Reactivity of 1,2,3-triazole-substituted 1-azabutadienes (vinamidines)

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Dedicated to Prof. Ferenc Fülöp on the occasion of his 60th birthday

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Abstract
The reactivity of the new 1,2,3-triazole-substituted vinamidines (*i.e.* 1-azabutadienes) was investigated. They were used as synthons to obtain new pyrazole, di-1,2,3-triazole as well as 4-amino-1,2,3-triazole derivatives. The Diels-Alder reaction with inverse electronic demand (using dimethyl 1,2,4,5-tetrazin-3,6-dicarboxylate as reagent) resulted in the formation of a new pyridazine derivative.

Keywords: 1-Azabutadiene, vinamidine, 1,2,3-triazole, reduction of vinamidines, cycloaddition, Diels-Alder reaction

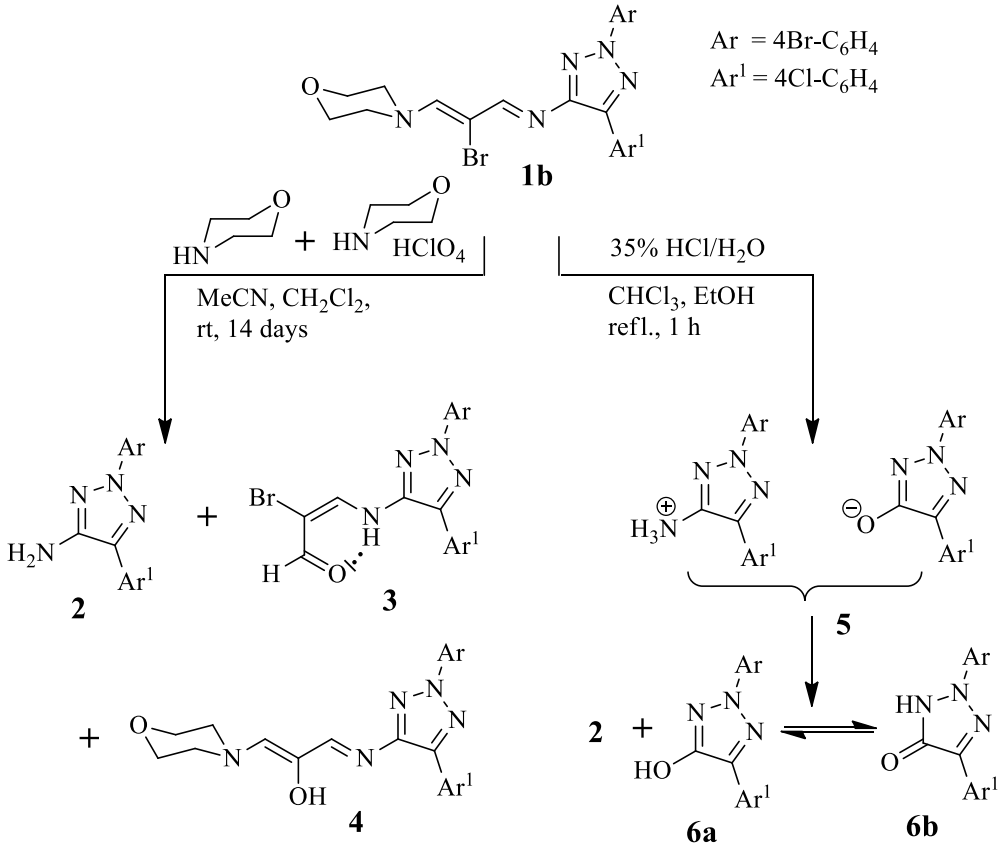
Introduction

The vinamidines and vinamidinium salts are valuable synthons in the synthesis of a variety of new compounds.[2-4] We studied the reactivity of two new 1-azadienes (**1a,b**), described by us recently.[1] These vinamidines were found to be fairly stable under the conditions of their preparation, although their aminolysis or hydrolysis could theoretically lead to the formation of aminotriazole **2**. This compound was isolated in low yield as byproduct in the reaction that gave **1b**.[1]

Results and Discussion

In order to study the possibility of formation of **2**, the 1-azadiene **1b** was reacted with an excess of morpholine in the presence of morpholinium perchlorate. A slow reaction took place at room

temperature and instead of the expected aminotriazole **2**[1] (which was isolated in very low, 2% yield), two other products were obtained: the 2-bromo-2-propenal-3-yl-aminotriazole **3**[1] (37%; being formed *via* the hydrolysis of the morpholine moiety) and the 3-hydroxy-4-morpholino-1-aza-1,3-butadien-1-yl derivative **4** (29%; being formed by the hydrolysis of the bromo substituent).



Scheme 1. Aminolysis and hydrolysis of vinamidine **1b**.

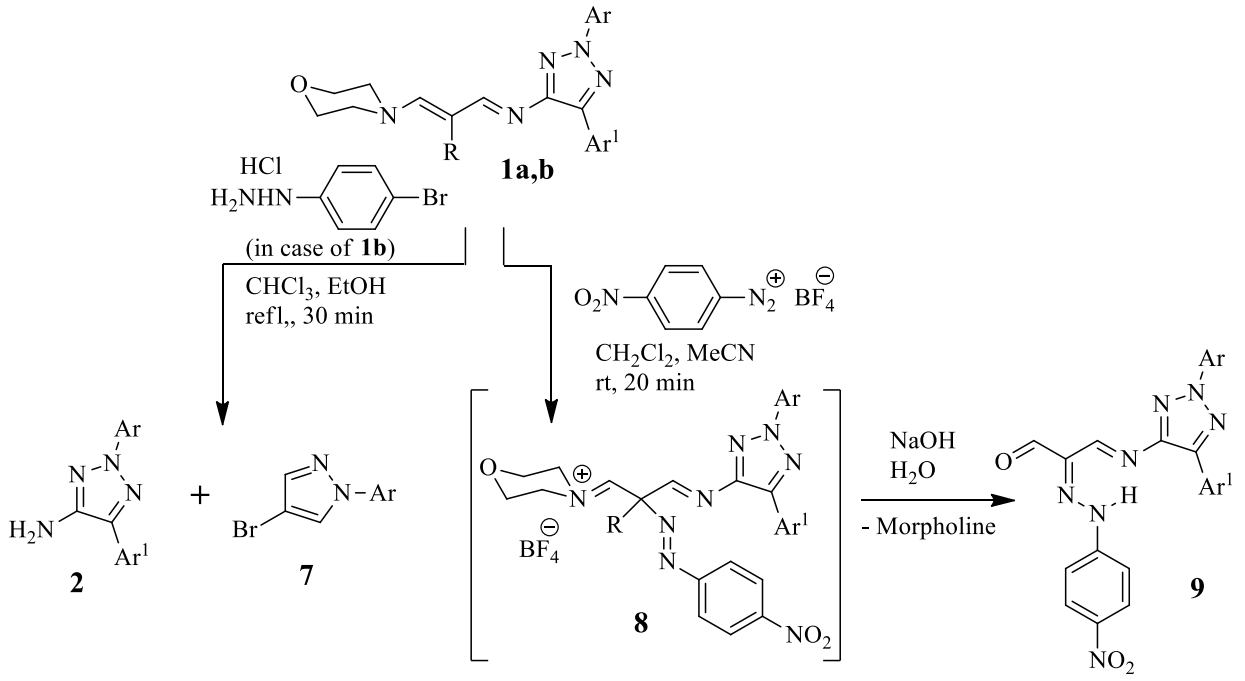
The structure elucidation of **4** showed that depending on the solvent it can also exist in zwitterionic form. The acidic hydroxy group at position 3 can protonate the N-atom at position 1 (or the N-atom of the morpholine substituent). As a result, the nitrogen atom in question became positively charged, while the oxygen was bearing a negative charge.

The reaction with morpholine showed that the aminolysis of **1b** was not a favoured process to give **2**, instead the hydrolysis of the morpholino or the bromo substituents took place under influence of traces of water in the solvent.

Under acidic conditions at room temperature the vinamidine **1b** is stable. At reflux temperature, however, the reaction of **1b** with aq. HCl resulted in (within 1 h) a yellow crystalline product. Its structure elucidation showed that the resulted compound (**5**) has a salt-type character and contains the protonated amine (**2**) and the hydroxytriazole anion **6** in 1 : 1

ratio. The two components were separated by column chromatography to give the pure **2** as well as **6**. This exists in equilibrium of two tautomeric forms, **6a** and **6b**, the latter being the dominant form (IR: 1644 cm^{-1}).

On the other hand, a successful aminolysis (hydrazinolysis) took place when the 1-azadiene **1b** was reacted with 4-bromophenylhydrazine: the aminotriazole **2** was obtained in 67% yield. The other product, isolated in excellent yield (81%), was 4-bromo-1-(4-bromophenyl)pyrazole (**7**)[5]. This compound was synthesized earlier by bromination of 1-phenylpyrazole or 1-(4-bromophenyl)pyrazole[5,6] and 4-bromo-1-phenylpyrazole.[7] W. Dieckmann and L. Platz[8] studied the reaction of chloro- and bromomalonaldehyde with aniline. They isolated 3-chloro- (or 3-bromo)-1-phenyl-4-(phenylamino)-1-azadienes. The reaction of these vinamidines with phenylhydrazine gave 4-chloro- (or 4-bromo)-1-phenylpyrazoles. The reaction, found by us, represents a modification of this method to produce 4-substituted pyrazoles.

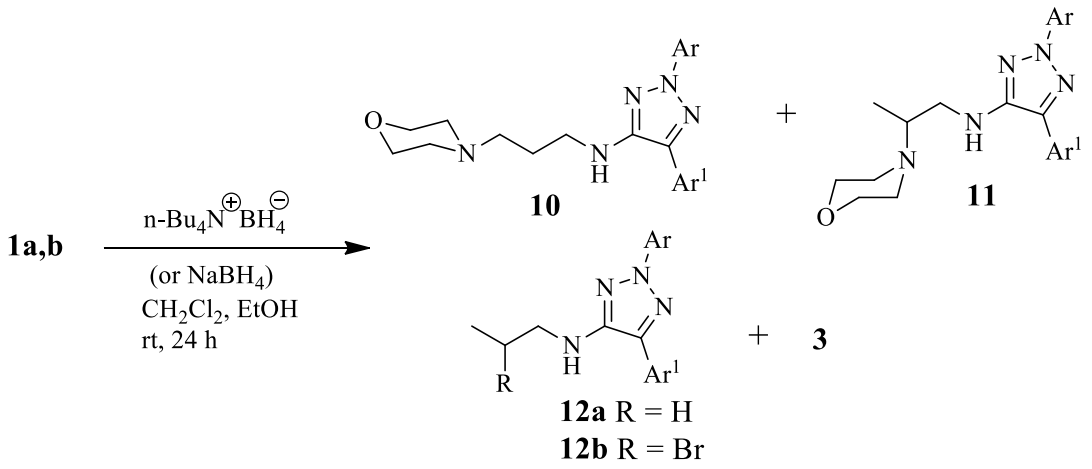


Scheme 2. Reaction of vinamidines **1a,b** with 4-bromophenylhydrazine and 4-nitrophenyldiazonium fluoroborate.

The reaction of **1a** with 4-nitrobenzenediazonium fluoroborate resulted in an unstable, insoluble orange solid as crude product (having very probably the structure **8**), that after work up with aq. NaOH (hydrolysis of the morpholino group) and chromatography, gave the hydrazone **9** (in 83% yield). It is interesting that the vinamidine **1b** gave the same hydrazone **9** (but in much lower yield) as was isolated in the case of **1a**. In this case, the aminotriazole **2** was formed as byproduct in comparable yield to **9**.

Interestingly, some hetaryl substituted dienamines[9] reacted with aryldiazonium salts similarly to vinamidines **1a,b** with formation of hydrazones, while 2-azadiene compounds[10] resulted in the formation of 1,2,4-triazole derivatives.

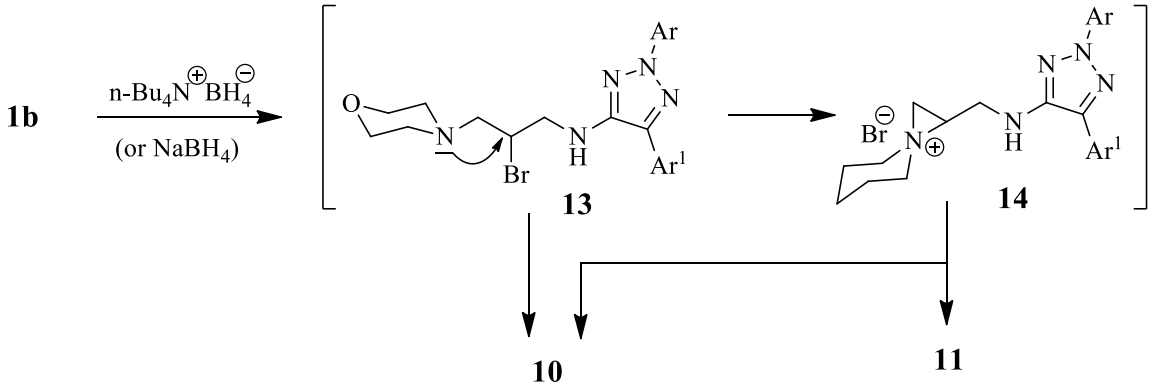
The reduction of vinamidines **1a** with tetrabutylammonium borohydride or sodium borohydride gave, as expected, the morpholinopropylamine derivative **10** as major product in 51% yield.



Scheme 3. Reduction of vinamidines **1a,b** with borohydride.

Similar reactions are described in the literature: Ch. Jutz *et al.*[11] carried out the reaction of vinamidines and vinamidinium salts with $NaBH_4$ to get 1,3-diaminopropane derivatives, while W. Schroth *et al.*[12] reduced vinamidines catalytically on Pd/C to get similarly 1,3-diaminopropane derivatives.

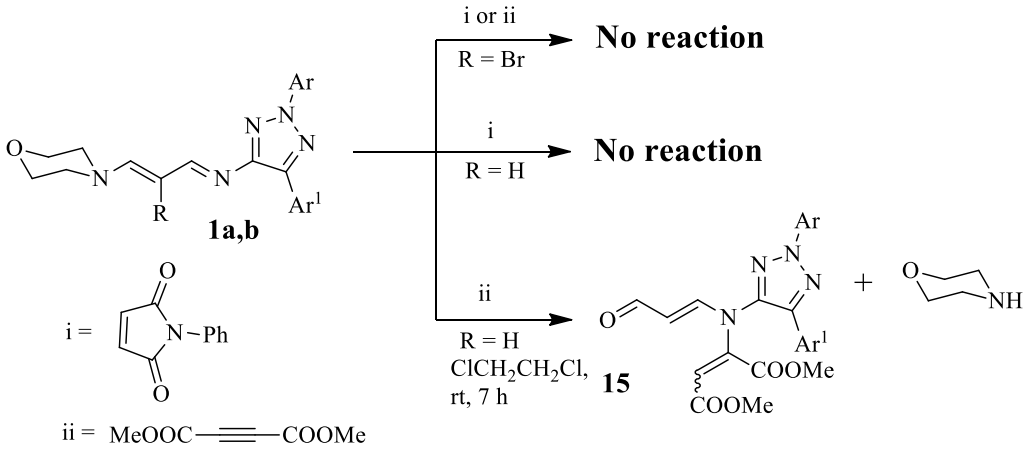
In the case of **1b** the isomeric derivative **11** was also obtained. Its formation can be explained by the reduction of the intermediate aziridinium salt **14** (Scheme 4), which was formed by an intramolecular attack of the nitrogen atom of morpholine on the *β*-C-atom of the first intermediate (**13**) of the reduction. As minor products of the reduction, propylamines **12a,b** were also isolated.



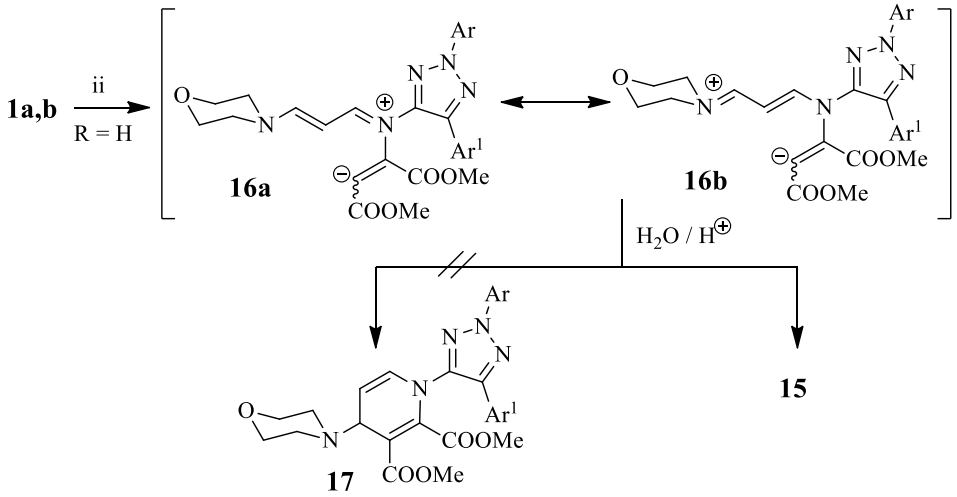
Scheme 4. Formation of isomeric morpholinopropylamine derivative **11**.

The ring opening of activated (like **14**) and non-activated aziridines is widely studied. S. Stankovic *et al.*[13] gave a detailed overview in a recent review about the regioselectivity found in the reaction of 2-substituted aziridines with nucleophiles (see also citations therein). The reaction is dependent on the activation and the nucleophile used. Usually the reaction occurs at the more hindered C-atom when the nucleophile is halogen (except fluoride), azide, and cyanide ion. Alcohols[14] and hydride anion[15] prefer the less hindered C-atom.

We found that the 1-azadienes **1a,b** did not react with *N*-phenylmaleinimide even at elevated temperature if heated for longer time (Scheme 5). The compound **1b** didn't react with dimethyl acetylenedicarboxylate at ambient temperature. After prolonged heating at 100 ºC a multicomponent mixture was formed, from which no definite product could have been isolated.



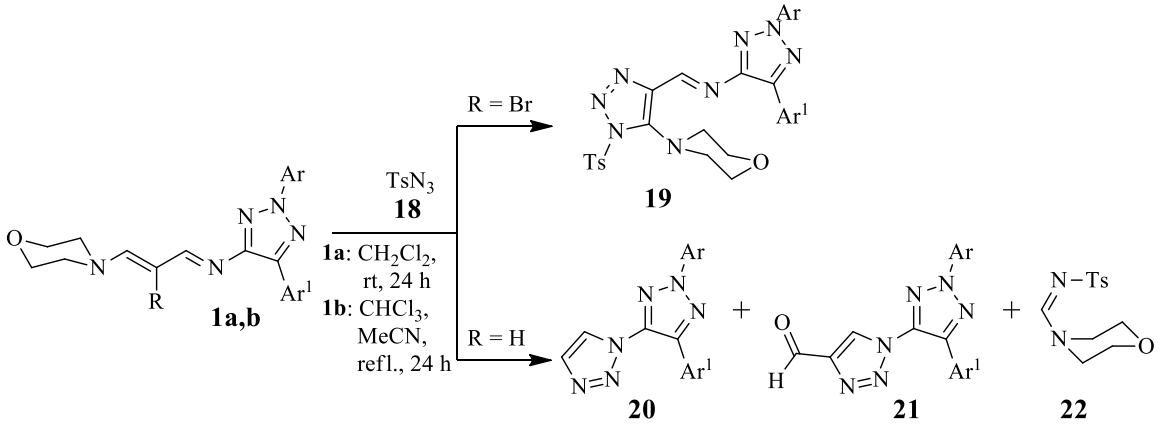
Scheme 5. Attempted Diels-Alder reactions of vinamidines **1a,b**.



Scheme 6. Intermediates in the formation of **15**.

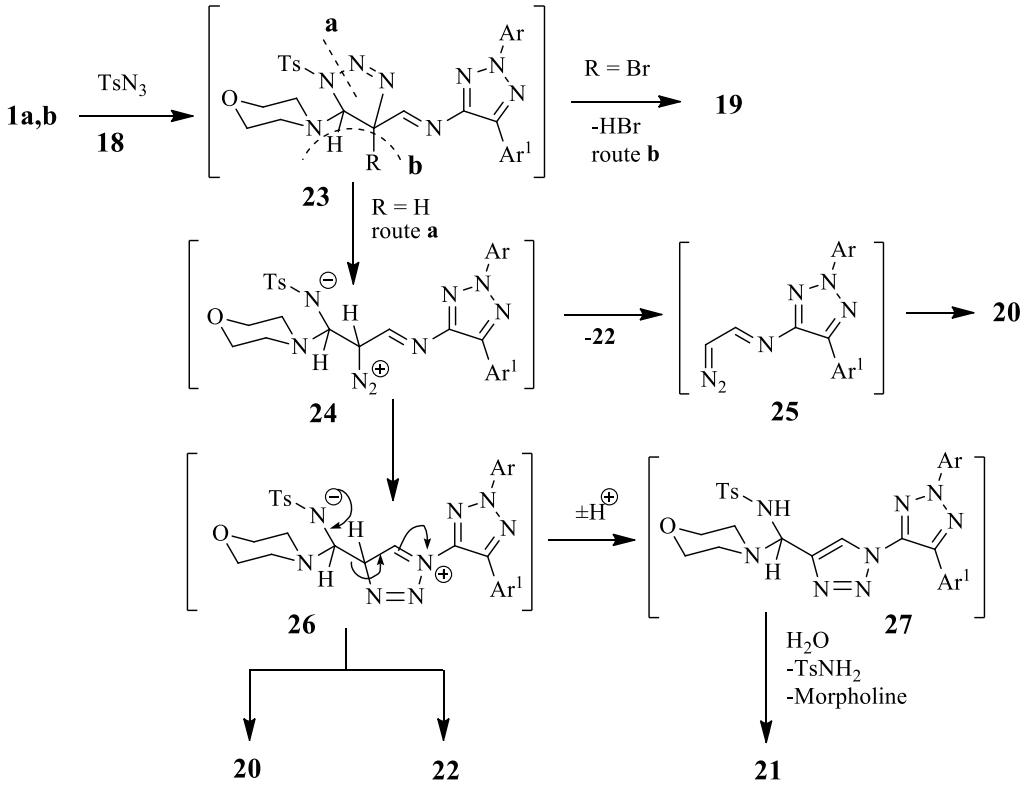
The less electrondeficiant aminoazabutadiene **1a**, however, did react with dimethyl acetylenedicarboxylate but instead of a cycloadduct (**17**), compound **15** was isolated in low (37%) yield. Its formation can be explained by the hydrolysis of the first intermediate (**16a** and **16b**) of the addition (see Scheme 6). According to the ^{1}H NMR the configuration of the double-bond of the propenal moiety of **15** is *trans* ($^3J_{HH}$=13.4 Hz), while the configuration of the double-bond of the diester could not be determined.

The reaction of **1b** with 4-toluenesulfonyl azide (**18**) led to the formation of **19** in low (15%) yield (Scheme 7). The isolation of this compound was important because it provides a proof for the reaction mechanism of this type of reactions. Earlier it was found[16] that the reaction of related systems, the aminobutadiens with 4-toluenesulfonyl azide (**18**) led to the formation of triazole- or tetrazole-substituted pyrazoles. An intermediate similar to **23** (Scheme 8) was postulated in that reaction, from which *N*-(4-toluenesulfonyl)morpholinoformimine (**22**)[17] could be cleaved to form a diazo intermediate (similar to **25**), which gave, after intramolecular cyclization, the isolated pyrazoles. In our case HBr could be easily eliminated from the first intermediate (**23**, R=Br) leading to the stable, isolated **19**.



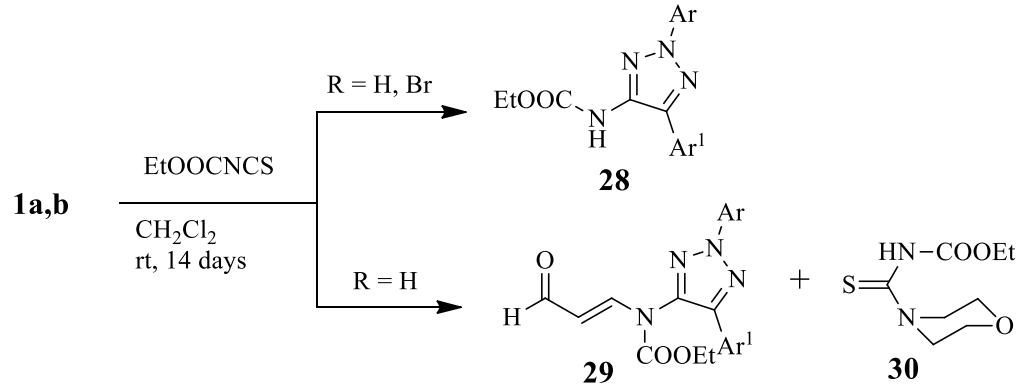
Scheme 7. Reaction of **1a,b** with 4-toluenesulfonyl azide.

If no bromine substituent was present (started from **1a**), a scission of the N-N bond adjacent to the tosyl group of intermediate **23** (R=H) took place to give **24** (Scheme 8).



Scheme 8. Explanation of formation of products with 4-toluenesulfonyl azide.

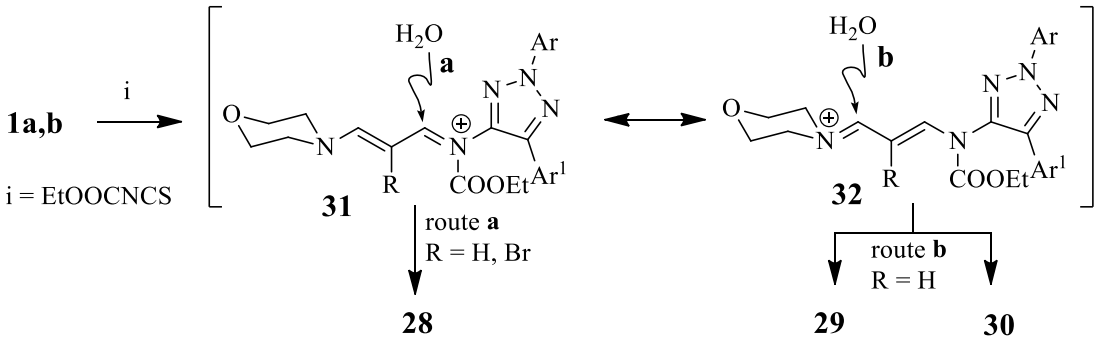
The diazo intermediate **24** could react further in two different ways. According to the first, *N*-(4-toluenesulfonyl)morpholinoformimine (**22**) was cleaved to give the triazolyltriazole derivative **20** (via intermediate **25**). The other possibility for the reaction of intermediate **24** was the cyclization to **26**. This could react further also in two possible ways: a deprotonation at the triazole ring and protonation at the tosyl group was leading to **27**. The hydrolysis of the aminal moiety furnished the other isolated product (**21**). The other possibility for the reaction of intermediate **26** was the cleavage of **22** to afford **20**.



Scheme 9. Reaction of ethoxycarbonyl isothiocyanate with **1a,b**.

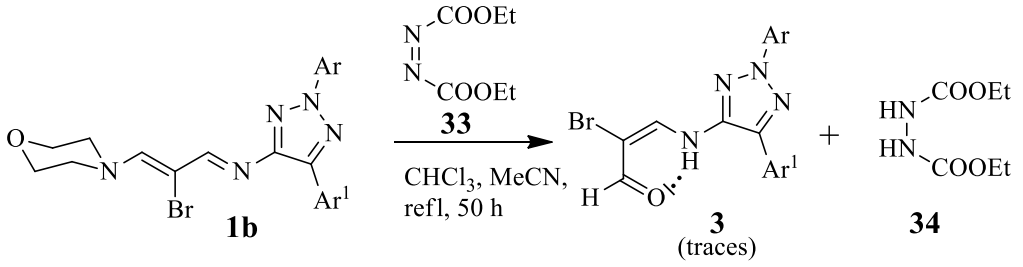
Isothiocyanates are widely used in [4+2][18,19] or [3+2][20] cycloaddition reactions. As the further reagent ethoxycarbonyl isothiocyanate was chosen in the reaction with **1a,b**.

Contrary to our expectations, this reagent proved to be only an acylating agent that formed in the first step very probably the intermediates **31** and **32** in a slow reaction at room temperature (2 weeks) (see Scheme 10). These intermediates were hydrolysed in two routes: the route **a** gave **28** while the other possible way (route **b**) gave **29**. In the course of the reaction, morpholine was liberated, which reacted with the reagent ethoxycarbonyl isothiocyanate to give 1-(ethoxycarbonyl)amino-1-morpholinomethanethione (**30**)[21].



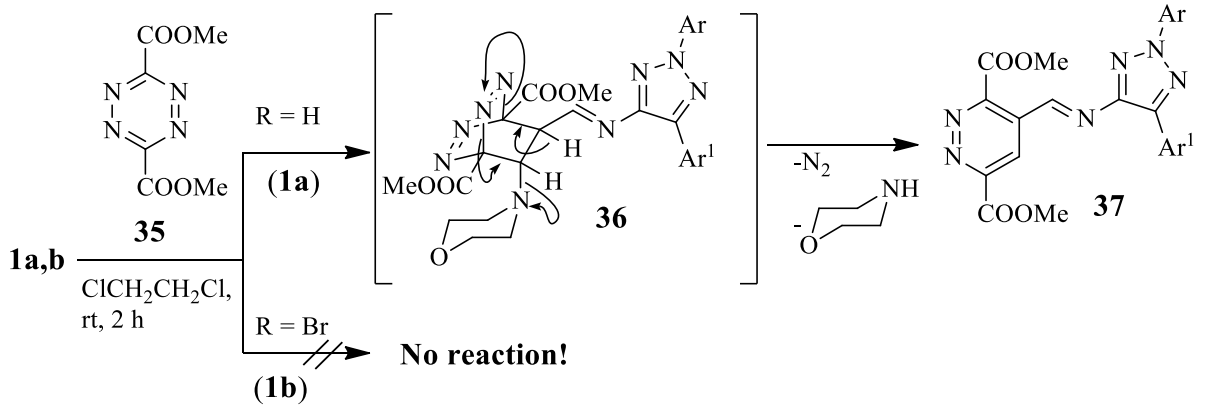
Scheme 10. Proposed intermediates leading to products **28-30**.

The last dienophile used was diethyl azodicarboxylate (**33**). Its prolonged heating (50 h) with **1b** in a 1 : 1 mixture of chloroform and acetonitrile gave a complex mixture from which *sym*-diethyl hydrazinedicarboxylate[22] (**34**, 24%) and traces of **3** were isolated.



Scheme 11. Attempted reaction of diethyl azodicarbocylate with **1b**.

The reaction of **1a,b** with dimethyl 1,2,4,5-tetrazinedicarboxylate (**35**) (a Diels-Alder reaction with inverse electron demand[23]) was also tried. When **1a** was reacted with 1 equivalent of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (**35**) in dichloroethane at room temperature, vigorous gas evolution was observed, the solution turned yellow within few minutes and crystals were separated. The structure elucidation of the product proved that the compound was the pyridazine derivative **37**.



Scheme 11. Reaction of vinamidines **1a,b** with dimethyl 1,2,4,5-tetrazinedicarboxylate (**35**).

Although the tetrazine derivative disappeared from the reaction mixture rapidly, the conversion of **1a** was only 78.4% (the isolated yield of **37** was 70%, based on the recovered **1a**). The repeated reaction with 2.4 equivalents of tetrazine resulted in the isolation of **37** in 91% yield!

The formation of **37** can be explained by the first addition of the activated, electron rich double bond next to the morpholine moiety of **1a** to the highly electrondeficiant aromatic ring (in positions 3 and 6) of tetrazine **35** forming the intermediate **36**. This bicyclic intermediate aromatizes by loosing N_2 and morpholine to give the isolated pyridazine derivative **37**.

The attempted reaction of **1b** with tetrazinedicarboxylate was unsuccessful. The vinamidine **1b** remained unchanged even after prolonged stirring in dichloroethane with **35**.

Conclusions

In the present paper we described the synthesis of new representatives of a few important azaheterocyclic ring systems (e.g., pyrazoles, 1,2,3-triazoles and pyridazines). The members of these ring systems have a wide range of applications.

The biological activity of pyrazole derivatives is recognized long ago as reviewed by R. E. Orth in as early as 1968.[24] Pyrazoles have been reported as potential anti-obesity agents.[25] They are promising scaffolds for the synthesis of antiinflammatory and/or antimicrobial agents[26] and show potential in the crop protection chemistry.[27] J.-Y. Yoon *et al*.[28] recently reviewed the advances in the regioselective synthesis of pyrazole derivatives.

The different 1,2,3-triazole derivatives have also important biological activities as reviewed earlier by R. Boehm and Ch. Karow[29] and recently by I. Pibiri and S. Buscemi.[30] The well known method making 1,2,3-triazole derivatives, the click chemistry, has a growing impact on the drug discovery.[31-33] The copper-free variations[34,35] enable to perform the click reaction in living animals.

Pyridazine derivatives (especially pyridazin-3-ones) have been considered as a magic moiety (wonder nucleus),[36] which posses almost all types of biological activities,[37] among others cardiovascular,[38] antimicrobial,[39] and analgesic.[40]

Experimental Section

General. Melting points were determined by a Büchi apparatus. IR spectra (KBr pellet) were recorded on Specord IR-75 and Bruker IFS-28 equipments. The ^{1}H-NMR spectra were measured on Varian XL-100 (100 MHz), Varian VXR-400 and Bruker DRX-400 instruments (400 MHz) at ambient temperature using TMS as internal standard. ^{13}C NMR spectra were recorded on a Bruker DRX-400 instrument. The yields of the reactions were not optimized.

Reaction of 2-(4-bromophenyl)-5-(4-chlorophenyl)-4-(4-morpholino-3-bromo-1-aza-1,3-butadien-1-yl)-1,2,3-triazole 1b with morpholine. A solution of **1b** (280 mg, 0.5 mmol) in a mixture of CH_2Cl_2 (5 ml) and acetonitrile (5 ml) was stirred with morpholine (210 mg, 0.21 ml, 2.4 mmol) and morpholinium perchlorate (95 mg, 0.5 mmol) at room temperature for 2 weeks. Water (20 ml) was added, the layers were separated and the upper layer was extracted with CH_2Cl_2 (2 x 10 ml). The combined organic extract was dried on $MgSO_4$, filtered and evaporated to dryness. The residue was chromatographed on silica gel with CH_2Cl_2 to give 3 products. *4-Amino-2-(4-bromophenyl)-5-(4-chlorophenyl)-1,2,3-triazole* (**2**). Yield 1.7%, 3 mg, mp 178-180ºC (Lit.[1] mp 178-180ºC). *4-[(2-Bromo-2-propenal-3-yl)amino]-2-(4-bromophenyl)-5-(4-chlorophenyl)-1,2,3-triazole* (**3**). Pale yellow crystals; yield 37%, 90 mg, mp 192-193ºC (acetonitrile) (Lit.[1] mp 191-192ºC). *2-(4-Bromophenyl)-5-(4-chlorophenyl)-4-(3-hydroxy-4-morpholino-1-aza-1,3-butadien-1-yl)-1,2,3-triazole* (**4**). Pale yellow crystals; yield 28.7%, 70 mg, mp 226-228ºC (acetonitrile). ^{1}H NMR (DMSO-d_6): δ_H 9.10 (s, 1H, H-2), 9.02 (br, 1H, OH), 7.99 (m, 2H, H-2',6'(4-Cl-phenyl)), 7.86 (m, 2H, H-2',6'(4-Br-phenyl)), 7.78 (m, 2H, H-3',5'(4-Br-phenyl)), 7.70 (s, 1H, H-4), 7.65 (m, 2H, H-3',5'(4-Cl-phenyl)), 3.64 (t, 4H, H-morpholino), 2.95 (t, 4H, H-morpholino). ^{1}H NMR ($CDCl_3$): δ_H 9.53 (d, $^3J_{HH}$=4.0 Hz, H-2) and 9.24 (s, H-2) ratio: 13:87, 8.24 (br, OH), 7.95 (m, 2H, H-2',6'(4-Cl-phenyl)), 7.76 (s, H-4) and 7.75 (s, H-4) ratio: 17:83, 7.67 (m, 2H, H-2',6'(4-Br-phenyl)), 7.62 (m, 2H, H-3',5'(4-Br-phenyl)), 7.55 (m, 2H, H-3',5'(4-Cl-phenyl)), 3.84 (t, H-morpholino) and 3.76 (t, H-morpholino) ratio: 15:85, 3.10 (m, H-morpholino) and 2.89 (m, H-morpholino) ratio: 85:15. ^{13}C NMR (DMSO-d_6): δ_C 188.21, 148.81, 145.58, 138.37, 137.47, 134.15, 133.09, 130.54, 129.59, 128.94, 128.19, 120.50, 120.17, 67.32, 50.10. Anal. Calcd for $C_{21}H_{19}BrClN_5O_2$ (417.76): C, 51.60; H, 3.92; N, 14.33%. Found: C, 51.46; H, 3.82; N, 14.18%.

Reaction of 2-(4-bromophenyl)-5-(4-chlorophenyl)-4-(4-morpholino-3-bromo-1-aza-1,3-butadien-1-yl)-1,2,3-triazole 1b with HCl/H_2O. A suspension of **1b** (280 mg, 0.5 mmol) in $CHCl_3$ (3 ml) and ethanol (3 ml) was refluxed with 35% HCl (1 ml) for 1 h. Water (15 ml) was added, neutralized by 2 N NaOH solution and the yellow precipitate was filtered off, washed

with water and recrystallized from DMF to give 120 mg (68.6%) of pale yellow prisms of **5** that is the salt of **2** with **6**, mp 275-276ºC. This salt (**5**, 80 mg, 0.11 mmol) was chromatographed on silica gel with CH_2Cl_2 to give two products: *5-aminotriazole* **2**, white crystals, yield 60%, 24 mg, mp 178-179ºC (Lit.[1] mp 178-180ºC). *2-(4-Bromophenyl)-5-(4-chlorophenyl)-1,2,3-triazole-5(1H)-one* **6b**. Yellow solid, yield 50%, 20 mg, mp 273-275ºC (DMF); IR (ν_{max}, cm^{-1}): 3413, 3066, 1644, 1582, 1547, 1488, 1412, 1317, 1291, 1263, 1197, 1180. ^{1}H NMR (pyridine-d_5, T = 353K): δ_H 8.80 (br, 1H, NH), 8.26 (m, 2H, H-2',6'(4-Cl-phenyl)), 8.07 (d, 2H, H-2',6'(4-Br-phenyl)), 7.72 (d, 2H, H-3',5'(4-Br-phenyl)), 7.53 (m, 2H, H-3',5'(4-Cl-phenyl)). ^{13}C NMR ($CDCl_3$): δ_C 168.9, 139.6, 137.0, 135.2, 129.6, 128.9, 128.1, 127.6, 117.5, 112.6. Anal. Calcd for $C_{14}H_9BrClN_3O$ (348.96): C, 47.96; H, 2.59; N, 11.99%. Found: C, 47.82; H, 2.71; N, 12.04%.

Reaction of 2-(4-bromophenyl)-5-(4-chlorophenyl)-4-(4-morpholino-3-bromo-1-aza-1,3-butadien-1-yl)-1,2,3-triazole 1b with 4-bromophenylhydrazine hydrochloride. A solution of the azadiene (**1b**, 280 mg, 0.5 mmol) in a mixture of ethanol (5 ml) and $CHCl_3$ (5 ml) was refluxed with 4-bromophenylhydrazine hydrochloride (120 mg, 0.5 mmol) for 30 min. The reaction mixture was cooled, the precipitated crystals were filtered off and recrystallized from ethanol to give white needles of **2** (120 mg, 67.6%), mp 179-180 ºC (Lit.[1] mp 178-180 ºC). The evaporation of the mother liquor of the first filtration to dryness and chromatography of the residue on silica gel with CH_2Cl_2 resulted in white needles of *4-bromo-1-(4-bromophenyl)pyrazole* (**7**). Yield 81.3%, 125 mg, mp 83-85 ºC (petroleum ether) (Lit.[5] mp 84.5-85 ºC). ^{1}H NMR ($CDCl_3$): δ_H 7.92 (s, 1H, H-3), 7.68 (s, 1H, H-5), 7.59 (m, 2H, H-2',6'(4-Br-phenyl)), 7.54 (m, 2H, H-3',5'(4-Br-phenyl)). Anal. Calcd for $C_9H_6Br_2N_2$ (301.99): C, 35.79; H, 2.00; N, 9.28%. Found: C, 35.56; H, 1.97; N, 9.04%.

Reaction of 1a with 4-nitrobenzenediazonium fluoroborate: formation of 3-[2-(4-bromophenyl)-5-(4-chlorophenyl)-2*H*-1,2,3-triazol-4-ylimino]-2-[(4-nitrophenyl)hydrazono]propionaldehyde (9). A solution of 4-nitrobenzenediazonium fluoroborate (80 mg, 0.33 mmol) in acetonitrile (5 ml) was added to a stirred solution of **1a** (150 mg, 0.31 mmol) in CH_2Cl_2 (5 ml) at room temperature. An orange solid was separated within 1 min. The suspension was stirred for 20 min and it was mixed with diethyl ether (15 ml) and filtered off, washed with diethyl ether. The crude product was suspended in water (10 ml), mixed with 20 % aq. NaOH solution (2 ml) and extracted with CH_2Cl_2 (4 x 5 ml). The organic extract was concentrated and chromatographed on silica gel with toluene to give an orange solid. Yield 83%, 150 mg, mp 268-270ºC. ^{1}H NMR ($CDCl_3$): δ_H 15.22 (br, 1H, NH), 9.70 (s, 1H, H-1), 9.45 (s, 1H, H-3), 8.31 (d, 2H, H-3,5(4-NO_2-phenyl)), 8.07 (d, 2H, H-2,6(4-NO_2-phenyl)), 7.93 (d, 2H, H-2,6(4-Cl-phenyl)), 7.67 (d, 2H, H-2,6(4-Br-phenyl)), 7.54 (d, 2H, H-3,5(4-Br-phenyl)), 7.39 (d, 2H, H-3,5(4-Cl-phenyl)). ^{13}C NMR ($CDCl_3$): δ_C 164.1, 162.7, 158.2, 146.5, 142.9, 142.2, 136.7, 131.0, 129.7, 129.0, 124.5, 123.7, 122.1, 116.6, 113.4. Anal. Calcd for $C_{23}H_{15}BrClN_7O_3$ (552.80): C, 49.98; H, 2.74; N, 17.74%. Found: C, 49.84; H, 2.78; N, 17.48%.

Reaction of 1b with 4-nitrobenzenediazonium fluoroborate. The reaction of **1b** (170 mg, 0.31 mmol) with 4-nitrobenzenediazonium fluoroborate (80 mg, 0.33 mmol) under the same reaction conditions and work up gave two compounds: *4-amino-2-(4-bromophenyl)-5-(4-chlorophenyl)-*

1,2,3-triazole (**2**). White crystals, yield 36.7%, 40 mg, mp 178-180ºC (Lit.[1] mp 178-180ºC). *3-[2-(4-Bromophenyl)-5-(4-chlorophenyl)-2H-1,2,3-triazol-4-ylimino]-2-[(4-nitrophenyl)hydrazono]-propionaldehyde* (**9**). Orange crystals, yield 31.7%, 57 mg, mp 269-271ºC. The compound was identical with that described above.

Reaction of 2-(4-bromophenyl)-5-(4-chlorophenyl)-4-(4-morpholino-1-aza-1,3-butadien-1-yl)-1,2,3-triazole 1a with tetrabutylammonium borohydride. A solution of **1a** (235 mg, 0.5 mmol) in CH_2Cl_2 (3 ml) and ethanol (3 ml) was stirred with tetrabutylammonium borohydride (270 mg, 1.05 mmol) at room temperature for 24 h. Water (10 ml) was added and extracted with CH_2Cl_2 (3 x 5 ml). The organic extract was dried on $MgSO_4$, filtered and evaporated, the residue was chromatographed on silica gel with CH_2Cl_2 to give two different products (26 mg, 11 % of starting material **1a** was also recovered). *2-(4-Bromophenyl)-5-(4-chlorophenyl)-4-(3-morpholinoprop-1-ylamino)-1,2,3-triazole* (**10**). White crystals, yield 50.9%, 108 mg, mp 125-126ºC (ethanol-water). ^{1}H NMR ($CDCl_3$): δ_H 7.79 (m, 2H, H-2',6'(4-Cl-phenyl)), 7.66 (m, 2H, H-2',6'(4-Br-phenyl)), 7.46 (m, 2H, H-3',5'(4-Br-phenyl)), 7.37 (m, 2H, H-3',5'(4-Cl-phenyl)), 5.08 (m, 1H, NH), 3.55 (m, 4H, H-morpholino), 3.42 (m, 2H, H-3), 2.46 (m, 2H, H-1), 2.39 (m, 4H, H-morpholino), 1.18 (d, 2H, H-2). ^{13}C NMR ($CDCl_3$): δ_C 151.54, 138.83, 133.95, 133.82, 132.09, 129.23, 128.85, 127.81, 127.69, 119.13, 118.85, 65.04, 57.01, 53.02, 43.14, 23.73. Anal. Calcd for $C_{21}H_{23}BrClN_5O$ (476.83): C, 52.90; H, 4.86; N, 14.69%. Found: C, 53.16; H, 4.88; N, 14.80%. *2-(4-Bromophenyl)-5-(4-chlorophenyl)-4-(prop-1-ylamino)-1,2,3-triazole* (**12a**). White crystals, yield 5.7% 10 mg, mp 175-177ºC. ^{1}H NMR ($CDCl_3$): δ_H 7.87 (m, 2H, H-2',6'(4-Cl-phenyl)), 7.69 (m, 2H, H-2',6'(4-Br-phenyl)), 7.55 (m, 2H, H-3',5'(4-Br-phenyl)), 7.45 (m, 2H, H-3',5'(4-Cl-phenyl)), 4.82 (br, 1H, NH), 3.36 (t, $^3J_{HH}$=1 Hz, 2H, N-CH_2), 1.74 (hept, $^3J_{HH}$=7.2 Hz, 2H, CH_2), 1.03 (t, $^3J_{HH}$=7.4 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ_C 162.1, 142.4, 138.9, 131.2, 127.7, 127.5, 126.6, 120.6, 118.8, 48.0, 22.5, 11.5. Anal. Calcd for $C_{17}H_{16}BrClN_4$ (391.72): C, 52.13; H, 4.12; N, 14.30%. Found: C, 52.28; H, 4.19; N, 14.18%.

Reaction of 2-(4-bromophenyl)-5-(4-chlorophenyl)-4-(4-morpholino-3-bromo-1-aza-1,3-butadien-1-yl)-1,2,3-triazole 1b with tetrabutylammonium borohydride. A solution of **1b** (550 mg, 1.0 mmol) in CH_2Cl_2 (3 ml) and ethanol (3 ml) was stirred with tetrabutylammonium borohydride (760 mg, 3 mmol) at room temperature for 24 h. Water (40 ml) was added and the mixture was extracted with CH_2Cl_2 (3 x 10 ml). The organic extract was dried on $MgSO_4$, filtered and evaporated, the residue was chromatographed on silica gel with CH_2Cl_2-methanol = 9:1 to give 4 different products. *4-[(2-Bromopropene-3-one-1-yl)amino]-2-(4-bromophenyl)-5-(4-chlorophenyl)-1,2,3-triazole* (**3**). White crystals, yield 2.3%, 13 mg, mp 189-191ºC (acetonitrile) (Lit.[1] mp 191-192ºC). *2-(4-Bromophenyl)-5-(4-chlorophenyl)-4-(3-morpholino-prop-1-ylamino)-1,2,3-triazole* (**10**). White crystals, yield 21.0%, 100 mg, mp 125-126ºC. The compound was identical with that described above. *2-(4-Bromophenyl)-5-(4-chlorophenyl)-4-(2-morpholinoprop-1-ylamino)-1,2,3-triazole* (**11**). White crystals, yield 31.5%, 150 mg, mp 112-114ºC (ethanol-water). ^{1}H NMR ($CDCl_3$): δ_H 7.88 (m, 2H, H-2',6'(4-Cl-phenyl)), 7.75 (m, 2H, H-2',6'(4-Br-phenyl)), 7.54 (m, 2H, H-3',5'(4-Br-phenyl)), 7.46 (m, 2H, H-3',5'(4-Cl-phenyl)), 5.08 (d, $^3J_{HH}$=7.3 Hz, 1H, NH), 3.67 (m, 4H, H-morpholino), 3.43 (m, 1H, H-1a), 3.17 (t, 1H, H-1b),

2.96 (m, 1H, H-2), 2.64 (m, 2H, H-morpholino), 2.47 (m, 2H, H-morpholino), 1.09 (d, $^3J_{HH}$=6.6 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ_C 151.6, 138.6, 133.6, 133.5, 131.8, 128.9, 127.3, 118.6, 67.2, 57.9, 47.9, 46.3, 11.0. Anal. Calcd for $C_{21}H_{23}BrClN_5O$ (476.83): C, 52.90; H, 4.86; N, 14.69%. Found: C, 53.00; H, 4.76; N, 14.87%. *2-(4-Bromophenyl)-4-(2-bromoprop-1-ylamino)-5-(4-chloro-phenyl)-1,2,3-triazole* (**12b**). White crystals, yield 6.8%, 32 mg, mp 108-110ºC (ethanol-water). ^{1}H NMR ($CDCl_3$): δ_H 7.86 (m, 2H, H-2',6'(4-Cl-phenyl)), 7.71 (m, 2H, H-2',6'(4-Br-phenyl)), 7.56 (m, 2H, H-3',5'(4-Br-phenyl)), 7.47 (m, 2H, H-3',5'(4-Cl-phenyl)), 4.55 (m, 1H, H-2), 4.40 (t, 1H, NH), 3.81 (m, 1H, H-1a), 3.55 (m, 1H, H-1b), 1.82 (d, $^3J_{HH}$=6.7 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ_C 150.5, 138.5, 133.9, 133.8, 131.9, 129.1, 128.5, 127.5, 118.9, 118.7, 52.6, 50.0, 23.3. Anal. Calcd for $C_{17}H_{15}Br_2ClN_4$ (470.63): C, 43.39; H, 3.21; N, 11.91%. Found: C, 43.60; H, 3.37; N, 11.89%.

Dimethyl 2-{[2-(4-bromophenyl)-5-(4-chlorophenyl)-2*H*-1,2,3-triazol-4-yl](3-oxopropenyl)-amino}but-2-enedioate (15). A solution of **1a** (120 mg, 0.25 mmol) in dichloroethane (3 ml) was stirred with dimethyl acetylenedicarboxylate (140 mg, 0.12 ml, 1 mmol) at room temperature for 7 h. The reaction mixture was chromatographed on silica gel with a mixture of hexane : ethyl acetate=8:2 to give white crystals. Yield 37%, 52 mg, mp 143-145ºC; ^{1}H NMR ($CDCl_3$): δ_H 9.37 (d, $^3J_{HH}$=7.6 Hz, 1H, C*H*O), 8.00 (m, 2H, H-2',6'(4-Cl-phenyl)), 7.73 (m, 2H, H-2',6'(4-Br-phenyl)), 7.68 (m, 2H, H-3',5'(4-Br-phenyl)), 7.45 (m, 2H, H-3',5'(4-Cl-phenyl)), 7.37 (d, 1H, $^3J_{HH}$=13.4 Hz, H-1 (propenyl)), 5.26 (dd, $^3J_{HH}$=13.4, 7.6 Hz, 1H, H-2 (propenyl)), 5.25 (s, 1H, H-3), 4.02 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$): δ_C 189.67, 165.23, 163.37, 148.91, 147.42, 142.42, 139.16, 137.90, 136.22, 132.69, 129.56, 127.79, 125.55, 122.58, 120.29, 113.99, 102.81, 53.95, 52.02. Anal. Calcd. for $C_{23}H_{18}BrClN_4O_5$ x $0.6H_2O$ (556.61): C, 49.63; H, 3.48; N, 10.06%. Found: C, 49.83; H, 3.54; N, 9.76%.

Reaction of 2-(4-bromophenyl)-5-(4-chlorophenyl)-4-(4-morpholino-1-aza-1,3-butadien-1-yl)-1,2,3-triazole 1a with 4-toluenesolfonyl azide (18). A solution of **1a** (235 mg, 0.5 mmol) in CH_2Cl_2 (5 ml) was stirred with 4-toluenesulfonyl azide (**18**, 300 mg, 1.5 mmol) at room temperature for 24 h and the reaction mixture was chromatographed on silica gel with CH_2Cl_2 to give different products. *4-Toluenesulfonylazide* (**18**). Yield 66.6%, 200 mg: recovered starting material. *N-(4-Toluenesulfonyl)morpholinoformimine* (**22**). Yield 24.6%, 33 mg, mp 175-177ºC (Lit.[17] mp. 174-176ºC); ^{1}H NMR ($CDCl_3$): δ_H 8.20 (s, 1H, H-formyl), 7.79 (m, 2H, H-2',6'(4-toluenesulfonyl)), 7.28 (m, 2H, H-3',5'(4-toluenesulfonyl)), 3.76 (m, 2H, H-morpholino), 3.69 (m, 4H, H-morpholino), 3.50 (m, 2H, H-morpholino), 2.42 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ_C 157.53, 142.68, 129.36, 126.58, 125.88, 66.80, 65.92, 50.30, 44.20, 21.48. Anal. Calcd for $C_{12}H_{16}N_2O_2S$ (252.34): C, 53.71; H, 6.01; N, 10.44%. Found: C, 53.54; H, 5.99; N, 10.45%. *2-(4-Bromophenyl)-5-(4-chlorophenyl)-4-(1,2,3-triazol-1-yl)-1,2,3-triazole* (**20**). White needles, yield 38.5%, 77 mg, mp 154-156ºC. ^{1}H NMR ($CDCl_3$): δ_H 8.06 (d, $^3J_{HH}$=1.1 Hz, 1H, H-4'), 8.04 (m, 2H, H-2',6'(4-Cl-phenyl)), 7.94 (d, $^3J_{HH}$=1.1 Hz, 1H, H-5'), 7.67 (m, 2H, H-2',6'(4-Br-phenyl)), 7.62 (m, 2H, H-3',5'(4-Br-phenyl)), 7.40 (m, 2H, H-3',5'(4-Cl-phenyl)). ^{13}C NMR ($CDCl_3$): δ_C 141.36, 137.98, 135.98, 134.18, 132.67, 129.27, 129.17, 129.13, 126.01, 125.32, 122.38, 120.32. Anal. Calcd for $C_{16}H_{10}BrClN_6$ (401.68): C, 47.84; H, 2.51; N, 20.92%. Found: C, 47.90; H, 2.56;

N, 20.75%. *2-(4-Bromophenyl)-5-(4-chlorophenyl)-4-(4-formyl-1,2,3-triazol-1-yl)-1,2,3-triazole* (**21**). White needles, yield 38.5%, 32 mg, mp 174-176ºC. ^{1}H NMR ($CDCl_3$): δ_H 10.28 (s, 1H, H-formyl), 8.59 (s, 1H, H-5"), 8.04 (m, 2H, H-2',6'(4-Cl-phenyl)), 7.70 (m, 2H, H-2',6'(4-Br-phenyl)), 7.65 (m, 2H, H-3',5'(4-Br-phenyl)), 7.44 (m, 2H, H-3',5'(4-Cl-phenyl)). ^{13}C NMR ($CDCl_3$): δ_C 184.34, 147.66, 141.50, 139.53, 137.80, 136.37, 132.78, 129.29, 126.74, 125.57, 122.79, 120.38. Anal. Calcd for $C_{17}H_{10}BrClN_6O$ (429.69): C, 47.84; H, 2.51; N, 20.92%. Found: C, 47.90; H, 2.56; N, 20.75%. *4-Toluenesulfonamide;* yield 36.8%, 32 mg, mp 133-135ºC (Lit.[41] mp 137ºC).

Reaction of 2-(4-bromophenyl)-4-(3-bromo-4-morpholino-1-aza-1,3-butadien-1-yl)-5-(4-chlorophenyl)-1,2,3-triazole 1b with 4-toluenesulfonyl azide (18). A solution of **1b** (280 mg, 0.5 mmol) in a mixture of $CHCl_3$ (5 ml) and acetonitrile (5 ml) was refluxed with 4-toluenesulfonyl azide (**18**, 300 mg, 1.5 mmol) for 24 h. The reaction mixture was evaporated to dryness, the residue was chromatographed on silica gel with CH_2Cl_2 to give two products. *4-[(2-Bromopropene-3-one-1-yl)amino]-2-(4-bromophenyl)-5-(4-chlorophenyl)-1,2,3-triazole* (**3**). Pale yellow crystals, yield 16.7%, 40 mg, mp 192-193ºC (acetonitrile) (Lit.[1] mp 191-192ºC). *2-(4-Bromophenyl)-5-(4-chlorophenyl)-4-[5-morpholino-1-(4-toluenesulfonyl)-1,2,3-triazol-4-methylidene]amino-1,2,3-triazole* (**19**). White needles, yield 15%, 50 mg, mp 245-247ºC. ^{1}H NMR ($CDCl_3$): δ_H 8.79 (s, 1H, H-formylimino), 8.06 (m, 2H, H-2',6'(4-Cl-phenyl)), 7.70 (m, 6H, H-2',3',5',6'(4-Br-phenyl) and 2',6'(4-toluenesulfonyl)), 7.43 (m, 2H, H-3',5'(4-Cl-phenyl)), 7.23 (m, 2H, H-3',5'(4-toluenesulfonyl)), 3.9 (m, 2H, H-morpholino)), 3.79 (m, 4H, H-morpholino)), 3.55 (m, 2H, H-morpholino)), 2.40 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ_C 154.4, 142.2, 141.5, 139.9, 139.2, 137.6, 137.4, 135.9, 132.5, 129.4, 129.1, 128.9, 126.1, 125.2, 122.4, 120.2, 66.5, 65.9, 48.6, 45.5, 21.2. Anal. Calcd for $C_{28}H_{24}BrClN_8O_3S$ (668.00): C, 50.34; H, 3.62; N, 16.78%. Found: C, 50.15; H, 3.56; N, 16.69%.

Reaction of 2-(4-bromophenyl)-5-(4-chlorophenyl)-4-(4-morpholino-1-aza-1,3-butadien-1-yl)-1,2,3-triazole 1a with ethoxycarbonyl isothiocyanate. A solution of **1a** (240 mg, 0.5 mmol) in CH_2Cl_2 (5 ml) was stirred with ethoxycarbonyl isothiocyanate (130 mg, 120 μL, 1 mmol) at room temperature for 2 weeks. The solvent was evaporated, the residue was chromatographed on silica gel with CH_2Cl_2 to give 3 different products. *2-(4-Bromophenyl)-5-(4-chlorophenyl)-4-(ethoxycarbonylamino)-1,2,3-triazole* (**28**). Pale yellow crystals, yield 10.0%, 42 mg, mp 195-197ºC (diethyl ether). ^{1}H NMR ($CDCl_3$): δ_H 7.99 (m, 2H, H-2',6'(4-Cl-phenyl)), 7.37 (s, 1H, NH), 7.67 (m, 2H, H-2',6'(4-Br-phenyl)), 7.52 (m, 2H, H-3',5'(4-Br-phenyl)), 7.41 (m, 2H, H-3',5'(4-Cl-phenyl)), 4.21 (q, $^3J_{HH}$=7.1 Hz, 2H, CH_2), 1.26 (t, $^3J_{HH}$=7.1 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ_C 154.0, 141.4, 140.7, 138.5, 135.0, 132.5, 129.1, 128.3, 128.0, 121.2, 120.0, 62.5, 14.4. Anal. Calcd for $C_{17}H_{14}BrClN_4O_2$ (421.70): C, 48.41; H, 3.35; N, 13.29%. Found: C, 48.60; H, 3.17; N, 13.49%. *2-(4-Bromophenyl)-5-(4-chlorophenyl)-4-[N-ethoxycarbonyl(2-propene-3-one-1-yl)-amino]-1,2,3-triazole monohydrate* (**29**). Pale yellow crystals, yield 32.9%, 81 mg, mp 168-170ºC. ^{1}H NMR ($CDCl_3$): δ_H 9.52 (d, $^3J_{HH}$=7.8 Hz, 1H, H-1), 8.26 (d, $^3J_{HH}$=14.2 Hz, 1H, H-3), 7.99 (m, 2H, H-2',6'(4-Cl-phenyl)), 7.66 (m, 2H, H-2',6'(4-Br-phenyl)), 7.60 (m, 2H, H-3',5'(4-Br-phenyl)), 7.43 (m, 2H, H-3',5'(4-Cl-phenyl)), 5.38 (dd, $J_{1,2}$=7.8, $J_{2,3}$=14.3 Hz, 1H, H-2), 4.25 (q,

$^3J_{HH}$=6.9 Hz, 2H, CH_2), 1.11 (t, $^3J_{HH}$=6.3 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ_C 190.85, 151.80, 148.92, 143.07, 139.12, 138.14, 135.81, 132.59, 129.46, 127.63, 126.52, 122.17, 120.25, 120.06, 114.34, 64.73, 14.03. Anal. Calcd for $C_{20}H_{16}BrClN_4O_3$ x H_2O (493.77): C, 48.65; H, 3.67; N, 11.35%. Found: C, 48.89; H, 3.47; N, 11.50%. *1-(Ethoxycarbonyl)amino-1-morpholino-methanethione* (**30**).[21] White crystals, yield 8.3%, 9 mg, mp 125-127ºC; ^{1}H NMR ($CDCl_3$): δ_H 4.18 (q, $^3J_{HH}$=7.1 Hz, 2H, CH_2), 3. 95 (m, 2H, H-morpholino), 3.80 (m, 4H, H-morpholino), 3.74 (m, 2H, H-morpholino), 1.30 (t, $^3J_{HH}$=7.1 Hz, 3H, CH_3). Anal. Calcd. for $C_8H_{14}N_2O_3S$ (218.43): C, 44.02; H, 6.46; N, 12.83%. Found: C, 43.88; H, 6.32; N, 12.93%.

Reaction of 2-(4-bromophenyl)-5-(4-chlorophenyl)-4-(3-bromo-4-morpholino-1-aza-1,3-butadien-1-yl)-1,2,3-triazole 1b with ethoxycarbonyl isothiocyanate. A solution of **1b** (280 mg, 0.5 mmol) in CH_2Cl_2 (5 ml) was stirred with ethoxycarbonyl isothiocyanate (70 mg, 63 µl, 0.5 mmol) at room temperature for 2 weeks. The solvent was evaporated, the residue was chromatographed on Silica gel with $CHCl_3$ to give 25 mg (11.9%) of pale yellow crystals of *2-(4-bromophenyl)-5-(4-chlorophenyl)-4-(ethoxycarbonylamino)-1,2,3-triazole* (**28**), mp 195-197ºC (diethyl ether). The compound was identical with that described above.

***sym*-Diethyl hydrazinedicarboxylate 34.** A solution of **1b** (280 mg, 0.5 mmol) in a mixture of $CHCl_3$ (5 ml) and acetonitrile (5 ml) was refluxed with diethyl azodicarboxylate (0.33 g, 0.3 ml, 1.9 mmol) for 50 h. The solvent was evaporated and the residue was chromatographed on silica gel with $CHCl_3$ as eluent to give traces of **2** (according to TLC) and *sym-diethyl hydrazinedicarboxylate* (**34**). White crystals, yield 24.2%, 80 mg, mp 130-132ºC (diethyl ether) (Lit.[22] mp 135ºC). ^{1}H NMR ($CDCl_3$): δ_H 6.45 (s, 2H, NH_2), 4.22 (q, $^3J_{HH}$=7.1 Hz, 4H, CH_2), 1.28 (t, $^3J_{HH}$=7.1 Hz, 6H, CH_3). Anal. Calcd for $C_6H_{12}N_2O_4$ x 0.5 H_2O (185.19): C, 38.91; H, 7.08; N, 15.13%. Found: C, 38.72; H, 6.86; N, 15.39%.

Dimethyl 4-{*N*-[2-(4-bromophenyl)-4-(4-chlorophenyl)-1,2,3-triazol-5-yl]}imino-formyl-pyridazine-3,6-di-carboxylate (34). A solution of **1a** (120 mg, 0.25 mmol) in dichloroethane (5 ml) was stirred with **35** (120 mg 0.6 mmol) at room temperature for 2 h. The precipitate was filtered off washed with dichloroethane (1 ml) to give 78 mg of yellow crystals. The mother liquor was chromatographed on silica gel with CH_2Cl_2-ethanol = 200:1 to give another quantity (51 mg) of product. Altogether 129 mg (91.5%) of pure product was obtained, mp 228-230ºC. ^{1}H NMR (DMSO-d_6): δ_H 9.60 (s, 1H, H-imino), 8.82 (s, 1H, H-5), 8.10 (m, 2H, H-2',6'(4-Cl-phenyl)), 8.03 (m, 2H, H-2',6'(4-Br-phenyl)), 7.82 (m, 2H, H-3',5'(4-Br-phenyl)), 7.60 (m, 2H, H-3',5'(4-Cl-phenyl)), 4.05 (s, 3H, OMe), 3.94 (s, 3H, OMe). ^{13}C NMR (DMSO-d_6): δ_C 164.88, 163.55, 159.57, 153.02, 151.92, 151.36, 142.16, 138.14, 134.51, 133.44, 133.08, 129.50, 129.28, 127.79, 127.71, 121.46, 120.75, 53.68, 53.66. Anal. Calcd for $C_{23}H_{16}BrClN_6O_4$ (555.80): C, 49.71; H, 2.90; N, 15.12%. Found: C, 49.47; H, 2.77; N, 14.98%.

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