikova,^{*a} Natalia N. Volkova,^a Ilya V. Efimov,^a
Jeroen Jacobs,^b Luc Van Meervelt,^b Wim Dehaen,^b and Vasiliy A. Bakulev^a

^a Institute of Chemical Technology, The Ural Federal University named after the first President of Russia B.N.Yeltsin, Mira str. 28, Yekaterinburg, 620002, Russia

^b Department of Chemistry, Celestijnenlaan 200F, KU Leuven, B-3001 Leuven, Belgium

E-mail: e.v.sadchikova@urfu.ru

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Abstract

A series of novel 3-azolylpyrazolo[5,1-*c*][1,2,4]triazines was synthesized by reaction of 3-substituted pyrazole-5-diazonium salts with β -azolyl enamines in an efficient fashion. The structures of the compounds prepared were characterized by NMR spectroscopy, mass-spectrometry, elemental and X-ray diffraction analyses. Plausible mechanisms were formulated.

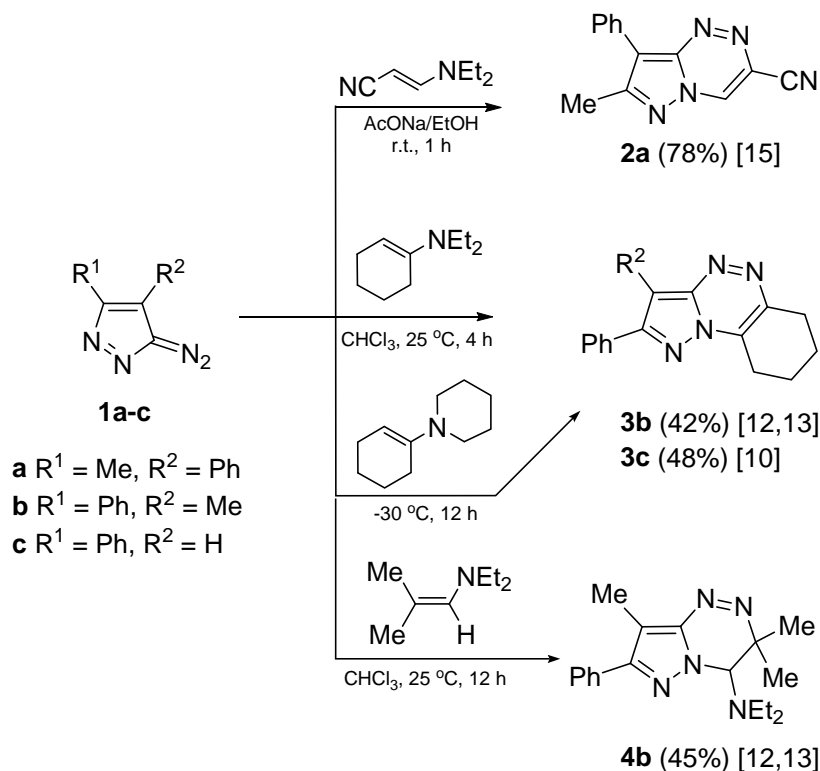
Keywords: 3-Substituted pyrazole-5-diazonium salts, enamines, pyrazolo[5,1-*c*][1,2,4]triazines

Introduction

Heterocyclic diazo compounds and the corresponding diazonium salts represent an important class of organic compounds due to their wide spectrum of reactivity in diverse reaction types. Similar to aromatic diazonium salts, they can couple with a very broad range of aromatic and heteroaromatic compounds^{1,2} as well as with active methylene reagents³⁻⁶ to form azo compounds and hydrazones, respectively. On the other hand, similarly to diazoalkanes, they react with alkenes,⁷⁻¹⁴ alkynes,⁸⁻¹⁰ enamines,^{10,12,13,15} ynamines,^{7,12,13,16} isocyanates¹⁷⁻²³ and isothiocyanates^{24,25} to furnish a huge variety of heterocyclic compounds. Thus, heterocyclic diazo compounds are important building blocks in organic synthesis and can be used as key precursors in the synthesis of various derivatives.

We turned our attention to reactions of diazopyrazoles **1** with enamines because they take place in a regioselective manner to form pyrazolo[5,1-*c*][1,2,4]triazines as exclusive products in good yields. Scheme 1 shows a few known examples for formation of pyrazolotriazines **2-4** by this reaction.^{10,12,13,15}

To the best of our knowledge 3-azolylpyrazolo[5,1-*c*][1,2,4]triazines are not described in the literature and reactions of β -azolyl enamines with diazo compounds and diazonium salts are not studied so far. At the same time both pyrazolotriazines and azoles, such as 1,2,3-thiadiazoles and isoxazoles, exhibit interesting biological and chemical properties.²⁶⁻³² Therefore, it is a challenging task to develop a new efficient synthetic method for their preparation. In continuation of our interest in the chemistry of diazoazoles and the synthesis of various types of triazines we have carefully studied the reactions of 3-substituted pyrazole-5-diazonium salts with enamines containing heterocyclic components.



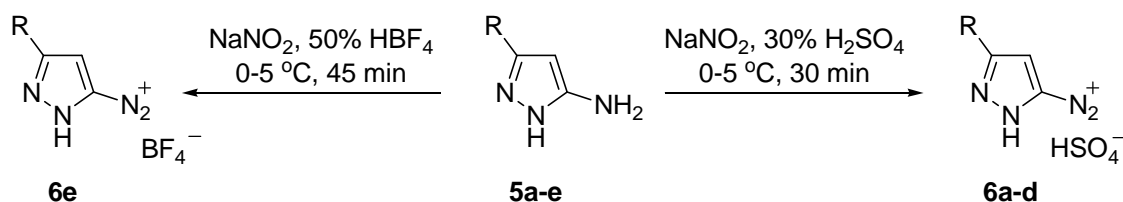
Scheme 1. Known examples for reaction of diazopyrazoles **1a-c** with enamines.

Results and Discussion

In the current research we have studied the reaction of 3-substituted pyrazole-5-diazonium salts **6a-e** with enamines **8a-f** containing isoxazole and thiadiazole moieties and found that this leads to the formation of pyrazolo[5,1-*c*][1,2,4]triazines **9a-l**.

To prepare pyrazole-5-diazonium salts **6a-d** we treated 3-aryl-1*H*-pyrazole-5-amines **5a-d** with sodium nitrite and sulfuric acid in water solution at 0–5 °C. The desired compounds **6a-d** were prepared in good yields as solid substances. In the case of 3-methyl-1*H*-pyrazole-5-amine **5e** we did not manage to isolate hydrosulfate salt **6e** as a solid. Therefore, it was alternatively

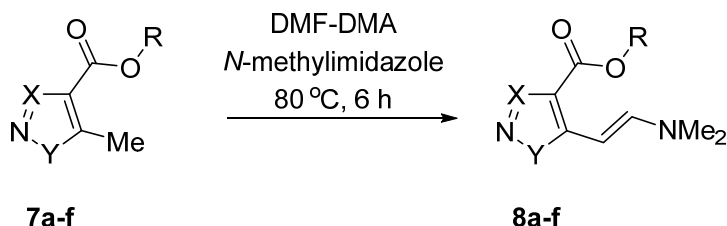
generated from aminopyrazole **5e** by reaction with sodium nitrite in an aqueous solution of HBF₄ at low temperature (Scheme 2) and tetrafluoroborate salt **6e** was used *in situ* in further studies.



5,6a R = Ph; **5,6b** R = 4-Tol; **5,6c** R = 4-MeOC₆H₄; **5,6d** R = 4-ClC₆H₄; **5,6e** R = Me

Scheme 2. Diazotization of 3-substituted 5-amino-1*H*-pyrazoles **5a-e**.

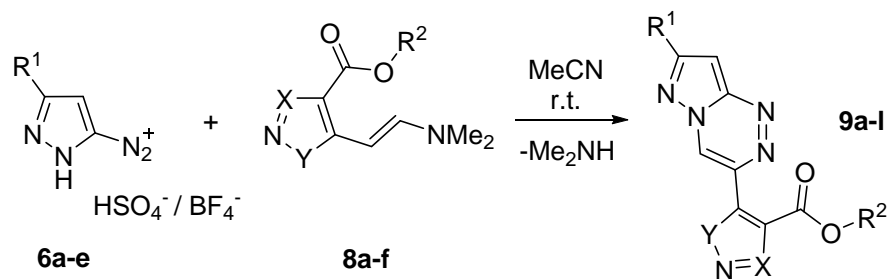
Enamines **8a-f** were prepared by treatment of the corresponding 5-methylthiadiazole-4-carboxylate **7a,b** or alkyl 5-methyl-3-arylisoxazole-4-carboxylates esters **7c-f** with DMF-DMA in the presence of *N*-methylimidazole under reflux for six hours as has been reported earlier^{33,34} (Scheme 3).



7,8 a,b X = N, Y = S, **a** R = Et, **b** R = Me;
7,8 c,d X = Ph-C, Y = O, **c** R = Me, **d** R = Et;
7,8 e X = 2-Cl-6-FC₆H₃-C, Y = O, R = Me;
7,8 f X = 3-FC₆H₄-C, Y = O, R = Et

Scheme 3. Synthesis of known 3-azolyl enamines **8a-f**.

Then with diazonium salts **6a-e** and azolyl enamines **8a-f** in hands we studied the reaction of 3-substituted pyrazole-5-diazonium salts **6a-e** with azolyl enamines **8a-f** (Scheme 4) and optimized the reaction conditions (Table 1).



Scheme 4. Synthesis of 3-azolyipyrazolo[5,1-*c*][1,2,4]triazines **9a-l**.

The study of the progress of the reaction mixture indicated that homogenous conditions were superior to heterogeneous ones (compare entries 2, 3 with entry 1). From the solvent screening it was found that acetonitrile was the best solvent (compare entry 3 with entries 1, 2 and entry 10 with entry 9). Furthermore, room temperature conditions performed better than heating at 45–50 °C (compare entries 3, 10, 14 with entries 4, 11, 15, respectively). Based on the low yields of the title compounds at 50 °C, the partial decomposition of the initial diazo compounds was assumed due to the temperature increase. Good yields of the desired pyrazolo[5,1-*c*][1,2,4]triazines **9** were obtained when the reaction was performed in acetonitrile at room temperature and these conditions were chosen as the optimal ones.

We have found the regioselective formation of novel 3-azolyipyrazolo[5,1-*c*][1,2,4]triazines **9a-l** in good to excellent yields (Table 1).

Table 1. Characteristics of 3-azolyipyrazolo[5,1-*c*][1,2,4]triazines **9a-l**

| Entry | Compds. | Product | Time (h) | Yield* (%) | Mp (°C) |
|-------|-----------|---------|-------------------|------------|---------|
| 1 | 9a | | 4 ^a | 46 | 180–181 |
| 2 | | | 2 ^b | 48 | |
| 3 | | | 1.5 ^c | 65 | |
| 4 | | | 0.75 ^d | 44 | |
| 5 | 9b | | 1.5 ^c | 71 | 194–195 |

Table 1. Continued

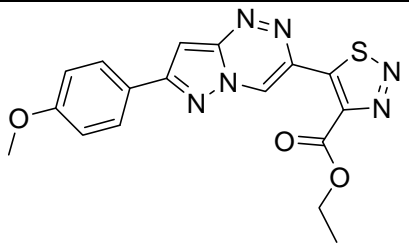
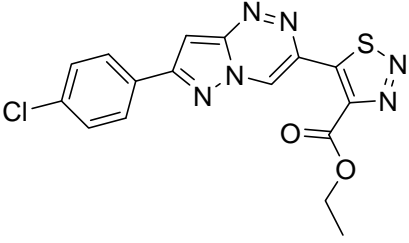
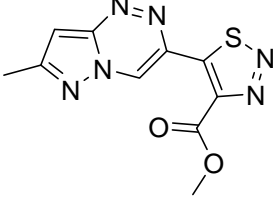
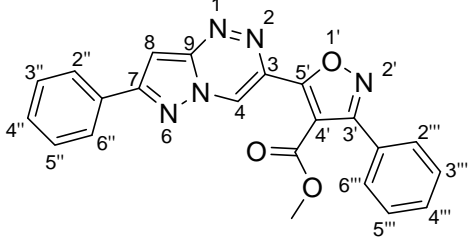
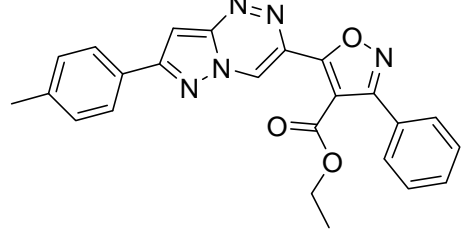
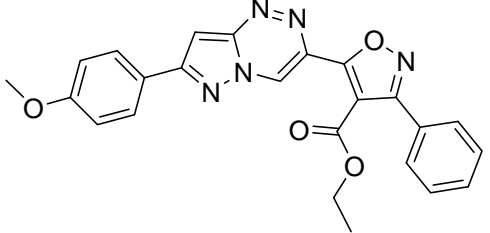
| Entry | Compds. | Product | Time (h) | Yield* (%) | Mp (°C) |
|-------|-----------|---|------------------|------------|---------|
| 6 | 9c |  | 3.5 ^c | 70 | 177–178 |
| 7 | 9d |  | 2.5 ^c | 67 | 245–246 |
| 8 | 9e |  | 1.2 ^c | 73 | 244–245 |
| 9 | 9f |  | 2.5 ^b | 53 | 232–233 |
| 10 | | | 1.5 ^c | 64 | |
| 11 | | | 0.8 ^d | 31 | |
| 12 | 9g |  | 2.5 ^c | 70 | 242–243 |
| 13 | 9h |  | 2.5 ^c | 57 | 230–231 |

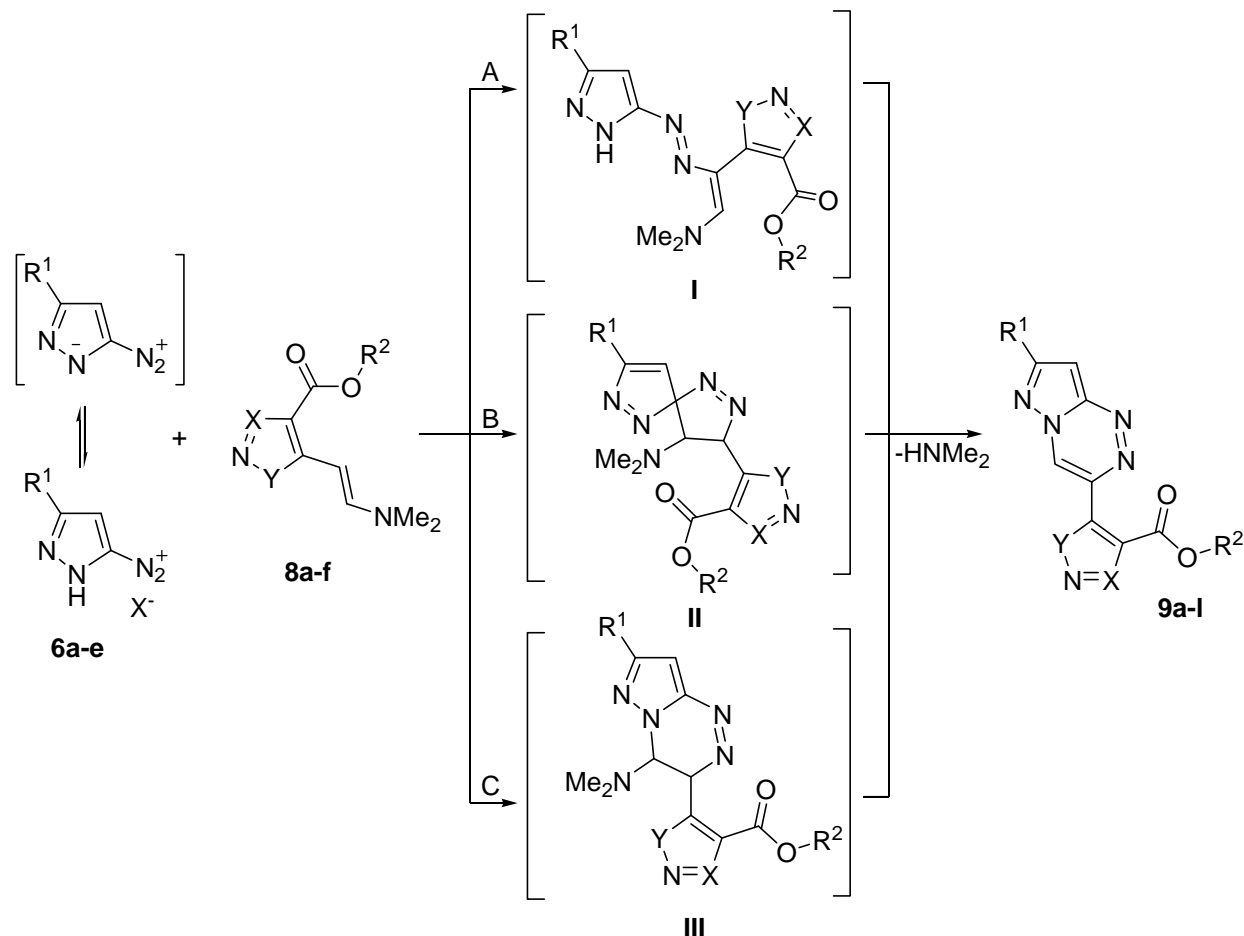
Table 1. Continued

| Entry | Comps. | Product | Time (h) | Yield* (%) | Mp (°C) |
|----------|-----------|---------|------------------------------------|------------|---------|
| 14 15 | 9i | | 2 ^c 0.7 ^d | 96 50 | 257–258 |
| 16 | 9j | | 4 ^c | 73 | 198–200 |
| 17 | 9k | | 3 ^c | 64 | 221–222 |
| 18 | 9l | | 4.5 ^c | 52 | 195–196 |

* Isolated yields of pyrazolotriazines **9** in two step process: **5**→**9**

^a CHCl₃, rt; ^b Pyridine, rt; ^c MeCN, rt; ^d MeCN, 45–50 °C; ^e MeCN, Na₂CO₃/ H₂O, rt

According to literature, we suggest three plausible mechanisms for the formation of the 3-azolyipyrazolo[5,1-*c*][1,2,4]triazines **9a-l** (Scheme 5). Compounds **9a-l** are assumed to be formed *via* coupling at C-2 of the activated double bond of enamines **8a-f** with the diazonium ions of **6a-e** to afford the azo intermediates **I** that undergo intramolecular cyclization *via* elimination of dimethylamine to final compounds **9**.³⁵



Scheme 5. Plausible mechanisms for the formation of 3-azolyipyrazolo[5,1-*c*][1,2,4]triazines **9a-l**.

While triazine system formation in the two steps formally corresponds to the route **A**, an alternate routes **B**, **C** involving initial 1,3 union **II** followed by a [1,5]-sigmatropic shift and elimination of dimethyl amine or 1,7-cycloaddition of **6** to **8** to yield **III**, which then aromatizes to form the title compounds **9a-l** are also possible.^{10,12,13,15}

We attempted to capture the intermediate **I** or **II** at a lower temperature (Scheme 5). However, it was difficult to check the presence of any intermediate product according to TLC. NMR experiments have shown that already 5 min after beginning of the reaction between cooled solutions of diazonium salt and enamine in dry DMSO-*d*₆ there were no longer signals of the starting compounds. Thus, unfortunately the trials to isolate either azo coupling intermediate or acyclic hydrazones failed.

The structures of the synthesized 3-azolyipyrazolo[5,1-*c*][1,2,4]triazines **9a-l** were confirmed by IR, ¹H, ¹³C NMR spectroscopy, mass spectrometry and elemental analysis.

In the IR spectra of **9a-l** bands are observed corresponding to the asymmetric (1544–1638 cm⁻¹) absorption modes of the N=N bonds typical for a triazine structure.

The mass spectra of the 3-azolyipyrazolo[5,1-*c*][1,2,4]triazines **9a-l** show a molecular ion peak (M^+) and decomposition under electron impact conditions with sequential cleavage of CO_2Et or CO_2Me thus pointing to the presence of ethoxy and methoxy carbonyl groups in the molecule, respectively. Ions with m/z 143, 177, 173, 157 point to the presence of 3-arylpyrazole fragments in the molecules bearing isoxazolyl moiety **9f-l**. For thiadiazolyl derivatives **9a-e** the general fragmentation is not the same. The occurrence of 1,2,3-thiazole fragment is confirmed by the characteristic processes³⁶ of loss of nitrogen molecule. Found together with the formation of the thiirene molecule there are also observed the pyrazole and pyrazolotriazine fragments with m/z 69 and 120, respectively.

The ^1H NMR spectra revealed the presence of the following signals: a singlet at δ_{H} 9.91-10.13 due to the H-4 proton of the triazine, a singlet at δ_{H} 7.89-8.09 due to the H-8 pyrazole proton and two multiplets in the region 7.04-8.18 due to the aromatic protons of pyrazole and triazine, respectively. The absence of a signal at δ_{H} 12.00-13.00 assigned to NH pyrazole proton, shows that this part of molecule has been involved in the reaction, and moreover the ^1H spectra are free of signals characteristic for the dimethylamine protons.

The ^{13}C NMR spectra revealed signals for all carbons of compounds **9a-l** and most significantly there is a C-4 signal at δ_{C} 95.22-96.84, proving triazine formation. The ^{13}C spectrum showed aromatic signals in the region δ_{C} 121.24-134.10 for both pyrazole and triazine aromatic carbons. At lower field one can see the signals due to the C=O group of the ester function and to quaternary carbons. The DEPT spectrum allows assigning exactly the signal at δ_{C} 124.12-124.84 as C-8 since it is connected with a proton.

In addition, in the comparison of the ^{13}C spectra of diazonium salts **6a-e** and pyrazolo[5,1-*c*][1,2,4]triazines **9a-l** we have noticed that the spectra of the former compounds exhibit signals of the carbon attached to diazonium function in the region δ_{C} 122.7-124.1 according to 2D HMBC spectra. On the other hand, the signals of the quaternary carbons of the final compounds are at lower field (δ_{C} 130.7-147.6). As for 3-*R*-pyrazole-5-diazonium salts this observation can be explained by the localization of the negative charge on the carbon of the pyrazole cycle.

Additional support for the structures of compounds **9a-l** as pyrazolo[5,1-*c*][1,2,4]triazines was given by X-ray analysis of a single crystal of **9e** which was successfully obtained by crystallization from tetrahydrofuran. The compound crystallizes into the monoclinic space group $\text{P2}_1/\text{n}$ (Fig. 1). Both rings are planar (rms deviations 0.001 and 0.002 Å for thiadiazole and pyrazolo[5,1-*c*][1,2,4]triazine rings, respectively) and make a dihedral angle of 4.40(7)°. This almost planar conformation is stabilized by an intramolecular C-H...O hydrogen bond [C6-H6...O2 with H6...O2 2.101(18) Å]. The molecules stack by π - π interactions into layers parallel to the plane (205). The shortest distance between these layers is between the centroids of neighboring thiadiazole and pyrazole rings [3.483(1) Å].

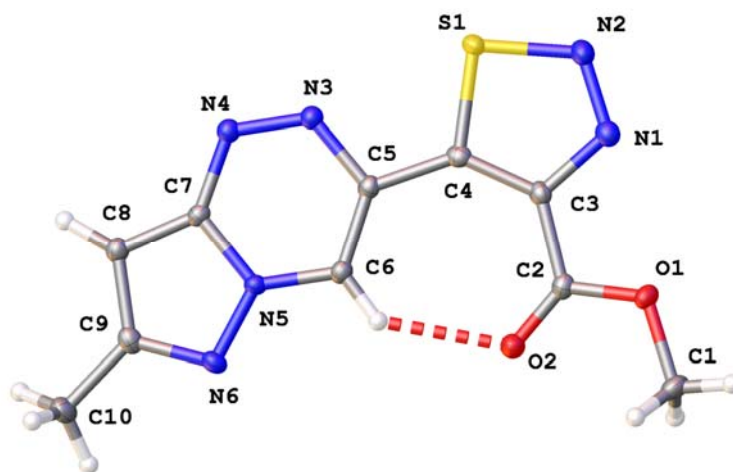


Figure 1. The molecular structure of **9e** with displacement ellipsoids drawn at the 50% probability level and intramolecular hydrogen bond drawn as dashed line.

Conclusions

We have demonstrated a simple, regioselective and convenient method for the synthesis of novel 3-substituted pyrazolo[5,1-*c*][1,2,4]triazines by reaction of pyrazole-5-diazonium salts with β -azoly enamines. In this context, twelve new reported 3-azoly pyrazolo[5,1-*c*][1,2,4]triazines were isolated and characterized. The crystal data for a representative compound pointed out its planar structure and formation of the intramolecular hydrogen bonding which stabilizes the molecule. Plausible mechanisms for the formation of the title compounds were proposed. The study of scope and limitation of this reaction is in progress in our laboratories.

Experimental Section

General. Melting points were determined on a Stuart SMP30 and are uncorrected. The ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer in $\text{DMSO-}d_6$ at 400 and 100 MHz, respectively. TMS was used as the internal standard. IR spectra were measured on a Bruker Alpha FT-IR spectrometer (ZnSe). The samples were examined directly as solids and ν_{max} values were given for the main absorption bands. The results of elemental analysis for the obtained compounds correspond to calculated data (Perkin Elmer 2400 II). The reactions were monitored and the purity of the products was checked by TLC with Silufol UV-254 (silica gel STC-1A as the sorbent) using the following solvent systems: chloroform/ethanol, 5:1; hexane/ethyl acetate, 3:1.

The single-crystal X-ray diffraction data for **9e** were collected on an Agilent SuperNova diffractometer with Eos CCD detector, MoK_α radiation, $\lambda = 0.71073 \text{ \AA}$. Data frames were

processed (unit cell determination, intensity data integration, correction for Lorentz and polarization effects, and empirical absorption correction) using CrysAlis PRO.³⁷ The structure was solved by direct methods and refined by full-matrix least-squares based on F^2 using the SHELX³⁸ and Olex2.³⁹ H atoms were found in difference density maps and refined freely with isotropic temperature factors.

The starting enamines: ethyl **8a** and methyl 5-[(*E*)-2-(*N,N*-dimethylamino)ethenyl]-1,2,3-thiadiazole-4-carboxylate **8b**, (*E*)-methyl **8c** and (*E*)-ethyl 5-[2-(*N,N*-dimethylamino)viny]-3-phenylisoxazole-4-carboxylate **8d**, (*E*)-methyl 3-(2-chloro-6-fluorophenyl)-5-[2-(*N,N*-dimethylamino)viny]isoxazole-4-carboxylate **8e**, (*E*)-ethyl 3-(3-fluorophenyl)-5-[2-(*N,N*-dimethylamino)viny]isoxazole-4-carboxylate **8f** were synthesized by known procedures.^{33,34}

General procedure for the synthesis of 3-aryl-1*H*-pyrazole-5-diazonium hydrosulfates (6a-d). A cooled solution of NaNO_2 (0.08 g, 1.2 mmol) in water (0.5 mL) was added dropwise to a stirring suspension of 3-aryl-5-aminopyrazole **5a-d** (1.0 mmol) in 30% H_2SO_4 (4 mL, 2 mmol) at 0 °C. The reaction mixture was stirred at this temperature for 30 min. Then, the formed precipitate was collected by filtration, washed with cold water (3 mL) and dried *in vacuo*.

3-Phenyl-1*H*-pyrazole-5-diazonium hydrosulfate (6a). Pale beige solid, yield 0.22 g, 81%, mp 129–130 °C (decomposition). ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ_{H} 8.10 (s, 1H, H-4), 7.90 (d, $^3J_{(\text{HH})}$ 7.3 Hz, 2H, H-2',6'), 7.61-7.55 (m, 3H, H-3',4',5'); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ_{C} 147.1 (C-3), 130.4 (C-1'), 129.5 (C-2',6'), 126.4 (C-3',5'), 126.8 (C-4'), 122.7 (C-5), 110.2 (C-4). FT-IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 3222 (NH), 2275 (N_2^+).

3-(*p*-Tolyl)-1*H*-pyrazole-5-diazonium hydrosulfate (6b). Beige solid, yield 0.21 g, 73%, mp 206–207 °C (decomposition). ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ_{H} 8.09 (s, 1H, H-4), 7.80 (d, $^3J_{(\text{HH})}$ 8.0 Hz, 2H, H-2',6'), 7.40 (d, $^3J_{(\text{HH})}$ 8.0 Hz, 2H, H-3',5'), 2.38 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ_{C} 146.7 (C-3), 140.7 (C-1'), 130.1 (C-2',6'), 126.4 (C-3',5'), 123.8 (C-5), 123.2 (C-4'), 109.4 (C-4). FT-IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 3217 (NH), 2280 (N_2^+).

3-(*p*-Methoxyphenyl)-1*H*-pyrazole-5-diazonium hydrosulfate (6c). Beige solid, yield 0.20 g, 67%, mp 204–205 °C (decomposition). ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ_{H} 8.00 (s, 1H, H-4), 7.87 (d, $^3J_{(\text{HH})}$ 8.7 Hz, 2H, H-2',6'), 7.12 (d, $^3J_{(\text{HH})}$ 8.7 Hz, 2H, H-3', 5'), 3.84 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ_{C} 161.2 (C-4'), 146.5 (C-3), 128.2 (C-2',6'), 124.1 (C-5), 118.2 (C-1'), 115.1 (C-3',5'), 109.4 (C-4). FT-IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 3247 (NH), 2271 (N_2^+).

3-(*p*-Chlorophenyl)-1*H*-pyrazole-5(3)-diazonium hydrosulfate (6d). Beige solid, yield 0.25 g, 84%, mp 154–156 °C (decomposition). ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ_{H} 8.13 (s, 1H, H-4), 7.91 (d, $^3J_{(\text{HH})}$ 8.5 Hz, 2H, H-2',6'), 7.65 (d, $^3J_{(\text{HH})}$ 8.5 Hz, 2H, H-3', 5'); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ_{C} 145.8 (C-3), 135.4 (C-1'), 129.7 (C-3',5'), 128.4 (C-2',6'), 125.3 (C-4'), 123.6 (C-5), 110.7 (C-4). FT-IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 3199 (NH), 2275 (N_2^+).

General procedure for the reaction of 3-substituted pyrazole-5-diazonium salts (6a-d) with 3-azolyl enamines (8a-f). To a stirred solution of diazonium salt **6a-d** (1 mmol) in MeCN (2 mL), a solution of enamine **8a-f** (1 mmol) in the same solvent (2 mL) was added at room temperature (see Table 1). The reaction mixture was stirring at this temperature for 0.7–4.5 h

(see Table 1). After disappearing of the starting compounds as checked by TLC, the formed precipitate was filtered off. The gummy product was purified by washing with diethyl ether (5–10 mL), then dried and recrystallized from a mixture of chloroform and acetonitrile.

3-(4'-Ethoxycarbonyl-1,2,3-thiadiazolyl)-7-phenylpyrazolo[5,1-c][1,2,4]triazine (9a). Yellow solid, yield 0.23 g, 65%, mp 180–181 °C. $^1\text{H NMR}$ (400 MHz, DMSO- d_6): δ_{H} 10.09 (s, 1H, H-4), 8.21 (d, $^3J_{\text{HH}}$ 7.2 Hz, 2H, H-2'',6''), 8.16 (s, 1H, H-8), 7.61–7.54 (m, 3H, H-3'',4'',5''), 4.49 (q, $^2J_{\text{HH}}$ 7.1 Hz, 2H, OCH_2CH_3), 1.35 (t, $^2J_{\text{HH}}$ 7.1 Hz, 3H, OCH_2CH_3); $^{13}\text{C NMR}$ (100 MHz, DMSO- d_6): δ_{C} 159.1, 157.4, 146.4, 140.0, 139.5, 139.2, 125.4, 125.0, 124.41, 121.2, 95.7, 86.8, 86.5, 56.8, 10.4. FT-IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 1708 (C=O), 1569 (N=N). *Anal.* Calcd. for $\text{C}_{16}\text{H}_{12}\text{N}_6\text{O}_2\text{S}$ (352.38): C, 54.54; H, 3.43; N, 23.85%. Found: C, 54.31; H, 3.46; N, 23.69%.

3-(4'-Ethoxycarbonyl-1,2,3-thiadiazolyl)-7-(*p*-tolyl)pyrazolo[5,1-c][1,2,4]triazine (9b). Mustard solid, yield 0.26 g, 71%, mp 194–195 °C. $^1\text{H NMR}$ (400 MHz, DMSO- d_6): δ_{H} 10.08 (s, 1H, H-4), 8.01 (d, $^3J_{\text{HH}}$ 7.8 Hz, 2H, H-3'',5''), 7.89 (s, 1H, H-8), 7.30 (d, $^3J_{\text{HH}}$ 7.8 Hz, 2H, H-2'',6''), 4.54 (q, $^2J_{\text{HH}}$ 7.0 Hz, 2H, OCH_2CH_3), 2.41 (s, 3H, CH_3), 1.46 (t, $^2J_{\text{HH}}$ 7.0 Hz, 3H, OCH_2CH_3); $^{13}\text{C NMR}$ (100 MHz, DMSO- d_6): δ_{C} 160.5, 158.5, 156.5, 149.9, 147.0, 140.1, 133.7, 129.5, 127.7, 126.6, 124.5, 96.0, 62.0, 20.8, 13.8. FT-IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 1706 (C=O), 1615 (N=N). *Anal.* Calcd. for $\text{C}_{17}\text{H}_{14}\text{N}_6\text{O}_2\text{S}$ (366.40): C, 55.73; H, 3.85; N, 22.94%. Found: C, 55.58; H, 4.03; N, 22.81%.

3-(4'-Ethoxycarbonyl-1,2,3-thiadiazolyl)-7-(*p*-methoxyphenyl)pyrazolo[5,1-c][1,2,4]triazine (9c). Mustard solid, yield 0.27 g, 70%, mp 177–178 °C. $^1\text{H NMR}$ (400 MHz, DMSO- d_6): δ_{H} 10.04 (s, 1H, H-4), 8.07 (d, $^3J_{\text{HH}}$ 7.4 Hz, 2H, H-3'',5''), 7.89 (s, 1H, H-8), 7.04 (d, $^3J_{\text{HH}}$ 7.4 Hz, 2H, H-2'',6''), 4.52 (q, $^2J_{\text{HH}}$ 7.0 Hz, 2H, OCH_2CH_3), 3.85 (s, 3H, OCH_3), 1.44 (t, $^2J_{\text{HH}}$ 7.0 Hz, 3H, OCH_2CH_3); $^{13}\text{C NMR}$ (100 MHz, DMSO- d_6): δ_{C} 160.9, 160.3, 158.4, 156.2, 149.9, 147.0, 133.4, 128.1, 124.2, 122.9, 114.4, 95.3, 61.9, 55.1, 13.6. FT-IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 1705 (C=O), 1607 (N=N). *Anal.* Calcd. for $\text{C}_{17}\text{H}_{14}\text{N}_6\text{O}_3\text{S}$ (382.40): C, 53.40; H, 3.69; N, 21.98%. Found: C, 53.28; H, 3.93; N, 21.57%.

3-(4'-Ethoxycarbonyl-1,2,3-thiadiazolyl)-7-(*p*-chlorophenyl)pyrazolo[5,1-c][1,2,4]triazine (9d). Yellow solid, yield 0.26 g, 67%, mp 245–246 °C. $^1\text{H NMR}$ (400 MHz, DMSO- d_6): δ_{H} 10.07 (s, 1H, H-4), 8.17 (d, $^3J_{\text{HH}}$ 8.0 Hz, 2H, H-3'',5''), 8.08 (s, 1H, H-8), 7.77 (d, $^3J_{\text{HH}}$ 8.0 Hz, 2H, H-2'',6''), 4.51 (q, $^2J_{\text{HH}}$ 7.0 Hz, 2H, OCH_2CH_3), 1.41 (t, $^2J_{\text{HH}}$ 7.0 Hz, 3H, OCH_2CH_3); $^{13}\text{C NMR}$ (100 MHz, DMSO- d_6): δ_{C} 160.5, 157.3, 156.4, 150.2, 147.6, 135.2, 134.1, 129.6, 129.3, 128.6, 125.1, 96.8, 62.2, 13.9. FT-IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 1717 (C=O), 1601 (N=N), 788 (C-Cl). *Anal.* Calcd. for $\text{C}_{16}\text{H}_{11}\text{ClN}_6\text{O}_2\text{S}$ (386.82): C, 49.68; H, 2.87; N, 21.53%. Found: C, 50.01; H, 3.12; N, 21.53%.

3-(4'-Methoxycarbonyl-1,2,3-thiadiazolyl)-7-methylpyrazolo[5,1-c][1,2,4]triazine (9e). A cooled solution of NaNO_2 (0.08 g, 1.2 mmol) in water (0.5 mL) was added dropwise to a stirring suspension of 3-methyl-5-aminopyrazole **5e** (0.097 g, 1.0 mmol) in 50% HBF_4 (2 mL) at 0 °C. The reaction mixture was stirred at this temperature until the disappearing of the starting amine. Then to the stirred diazo solution of 3-methyl-1*H*-pyrazole-5-diazonium tetrafluoroborate **6e** in HBF_4 a solution of enamine **8b** (2 mmol) in MeCN (1 mL) and 20% aqueous solution of

Na₂CO₃ (5 mL) were added at room temperature. The reaction mixture was stirring at this temperature for 1,2 h. After disappearing of the starting compounds checked by TLC the formed precipitate was filtered off. The crude product was recrystallized from a mixture of ethanol and acetonitrile. Yellow solid, yield 0.20 g, 73%, mp 244–245 °C. ¹H NMR (400 MHz, DMSO-*d*₆): δ_H 9.98 (s, 1H, H-4), 7.41 (s, 1H, H-8), 4.00 (s, 3H, OCH₃), 2.60 (s, 3H, CH₃); ¹³C NMR (100 MHz, DMSO-*d*₆): δ_C 160.8, 158.6, 156.4, 149.3, 146.9, 133.0, 124.3, 98.8, 52.7, 14.0. FT-IR (ν_{max}/cm⁻¹): 1716 (C=O), 1574 (N=N). *Anal.* Calcd. for C₁₀H₈N₆O₂S (276.28): C, 43.47; H, 2.92; N, 30.42%. Found: C, 43.72; H, 2.85; N, 30.32%.

3-(3'-Phenyl-4'-methoxycarbonylisoxazolyl)-7-phenylpyrazolo[5,1-*c*][1,2,4]triazine (9f).

Yellow solid, yield 0.25 g, 64%, mp 232–233 °C. ¹H NMR (400 MHz, DMSO-*d*₆): δ_H 9.88 (s, 1H, H-4), 8.16 (d, ³J_(HH) 7.0 Hz, 2H, H-2'',6''), 7.98 (s, 1H, H-8), 7.73 (d, ³J_(HH) 5.5 Hz, 2H, H-2''',6'''), 7.49–7.54 (m, 6H, H-3'',4'',5'',3''',4''',5'''), 3.79 (s, 3H, OCH₃); ¹³C NMR (100 MHz, DMSO-*d*₆): δ_C 166.1, 161.7, 161.7, 158.4, 150.4, 132.4, 130.7, 130.3, 130.2, 129.0, 128.6, 128.4, 127.8, 127.1, 126.8, 124.8, 96.4, 52.4. FT-IR (ν_{max}/cm⁻¹): 1733 (C=O), 1631 (N=N). *Anal.* Calcd. for C₂₂H₁₅N₅O₃ (397.40): C, 66.49; H, 3.80; N, 17.62%. Found: C, 66.85; H, 3.86; N, 17.73%.

3-(3'-Phenyl-4'-ethoxycarbonylisoxazolyl)-7-(*p*-tolyl)pyrazolo[5,1-*c*][1,2,4]triazine (9g).

Yellow solid, yield 0.30 g, 70%, mp 242–243 °C. ¹H NMR (400 MHz, DMSO-*d*₆): δ_H 9.87 (s, 1H, H-4), 8.05 (d, ³J_(HH) 7.7 Hz, 2H, H-3'',5''), 7.93 (s, 1H, H-8), 7.73 (d, ³J_(HH) 6.6 Hz, 2H, H-2''',6'''), 7.50–7.60 (m, 3H, H-3',4',5'), 7.34 (d, ³J_(HH) 7.7 Hz, 2H, 2'',6''-H), 4.26 (q, ²J_(HH) 7.0 Hz, 2H, OCH₂CH₃), 3.08 (s, 3H, CH₃), 1.15 (t, ²J_(HH) 7.0 Hz, 3H, OCH₂CH₃); ¹³C NMR (100 MHz, DMSO-*d*₆): δ_C 166.1, 161.8, 161.0, 158.4, 150.4, 140.1, 132.2, 130.3, 129.6, 128.5, 128.5, 127.9, 127.2, 126.7, 124.8, 115.0, 96.0, 61.3, 20.9, 13.3. FT-IR (ν_{max}/cm⁻¹): 1731 (C=O), 1636 (N=N). *Anal.* Calcd. for C₂₄H₁₉N₅O₃ (425.45): C, 67.76; H, 4.50; N, 16.46%. Found: C, 67.32; H, 4.69; N, 16.08%.

3-(3'-Phenyl-4'-ethoxycarbonylisoxazolyl)-7-(*p*-methoxyphenyl)pyrazolo-[5,1-*c*][1,2,4]triazine (9h).

Mustard solid, yield 0.25 g, 57%, mp 230–231 °C. ¹H NMR (400 MHz, DMSO-*d*₆): δ_H 9.81 (s, 1H, H-4), 8.11 (d, ³J_(HH) 8.05 Hz, 2H, H-3'',5''), 7.94 (s, 1H, H-8), 7.73 (d, ³J_(HH) 5.0 Hz, 2H, H-2''',6'''), 7.56–7.51 (m, 3H, H-3''',4''',5'''), 7.12 (d, ³J_(HH) 8.05 Hz, 2H, H-2'',6''), 4.24 (q, ²J_(HH) 7.0 Hz, 2H, OCH₂CH₃), 3.86 (s, 3H, OCH₃), 1.10 (t, ²J_(HH) 7.0 Hz, 3H, OCH₂CH₃); ¹³C NMR (100 MHz, DMSO-*d*₆): δ_C 166.0, 160.9, 160.8, 158.3, 150.2, 132.0, 130.0, 128.4, 128.3, 128.2, 128.2, 127.1, 126.6, 124.4, 123.0, 114.4, 95.3, 61.1, 55.1, 13.1. FT-IR (ν_{max}/cm⁻¹): 1728 (C=O), 1631 (N=N). *Anal.* Calcd. for C₂₄H₁₉N₅O₄ (441.45): C, 65.30; H, 4.34; N, 15.86%. Found: C, 65.37; H, 4.41; N, 15.95%.

3-(3'-Phenyl-4'-methoxycarbonylisoxazolyl)-7-(*p*-chlorophenyl)pyrazolo-[5,1-*c*][1,2,4]triazine (9i).

Yellow solid, yield 0.41 g, 96%, mp 257–258 °C. ¹H NMR (400 MHz, DMSO-*d*₆): δ_H 9.94 (s, 1H, H-4), 8.20 (d, ³J_(HH) 8.0 Hz, 2H, H-3'',5''), 8.13 (s, 1H, H-8), 7.72 (d, ³J_(HH) 8.0 Hz, 2H, H-2'',6''), 7.64–7.58 (m, 5H, H-2''',3''',4''',5''',6'''), 3.75 (s, 3H, OCH₃); ¹³C NMR (100 MHz, DMSO-*d*₆): δ_C 165.9, 161.6, 161.5, 157.0, 150.3, 134.9, 132.4, 130.2, 129.5, 129.0, 128.6, 128.5, 128.4, 128.2, 127.0, 124.7, 99.2, 96.5, 52.2. FT-IR (ν_{max}/cm⁻¹):

1729 (C=O), 1638 (N=N), 808 (C-Cl). *Anal.* Calcd. for C₂₃H₁₆ClN₅O₃ (431.84): C, 61.19; H, 3.27; N, 16.22%. Found: C, 59.78; H, 3.01; N, 15.96%.

3-[3'-(2'''-Chloro-6'''-fluorophenyl)-4'-methoxycarbonylisoxazolyl]-7-(*p*-methylphenyl)-pyrazolo[5,1-*c*][1,2,4]triazine (9j). Yellow solid, yield 0.34 g, 73%, 198–200 °C. ¹H NMR (400 MHz, DMSO-*d*₆): δ_H 9.98 (s, 1H, H-4), 8.05 (d, ³J_(HH) 8.0 Hz, 2H, H-3'',5''), 7.91 (s, 1H, H-8), 7.63 (dd, ²J_(HH) 8.3 Hz, ³J_(HH) 4.6 Hz, 1H, H-5'''), 7.47 (d, ³J_(HH) 8.1 Hz, 1H, H-3'''), 7.35 (dd, ²J_(HH) 8.3 Hz, ³J_(HH) 8.1 Hz, 1H, H-4'''), 7.33 (d, ³J_(HH) 8.0 Hz, 2H, H-2'',6''), 3.68 (s, 3H, OCH₃), 2.44 (s, 3H, CH₃); ¹³C NMR (100 MHz, DMSO-*d*₆): δ_C 166.6, 160.4, 159.3, 157.7, 154.9, 149.5, 139.3, 132.8, 132.3, 130.9, 128.8, 127.0, 125.9, 125.4, 124.8, 114.8, 113.8, 110.0, 95.2, 51.4, 20.0. FT-IR (ν_{max}/cm⁻¹): 1720 (C=O), 1587 (N=N), 1440 (C-F), 833 (C-Cl), 785 (C-Cl). *Anal.* Calcd. for C₂₃H₁₅ClFN₅O₃ (463.86): C, 59.56; H, 3.26; N, 15.10%. Found: C, 59.13; H, 3.09; N, 15.05%.

3-[3'-(2'''-Chloro-6'''-fluorophenyl)-4'-methoxycarbonylisoxazolyl]-7-(*p*-chlorophenyl)-pyrazolo[5,1-*c*][1,2,4]triazine (9k). Orange solid, yield 0.31 g, 64%, mp 221–222 °C. ¹H NMR (400 MHz, DMSO-*d*₆): δ_H 10.05 (s, 1H, H-4), 8.20 (d, ³J_(HH) 8.0 Hz, 2H, H-3'',5''), 8.08 (s, 1H, H-8), 7.65 (dd, ²J_(HH) 8.0 Hz, ³J_(HH) 6.5 Hz, 1H, H-5'''), 7.55 (d, ³J_(HH) 8.0 Hz, 2H, H-2'',6''), 7.49 (d, ³J_(HH) 8.5 Hz, 1H, H-3'''), 7.37 (dd, ²J_(HH) 8.5 Hz, ³J_(HH) 8.0 Hz, 1H, H-4'''), 3.68 (s, 3H, OCH₃); ¹³C NMR (100 MHz, DMSO-*d*₆): δ_C 166.2, 160.5, 158.7, 157.0, 155.8, 150.5, 138.2, 131.3, 130.3, 128.7, 127.0, 126.7, 125.4, 124.7, 123.8, 111.9, 110.0, 96.8, 95.4, 50.7. FT-IR (ν_{max}/cm⁻¹): 1722 (C=O), 1544 (N=N), 1448 (C-F), 836 (C-Cl), 783 (C-Cl). *Anal.* Calcd. for C₂₂H₁₂Cl₂FN₅O₃ (484.28): C, 54.56; H, 2.50; N, 14.46%. Found: C, 54.43; H, 2.60; N, 14.11%.

3-[3'-(*m*-Fluorophenyl)-4'-ethoxycarbonylisoxazolyl]-7-phenylpyrazolo[5,1-*c*][1,2,4]triazine (9l). Yellow solid, yield 0.22 g, 52%, mp 195–196 °C. ¹H NMR (400 MHz, DMSO-*d*₆): δ_H 10.00 (s, 1H, H-4), 8.22–8.16 (m, 3H, 2 H_{Ar}, H-8), 7.65–7.45 (m, 7H, 7 H_{Ar}), 4.24 (q, ²J_(HH) 6.9 Hz, 2H, OCH₂CH₃), 1.09 (t, ²J_(HH) 6.9 Hz, 3H, OCH₂CH₃); ¹³C NMR (100 MHz, DMSO-*d*₆): δ_C 166.8, 161.1, 160.8, 160.6, 158.4, 150.5, 132.3, 130.9, 130.8, 130.4, 129.2, 126.9, 125.5, 125.0, 115.9, 115.7, 110.5, 99.5, 96.5, 61.5, 13.4. FT-IR (ν_{max}/cm⁻¹): 1723 (C=O), 1631 (N=N), 1459 (C-F). *Anal.* Calcd. for C₂₃H₁₆FN₅O₃ (429.41): C, 64.33; H, 3.76; N, 16.31%. Found: C, 63.98; H, 3.55; N, 16.43%.

Crystal Data for 9e. (*M* = 276.28 g/mol), monoclinic, space group P2₁/n (no. 14), *a* = 5.73223(14) Å, *b* = 16.3235(4) Å, *c* = 12.0595(3) Å, β = 91.991(2)°, *V* = 1127.73(5) Å³, *Z* = 4, *T* = 100.01(10) K, μ(MoKα) = 0.296 mm⁻¹, *D*_{calc} = 1.627 g/cm³, 4626 reflections measured (5° ≤ 2θ ≤ 52.74°), 2302 unique (*R*_{int} = 0.0189, *R*_{sigma} = 0.0308) which were used in all calculations. The final *R*₁ was 0.0349 (>2σ(I)) and *wR*₂ was 0.0865 (all data).

Single crystal data for compound 9e (CCDC 1437673) has been deposited in the Cambridge Crystallographic Data Center and it can be obtained free of charge via <http://www.ccdc.cam.ac.uk/conts/retrieving.html> (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

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