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The chemistry of [1,2,3]triazolo[1,5-*c*]pyrimidine

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Abstract—Reactions of [1,2,3]triazolo[1,5-*c*]pyrimidine **2** with some electrophiles and nucleophiles are reported. Triazole ring opening and loss of nitrogen is the principal reaction with electrophiles. With strong acids protonation on N6 competes successfully. Derivatives in which the pyrimidine ring has been opened are obtained in reactions with nucleophiles. No stable simple substitution compounds were found.

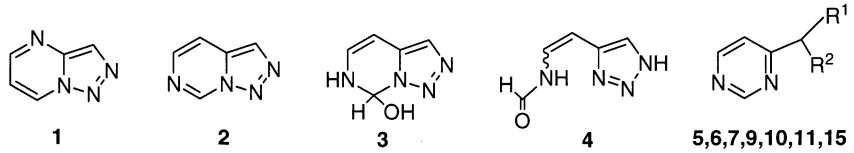
1. Introduction

The triazolopyrimidines with a bridgehead nitrogen are interesting compounds that can be considered as purine analogues. Little is reported in the literature about the two systems [1,2,3]triazolo[1,5-*a*]pyrimidine **1** and [1,2,3]-triazolo[1,5-*c*]pyrimidine **2**. In the latter series, the parent structure has been synthesised via the oxidative ring closure of pyrimidine-4-carboxaldehyde hydrazone.[1] Addition of trifluoroacetic acid to a wet DMSO or chloroform solution of **2** gave the covalent hydrate **3** which was suggested to be in equilibrium with the open form **4**.[1] The reaction between triazolopyrimidine **2** and acetic acid giving 4-acetoxy-methylpyrimidine **5** in 80% yield, some attempts to bromination with NBS[2] and the reaction with bromine to give 4-dibromomethylpyrimidine **6** were also described.[3] No evidence of lithiation was obtained under a variety of conditions.[3] No more reactions have been reported (Fig. 1).

Our experience in the field of [1,2,3]triazolo[1,5-*a*]pyridine chemistry,[4] and the potential applications of the analogous triazolopyrimidine derivatives as angiotensin II receptor antagonists,[5] with affinity toward adenosine receptors,[6] as platelet aggregation inhibitors,[7] herbicides,[8,9] or as model systems for various naturally occurring metal coordination compounds,[10] led us to study the chemistry of the [1,2,3]triazolo[1,5-*c*] pyrimidine **2**. We report here a number of reactions between compound **2** and some electrophiles and nucleophiles, giving different types of ring-opening and ring-transformation reactions. No stable simple substitution compounds were found.

2. Results and discussion

[1,2,3]Triazolo[1,5-*c*]pyrimidine **2** was prepared by the method of Maury et al.[1] using manganese dioxide as oxidant. Compound **2** is unstable and in the solid state at room temperature was slowly transformed into the hydrate **4**. All the reactions studied were difficult to perform, and the yields moderate to low.



1 **2** **3** **4** **5,6,7,9,10,11,15**

5 R^1= H, R^2= $OCOCH_3$, **6** R^1= R^2= Br, **7** R^1= H, R^2= OH, **9** R^1= H, R^2= O=,
10 R^1= OH, R^2= O=, **11** R^1= H, R^2= ONO_2, **15** R^1= H, R^2= Br

Figure 1.

Keywords: triazolopyrimidines; electrophilic and nucleophilic reactions.
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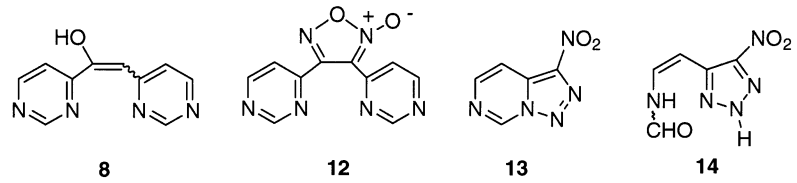
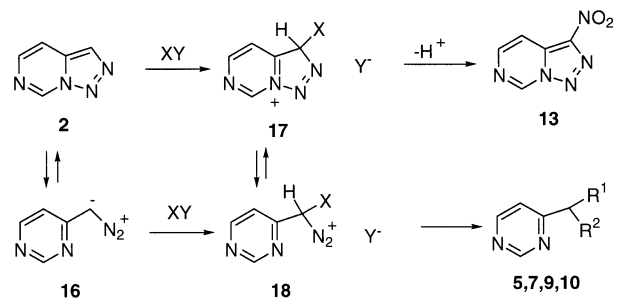


Figure 2.

The reported reactions with bromine and acetic acid cause triazole ring opening and loss of nitrogen to give 4-substituted pyrimidines,[2,3] in a way similar to that known for triazolopyridines.[11,12] Jones et al.[12] also discovered that triazolopyridines undergo triazole ring opening with loss of nitrogen with hot aqueous sulphuric acid and with selenium dioxide, and we studied the behaviour of compound **2** towards these two reagents. The triazolopyrimidine reacts rapidly with warm dilute sulphuric acid to give a complex mixture, but a ^{1}H NMR study showed the main product in the mixture to be pyrimidin-4-ylmethan-1-ol **7**.[13] Attempts to separate the mixture by chromatography were unsuccessful. A different result was found when the reaction was done with concentrated sulphuric acid, when a yellow solid was formed. This compound shows a molecular ion of 200.0698 corresponding to a molecular formula of $C_{10}H_8N_4O$. A careful study of its ^{1}H and ^{13}C NMR spectral data suggested the presence of two different 4-substituted pyrimidines, and an enol. A trisubstituted alkene was also present (singlet at 6.87 ppm, and a signal for quaternary carbon at 159.67 and for CH at 97.00 ppm in the ^{1}H and ^{13}C NMR spectra, respectively). We propose the structure **8** for this compound.

The five-membered ring of triazolopyrimidine was also opened by selenium dioxide. We have used boiling dioxane as the solvent, and a mixture of 4-pyrimidinylcarbaldehyde **9**,[14] (77%) and 4-pyrimidinylcarboxylic acid **10**,[15] (18%) was obtained.

Nitration was attempted using a mixture of nitric acid with acetic anhydride as reagent and the temperature was kept below 10°C,[11] when an intractable mixture was obtained. With fuming nitric acid as co-reagent at room temperature, we had difficulties in obtaining reproducible results. (CAUTION: an explosion and fire were caused in one experiment). In the first attempt an unstable yellow compound was formed, and spectroscopic analysis showed a 4-pyrimidinylmethane substituted by a deshielding group. We assigned to the compound tentatively the structure of 4-pyrimidinylmethyl nitrate **11**. Repeating the experiment



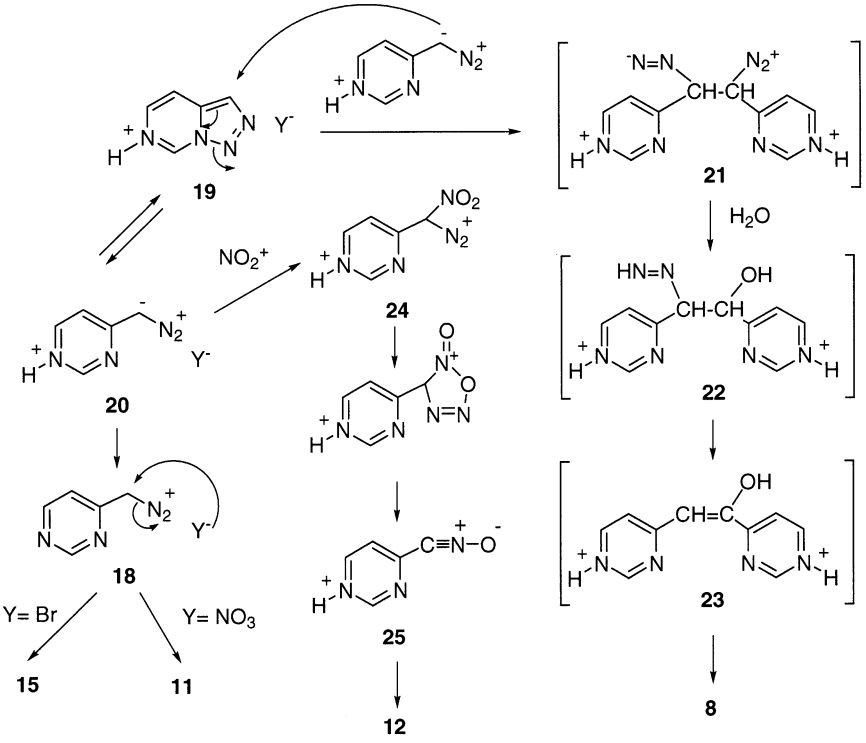
Scheme 1.

we had NMR evidence of the formation of this compound but we could not isolate it. We also identified the 4-pyrimidinylcarbaldehyde **9** in the crude reaction mixture, and found an unexpected yellow compound in small yield, with molecular weight 242.0545 consistent with a molecular formula of $C_{10}H_6N_6O_2$. The ^{1}H and ^{13}C NMR spectra showed two different 4-substituted pyrimidines; in addition in the ^{13}C NMR spectrum were two signals for quaternary carbons at 149.72 and 111.78 ppm. Significant peaks at 1684, 1575 and 1384 cm^{-1}, and M^+, $(M-30)^+$, $(M-60)^+$ (attributable to loss of NO and N_2O_2) in the IR and MS spectra respectively lead to the assigned structure of the furoxan **12**.

Different results were obtained when the nitrating agent was nitronium tetrafluoroborate in dry acetonitrile. The crude reaction mixture was also difficult to handle but we could isolate and identify by their analytical and spectroscopic properties two compounds, 3-nitrotriazolopyrimidine **13** and its hydrate, shown in the open chain form **14**. The complexity of the NMR spectra of compound **14** suggests the presence of rotamers. We assume that the reaction is an electrophilic substitution at the 3 position of the triazolopyrimidine ring (given later), that the compound **13** formed is unstable and during the purification **14** was formed (Fig. 2).

Attempts to prepare quaternary triazolopyrimidinium salts of the parent **2** were unsuccessful. A solution of HBr in acetic acid was added slowly to a solution of compound **2** in ether. A white precipitate was formed which melted at 123–125°C, after solution in DMSO the free base was shown by HRMS to have formula $C_5H_5BrN_2$. The ^{1}H NMR spectrum in DMSO-d_6 showed the characteristic pattern of a 4-substituted pyrimidine which we attributed to 4-bromomethylpyrimidine **15**.[13] Methyl iodide and isopropyl bromide do not react with **2** under several different conditions; neither methyl bromoacetate nor phenacyl bromide alkylate compound **2**, giving complex mixtures and intractable gums.

The mode of formation of compounds **7**–**13** and **15** are discussed together. It is well known that triazolopyrimidines have ring-chain tautomerism (**2**⇌**16**).[16] Maury et al.[2] suggested that the formation of 4-acetoxymethylpyrimidine **5** (X=H, Y=OCOCH$_3$) must be attributed to this tautomerism, or more likely to the tautomerism **17**⇌**18** of the intermediate in electrophilic substitution in this case by a proton, with subsequent attack by acetate as nucleophile, with loss of nitrogen (Scheme 1). We believe that compounds **7** and **9** could be formed similarly, by attack by a proton or selenium dioxide, as electrophiles,[12] to the more nucleophilic carbon with ring opening to the diazoalkane. Subsequent attack by a nucleophile is accompanied by



Scheme 2.

elimination of nitrogen, or of nitrogen and selenium monoxide, respectively. Oxidation of the aldehyde **9** gives acid **10**. If the electrophile is an electron-withdrawing group, such as NO_2, the intermediate **18** will be longer-lived and deprotonation of the cyclic form **17** could compete successfully with loss of nitrogen giving electrophilic substitution in C3,[11] which explains the formation of compound **13**.

In reactions with strong acids, such as concentrated sulphuric acid, fuming nitric acid, or hydrogen bromide, protonation on the more basic nitrogen occurs preferentially, and salts **19** are formed (Scheme 2).

We suggest that the position of protonation is N6, and this is supported by molecular orbital calculations. Ab initio molecular orbital calculations were performed using the GAUSSIAN 94 package.[17] The geometry was fully optimised at the RHF/6-31G* level. The charge distribution was computed for **2** using the natural population analysis method. The calculated values using the NBO population analysis are given in Table 1. The ab initio calculations predict N6 as the site of protonation with the underlying assumption that this position is related to atomic charges at the nitrogen atoms. This prediction is in accord with the result of an NMR $Eu(FOD)_3$ experiment (Table 2).

Salts **19** (**a**, Y=SO_4^-; **b**, Y=NO_3; **c**, Y=Br) show ring-chain tautomerism (**19**⇌**20**) in solution. With concentrated sulphuric acid, the diazo form **20a** attacks the cyclic form **19a** to give the intermediate **21**, displacement of nitrogen by water gives **22** which undergoes radical azo decomposition with radical H abstraction,[18] forming the salt **23**. Treatment with $NaHCO_3$ give the free base **8**. In fuming nitric acid, a proton transfer occurs from the diazo form **20b** to give diazonium salt **18b**, then a nucleophilic displacement by nitrate ion could explain formation of **11**. Hydrolysis of the nitrate gives **9**. Alternatively **20b** may be attacked by the nitronium ion NO_2^+, from the self-dissociation of pure nitric acid, forming the intermediate **24** which undergoes an intramolecular addition followed by loss of nitrous oxide and deprotonation to give the nitrile oxide **25**. This undergoes spontaneous 3+2 dimerisation to give furoxan **12**.[19] When the reaction is done with HBr the salt **19c** is stable enough and insoluble in ether to precipitate as a white solid, but in DMSO solution the tautomeric form **20c** quickly suffers proton transfer and displacement of nitrogen by bromide giving **15**.

The easy formation of the hydrates **4** and **14** led us to think that position **7** of triazolopyrimidine could be activate towards nucleophiles. Methanol, ethanol, isoamyl alcohol, phenol or thiophenol fail to react with **2**. Sodium methoxide in methanol reacted forming again the hydrate **4**, probably through **26**. Aromatic amines like aniline and

Table 1. Natural population analysis

Atoms	N1	N2	N6	N8
NC[a]	−0.079	−0.213	−0.549	−0.273

[a] NC=Natural charge.

Table 2. δ values in ^{1}H NMR spectra

	H3	H4	H5	H7
2	8.05	7.6	7.9	9.5
2+$Eu(FOD)_3$	8.2	7.7	8.3	10.0

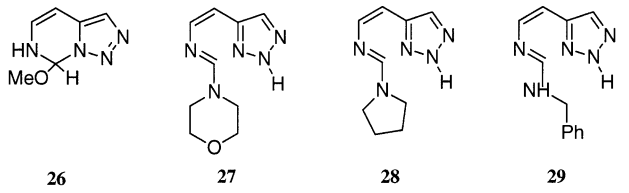


Figure 3.

p-methylaniline are unreactive. More reactive are the aliphatic amines, the secondary amines morpholine and pyrrolidine give pyrimidine derivatives **27** and **28** with moderate yields, and these reactions could be explained by a nucleophilic attack on C7. Benzylamine also reacts but the only isolated compound from the crude mixture was *N*-benzylformamide formed by hydrolysis of the initially formed derivative **29** (Fig. 3).

The most interesting result was when the reagent was potassium cyanide. A white solid was formed, and shown by HRMS to have formula $C_{10}H_8N_8$. From the analysis of the ^1H and ^{13}C NMR data we deduced that a 4-susbstituted pyrimidine structure is present ($C_4H_3N_2$) as well as a 2-(2*H*-1,2,3-triazol-4-yl)-1-ethenyl group ($C_4H_4N_3$). The new compound also has 2C [δ 145.35 (C) and 125.77 (CH)], 1H (δ 9.62 s), and 3N, indicating the presence of a disubstituted triazole. We propose the structure **30**. The observed fragmentation pattern in the mass spectrum is consistent with the proposal, and COSY, NOESY, DEPT and HSQC experiments also corroborate the structure **30** (Fig. 4).

We propose the following mechanism (Scheme 3) in which the triazolopyrimidine has an electrophilic (C7) and a nucleophilic (C3) centre, behaviour in line with the known chemistry of [1,2,3]triazolo[1,5-*c*]pyrimidine **2**. The cyanide ion is a soft nucleophile at carbon and attacks

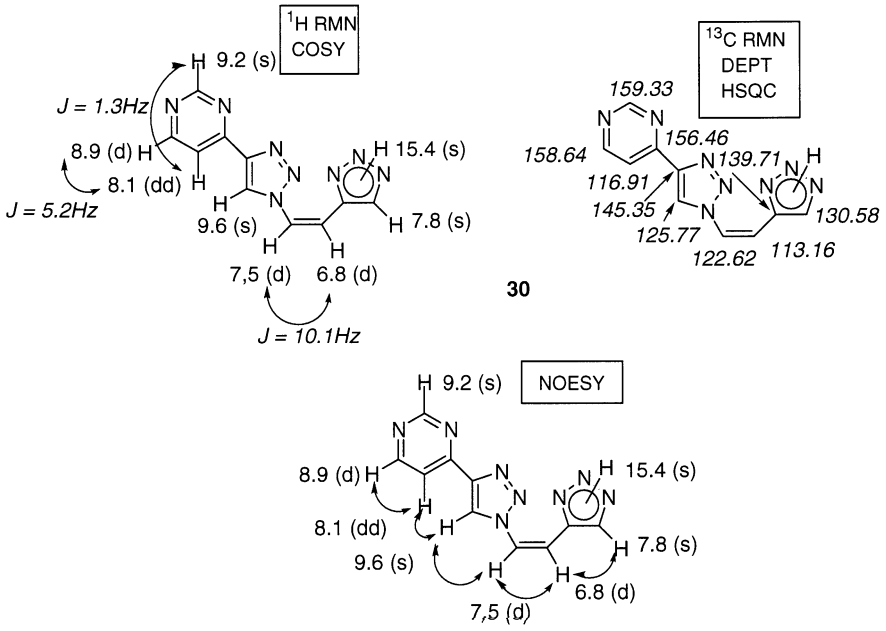
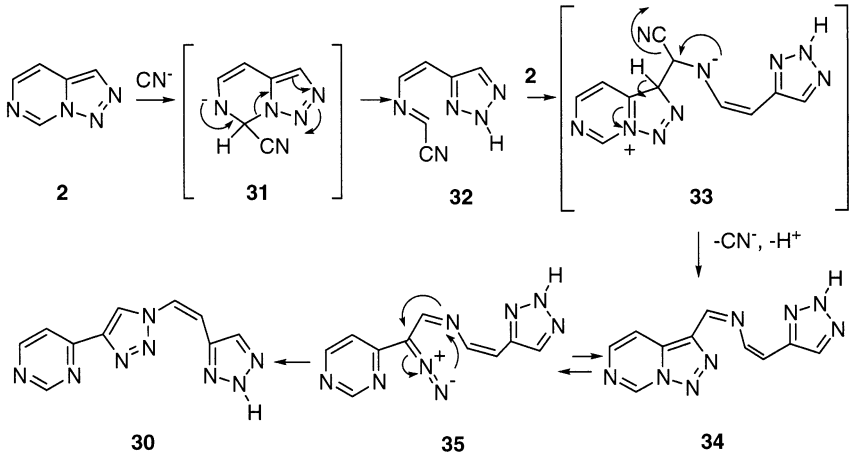


Figure 4.



Scheme 3.

triazolopyrimidine at C7 giving the intermediate **31**, converted into **32**, as in the nucleophilic reactions described earlier. Triazolopyrimidine, acting as a nucleophile, reacts with **32** giving a new intermediate **33**, which loses a cyanide ion and a proton to give triazolopyrimidine derivative **34**, in equilibrium with the diazo tautomer **35**. This intermediate may undergo a new ring-chain tautomerism,[20] giving a 1,4-disubstituted-1,2,3-triazole. This type of rearrangement has a precedent in the chemistry of [1,2,3]triazolo[1,5-*a*]-pyridines.[21]

3. Experimental

3.1. General

Melting points were determined on a Kofler heated stage. NMR spectra were determined on a Bruker 300 MHz instrument. HRMS (EI) determinations were made using a VG Autospec Trio 1000 (Fisons). Chromatography was performed on a Flash 40 column using silica. Infrared spectra were recorded in KBr discs on a Bio-Rad FTS-7.

3.1.1. [1,2,3]Triazolo[1,5-*c*]pyrimidine 2.[1] To a solution of 4-pyrimidinecarboxaldehyde hydrazone (0.9 g, 7.37 mmol) in dichloromethane (28 mL), manganese dioxide (1.68 g) was added. The mixture was heated to reflux 3 h. Then was cooled, filtered and the filtrate evaporated. The reaction crude was purified by crystallisation from ethyl acetate/hexane (52% yield).

3.1.2. Pyrimidin-4-ylmethan-1-ol 7. A solution of triazolopyrimidine **2** (0.25 g, 2 mmol) in sulphuric acid 2.5 M (10 mL) was heated to reflux for 1 h, then cooled, neutralised with a solution of sodium hydroxide, extracted with dichloromethane, dried and evaporated. The crude product was a complex mixture that could not be purified. The main product in the mixture, analysed by NMR, was pyrimidinylmethanol **7**.[13] ^{1}H NMR (250 MHz) δ ($CDCl_3$) 9.10 (1H, s), 8.70 (1H, d, J=5.1 Hz), 7.45 (1H, d, J=5.1 Hz), 4.79 (2H, s), 4.20 (1H, bs, OH). ^{13}C NMR δ ($CDCl_3$) 168.79 (C), 157.93 (CH), 156.91 (CH), 117.79 (CH), 63.60 (CH_2).

3.1.3. 1,2-Di(4-pyrimidinyl)-1-ethene-1-ol 8. To triazolopyrimidine **2** (0.1 g, 0.83 mmol) concentrated sulphuric acid (2 mL) was added, stirred 2–3 min, and neutralised with a solution of sodium bicarbonate, extraction with dichloromethane, drying, and evaporation giving a red solid, which was purified by column chromatography. Elution with ethyl acetate/hexane gave a yellow solid that was identified as 1,2-di(4-pyrimidinyl)-1-ethene-1-ol **8** (53% yield). Mp 221–223°C (ethyl acetate). HRMS found for M^+ 200.0700; $C_{10}H_8N_4O$ requires 200.0698. λ_{max} (nm) (log ϵ) (EtOH) 340 (4.17), 397 (3.6), 423 (3.4). ν_{max} (KBr) (cm^{-1}) 3450 (broad), (OH), 1639, 1599, 1579, 1468, 1393, 1278, 863. ^{1}H NMR δ ($CDCl_3$) 14.5 (1H, bs, OH), 9.18 (1H, d, J=1.5 Hz, H2′), 8.95 (1H, d, J=1.5 Hz, H2″), 8.83 (1H, d, J=5.4 Hz, H6′), 8.55 (1H, d, J=5.6 Hz, H6″), 7.85 (1H, dd, J_1=1.5 Hz, J_2=5.4 Hz, H5′), 7.09 (1H, dd, J_1=5.6 Hz, J_2=1.5 Hz, H5″), 6.87(1H, s, H2). ^{13}C NMR δ ($CDCl_3$) 164.16 (C4′ or C4″), 163.27 (C4″ or C4′), 159.67 (C1), 159.06 (CH, C2′ or C2″), 158.69 (CH, C2″ or C2′), 157.25 (CH, C6″), 155.43 (CH, C6′), 119.22 (CH, C5″), 117.54 (CH, C5′), 97.00 (CH, C2). MS (%), 200 (M^+, 63), 172 (M^+-CO, 26), 171 (17), 121 ($M^+-C_4H_3N_2$, 100), 93 (35), 79 [$(C_4H_3N_2)^+$, 10], 66 (13), 52 (10).

3.1.4. Reaction of triazolopyrimidine 2 with selenium dioxide. To a suspension of selenium dioxide (0.5 g, 4.5 mmol) in dioxane (10 mL) at 50°C, a solution of triazolopyrimidine **2** (0.215 g, 1.8 mmol) in dioxane (5 mL) was added. The suspension was refluxed for 4 h, then filtered, and the filtrate evaporated giving a crude solid (0.2 g), which was purified by chromatography. Elution with ethyl acetate/hexane gave 4-pyrimidinylcarbaldehyde **9**.[14] (77%). ^{1}H NMR δ ($CDCl_3$) 10.07 (1H, s), 9.49 (1H, s), 9.06 (1H, d, J=4.8 Hz), 7.86 (1H, dd, J_1=1, 4 Hz, J_2=4.8 Hz). ^{13}C NMR δ ($CDCl_3$) 192.20 (CH), 159.25 (CH), 158.75 (CH), 157.00 (C), 116.50 (CH). Subsequently 4-pyrimidinylcarboxylic acid **10** was eluted (18%).[15] Mp 236–237°C, ^{1}H NMR δ (DMSO-d_6) 9.37 (1H, s), 9.07 (1H, d, J=5 Hz), 8.0 (1H, dd, J_1=1, 3 Hz, J_2=5 Hz). ^{13}C NMR δ (DMSO-d_6) 164.95 (C), 159.01 (CH), 158.31 (CH), 155.39 (C), 120.40 (CH).

3.1.5. Reaction of triazolopyrimidine 2 with fuming nitric acid. In one experiment, fuming nitric acid (1 mL) was added to triazolopyrimidine **2** (0.033 g, 0.28 mmol), stirred 1–2 min, neutralised with a solution of sodium bicarbonate, extracted with dichloromethane, dried and evaporated giving a red solid, 4-pyrimidinylmethyl nitrate **11**. ^{1}H NMR δ ($CDCl_3$) 9.16 (1H, s, H2′), 8.74 (1H, d, J=5 Hz, H6′), 7.31 (1H, d, J=5 Hz, H5′), 5.47 (2H, s, H1). ^{13}C NMR δ ($CDCl_3$) 162.25 (C4′), 159.34 (CH, C2′), 158.33 (CH, C6′), 118.35 (CH, C5′), 72.49 (CH_2, C1). Similar procedure gives a mixture of **11** and **9**. (CAUTION: an explosion and fire occurred). In another experiment, fuming nitric acid (1 mL) was added to cooled (ice bath) triazolopyrimidine **2** (0.033 g, 0.28 mmol) under an inert atmosphere, stirred 15 min, neutralised with a solution of sodium bicarbonate, extracted with dichloromethane, dried and evaporated giving a mixture. NMR analysis of the mixture showed nitrate **11**, aldehyde **9**, triazolopyrimidine hydrate **4** and furoxan **12**. By flash chromatography we isolated only compound **12**, as an oil. HRMS found for M^+ 242.0545; $C_{10}H_6N_6O_2$ requires 242.0552. ν_{max} (KBr) (cm^{-1}) 1684 (C=N–O), 1575 (C=NO_2), 1384 (N–O). ^{1}H NMR δ ($CDCl_3$) 9.19 (1H, d, J=1.3 Hz, H2″), 9.06 (1H, d, J=1.3 Hz, H2′), 8.95 (1H, d, J=5.3 Hz, H6″), 8.91 (1H, d, J=5.3 Hz, H6′), 8.02 (1H, dd, J_1=5.3 Hz, J_2=1.3 Hz, H5″), 7.84 (1H, dd, J_1=1.3 Hz, J_2=5.3 Hz, H5′). ^{13}C NMR δ ($CDCl_3$) 157.72 (CH, C2′ or C2″), 157.56 (CH, C2″ or C2′), 157.49 (CH, C6′ or C6″), 157.38 (CH, C6″ or C6′), 153.23 (C4′ or C4″), 152.81 (C4″ or C4′), 149.72 (C4), 119.24 (CH, C5′ or C5″), 118.55 (CH, C5″ or C5′), 111.78 (C3). MS (%) 242 (M^+, 81), 226 (56), 212 (M^+-NO, 94), 196 (7), 182 ($M^+-N_2O_2$, 100), 121 (8), 105 (37), 91 (9), 79 (32).

3.1.6. Reaction of triazolopyrimidine 2 with nitronium tetrafluoroborate. To a solution of nitronium tetrafluoroborate (0.68 g, 5.12 mmol) in dry acetonitrile (5 mL) at 0–5°C under nitrogen, a solution of triazolopyrimidine **2** (0.5 g, 4.16 mmol) in dry acetonitrile (7 mL) was added slowly (25 min). The solution was stirred at room temperature for 1.5 h, becoming red. Evaporation gave a crude

product which showed by TLC only one impure compound. Purification by flash 40 chromatography. Elution with ethyl acetate/hexane 3:1 gave nevertheless two compounds. First a small amount of 3-nitrotriazolopyrimidine **13** was eluted, mp 158–160°C (ethyl acetate/hexane). HRMS found for M^+ 165.0288; $C_5H_3N_5O_2$ requires 165.0286. $\nu_{max.}$ (KBr) (cm^{-1}) 3076, 1626, 1510 (NO_2), 1496, 1409, 1392 (NO_2), 1244. ^1H NMR (250 MHz) δ ($CDCl_3$) 9.73 (1H, d, J=1.8 Hz, H7), 8.50 (1H, d, J=8.2 Hz, H5), 8.33 (1H, dd, J_1=1.8 Hz, J_2=8.2 Hz, H4). ^1H NMR (250 MHz) δ (DMSO-d_6) 10.33 (1H, s, H7), 8.58 (1H, d, J=8.2 Hz, H5), 8.34 (1H, d, J=8.2 Hz, H4). MS (EI) (%) 165 (M^+, 65), 86 ($M^+-C_4H_3N_2$, 10), 79 ($M^+-CN_3O_2$, 73), 66 [$M^+-(CN_3O_2+CH)$, 100), 52 [$M^+-(CN_3O_2+HCN)$, 45]. Then *N*-[(*Z*)-2-(5-nitro-2*H*-1,2,3-triazol-4-yl)-1-ethenyl] methanamide **14** was eluted (46%). Mp 141–142°C (ethyl acetate/hexane). HRMS found for M^+ 183.0398; $C_5H_5N_5O_3$ requires 183.0392. $\nu_{max.}$ (KBr) (cm^{-1}) 3360 (sharp, NH), 3145 (broad, NH), 1709 (CO), 1654, 1543, 1505 (NO_2), 1408. ^1H NMR δ (DMSO-d_6) (main rotamers) 10.55 (1H, d, J=12.7 Hz, HN), 8.30 (1H, s, CHO), 7.17 (1H, dd, J_1=12.7 Hz, J_2=10.7 Hz, H1), 6.10 (1H, d, J=10.7 Hz, H2), (minor rotamers) 10.25 (1H, bs, NH), 8.41 (1H, d, J=10 Hz, CHO), 7.13 (1H, dd, J_1=10 Hz, J_2=9.2 Hz, H1), 5.97 (1H, d, J=9.2 Hz, H2). ^{13}C NMR δ (DMSO-d_6) (main rotamers) 160.78 (CH, CHO), 150.0 (C4′), 138.99 (C5′), 125.64 (CH, C1), 95.36 (CH, C2), (minor rotamers) 164.49 (CH, CHO), 150.0 (C4′), 138.99 (C5′), 130.77 (CH, C1), 93.67 (CH, C2). MS (EI) (%) 183 (M^+, 11), 165 (M^+-H_2O, 37), 79 (51), 66 (100).

3.1.7. 4-Bromomethylpyrimidine 15. A solution of HBr in acetic acid was added slowly to a solution of compound **2** (0.1 g, 0.83 mmol) in ether (2 mL). A white precipitate was formed, filtered, and washed with ether. Mp 123–125°C. $\nu_{max.}$ (KBr) (cm^{-1}) 3380 (broad HN^+), 1624, 1608, 1589, 1473, 1396, 624. The solid was dissolved in DMSO-d_6 and analysed by HRMS. Found for M^+173.9607, 171.9629; $C_5H_5N_2Br$ requires 173.9615, 171.9636. ^1H NMR δ (DMSO-d_6) 9.17 (1H, s, H2′), 8.83 (1H, d, J=5.5 Hz, H6′), 7.68 (1H, d, J=5.5 Hz, H5′), 4.64 (2H, s, H1). ^{13}C NMR δ (DMSO-d_6) 158.90 (CH, C2′), 158.62 (CH, C6′), 121.42 (CH, C5′), 33.07 (CH_2, C1), corresponding to 4-bromomethylpyrimidine **15**.[13]

3.1.8. Reaction of triazolopyrimidine 2 with sodium methoxide. To a solution of triazolopyrimidine **2** (0.5 g, 4.2 mmol) in dry methanol (6 mL) a solution of sodium methoxide (0.27 g, 5 mmol) in dry methanol (2 mL) was added. The solution became red, was stirred for 24 h at room temperature and then refluxed for 24 h The solution was concentrated and the only identified compound was almost pure *N*-[2-(1*H*-1,2,3-triazol-4-yl) vinyl]carboxamide **4**.

3.1.9. Reaction of triazolopyrimidine 2 with morpholine or pyrrolidine. A solution of triazolopyrimidine **2** and one equivalent amount of morpholine or pyrrolidine in dry acetonitrile was refluxed. The solvent was then evaporated and the reaction crude was treated with ether, a yellow solid precipitate. Reaction with morpholine was refluxed 24 h, the solid was filtered and recrystallised from chloroform/hexane to give 4-[4-(2*H*-1,2,3-triazol-4-yl)-2-azabuta-1,3-dienyl] morpholine **27**, (41%). Mp 105°C (Cl_3CH/Hexane). HRMS found for M^+207.1118; $C_9H_{13}N_5O$ requires 207.1120. ν_{max} (KBr) (cm^{-1}) 3312 (broad, NH), 3184 (broad, NH), 3037, 1666 (C=N), 1527, 1455, 1376, 971. ^1H NMR (250 MHz) δ ($CDCl_3$) 8.55 (1H, bs, NH), 7.55 (1H, s, H1′ or H5′), 7.52 (1H, s, H5′ or H1′), 6.70 (1H, d, J=7.6 Hz, H3′), 5.56 (1H, d, J=7.6 Hz, H4′), 3.80–3.68 (4H, m, H2+H6), 3.3 (2H, m, H3 or H5), 2.8 (2H, m, H5 or H3). ^{13}C NMR δ ($CDCl_3$) 157.00 (CH, C1′), 141.89 (CH, C5″), 137.00 (C4″), 129.79 (CH, C3′), 99.23 (CH, C4′), 67.64 (CH_2, C2+C6), 45.98 (CH_2, C3+C5). MS (%), 207 (M^+, 16), 180 (M^+-HCN, 8), 138 (65), 120 (28), 110 [$(C_4H_6N_4)^+$, 100], 92 (10), 87 (17), 65 (29). The filtrated was purified by flash 40 chromatography, elution with ethyl acetate/hexane 3:1 give triazolopyrimidine (9%) and compound **4** (10%). Reaction with pyrrolidine was refluxed 5 h, then was stirred 24 h at room temperature, giving 4-(3-aza-4-pyrrolidinylbuta-1,3-dienyl)-2*H*-1,2,4-triazole **28** almost pure. Mp 75–77°C. HRMS found for M^+ 191.1174; $C_9H_{13}N_5$ requires 191.1170. ν_{max} (KBr) (cm^{-1}) 3306 (sharp), 3191 (broad NH), 2935, 1660 (C=N), 1540, 1457, 1380, 964. ^1H NMR (250 MHz) δ ($CDCl_3$) 7.71 (1H, s, H5), 7.45 (1H, s, H4′), 6.74 (1H, d, J=7.3 Hz, H2′), 5.49 (1H, d, J=7.3 Hz, H1′), 3.52–3.43 (5H, m), 1.98–1.86 (4H, m). ^{13}C NMR δ ($CDCl_3$), 154.52 (CH, C4′), 142.63 (CH, C5), 136.23 (C4), 129.27 (CH, C2′), 97.70 (CH, C1′), 49.02 (CH_2, C2″ or C5″), 45.97 (CH_2, C5″ or C2″), 25.08 (CH_2, C3″ or C4″), 24.41 (CH_2, C4″ or C3″). MS (%), 191 (M^+, 55), 163 (M^+-N_2, 8), 121 (21), 120 [$(C_5H_4N_4)^+$, 100], 110 [$(C_4H_6N_4)^+$, 84],, 92 (30), 71 (39), 70 (79), 65 (94).

3.1.10. Reaction of triazolopyrimidine 2 with benzylamine. A solution of triazolopyrimidine **2** (0.1 g, 0.83 mmol) and benzylamine (0.098 g, 0.9 mmol) in dry acetonitrile (10 mL) was heated at 120°C 2 days in a steel sealed vessel. Then the solvent was evaporated and the crude product purified by chromatotron eluting with ethyl acetate/hexane 2:1. Triazolopyrimidine **2** was first eluted (0.058 g) and then *N*-benzylformamide (0.055 g, 50%).

3.1.11. Reaction of triazolopyrimidine 2 with potassium cyanide. To a solution of triazolopyrimidine **2** (0.3 g, 2.6 mmol) in dry acetonitrile (10 mL) potassium cyanide (0.195 g, 2.9 mmol) was added and heated at 120°C 3 days in a steel sealed vessel. Then the solvent was evaporated and the crude purified by column chromatography, eluting with ethyl acetate a white solid was isolated and identified as (*Z*)-1-[4-(4-pyrimidinyl)-1*H*-1,2,3-triazolo-1-yl]-2-(2*H*-1,2,3-triazo-4-yl)-1-ethene **30** (0.105 g, 35% yield). Mp 234–235°C (AcOEt). HRMS found for M^+240.0871; $C_{10}H_8N_8$ requires 240.0871. ν_{max} (KBr) (cm^{-1}) 3438 (broad), 3137, 2916, 2852, 1600. λ_{max}(nm) (log ϵ) (EtOH) 281 (4.04), 240 (4.02), 234 (4.00), 224 (4.03), 220 (4.03). ^1H NMR δ (DMSO-d_6) 15.40 (1H, s), 9.62 (1H, s), 9.20 (1H, d, J=1.3 Hz), 8.90 (1H, d, J=5.2 Hz) 8.12 (1H, dd, J_1=5.2 Hz, J_2=1.3 Hz), 7.80 (1H, s), 7.49 (1H, d, J_1=10.1 Hz), 6.78 (1H, d, J=10.1 Hz). ^{13}C NMR δ (DMSO-d_6) 159.33 (CH), 158.64 (CH), 156.46 (C), 145.35 (C), 139.71 (C), 130.58 (CH), 125.77 (CH), 122.62 (CH), 116.91 (CH), 113.16 (CH). MS (%) 240 (M^+, 24), 213 (M^+-HCN, 12), 212 (M^+-N_2, 24), 184 (M^+-2N_2, 17), 183 (72), 171 (35), 158 (29), 157 (69), 156 (81), 149 (13), 147 (34), 131 (23), 129 (43), 119 (32), 106 (76), 105

$[(C_6H_5N_2)^+, 100]$, 104 (25), 103 (30), 91 (14), 80 (46), 79 (37), 52 (55).

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