



Reaction of 1-substituted 3,5-diamino-1,2,4-triazoles with β -keto esters: synthesis and new rearrangement of mesoionic 3-amino-2*H*-[1,2,4]triazolo-[4,3-*a*]pyrimidin-5-ones

Victor M. Chernyshev^{a,*}, Alexander V. Astakhov^a, Zoya A. Starikova^b

^a South-Russia State Technical University, 346428 Novocherkassk, Russian Federation

^b A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 119991 Moscow, Russian Federation

ARTICLE INFO

Article history:

Received 19 November 2009

Received in revised form 5 February 2010

Accepted 1 March 2010

Available online 6 March 2010

Keywords:

[1,2,4]Triazolo[4,3-*a*]pyrimidin-5-ones

Mesoionic

Rearrangement

1-Substituted 1*H*-1,2,4-triazole-3,5-

diamines

β -Keto esters

Condensation

ABSTRACT

Reaction of 3,5-diamino-1-*R*-1,2,4-triazoles (*R*=Ph, Bn) with β -keto esters results in the reversible formation of *N*-(5-amino-1-*R*-1,2,4-triazol-3-yl)-substituted enaminoesters (**8**). Subsequent transformations depended on the reaction conditions. Compounds **8** undergo intermolecular reactions of condensation and amidation in the absence of solvent. However, in the presence of acetic acid they form 3-amino-5-oxo-2-*R*-2,5-dihydro-[1,2,4]triazolo[4,3-*a*]pyrimidin-4-ium-8-ides (**10**) followed by rearrangement to 3-amino-1-*R*-[1,2,4]triazolo[4,3-*a*]pyrimidin-5-ones (**11**). The transformation of **10** into **11** represents a new type of rearrangement in the azolopyrimidine series. Heating of enaminoesters **8** in ethanol with sodium ethoxide present, proved to be a suitable method for the preparation of the mesoionic compounds **10**.

© 2010 Elsevier Ltd. All rights reserved.

1. Introduction

The cyclocondensation of aminoazoles with β -keto esters is a powerful method for the preparation of azolopyrimidinones with a nodal nitrogen atom.^{1,2} These compounds are analogs of purine bases³ and exhibit various types of biological activity, including antihypertensive,^{1g} serotonin antagonist,^{1e,4a} anti-inflammatory,^{4b} analgesic,^{4c} antimicrobial,^{4d,e} antifungal,^{4f} cytotoxic,^{4g,h} and anti-tumor activities.⁴ⁱ They can also serve as synthetic precursors for the preparation of pharmacologically valuable amino derivatives of azolopyrimidines.^{1h,5} Condensation of *N*-unsubstituted 3(5)-amino-1,2,4-triazoles with various β -keto esters results in the predominant formation of 1,2,4-triazolo[1,5-*a*]pyrimidin-7-ones and represents a significant method of preparation of this type of compounds.^{2,5a} So far, the analogous reaction of 1-substituted 3-amino- and 5-amino-1,2,4-triazoles has not been thoroughly investigated. According to the literature data,⁶ 1-aryl-substituted 3,5-diamino-1,2,4-triazoles (**1**) and ethyl acetoacetate (**7a**) form products **2–4** depending on the molar ratio and heating temperature in a solventless reaction (Fig. 1). Compound **4** affords a derivative of 1,2,4-triazolo[1,5-*a*]pyrimidin-

7-one (**5**) when treated with warm alcoholic alkali or when heated at 210–215 °C.^{6b} According to patent data, triazole **1** (*Ar*=Ph) forms diamides **6** in refluxing xylene with an excess of ethyl acetoacetate.⁷ However, this information was subsequently revised, and the reaction products were claimed to be amides **2** (Fig. 1).^{6c} In our opinion, the structures of compounds **2–6** were not accurately proven owing to the absence of any analytical data except elemental analysis in the cited literature.

It is well known that the interaction of 1-substituted 3-amino- and 5-amino-1,2,4-triazoles with 1,3-bielectrophiles, such as 1,3-diketones^{8a,b} or diethyl ethoxymethylenemalonates^{8c} leads to 1,2,4-triazolo[4,3-*a*]pyrimidine derivatives. Consequently, under certain conditions the reaction of 1-substituted 3-amino- and 5-amino-1,2,4-triazoles with β -keto esters would be expected to afford triazolopyrimidinones and would thus be a suitable method for the preparation of these compounds.

This article reports our results from the reinvestigation of the reaction of 1-*R*-3,5-diamino-1,2,4-triazoles (**1a**, *R*=Ph, **1b**, *R*=Bn) with β -keto esters. Furthermore, it describes some interconversion between the products formed. The choice of diamines **1** as substrates was predicated on having greatly varied nucleophilicity of amino groups in positions 3 and 5 of triazole ring.⁹ We believe that 1-substituted 3,5-diamino-1,2,4-triazoles are convenient models for a comparative investigation of the reactivity of 3-amino- and

* Corresponding author. Tel.: +7 903 437 24 03; fax: +7 86 352 276 19; e-mail address: chern13@yandex.ru.

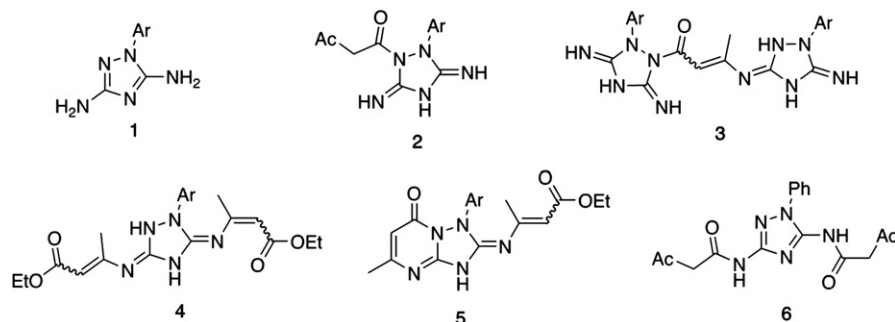
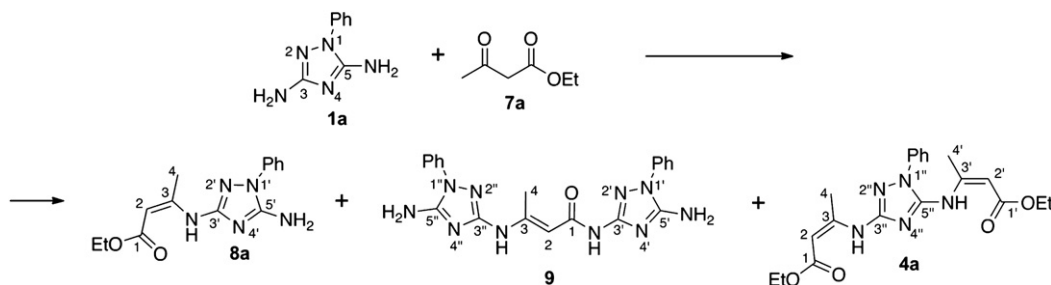


Figure 1. Structures of products of the reaction of 1-substituted 3,5-diamino-1,2,4-triazoles (**1**) with ethyl acetoacetate according to the literature data.^{6,7}

5-amino-1,2,4-triazoles toward electrophiles. Moreover, this would afford a new approach to the selective synthesis of triazolopyrimidinones with different annulation of triazole and pyrimidine.

2. Results and discussion

We first reproduced the literature results of the reaction of compounds **1** and β -keto esters.^{6,7} According to Papini's findings, heating of 1-arylsubstituted 3,5-diamino-1,2,4-triazoles with ethyl acetoacetate (**7a**) in molar ratios from 1:1 to 1:2 at 100–120 °C without solvent resulted in the formation of compounds **2** (Fig. 1).^{6a} However, we established that a mixture of three major products (**4a**, **8a**, and **9**) was formed in the reaction of compound **1a** with ester **7a** in the absence of solvent at 100–105 °C and molar ratios of **1a**:**7a** from 1:1 to 1:2 (Scheme 1). Compound **9** is sparingly soluble in most organic solvents and was isolated by crystallization. Products **4a** and **8a** were separated by column chromatography. In accordance with HPLC analysis of the reaction mixtures, prolongation of the reaction time decreased the yield of **8a** and increased the yield of **9**, and also caused the appearance of several small peaks of unidentified compounds (Table 1).



Scheme 1. The reaction of compounds **1a** and **7a** without solvent at 100–105 °C.

Table 1

HPLC data from monitoring the reaction between **1a** and **7a** without solvent at 100–105 °C

Entry	Molar ratio 1a : 7a =1:1		Molar ratio 1a : 7a =1:2	
	Yield in 4 h (%)	Yield ^a in 60 h (%)	Yield in 4 h (%)	Yield ^a in 60 h (%)
1a	27	8	17	8
8a	56	22	64	36
9	12	56	4	12
4a	5	7	15	22

^a There were several small peaks observed from unidentified compounds.

Using HPLC, we also determined that pure compound **8a** gradually decomposed to give a mixture of diamine **1a** and products **9** and **4a** when heated past its melting point and maintained at

100 °C. The yields of **1a** and **9** increased with longer heating time (Table 2). The results obtained allowed us to assume that the formation of compounds **4a**, **8a**, and **9** may be described by four major reactions (Scheme 2). Apparently, the first three reactions are reversible and relatively fast. The fourth reaction is irreversible and relatively slow.

Table 2

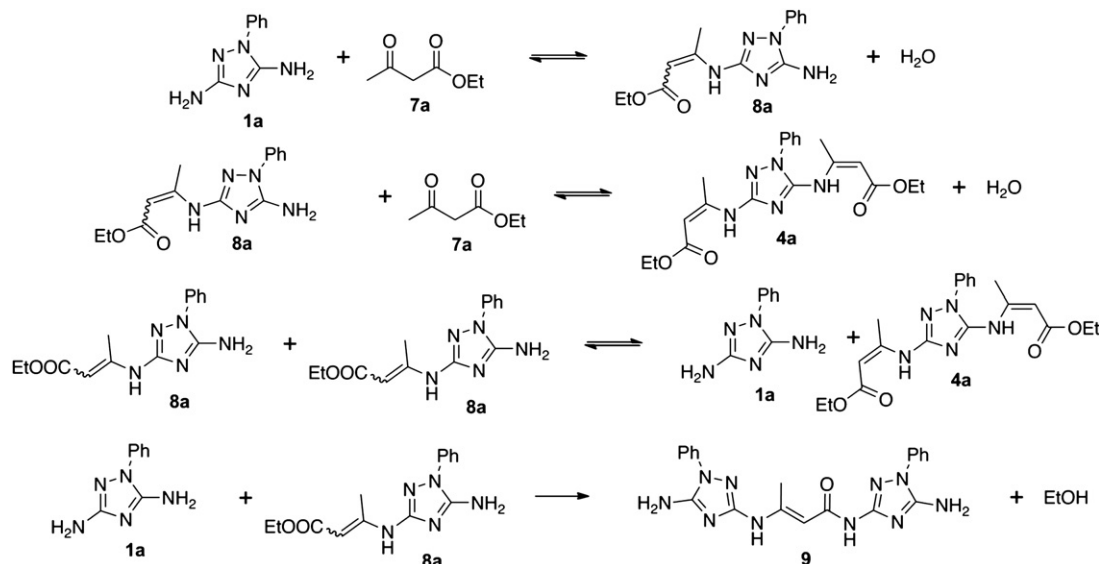
HPLC data from monitoring the decomposition of compound **8a** at 100 °C

Entry	Yield in 4 h (%)	Yield ^a in 60 h (%)
1a	14	37
8a	69	39
9	2	20
4a	15	4

^a There were several small peaks observed from unidentified compounds.

We were not able to detect compound **2** (or its isomer with an acetoacetamide group) in the reaction mixtures, which according to the literature data was the main product under these conditions.^{6a} Papini claimed that compound **2** was also obtained by refluxing diamine **1a** with excess of the ester **7a** in xylene.^{6c}

However, Bavley assigned the structure **6** to the reaction product (Fig. 2).⁷ By reproducing the described procedures,^{6c,7} we obtained compound **9** as the main product in both cases. Therefore, we concluded that impure compound **9** was obtained rather than compounds **2** (Ar=Ph) and **6**, as was described in the literature,^{6a,c,7} and that the inconsistencies in elemental analysis were caused by impurities. It is noteworthy that Papini also described the synthesis of compound **3** (Ar=Ph, Fig. 1) by heating diamine **1a** with neat β -keto ester **7a** at 140–150 °C in the molar ratio of **1a**:**7a** of 2:1.^{6a} However, again we obtained compound **9** in 40% yield under these conditions. The melting point and other properties described by Papini for compound **3** are in good agreement with the properties of compound **9**. Therefore, taking into account current data

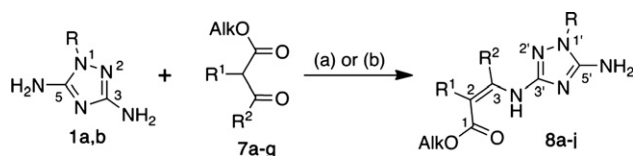


Scheme 2. The major reactions of formation of compounds **4a**, **8a**, and **9** from **1a** and **7a** under solvent free conditions at 100–105 °C.

on the structure of acyl derivatives of 1-substituted 3,5-diamino-1,2,4-triazoles,^{9a,b,d} we concluded that Papini obtained compound **9** rather than its isomer **3**. The highest yield and purity of compound **9** was obtained by heating compounds **1a** and **7a** without solvent at 140–150 °C for 1 h or refluxing them in xylene for 5 h at the molar ratio of **1a**:**7a**=1:1.

The properties of compound **4a**, obtained by the present authors from heating of **1a** with an excess of **7a**, are in good agreement with the one described by Papini and Checchi for compound **4** (Ar=Ph).^{6b} Considering the modern knowledge of tautomerism of C-amino-1,2,4-triazoles and their derivatives¹⁰ as well as triazolyl substituted enaminoesters,¹¹ it is reasonable to conclude that the tautomeric form **4a** is more appropriate for describing the structure of the compound synthesized. The literature procedure^{6b} was used for the synthesis of compound **4a**, reducing the reaction time to 1 h to improve the yield and selectivity.

The synthesis of compound **8a** was accomplished by refluxing diaminotriazole **1a** with a small excess of β-keto ester **7a** in either ethanol or tetrahydrofuran. Compounds **8b–j** were synthesized analogously in 40–73% yields (Scheme 3, Table 3). It should be noted that the enaminoesters **8a–j** are quite stable, which is in contrast to similar derivatives of C-amino-1,2,4-triazoles unsubstituted at the cyclic nitrogen atom. These latter compounds are usually not isolatable because of rapid cyclization into [1,2,4]triazolo[1,5-*a*]pyrimidin-7-ones.^{2f}



Scheme 3. Synthesis of compounds **8a–j**. Reaction conditions: (a) EtOH (or MeOH for **8g**), reflux; (b) THF, reflux.

The structures of compounds **4a**, **8**, and **9** were confirmed by both elemental analysis and spectral data (IR, ¹H, and ¹³C NMR, and mass spectroscopy). The direction of the condensation and acylation reactions of diamines **1** at the 3-NH₂ conforms with the previously observed selectivity of reactions of 1-substituted 3,5-diamino-1,2,4-triazoles with electrophiles,⁹ and it was corroborated by ¹H NMR spectra of compounds **8a–j** and **9**, in which the signal of unreacted

Table 3

Yields of compounds **8a–j**

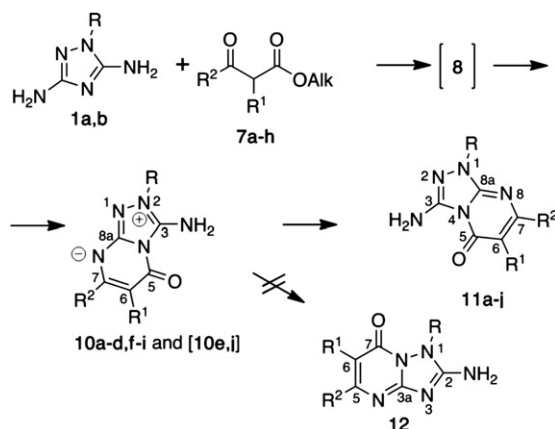
Compound	β-Keto ester	R	R ¹	R ²	Alk	Yield, %
8a	7a	Ph	H	Me	Et	60 (a), 75 (b)
8b	7b	Ph	<i>n</i> -Bu	Me	Et	40 (a)
8c	7c	Ph	Bn	Me	Et	40 (a)
8d	7d	Ph	4-MeC ₆ H ₄	Me	Et	41 (a)
8e	7e	Ph	Cl	Me	Et	57 (b)
8f	7f	Ph	H	<i>n</i> -Pr	Et	45 (a)
8g	7g	Ph	H	<i>i</i> -Pr	Me	42 (a)
8h	7a	Bn	H	Me	Et	73 (a)
8i	7e	Bn	Cl	Me	Et	46 (a)
8j	7f	Bn	H	<i>n</i> -Pr	Et	54 (a)

NH₂ (6.48–6.65 ppm in DMSO-*d*₆) was typical for 1-substituted 5-amino-1,2,4-triazoles.^{9a–c,12} If these reactions had occurred at the 5-NH₂ the signal of the amino group in the compounds formed should be in the 4.5–5.4 ppm range like those from other 1-substituted 3-amino-1,2,4-triazoles.^{9a–c,12} The direction of the reactions was unambiguously established by the NOESY spectra of compounds **8a** and **9**, which both contain correlation peaks between the spatially close protons of 5-NH₂ and the phenyl group. In analogy to other enaminoesters, compounds **4a**, **8**, and **9** can exist as *E* and *Z* stereoisomers.^{11,13} According to the ¹H and ¹³C NMR spectra, compounds **4a** and **8** are (*Z*)-isomers because the signals of their enaminoester fragments are in close agreement with the literature data for the (*Z*)-enaminoesters.^{13a–d} The (*E*)-isomer was only detected in uncrystallized samples of compound **8a**, that had been obtained by refluxing the reagents in tetrahydrofuran (content of (*E*)-isomer 19%) or acetic acid (content of (*E*)-isomer 47%). ¹H NMR spectra of the (*E*) and (*Z*) isomers of **8a** are substantially different. The H-2 and NH signals of the enaminoester fragment (see Scheme 3) of the (*Z*)-isomer were observed at 4.75 and 10.59 ppm, respectively, whereas the same signals of the (*E*)-isomer were found at 6.31 and 9.09 ppm, respectively. Differentiation of the (*E*) and (*Z*) isomers of compound **8a** was based on the NOESY spectrum, in which the cross-peak between the H-2 and CH₃ at C-3 was observed only for the (*Z*)-isomer. The assignment of signals in the ¹³C NMR spectra was performed on the basis of the HMBC spectrum of compound **8a**, which contained correlation peaks between the protons of the ethoxy group (4.06 ppm) and the carbonyl carbon (169.5 ppm), the protons of the methyl group (2.32 ppm) and C-2 (88.1 ppm), and H-2 (4.75 ppm) and C-3 (157.1 ppm). The signals of the carbons that

showed no correlation peaks with any protons were assigned to the triazole ring. Owing to the absence of a cross-peak between the H-2 and the protons of the methyl group in the NOESY spectrum of compound **9**, this substance was concluded to exist in the (*E*)-isomer form.

Eventually, it was concluded that for the conditions described above, the interaction between compounds **1** and **7** does not result in the formation of annulated products. It is known that the synthesis of triazolopyrimidines is generally performed by condensation of aminotriazoles with β -keto esters in glacial acetic acid under reflux.² Therefore, we investigated the reaction of diamines **1a,b** with β -keto esters **7a–h** in the presence of acetic acid to probe the possibility of synthesis of annulated heterocycles.

The HPLC analysis revealed that compound **8a**, isolated from the reaction mixture, was initially formed when heating compounds **1a** and **7a** to reflux in glacial acetic acid. Upon further heating, the enaminoester **8a** gradually disappeared and two new compounds were formed. Following isolation by column chromatography and analysis they were proven to be the isomeric [1,2,4]triazolo[4,3-*a*]pyrimidin-5-ones **10a** and **11a** (Scheme 4). It was also established that higher yields of the triazolopyrimidines could be achieved by gradual evaporation of acetic acid when heating the reaction mixture until its temperature reached 145–150 °C and then maintained at 145–150 °C for five hours (Table 4).



Scheme 4. The reaction of compounds **1** and **7** in the presence of AcOH at 140–150 °C.

Table 4

Yields of compounds **10a–j** and **11a–j** isolated from the reaction of **1a,b** with **7a–h** in the presence of AcOH at 140–150 °C for 5 h

Compound	R	R ¹	R ²	Compound (yield, %)
a	Ph	H	Me	10a (10), 11a (21)
b	Ph	<i>n</i> -Bu	Me	10b (19), 11b (35)
c	Ph	Bn	Me	10c (11), 11c (42)
d	Ph	4-MeC ₆ H ₄	Me	10d (23), 11d (23)
e	Ph	Cl	Me	11e (13) ^a
f	Ph	H	<i>n</i> -Pr	10f (12), 11f (21)
g	Ph	H	<i>i</i> -Pr	10g (27), 11g (38)
h	Bn	H	Me	10h (10), 11h (20)
i	Bn	H	<i>n</i> -Pr	10i (14), 11i (28)
j	Ph	H	CF ₃	11j (14) ^a

^a Compounds **10e** and **10j** were not isolated.

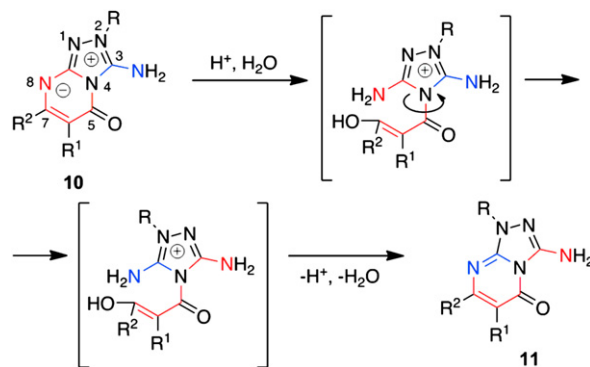
According to HPLC analysis, the yield of compound **10a** decreased and the yield of **11a** increased with prolonged reaction time. For example, after heating for 3 h the yields of compounds **10a** and **11a** amounted to 17% and 18%, respectively, while after 20 h compound **10a** was not detected in the reaction mixture, and the yield of triazolopyrimidinone **11a** rose to 30%. This observation led to the hypothesis that the mesoionic compound **10a** gradually rearranges into compound **11a** (Scheme 4). This rearrangement was

clearly confirmed by heating of pure compound **10a** in the presence of acetic acid at 150–160 °C for 10 h. The HPLC analysis of the resulting mixture revealed that all of compound **10a** had been consumed and that compound **11a** had formed in 18% yield. We also observed several new sparingly soluble and unidentified compounds, indicating that the rearrangement was accompanied by substantial decomposition of compound **10a**. Compound **11a** is more thermally stable, and the degree of decomposition was only 12% after heating for 10 h at the same conditions as those for **10a**.

The reactions of compounds **1a,b** with β -keto esters **7a–d,f,g** occurred analogously to those described above, affording the mixtures of compounds **10b–d,f,i** and **11b–d,f,i** (Scheme 4, Table 4). However, only compounds **11e** (13%) and **11j** (14%) were obtained from the reaction of **1a** with **7e** and **7h** (R¹=H, R²=CF₃, Alk=Et), respectively. Compound **10e** was detected chromatographically and not isolated owing to a very low yield. The corresponding mesoionic CF₃-substituted triazolopyrimidinone **10j** was not detected even by HPLC and thin-layer chromatography. Apparently, this is a result of the mesoionic [1,2,4]triazolo[4,3-*a*]pyrimidin-5-ones containing electron withdrawing substituents in the positions 6 and 7 being unstable. Additionally, it is clear that the thermal instability of the mesoionic compounds **10** is responsible for the low total yield of triazolopyrimidinones in the reactions of diaminotriazoles **1a,b** with β -keto esters **7a–h**.

The rearrangement of compounds **10** into compounds **11** was concluded to be irreversible because compounds **10** were not detected in the reaction mixtures after heating of pure compounds **11** at 150–160 °C in the presence of acetic acid. This indicates that compounds **11** are substantially more thermodynamically stable than compounds **10**.

One of the most investigated rearrangements of azolopyrimidines is the Dimroth rearrangement of 1,2,4-triazolo[4,3-*a*]pyrimidines into the thermodynamically more stable 1,2,4-triazolo[1,5-*a*]pyrimidines.^{1b,2a,f,8a,14} It is noteworthy that the rearrangement observed in the present investigation results in the formation of 1-substituted 3-amino-[1,2,4]triazolo[4,3-*a*]pyrimidin-5(1*H*)-ones **11** instead of the expected 1-substituted 2-amino-[1,2,4]triazolo[1,5-*a*]pyrimidin-7(1*H*)-ones **12** (Scheme 4). As far as we are aware, an analogous rearrangement of azolopyrimidines has not been described in the literature. While the mechanism of this rearrangement needs a separate investigation, it is appropriate to propose that it is analogous to the ANRORC mechanism of Dimroth rearrangement.¹⁵ However, instead of N⁴–C⁵ bond cleavage, the fission occurs at the C⁷–N⁸ bond, followed by rotation around the N–CO bond, and finally reformation of the ring (Scheme 5). A water or acetic acid molecule can act as a nucleophile. The Dimroth rearrangement is probably hindered by an intramolecular hydrogen bond between the amino and carbonyl groups, which strengthen the 4–5 bond. Nevertheless, other possible mechanisms of the observed rearrangement cannot be ruled out.



Scheme 5. The proposed mechanism of the rearrangement of compounds **10**.

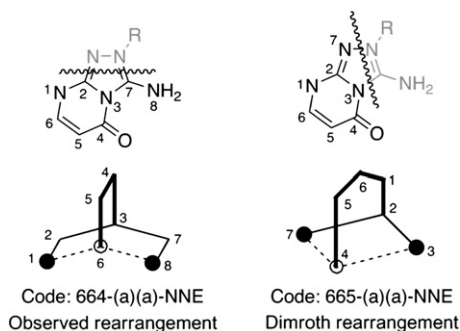
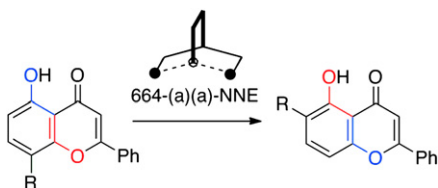


Figure 2. Ring-bond-redistribution graphs (G_2) and codes for the observed rearrangement and for the Dimroth^{15b,17c} rearrangement according to the Babaev-Zefirov classification.¹⁷

This rearrangement relates to degenerate ring transformations, because it results in the formation of the same heterocyclic system,^{15b,c} and it represents a rare example of fission of the 7–8 bond in the azaindolizine system for which cleavage of the 4–5 bond is more typical.¹⁶ We can see that this rearrangement differs from the Dimroth rearrangement by considering the rearrangement of the pyrimidine cycle (Fig. 2), which occurs via the interchange of an endocyclic heteroatom by an adjacent exocyclic heteroatom.^{15b} In the case of compounds **10**, the Dimroth rearrangement should result in replacement of N-3 by N-7 (see numbering at Fig. 2). However, we observed the interchange of two endocyclic atoms (C and N) by their analogous atoms of the side chain (Scheme 5, Fig. 2). According to the Babaev-Zefirov ring-bond-redistribution (RBR) graphs classification¹⁷ of heterocyclic ring transformations, a topological difference between the Dimroth and the observed rearrangements is illustrated by Figure 2. The observed rearrangement has a code of 664-(a)(a)-NNE, whereas the code for the Dimroth rearrangement of azines is 665-(a)(a)-NNE.^{15b,17b,c} Topologically the observed rearrangement is similar to the rearrangement of 5-hydroxyflavones (Scheme 6),¹⁸ which has the same type, class and sort, but relates to another family.^{17c}



Scheme 6. The rearrangement of 5-hydroxyflavones,¹⁸ its G_2 RBR graph and code.^{17c}

The structures of compounds **10** and **11** were confirmed by elemental analysis and spectral data. The ^1H NMR spectra of compounds **10** and **11** display signals for one tautomeric form only. The two proton singlet of the amino group supports the proposed amino tautomer for both compounds **10** and **11** in DMSO solutions. There are substantial differences between the spectra of the isomers. Thus, the signal of amino group of compounds **10** is observed at 8.38–8.45 ppm, whereas for the compounds **11** it is shifted upfield to 6.86–7.24 ppm. The signal of H-6 is found at 5.14–5.22 ppm for **10a,f–i** and at 5.54–5.75 ppm for isomeric **11a,f–i**. Furthermore, the relatively narrow multiplet of the phenyl protons at 7.47–7.68 ppm indicates that the benzene and triazole cycles are not coplanar in compounds **10a–g**, while the three multiplets of the phenyl protons in a reasonably wide range (7.23–8.11 ppm) indicate coplanarity¹⁹ between the same groups in compounds **11a–g,j**.

The ^{13}C NMR spectra of compounds **10** and **11** are quite similar to the spectrum of compound **13**.^{2b,c} On the other hand, they differ considerably from the spectra of isomers **12**,^{20a,b} which could be

formed from either alternative direction of the cyclization of enaminoesters **8** or Dimroth rearrangement of compounds **10** (Fig. 3). The signal of C-3 is shifted upfield by 18–23 ppm in comparison with the analogous signal of C-2 in compounds **12**. The main difference between the spectra of isomers **10** and those of **11** is observed for the signal of C-6, which is shifted upfield by 6.2–9.0 ppm for compounds **10**. It is also notable that the differences between the chemical shifts of the triazole carbons C-3 and C-8a in compounds **10** (6.5–9.0 ppm) are significantly higher than in compounds **11** (less than 1.9 ppm). Moreover, in the spectra of compounds **10** the signals of C-5 and C-7 are shifted downfield by 0.3–1.3 ppm and 1.3–3.2 ppm as compared to those from the spectra of isomeric compounds **11**. Assignments of the signals in the ^{13}C NMR spectra were accomplished with the HSQC and HMBC spectra of compounds **10b,h**, **11h** and the proton coupled ^{13}C spectra of **10a,d,g,i** and **11a,d,i**.

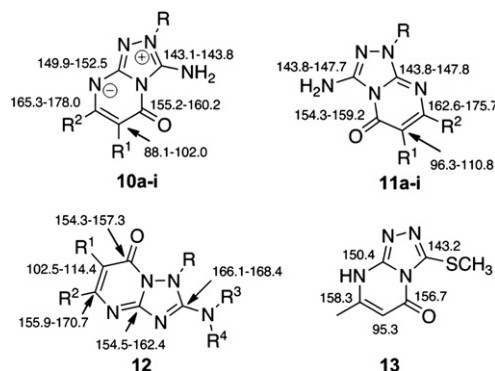


Figure 3. The characteristic signals in the ^{13}C NMR spectra of compounds **10–13**.

UV spectroscopy in neutral solution was successfully used to differentiate between isomeric triazolopyrimidinones.^{2b–d} We found considerable differences in the UV spectra of the isomeric compounds **10a–g** and **11a–g**. Compounds **10a–g** show two absorption bands appearing at 234–238 nm (high intensity) and 335–348 nm (low intensity), whereas compounds **11a–g** display three maxima at 220–231 nm (medium intensity), 270–276 nm (low intensity), and 331–349 nm (high intensity). The UV spectra of the benzyl derivatives **10h,i** and **11h,i** are quite similar and unsuitable for the identification of the isomers.

The structure of compounds **10** and **11** was confirmed unambiguously by X-ray diffraction studies of compounds **10a** and **11d**. In the ensuing discussion of the structures, the crystallographic numbering system will be used (Figs. 4 and 5). The X-ray diffraction data of the molecule of triazolopyrimidinone **10a** shows that it is non-planar, with the plane of the phenyl group and the plane of the triazole cycle having a dihedral angle of 34.6°. In addition, there is a small dihedral angle of 3.3° between the planes of the triazole and the pyrimidine rings. The greatest deviation from the plane of the triazole ring is observed for C(7) (0.142 Å). The nitrogen atom of the amino group is in a trigonal pyramidal configuration (sum of valence angles is 356.2°) and deviates from the triazole plane by only 0.02 Å. There is an intramolecular hydrogen bond N(3)H...O(1) in the molecule [N(3)H...O 2.782(1), N–H 0.87, O...H 2.10 Å, angle OHN 135°]. The O(1)–C(5) bond length of 1.234(2) Å is in agreement with the corresponding values in other [1,2,4]triazolo[4,3-*a*]pyrimidin-5(1*H*)-ones and related systems (1.203–1.248 Å).²¹ The bonds C(7)–N(8) and N(8)–C(8a) have almost equal lengths of 1.351(2) and 1.346(2) Å, respectively. It should be noted that the N(4)–C(3) bond (1.369(2) Å) is longer than the N(2)–C(3) and N(3)–C(3) bonds (1.341(2) Å and 1.324(1) Å, respectively). This makes it reasonable to assume that the resonance structures A and B (Scheme 7) are the main contributors to the description of the structure of compounds **10**.

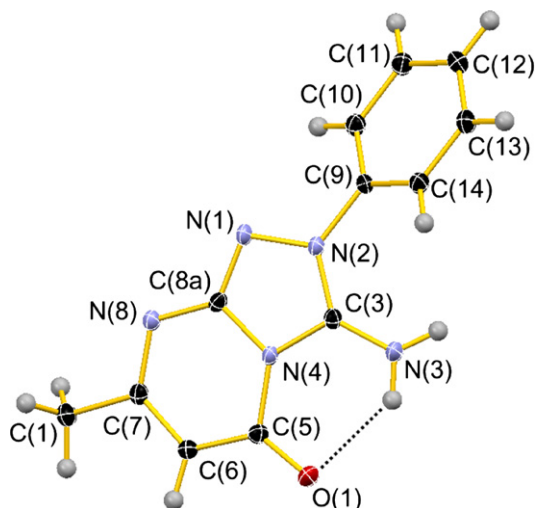


Figure 4. The X-ray crystallographic structure of compound **10a**.

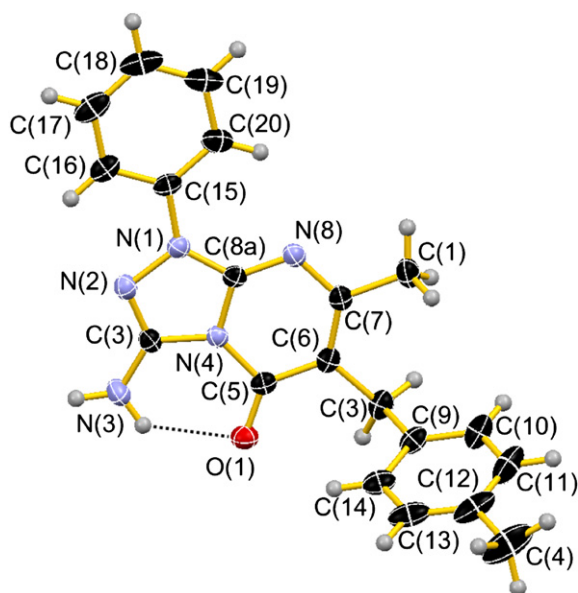
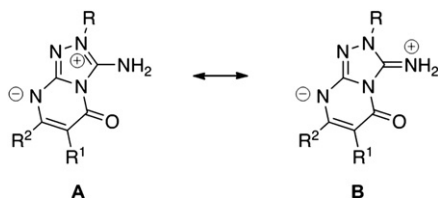


Figure 5. The X-ray crystallographic structure of compound **11d**.

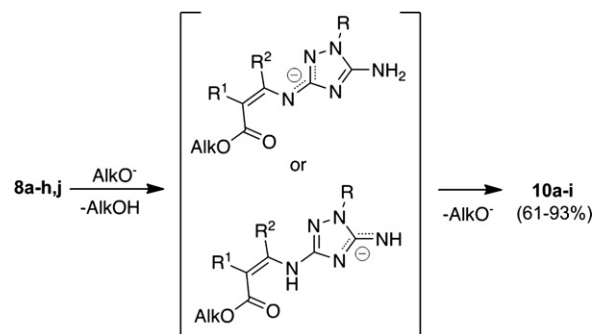


Scheme 7. The resonance structures of compounds **10**.

The triazolopyrimidine fragment of the molecule **11d** is planar, with the maximal deviation of atoms from the mean-square plane not exceeding 0.028 Å. The nitrogen atom of the amino group is in a trigonal pyramidal configuration (sum of valence angles is 356.7°) and deviates from the triazole plane by only 0.073 Å. Conjugation between the unshared electron pair of N(3) and the π system of the bicyclic fragment leads to a shortening of the N(3)–C(3) bond (1.340(1) Å) relative to the standard length of a purely single N_{sp^2} – C_{sp^2} bond (1.43–1.45 Å).²² The benzene and triazole rings are almost coplanar with a dihedral angle of 6.44°. There is an intramolecular hydrogen bond N(3)H \cdots O(1) in the molecule [N(3) \cdots O

2.791(2), N–H 0.87, O \cdots H 2.12 Å, angle OHN is 133°]. The N(2)–C(3) and N(8)–C(8a) bonds have a pronounced double character (1.298(2) and 1.312(2) Å, respectively). The lengthening of the C(5)–O(1) [1.239(1) Å] and C(6)–C(7) [1.385(1) Å] bonds as compared to the average values (1.211 and 1.326 Å, respectively),²² as well as the shortening of the C(5)–C(6) [1.422(2) Å] and C(7)–N(8) [1.368(2) Å] bonds with regards to the average values (1.464 Å and 1.45 Å) indicate a pronounced conjugation in the O(1)C(5)C(6)C(7)N(8) fragment.

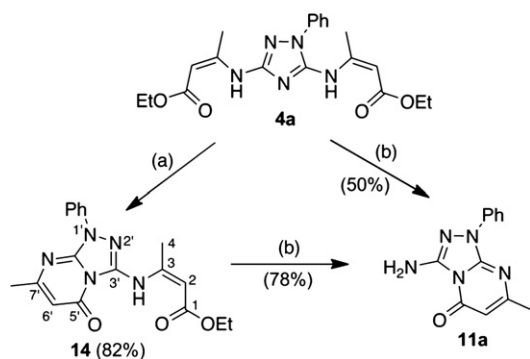
At this point, the condensation of diaminotriazoles **1** with β -keto esters **7** in acetic acid has not afforded the mesoionic triazolopyrimidinones **10** in good yields, and thus we tried to find another method for the selective preparation of these compounds. We established that enaminoesters **8a–h,j** are readily cyclized to compounds **10a–i** in high yields under refluxing conditions in ethanol or methanol in the presence of sodium alcoholates. Apparently, dissociation of hydrogen from the enamine NH or a sufficiently acidic amino group²³ to afford the corresponding nucleophilic anion precedes the intramolecular acylation, resulting in the formation of the triazolopyrimidinones **10** (Scheme 8). According to TLC and HPLC data, the crude samples of compounds **10** did not contain impurities in detectable amounts, except for compound **10e**, which contained traces of the rearranged product **11e**. Fortunately, **11e** could be completely removed by a single crystallization. Thus, the direction of the cyclization of enaminoesters **8** under basic conditions differs from the analogous cyclization of enaminoesters of triazoles that are unsubstituted at the endocyclic nitrogen's, which produce [1,2,4]triazolo[1,5-*a*]pyrimidin-7-ones.²⁴



Scheme 8. The selective synthesis of mesoionic compounds **10a–i**.

It is noteworthy that compound **4a** was converted to compound **14** in high yield by heating to reflux in an ethanolic solution of sodium ethoxide for a short time (Scheme 9). Thus, the formation of the more thermodynamically stable product from two possible directions of cyclization was accomplished. The ^1H and ^{13}C NMR spectra of compound **14** contain the signals characteristic for both the (*Z*)-enaminoester and the pyrimidinone fragments. Assignment of signals in the ^{13}C NMR spectra was performed using the HMBC spectrum. The (*Z*) form of compound **14** was unambiguously confirmed by the NOESY spectrum, which contains a cross-peak between the signals of H-2 (5.06 ppm) and CH_3 (2.46 ppm) of the enaminoester fragment. The absence of cross-peaks between the enaminoester signals and the protons of the phenyl ring shows that these groups are remote and that is only possible for compound **14**. The ^1H NMR spectrum is in accord with the phenyl and triazole rings being coplanar and is analogous to compounds **11a–h**. Because the physicochemical properties of the compound **14** are very close to the ones described for **5** (Fig. 1), it is plausible that compound **14**, rather than **5**, was obtained in the published work.^{6b}

Hydrolysis of compound **14** in alkaline water–ethanol solution afforded compound **11a**, which could also be obtained in one step from **4a** under analogous conditions (Scheme 9).



Scheme 9. The synthesis of compounds **11a** and **14** from **4a**. Reagents and conditions: (a) EtONa, EtOH, reflux; (b) NaOH, EtOH–H₂O, reflux.

3. Conclusion

The direction of the reaction of 1-substituted 3,5-diamino-1,2,4-triazoles **1** with β -keto esters differs significantly from that of the analogous reaction of C-amino-1,2,4-triazoles, unsubstituted at the endocyclic nitrogen atoms. Initially a reversible condensation occurs to afford the rather stable 5-amino-1-*R*-1,2,4-triazol-3-yl-substituted enaminoesters **8**, which then, depending on the reaction conditions, undergo intermolecular condensation and amidation or cyclization to form mesoionic 3-amino-2-*R*-[1,2,4]triazolo[4,3-*a*]pyrimidin-5-ones (**10**). In contrast to [1,2,4]triazolo[4,3-*a*]pyrimidin-5-ones that are unsubstituted at N-2, for which the Dimroth rearrangement into the thermodynamically more stable [1,2,4]triazolo[1,5-*a*]pyrimidin-7-ones is inherent, compounds **10** undergo the unusual and irreversible rearrangement into 3-amino-1-*R*-[1,2,4]triazolo[4,3-*a*]pyrimidin-5-ones (**11**) under heating conditions. A suitable method for the synthesis of the mesoionic compounds **10**, based on the selective cyclization of the enaminoesters **8** by heating in alcoholic alkali solutions, was developed.

Substantial difference in nucleophilicity of the amino groups in the positions 3 and 5 of 1-substituted 3,5-diamino-1,2,4-triazoles allows to employ the reaction between these compounds and β -keto esters for the selective synthesis of isomeric [1,2,4]triazolo[4,3-*a*]pyrimidines.

4. Experimental

4.1. General

The melting points were determined in open capillary tubes in a Thiele apparatus and are uncorrected. IR spectra were recorded on a Varian Excalibur 3100 FT-IR spectrometer using a single reflection ATR system as a sampling accessory. ¹H and ¹³C NMR spectra were recorded on a Bruker DRX 500 instrument at 500 MHz and 125 MHz, respectively, and a Bruker Avance 600 instrument at 600 MHz (150 MHz for ¹³C) or Varian Unity 300 at 300 MHz (75 MHz for ¹³C) in DMSO-*d*₆ and using TMS as an internal standard. Mass spectra were recorded in the form of *m/z* (intensity relative to base 100) on a Finnigan MAT INCOS 50 instrument using electron impact ionization. UV spectra were obtained with a Specord UV-vis spectrophotometer in aqueous solutions. Elemental analyses were determined using a Perkin–Elmer 2400 Elemental Analyzer. HPLC analyses were performed on a Milichrom-5 chromatograph equipped with a Nucleosil-C₁₈ column (acetonitrile/water as the mobile phase) and a UV detector. Chromatographic purification of products was accomplished using column chromatography on Al₂O₃ 230–400 mesh.

Starting compounds **1a**,²⁵ **1b**,²⁶ and **7d**²⁷ were obtained by known methods. All other chemicals are commercially available.

4.2. (Z)-N-(5-Amino-1-phenyl-1H-1,2,4-triazol-3-yl)-3-(5-amino-1-phenyl-1H-1,2,4-triazol-3-ylamino)but-2-enamide (**9**)

Method A. A stirred mixture of triazole **1a** (1.00 g, 5.71 mmol) and ethyl acetoacetate **7a** (0.74 g, 5.71 mmol) was heated at 140–150 °C for 1 h, then diluted with ethanol (5 mL) and cooled to room temperature. The precipitate formed was filtered off and recrystallized from DMF–ethanol mixture (1:3) to give white-yellowish prisms (0.47 g, 40%) of **9**, mp 240–241.5 °C, lit.^{6a} mp 240–241 °C. IR (ATR) ν (cm^{−1}): 3432, 3387, 3247, 3102, 1634, 1612, 1577, 1551, 1511. ¹H NMR (300 MHz) δ : 2.30 (s, 3H, CH₃), 5.19 (br s, 1H, CH), 6.48 (s, 2H, NH₂), 6.54 (s, 2H, NH₂), 7.28–7.54 (m, 10H, 2Ph), 9.73 (s, 1H, NH), 11.52 (s, 1H, NH). ¹³C NMR (125 MHz) δ : 21.9 (CH₃), 91.0 (CH), 122.2, 122.4, 126.4, 126.5, 129.2, 129.4, 137.3, 137.4 (carbons of phenyls), 153.6, 153.8, 154.3, 154.3 (carbons of triazoles), 156.0 (C-3), 167.5 (CO). Anal. Calcd for C₂₀H₂₀N₁₀O: C, 57.68; H, 4.84; N, 33.63. Found: C, 57.71; H, 4.69; N, 33.34.

Method B. A mixture of triazole **1a** (1.00 g, 5.71 mmol), keto ester **7a** (0.74 g, 5.71 mmol), and xylene (5 mL) was heated to reflux for 5 h. Then xylene was evaporated to a volume of about 2 mL and the reaction mixture was cooled to room temperature. The precipitate formed was filtered off and recrystallized from DMF–ethanol mixture (1:3) to give **9** (0.67 g, 56%).

4.3. (2Z,2'Z)-Diethyl 3,3'-(1-phenyl-1H-1,2,4-triazole-3,5-diyl)bis(azanediyl)dibut-2-enoate (**4a**)

A magnetically stirred mixture of triazole **1a** (1.00 g, 5.71 mmol) and ethyl acetoacetate **7a** (2.96 g, 22.84 mmol) was heated at 140–150 °C for 1 h, then diluted with ethanol (5 mL) and cooled to room temperature. The precipitate formed was filtered off and recrystallized from ethanol to give colorless prisms (0.91 g, 40%) of **4a**, mp 121–122 °C, lit.^{6b} mp 120–122 °C. IR (ATR) ν (cm^{−1}): 3206, 3066, 2984, 2935, 1666, 1627, 1581, 1556, 1529. ¹H NMR (300 MHz) δ : 1.13, 1.19 (both t, *J* = 7.1 Hz, 3H each, OCH₂CH₃), 2.34, 2.35 (both s, 3H each, CH₃), 3.99, 4.08 (both q, *J* = 7.1 Hz, 2H each, OCH₂CH₃), 4.83, 4.98 (both s, 1H each, CH), 7.47–7.63 (m, 5H, Ph), 10.82 (s, 1H, NH), 11.09 (s, 1H, NH). ¹³C NMR (125 MHz) δ : 14.2, 14.3, 21.1, 21.3, 58.9, 59.2, 88.9, 92.1, 124.4, 128.8, 129.8, 135.5, 147.4, 155.4, 155.7, 156.7, 169.0, 169.3. MS (EI, 70 eV), *m/z* (%): 399 (M⁺, 62), 307 (100), 280 (27), 266 (21), 240 (29), 200 (20), 190 (28), 110 (16), 77 (53), 67 (14), 42 (10). Anal. Calcd for C₂₀H₂₅N₅O₄: C, 60.14; H, 6.31; N, 17.53. Found: C, 60.28; H, 6.35; N, 17.25.

4.4. General procedure for the synthesis of compounds **8a–g**

Method A. A solution of diaminotriazole **1a,b** (6 mmol) and appropriate β -keto ester **7a–f** (6.6 mmol) in EtOH (2 mL) or **7g** in MeOH (2 mL) was heated to reflux for 5 h, then water (5 mL) was added. After cooling, the precipitate formed was isolated by filtration and recrystallized from ethanol.

Method B. A solution of diaminotriazole **1a** (6 mmol) and appropriate β -keto ester **7a,e** (6.6 mmol) in 10 mL of tetrahydrofuran was heated to reflux for 5 h. Then the solution was evaporated to a volume of about 4 mL and the reaction mixture was diluted with water (5 mL). The precipitate formed was isolated by filtration and recrystallized from ethanol.

Method C. A mixture of compound **1a** (0.5 g, 2.85 mmol), keto ester **7a** (0.41 g, 3.14 mmol), and acetic acid (1 mL) was refluxed for 15 min, cooled to room temperature, diluted with water (5 mL), and extracted with chloroform (3 × 5 mL). The extract was evaporated to a volume of about 1 mL and subjected to a column chromatography (Al₂O₃, CHCl₃) to give compound **8a**.

4.4.1. Ethyl 3-(5-amino-1-phenyl-1H-1,2,4-triazol-3-ylamino)but-2-enoate (8a). Yield 1.03 g (60%, Method A, pure (Z)-isomer), 1.29 g (75%, Method B, mixture of (E,Z)-isomers), 0.12 g (15%, Method C, mixture of (E,Z)-isomers) of colorless plates. Mp 115–116 °C (pure (Z)-isomer). IR (ATR) for (Z)-isomer, ν (cm⁻¹): 3441, 3305, 3131, 2984, 1648, 1620, 1578, 1552, 1516. ¹H NMR for (Z)-isomer (300 MHz) δ : 1.18 (t, J =7.1 Hz, 3H, OCH₂CH₃), 2.32 (s, 3H, CH₃), 4.06 (q, J =7.1 Hz, 2H, OCH₂CH₃), 4.75 (s, 1H, CH), 6.57 (s, 2H, NH₂), 7.48–7.54 (m, 5H, Ph), 10.59 (s, 1H, NH). ¹³C NMR for the (E)-isomer (300 MHz) δ : 1.14 (t, J =7.1 Hz, 3H, OCH₂CH₃), 2.31 (s, 3H, CH₃), 3.90 (q, J =7.1 Hz, 2H, OCH₂CH₃), 6.31 (s, 1H, CH), 6.49 (s, 2H, NH₂), 7.28–7.35 (m, 5H, Ph), 9.09 (s, 1H, NH). ¹³C NMR (125 MHz) for the (Z)-stereoisomer δ : 14.4 (OCH₂CH₃), 21.5 (CH₃), 58.7 (OCH₂CH₃), 88.1 (C-2 of butenoate), 122.4, 126.7, 129.5, 137.3 (carbons of Ph), 153.9, 155.5 (carbons of triazole), 157.1 (C-3 of butenoate), 169.5 (CO). MS (EI, 70 eV) for the mixture of (E,Z)-stereoisomers, m/z (%): 287 (M⁺, 56), 241 (56), 214 (55), 200 (19), 123 (41), 119 (39), 105 (13), 96 (12), 91 (28), 77 (100), 68 (17), 51 (20), 43 (17). Anal. Calcd for C₁₄H₁₇N₅O₂: C, 58.52; H, 5.96; N, 24.37. Found: C, 58.74; H, 5.99; N, 24.25.

4.4.2. (Z)-Ethyl 2-(1-(5-amino-1-phenyl-1H-1,2,4-triazol-3-ylamino)-ethylidene)hexanoate (8b). Yield 0.82 g (40%, Method A) of colorless needles, mp 123–124 °C. IR (ATR) ν (cm⁻¹): 3444, 3422, 3288, 3163, 2964, 1620, 1573, 1545, 1499. ¹H NMR (600 MHz) δ : 0.88 (t, J =7.2 Hz, 3H, (CH₂)₃CH₃), 1.21 (t, J =7.1 Hz, 3H, OCH₂CH₃), 1.27–1.33 (m, 4H, CH₂(CH₂)₂CH₃), 2.24 (t, J =7.4 Hz, 2H, CH₂(CH₂)₂CH₃), 2.39 (s, 3H, CH₃), 4.10 (q, J =7.1 Hz, 2H, OCH₂CH₃), 6.49 (s, 2H, NH₂), 7.30 (t, J =7.2 Hz, 1H, Ph), 7.47 (m, 2H, Ph), 7.53 (d, J =7.7 Hz, 2H, Ph), 11.31 (s, 1H, NH). ¹³C NMR (150 MHz) δ : 13.8 (CH₃), 14.2 (CH₃), 16.7 (CH₃), 21.9 (CH₂), 26.0 (CH₂), 32.2 (CH₂), 59.0 (OCH₂CH₃), 98.5 (C-2 of hexanoate), 122.1, 126.3, 129.3, 137.2 (carbons of Ph), 153.6 (C-3 of hexanoate), 153.6, 156.0 (carbons of triazole), 169.9 (CO). MS (EI, 70 eV), m/z (%): 343 (M⁺, 16), 300 (74), 270 (11), 254 (44), 200 (39), 175 (100), 133 (28), 119 (33), 91 (74), 77 (85), 64 (23), 51 (32), 43 (44). Anal. Calcd for C₁₈H₂₅N₅O₂: C, 62.95; H, 7.34; N, 20.39. Found: C, 63.11; H, 7.30; N, 20.07.

4.4.3. (Z)-Ethyl 3-(5-amino-1-phenyl-1H-1,2,4-triazol-3-ylamino)-2-benzylbut-2-enoate (8c). Yield 0.91 g (40%, Method A) of colorless plates, mp 132–133 °C. IR (ATR) ν (cm⁻¹): 3430, 3300, 3106, 2984, 1640, 1613, 1576, 1543, 1491. ¹H NMR (500 MHz) δ : 1.14 (t, J =7.1 Hz, 3H, OCH₂CH₃), 2.40 (s, 3H, CH₃), 3.67 (s, 2H, CH₂), 4.09 (q, J =7.1 Hz, 2H, OCH₂CH₃), 6.53 (s, 2H, NH₂), 7.13–7.54 (m, 10H, 2Ph), 11.47 (s, 1H, NH). ¹³C NMR (125 MHz) δ : 14.1 (OCH₂CH₃), 17.2 (CH₃ of butenoate), 31.8 (CH₂Ph), 59.2 (OCH₂CH₃), 96.9 (C-2 of butenoate), 122.2, 125.5, 126.4, 127.5, 128.1, 129.3, 137.1, 141.6 (carbons of phenyl), 153.7, 155.3, 155.8 (carbons of triazole and C-3 of butenoate), 169.8 (CO). MS (EI, 70 eV), m/z (%): 377 (M⁺, 5), 286 (16), 200 (21), 176 (21), 144 (12), 135 (10), 128 (25), 119 (47), 91 (64), 77 (100), 65 (24), 51 (29), 43 (19). Anal. Calcd for C₁₈H₂₃N₅O₂: C, 66.83; H, 6.14; N, 18.55. Found: C, 66.60; H, 6.06; N, 18.78.

4.4.4. (Z)-Ethyl 3-(5-amino-1-phenyl-1H-1,2,4-triazol-3-ylamino)-2-(4-methylbenzyl)but-2-enoate (8d). Yield 0.96 g (41%, Method A) of yellowish needles, mp 142.5–144 °C. IR (ATR) ν (cm⁻¹): 3464, 3301, 3092, 2980, 1619, 1581, 1544, 1499. ¹H NMR (500 MHz) δ : 1.15 (t, J =7.1 Hz, 3H, OCH₂CH₃), 2.23 (s, 3H, CH₃), 2.39 (s, 3H, CH₃), 3.61 (s, 2H, CH₂), 4.08 (q, J =7.1 Hz, 2H, OCH₂CH₃), 6.52 (s, 2H, NH₂), 7.03–7.54 (m, 9H, Ar), 11.46 (s, 1H, NH). ¹³C NMR (125 MHz) δ : 14.1 (OCH₂CH₃), 17.1 (CH₃ of butenoate), 20.5 (CH₃ of methylbenzyl), 31.3 (CH₂ of methylbenzyl), 59.2 (OCH₂CH₃), 97.1 (C-2 of butenoate), 122.1, 126.4, 127.4, 128.7, 129.3, 134.3, 137.1, 138.5 (Ar), 153.7, 155.2, 155.8 (carbons of triazole and C-3 of butenoate), 169.8 (CO). MS (EI, 70 eV), m/z (%): 391 (M⁺, 15), 345 (22), 318 (22), 286 (30), 225 (11), 200 (27), 176 (21), 143 (14), 128 (20), 119 (39), 115 (14), 105 (40), 91 (39), 77 (100), 65 (25), 51 (31), 43 (25), 42 (20). Anal. Calcd

for C₂₂H₂₅N₅O₂: C, 67.50; H, 6.44; N, 17.89. Found: C, 67.69; H, 6.36; N, 17.57.

4.4.5. (E)-Ethyl 3-(5-amino-1-phenyl-1H-1,2,4-triazol-3-ylamino)-2-chlorobut-2-enoate (8e). Yield 1.1 g (57%, Method B) of yellowish needles, mp 144–146 °C. IR (ATR) ν (cm⁻¹): 3474, 3433, 3315, 3166, 2994, 1646, 1608, 1570, 1546, 1501. ¹H NMR (300 MHz) δ : 1.25 (t, J =7.1 Hz, 3H, OCH₂CH₃), 2.59 (s, 3H, CH₃), 4.19 (q, J =7.1 Hz, 2H, OCH₂CH₃), 6.65 (s, 2H, NH₂), 7.34–7.54 (m, 5H, Ph), 11.06 (s, 1H, NH). ¹³C NMR (125 MHz) δ : 14.1 (OCH₂CH₃), 18.3 (CH₃), 60.7 (OCH₂CH₃), 93.8 (C-2 of butenoate), 122.3, 126.7, 129.3, 136.9 (carbons of Ph), 153.8, 154.9, 155.1 (carbons of triazole and C-3 of butenoate), 166.2 (CO). MS (EI, 70 eV), m/z (%): 321 (M⁺, 17), 286 (40), 258 (17), 240 (47), 200 (12), 175 (15), 119 (27), 91 (26), 77 (100), 64 (18), 51 (46), 43 (39), 42 (26). Anal. Calcd for C₁₄H₁₆ClN₅O₂: C, 52.26; H, 5.01; N, 21.77. Found: C, 52.19; H, 5.11; N, 21.41.

4.4.6. (Z)-Ethyl 3-(5-amino-1-phenyl-1H-1,2,4-triazol-3-ylamino)-hex-2-enoate (8f). Yield 0.85 g (45%, Method A) of colorless plates, mp 153–154 °C. IR (ATR) ν (cm⁻¹): 3442, 3303, 3145, 2965, 1648, 1615, 1579, 1550, 1511. ¹H NMR (500 MHz) δ : 0.93 (t, J =7.3 Hz, 3H, CH₂CH₂CH₃), 1.20 (t, J =7.1 Hz, 3H, OCH₂CH₃), 1.57 (m, 2H, CH₂CH₂CH₃), 2.73 (t, J =7.6 Hz, 2H, CH₂CH₂CH₃), 4.08 (q, J =7.1 Hz, 2H, OCH₂CH₃), 4.86 (s, 1H, CH), 6.56 (s, 2H, NH₂), 7.31–7.55 (m, 5H, Ph), 10.59 (s, 1H, NH). ¹³C NMR (125 MHz) δ : 13.5 (CH₂CH₂CH₃), 14.3 (OCH₂CH₃), 21.1 (CH₂CH₂CH₃), 34.8 (CH₂CH₂CH₃), 58.6 (OCH₂CH₃), 87.5 (C-2 of hexenoate), 121.9, 126.3, 129.3, 137.1 (carbons of Ph), 153.7, 155.1, 160.5 (carbons of triazole and C-3 of hexenoate), 169.3 (CO). MS (EI, 70 eV), m/z (%): 315 (M⁺, 49), 287 (14), 270 (10), 254 (29), 242 (64), 228 (19), 212 (19), 200 (15), 187 (14), 175 (13), 160 (10), 134 (11), 119 (48), 105 (12), 91 (30), 77 (100), 68 (20), 51 (22), 43 (27), 41 (23), 39 (19). Anal. Calcd for C₁₆H₂₁N₅O₂: C, 60.94; H, 6.71; N, 22.21. Found: C, 61.14; H, 6.65; N, 22.05.

4.4.7. (Z)-Methyl 3-(5-amino-1-phenyl-1H-1,2,4-triazol-3-ylamino)-4-methylpent-2-enoate (8g). Yield 0.76 g (42%, Method A) of colorless plates, mp 156–157 °C. IR (ATR) ν (cm⁻¹): 3439, 3291, 3093, 2962, 1623, 1581, 1552, 1521, 1500. ¹H NMR (300 MHz) δ : 1.12 (m, 6H, 2CH₃), 3.59 (s, 3H, OCH₃), 3.85 (m, 1H, CH), 4.80 (s, 1H, CH), 6.60 (s, 2H, NH₂), 7.30–7.53 (m, 5H, Ph), 11.68 (s, 1H, NH). ¹³C NMR (125 MHz) δ : 21.1 (2CH₃), 28.4 (CH(CH₃)₂), 50.3 (OCH₃), 83.4 (C-2 of pentenoate), 122.2, 126.5, 129.3, 137.1 (carbons of Ph), 153.7, 155.0 (carbons of triazole), 167.1 (C-3 of pentenoate), 170.1 (CO). MS (EI, 70 eV), m/z (%): 301 (M⁺, 31), 254 (11), 242 (22), 119 (17), 93 (17), 91 (31), 77 (100), 68 (19), 65 (16), 59 (20), 51 (38), 43 (63), 42 (18), 41 (35). Anal. Calcd for C₁₅H₁₉N₅O₂: C, 59.79; H, 6.36; N, 23.24. Found: C, 59.64; H, 6.50; N, 23.48.

4.4.8. (Z)-Ethyl 3-(5-amino-1-benzyl-1H-1,2,4-triazol-3-ylamino)-but-2-enoate (8h). Yield 1.32 g (73%, Method A) of colorless plates, mp 137–138 °C. IR (ATR) ν (cm⁻¹): 3429, 3295, 3127, 2985, 1627, 1576, 1539, 1496. ¹H NMR (300 MHz) δ : 1.16 (t, J =7.1 Hz, 3H, OCH₂CH₃), 2.22 (s, 3H, CH₃), 4.03 (q, J =7.1 Hz, 2H, OCH₂CH₃), 4.66 (s, 1H, CH), 5.00 (s, 2H, CH₂), 6.49 (s, 2H, NH₂), 7.21–7.33 (m, 5H, Ph), 10.48 (s, 1H, NH). ¹³C NMR (125 MHz) δ : 14.7 (OCH₂CH₃), 21.6 (CH₃), 49.2 (CH₂Ph), 58.9 (OCH₂CH₃), 87.6 (C-2 of butenoate), 127.5, 127.7, 128.8, 137.4 (carbons of Ph), 155.11, 155.13, 157.6 (carbons of triazole and C-3 of butenoate), 169.6 (CO). MS (EI, 70 eV), m/z (%): 301 (M⁺, 21), 228 (12), 91 (100), 65 (16), 43 (19), 42 (13). Anal. Calcd for C₁₅H₁₉N₅O₂: C, 59.79; H, 6.36; N, 23.24. Found: C, 59.88; H, 6.33; N, 23.01.

4.4.9. (E)-Ethyl 3-(5-amino-1-benzyl-1H-1,2,4-triazol-3-ylamino)-2-chlorobut-2-enoate (8i). Yield 0.93 g (46%, Method A) of yellowish plates, mp 183–184 °C. IR (ATR) ν (cm⁻¹): 3414, 3312, 3146, 2990, 1619, 1572, 1521, 1495. ¹H NMR (500 MHz) δ : 1.24 (t, J =7.1 Hz, 3H,

OCH₂CH₃), 2.21 (s, 3H, CH₃), 4.17 (q, $J=7.1$ Hz, 2H, OCH₂CH₃), 5.03 (s, 2H, CH₂), 6.52 (s, 2H, NH₂), 7.22–7.36 (m, 5H, Ph), 10.93 (s, 1H, NH). ¹³C NMR (125 MHz) δ : 14.6 (OCH₂CH₃), 18.6 (CH₃), 49.2 (CH₂Ph), 61.0 (OCH₂CH₃), 93.4 (C-2 of butenoate), 127.7, 127.8, 128.8, 137.3 (carbons of Ph), 154.7, 155.2, 155.6 (carbons of triazole and C-3 of butenoate), 166.7 (CO). MS (EI, 70 eV), m/z (%): 335 (M⁺, 1.5), 91 (100), 65 (17), 43 (14), 39 (13). Anal. Calcd for C₁₅H₁₈ClN₅O₂: C, 53.65; H, 5.40; N, 20.86. Found: C, 53.81; H, 5.54; N, 20.63.

4.4.10. (Z)-Ethyl 3-(5-amino-1-benzyl-1H-1,2,4-triazol-3-ylamino)-hex-2-enoate (8j). Yield 1.07 g (54%, Method A) of colorless plates, mp 142–143 °C. IR (ATR) ν (cm⁻¹): 3449, 3297, 3127, 2961, 1641, 1615, 1590, 1543, 1521. ¹H NMR (600 MHz) δ : 0.82 (t, $J=6.9$ Hz, 3H, CH₃), 1.17 (t, $J=7.1$ Hz, 3H, OCH₂CH₃), 1.44 (m, 2H, CH₂), 2.62 (t, $J=7.2$ Hz, 2H, CH₂), 4.04 (q, $J=7.1$ Hz, 2H, OCH₂CH₃), 4.66 (s, 1H, CH), 5.01 (s, 2H, CH₂), 6.43 (s, 2H, NH₂), 7.22–7.33 (m, 5H, Ph), 10.44 (s, 1H, NH). ¹³C NMR (150 MHz) δ : 13.5 (CH₃), 14.3 (CH₃), 21.1 (CH₂), 34.7 (CH₂), 48.9 (CH₂Ph), 58.5 (OCH₂CH₃), 86.7 (C-2 of hexenoate), 127.30, 127.35, 128.3, 137.0 (carbons of Ph), 154.4 (C-3 of triazole), 154.7 (C-5 of triazole), 160.9 (C-3 of hexenoate), 169.3 (CO). MS (EI, 70 eV), m/z (%): 329 (M⁺, 23), 301 (11), 256 (24), 238 (11), 91 (100). Anal. Calcd for C₁₇H₂₃N₅O₂: C, 61.99; H, 7.04; N, 21.26. Found: C, 62.21; H, 7.22; N, 20.95.

4.5. (2Z,2'Z)-Diethyl 3,3'-(1-phenyl-1H-1,2,4-triazole-3,5-diyl)bis(azanediyldibut-2-enoate (4a), ethyl 3-(5-amino-1-phenyl-1H-1,2,4-triazol-3-ylamino)but-2-enoate (8a), (E)-N-(5-amino-1-phenyl-1H-1,2,4-triazol-3-yl)-3-(5-amino-1-phenyl-1H-1,2,4-triazol-3-ylamino)but-2-enamide (9)

A mixture of triazole **1a** (1.00 g, 5.71 mmol) and ethyl acetate **7a** (1.11 g, 8.57 mmol) was heated at 100–105 °C and stirring for 60 h, then cooled to room temperature and diluted with 1,2-dichloroethane (10 mL). The precipitate formed was filtered off and dried at 100 °C to give crude compound **9** (400 mg, 40%). An analytical sample was obtained by crystallization of crude **9** from DMF–ethanol mixture (1:3). The mother liquor was concentrated in vacuo giving a residue, which was subjected to a column chromatography (Al₂O₃, CHCl₃) to give product **4a** (336 mg, 15%) with $R_f=0.98$ and product **8a** (410 mg, 25%) with $R_f=0.3$.

4.6. General procedures for the synthesis of compounds 10a–i and 11a–j

Method A. A magnetically stirred mixture of triazole **1a,b** (2.85 mmol), compound **7a–h** (3.14 mmol) and acetic acid (2 mL) was heated to reflux for 15 min, then acetic acid was distilled off until the temperature of the reaction mixture raised to 145–150 °C. The reaction mixture was heated at the same temperature and stirred for 5 h, cooled to room temperature, dissolved in chloroform and subjected to a column chromatography (Al₂O₃, CHCl₃) to give products **10a–d, f–i**, and **11a–j**.

Method B. Compound **8a–hj** (2 mmol) was added to a solution of sodium (0.14 g, 6.0 mmol) in absolute EtOH or MeOH (10 mL). The resultant mixture was heated to reflux for 20 min, cooled to room temperature and neutralized by addition of acetic acid. Then solvent was evaporated to a volume of about 1 mL and the resultant solution was diluted with water (5 mL) to give product **10a–i**. Samples for elemental analysis were obtained by crystallization of crude products from ethanol.

Method C. A magnetically stirred mixture of compound **10a** (400 mg, 1.66 mmol) and acetic acid (0.4 mL) in a glass ampoule placed in oil bath was heated at 150–160 °C for 10 h. After cooling to room temperature the ampoule was unsealed (caution: excessive pressure!) and the reaction mixture was diluted with DMF to

a volume of 5 mL. According to HPLC analysis, the yield of **11a** was 18% and the compound **10a** was absent in the reaction mixture. DMF solution (4 mL) was evaporated to dryness at reduced pressure and the residue was extracted with hot chloroform (5 mL). The extract was subjected to a column chromatography (Al₂O₃, CHCl₃) to give 48 mg (yield 15%) of compound **11a**.

Method D. A solution of NaOH (90 mg, 2.25 mmol) in water (8 mL) was added to a magnetically stirred suspension of compound **14** (400 mg, 1.13 mmol) in ethanol (15 mL) and the resulted mixture was heated to reflux for 20 min, then cooled to room temperature and neutralized by addition of acetic acid. Then the resultant solution was evaporated to a volume of about 8 mL and diluted with cold water (10 mL) to give 210 mg (78%) of pure compound **11a**.

Method E. A solution of NaOH (96 mg, 2.40 mmol) in water (8 mL) was added to a magnetically stirred suspension of compound **4a** (400 mg, 1.00 mmol) in ethanol (15 mL). The resulted mixture was heated to reflux for 20 min, then treated by analogy with method D to give 121 mg (50%) of pure compound **11a**.

4.6.1. 3-Amino-7-methyl-5-oxo-2-phenyl-5H-[1,2,4]triazolo[4,3-a]pyrimidin-2-ium-8-ide (10a). Yield 69 mg (10%, Method A), 352 mg (73%, Method B) of colorless plates, mp 210–211 °C; $R_f=0.15$. IR (ATR) ν (cm⁻¹): 3293, 2889, 1687, 1655, 1588, 1503. UV, λ_{max} , nm ($\epsilon \cdot 10^{-3}$): 234 (22.1) and 344 (11.3). ¹H NMR (300 MHz) δ : 2.12 (s, 3H, CH₃), 5.20 (s, 1H, CH), 7.49–7.65 (m, 5H, Ph), 8.38 (s, 2H, NH₂). ¹³C NMR (75 MHz) δ : 24.7 (CH₃), 90.4 (C-6), 124.5, 128.9, 129.5, 134.8 (carbons of Ph), 143.3 (C-3), 151.9 (C-8a), 159.5 (CO), 169.1 (C-7). MS (EI, 70 eV), m/z (%): 241 (M⁺, 91), 212 (11), 123 (33), 119 (44), 105 (16), 94 (23), 91 (22), 77 (100), 68 (21), 64 (20), 51 (57), 42 (17), 39 (69). Anal. Calcd for C₁₂H₁₁N₅O: C, 59.74; H, 4.60; N, 29.03. Found: C, 59.87; H, 4.47; N, 29.21.

4.6.2. 3-Amino-6-butyl-7-methyl-5-oxo-2-phenyl-5H-[1,2,4]triazolo[4,3-a]pyrimidin-2-ium-8-ide (10b). Yield 161 mg (19%, Method A), 363 mg (61%, Method B) of colorless needles, mp 201–202 °C; $R_f=0.21$. IR (ATR) ν (cm⁻¹): 3199, 2923, 1660, 1582, 1492. UV, λ_{max} , nm ($\epsilon \cdot 10^{-3}$): 238 (22.6) and 348 (10.4). ¹H NMR (600 MHz) δ : 0.90 (t, $J=7.2$ Hz, 3H, (CH₂)₃CH₃), 1.29–1.40 (m, 4H, 2CH₂), 2.20 (s, 3H, CH₃), 2.35 (t, $J=7.4$ Hz, 2H, CH₂), 7.47–7.66 (m, 5H, Ph), 8.45 (br s, 2H, NH₂). ¹³C NMR (150 MHz) δ : 13.9 (CH₃), 22.1 (CH₂), 22.6 (CH₃), 24.2 (CH₂), 31.3 (CH₂), 102.0 (C-6), 124.1, 128.6, 129.5, 135.1 (carbons of phenyl), 143.1 (C-3), 149.9 (C-8a), 159.3 (CO), 165.3 (C-7). MS (EI, 70 eV), m/z (%): 297 (M⁺, 14), 254 (100), 200 (34), 119 (24), 91 (20), 77 (79), 65 (22), 55 (12), 53 (21), 51 (30), 43 (20), 39 (29). Anal. Calcd for C₁₆H₁₉N₅O: C, 64.63; H, 6.44; N, 23.55. Found: C, 64.47; H, 6.53; N, 23.28.

4.6.3. 3-Amino-6-benzyl-7-methyl-5-oxo-2-phenyl-5H-[1,2,4]triazolo[4,3-a]pyrimidin-2-ium-8-ide (10c). Yield 104 mg (11%, Method A), 616 mg (93%, Method B) of colorless needles, mp 202–203 °C; $R_f=0.23$. IR (ATR) ν (cm⁻¹): 3286, 2904, 1658, 1586, 1491. UV, λ_{max} , nm ($\epsilon \cdot 10^{-3}$): 238 (24.7) and 344 (11.1). ¹H NMR (500 MHz) δ : 2.14 (s, 3H, CH₃), 3.75 (s, 2H, CH₂), 7.12–7.26 (m, 5H, Ph), 7.50–7.67 (m, 5H, Ph), 8.45 (br s, 2H, NH₂). ¹³C NMR (125 MHz) δ : 23.2 (CH₃), 29.8 (CH₂), 100.7 (C-6), 124.4, 125.5, 127.8, 128.1, 128.9, 129.5, 135.0, 141.6 (carbons of phenyls), 143.2 (C-3), 150.4 (C-8a), 159.5 (CO), 166.7 (C-7). MS (EI, 70 eV), m/z (%): 331 (M⁺, 26), 211 (11), 200 (12), 143 (11), 134 (14), 128 (19), 119 (31), 115 (12), 103 (12), 91 (56), 77 (100), 67 (15), 65 (29), 51 (48), 42 (17), 39 (24). Anal. Calcd for C₁₉H₁₇N₅O: C, 68.87; H, 5.17; N, 21.13. Found: C, 69.05; H, 5.13; N, 21.01.

4.6.4. 3-Amino-7-methyl-6-(4-methylbenzyl)-5-oxo-2-phenyl-5H-[1,2,4]triazolo[4,3-a]pyrimidin-2-ium-8-ide (10d). Yield 226 mg (23%, Method A), 553 mg (80%, Method B) of yellowish needles, mp 211.5–212.5 °C; $R_f=0.24$. IR (ATR) ν (cm⁻¹): 3199, 3054, 2920, 1666, 1580, 1492. UV, λ_{max} , nm ($\epsilon \cdot 10^{-3}$): 220 sh (19.9), 238 (23.8), and 347

(10.6). ^1H NMR (300 MHz) δ : 2.12 (s, 3H, CH₃), 2.24 (s, 3H, CH₃), 3.70 (s, 2H, CH₂), 7.05 (d, $J=7.9$ Hz, 2H, Ar), 7.11 (d, $J=7.9$ Hz, 2H, Ar), 7.49–7.68 (m, 5H, Ph), 8.43 (br s, 2H, NH₂). ^{13}C NMR (150 MHz) δ : 20.6 (CH₃), 23.2 (CH₃), 29.4 (CH₂), 101.0 (C-6), 124.4, 127.7, 128.7, 128.9, 129.6, 134.3, 135.0, 138.5 (carbons of benzene rings), 143.2 (C-3), 150.3 (C-8a), 159.6 (CO), 167.0 (C-7). MS (EI, 70 eV), m/z (%): 345 (M^+ , 24), 225 (11), 200 (14), 143 (13), 134 (16), 128 (20), 119 (32), 115 (19), 105 (38), 91 (32), 77 (100), 67 (16), 65 (28), 51 (41), 42 (15), 39 (28). Anal. Calcd for $\text{C}_{20}\text{H}_{19}\text{N}_5\text{O}$: C, 69.55; H, 5.54; N, 20.28. Found: C, 69.78; H, 5.66; N, 20.41.

4.6.5. 3-Amino-6-chloro-7-methyl-5-oxo-2-phenyl-5H-[1,2,4]triazolo[4,3-*a*]pyrimidin-2-ium-8-ide (10e). Yield 629 mg (80%, Method B) of yellowish prisms, mp 260–262 °C; $R_f=0.16$. IR (ATR) ν (cm^{-1}): 3348, 3244, 3212, 3064, 1680, 1647, 1587, 1483. UV, λ_{max} , nm ($\epsilon \cdot 10^{-3}$): 238 (23.8) and 347 (10.4). ^1H NMR (500 MHz) δ : 2.31 (s, 3H, CH₃), 7.52–7.64 (m, 5H, Ph), 8.40 (s, 2H, NH₂). ^{13}C NMR (125 MHz) δ : 24.3 (CH₃), 96.8 (C-6), 125.3, 129.8, 130.1, 135.0 (carbons of Ph), 143.6 (C-3), 150.1 (C-8a), 155.2 (CO), 165.7 (C-7). MS (EI, 70 eV), m/z (%): 275 (94), 200 (20), 119 (50), 91 (17), 77 (100), 67 (14), 64 (15), 51 (37), 39 (17). Anal. Calcd for $\text{C}_{12}\text{H}_{10}\text{ClN}_5\text{O}$: C, 52.28; H, 3.66; N, 25.40. Found: C, 51.98; H, 3.51; N, 25.43.

4.6.6. 3-Amino-5-oxo-2-phenyl-7-propyl-5H-[1,2,4]triazolo[4,3-*a*]pyrimidin-2-ium-8-ide (10f). Yield 92 mg (12%, Method A), 420 mg (78%, Method B) of colorless needles, mp 147 °C dec; $R_f=0.16$. IR (ATR) ν (cm^{-1}): 3303, 2961, 1678, 1597, 1537, 1520. UV, λ_{max} , nm ($\epsilon \cdot 10^{-3}$): 234 (24.1) and 336 (10.7). ^1H NMR (500 MHz) δ : 0.91 (t, $J=7.4$ Hz, 3H, CH₃), 1.63 (m, 2H, CH₂), 2.35 (t, $J=7.5$ Hz, 2H, CH₂), 5.20 (s, 1H, CH), 7.49–7.67 (m, 5H, Ph), 8.37 (br s, 2H, NH₂). ^{13}C NMR (125 MHz) δ : 14.1 (CH₃), 21.7 (CH₂), 40.5 (CH₂), 90.5 (C-6), 124.9, 129.3, 130.0, 135.4 (carbons of Ph), 143.8 (C-3), 152.5 (C-8a), 160.2 (CO), 173.2 (C-7). MS (EI, 70 eV), m/z (%): 269 (M^+ , 13), 254 (14), 241 (100), 212 (15), 119 (27), 93 (30), 77 (98), 67 (19), 65 (20), 51 (37), 43 (18), 39 (44). Anal. Calcd for $\text{C}_{14}\text{H}_{15}\text{N}_5\text{O}$: C, 62.44; H, 5.61; N, 26.01. Found: C, 62.57; H, 5.49; N, 25.73.

4.6.7. 3-Amino-7-isopropyl-5-oxo-2-phenyl-5H-[1,2,4]triazolo[4,3-*a*]pyrimidin-2-ium-8-ide (10g). Yield 207 mg (27%, Method A), 463 mg (86%, Method B) of colorless prisms, mp 149 °C dec; $R_f=0.18$. IR (ATR) ν (cm^{-1}): 3279, 2964, 1678, 1649, 1585, 1533, 1502. UV, λ_{max} , nm ($\epsilon \cdot 10^{-3}$): 234 (22.9) and 335 (8.6). ^1H NMR (300 MHz) δ : 1.15 (d, $J=6.6$ Hz, 6H, 2CH₃), 2.62 (m, 1H, CH of *i*-Pr), 5.22 (s, 1H, CH), 7.50–7.66 (m, 5H, Ph), 8.37 (br s, 2H, NH₂). ^{13}C NMR (150 MHz) δ : 21.5 (2CH₃), 36.2 (CH), 88.1 (C-6), 124.6, 129.1, 129.6, 135.9 (carbons of Ph), 143.2 (C-3), 152.3 (C-8a), 160.1 (CO), 178.0 (C-7). MS (EI, 70 eV), m/z (%): 269 (M^+ , 23), 254 (33), 241 (24), 119 (18), 105 (13), 93 (19), 91 (18), 77 (100), 67 (17), 65 (19), 53 (17), 51 (38), 43 (19), 41 (30), 39 (28). Anal. Calcd for $\text{C}_{14}\text{H}_{15}\text{N}_5\text{O}$: C, 62.44; H, 5.61; N, 26.01. Found: C, 62.21; H, 5.52; N, 25.71.

4.6.8. 3-Amino-2-benzyl-7-methyl-5-oxo-5H-[1,2,4]triazolo[4,3-*a*]pyrimidin-2-ium-8-ide (10h). Yield 81 mg (10%, Method A), 424 mg (83%, Method B) of colorless plates, mp 191–193 °C; $R_f=0.10$. IR (ATR) ν (cm^{-1}): 3283, 3081, 1657, 1583, 1538, 1516. UV, λ_{max} , nm ($\epsilon \cdot 10^{-3}$): 225 (17.0), 264 (4.7), and 330 (10.6). ^1H NMR (500 MHz) δ : 2.08 (s, 3H, CH₃), 5.15 (s, 1H, CH), 5.23 (s, 2H, CH₂), 7.31–7.39 (m, 5H, Ph), 8.40 (s, 2H, NH₂). ^{13}C NMR (125 MHz) δ : 25.2 (CH₃), 49.8 (CH₂), 90.6 (C-6), 128.15, 128.30, 128.97, 135.3 (carbons of Ph), 143.7 (C-3), 152.4 (C-8a), 159.5 (CO), 169.4 (C-7). MS (EI, 70 eV), m/z (%): 255 (M^+ , 0.8), 91 (100), 68 (19), 65 (45), 51 (15), 39 (67). Anal. Calcd for $\text{C}_{13}\text{H}_{13}\text{N}_5\text{O}$: C, 61.17; H, 5.13; N, 27.43. Found: C, 61.33; H, 5.21; N, 27.09.

4.6.9. 3-Amino-2-benzyl-5-oxo-7-propyl-5H-[1,2,4]triazolo[4,3-*a*]pyrimidin-2-ium-8-ide (10i). Yield 113 mg (14%, Method A), 448 mg

(79%, Method B) of colorless plates, mp 179–179.5 °C; $R_f=0.17$. IR (ATR) ν (cm^{-1}): 3244, 3107, 2962, 1652, 1583, 1538, 1511. UV, λ_{max} , nm ($\epsilon \cdot 10^{-3}$): 225 (18.4), 264 (4.5), and 329 (10.1). ^1H NMR (600 MHz) δ : 0.86 (t, $J=6.6$ Hz, 3H, CH₃), 1.58 (m, 2H, CH₂), 2.29 (t, $J=6.6$ Hz, 2H, CH₂), 5.14 (s, 1H, CH), 5.22 (s, 2H, CH₂), 7.20–7.33 (m, 5H, Ph), 8.39 (br s, 2H, NH₂). ^{13}C NMR (150 MHz) δ : 13.7 (CH₃), 21.2 (CH₂), 40.1 (CH₂), 49.5 (CH₂), 89.8 (C-6), 127.86, 127.91, 128.6, 134.8 (carbons of Ph), 143.3 (C-3), 152.1 (C-8a), 159.3 (CO), 172.5 (C-7). MS (EI, 70 eV), m/z (%): 283 (M^+ , 3), 91 (100), 65 (21), 39 (17). Anal. Calcd for $\text{C}_{15}\text{H}_{17}\text{N}_5\text{O}$: C, 63.59; H, 6.05; N, 24.72. Found: C, 63.81; H, 6.11; N, 24.47.

4.6.10. 3-Amino-7-methyl-1-phenyl-[1,2,4]triazolo[4,3-*a*]pyrimidin-5(1H)-one (11a). Yield 144 mg (21%) of colorless needles, mp 176–177 °C; $R_f=0.75$. IR (ATR) ν (cm^{-1}): 3424, 3262, 3200, 3143, 1702, 1678, 1656, 1581, 1499. UV, λ_{max} , nm ($\epsilon \cdot 10^{-3}$): 227 (9.8), 270 (4.1), and 331 (12.6). ^1H NMR (300 MHz) δ : 2.25 (s, 3H, CH₃), 5.74 (s, 1H, CH), 7.13 (s, 2H, NH₂), 7.26 (m, 1H, Ph), 7.50 (m, 2H, Ph), 8.07 (m, 2H, Ph). ^{13}C NMR (75 MHz) δ : 24.2 (CH₃), 99.0 (C-6), 119.1, 125.3, 128.9, 137.0 (carbons of Ph), 146.1, 146.2 (carbons of triazole), 158.6 (CO), 167.3 (C-7). MS (EI, 70 eV), m/z (%): 241 (M^+ , 51), 133 (18), 126 (32), 109 (74), 103 (26), 91 (100), 77 (64), 68 (25), 64 (31), 51 (39), 39 (51). Anal. Calcd for $\text{C}_{12}\text{H}_{11}\text{N}_5\text{O}$: C, 59.74; H, 4.60; N, 29.03. Found: C, 59.50; H, 4.71; N, 29.19.

4.6.11. 3-Amino-6-butyl-7-methyl-1-phenyl-[1,2,4]triazolo[4,3-*a*]pyrimidin-5(1H)-one (11b). Yield 397 mg (35%) of colorless needles, mp 155–156 °C; $R_f=0.89$. IR (ATR) ν (cm^{-1}): 3429, 3284, 2951, 1701, 1667, 1577, 1484. UV, λ_{max} , nm ($\epsilon \cdot 10^{-3}$): 220 (10.5), 275 (6.1), and 349 (17.1). ^1H NMR (300 MHz) δ : 0.90 (t, $J=7.0$ Hz, 3H, (CH₂)₃CH₃), 1.36 (m, 4H, 2CH₂), 2.31 (s, 3H, CH₃), 2.42 (t, $J=7.3$ Hz, 2H, CH₂), 7.16 (s, 2H, NH₂), 7.23 (m, 1H, Ph), 7.48 (m, 2H, Ph), 8.08 (m, 2H, Ph). ^{13}C NMR (125 MHz) δ : 13.8 (CH₂)₃CH₃, 22.0 (CH₂), 22.4 (CH₂), 24.3 (CH₃), 30.5 (CH₂), 110.8 (C-6), 118.4, 124.8, 128.8, 137.2 (carbons of Ph), 143.9, 145.8 (carbons of triazole), 158.7 (CO), 162.6 (C-7). MS (EI, 70 eV), m/z (%): 297 (M^+ , 36), 254 (100), 77 (67), 67 (15), 55 (14), 51 (31), 43 (23), 41 (35), 39 (30). Anal. Calcd for $\text{C}_{16}\text{H}_{19}\text{N}_5\text{O}$: C, 64.63; H, 6.44; N, 23.55. Found: C, 64.87; H, 6.28; N, 23.69.

4.6.12. 3-Amino-6-benzyl-7-methyl-1-phenyl-[1,2,4]triazolo[4,3-*a*]pyrimidin-5(1H)-one (11c). Yield 397 mg (42%) of colorless needles, mp 223–224 °C; $R_f=0.87$. IR (ATR) ν (cm^{-1}): 3436, 3290, 1670, 1577, 1483. UV, λ_{max} , nm ($\epsilon \cdot 10^{-3}$): 220 sh (15.1), 273 (6.9), and 349 (18.1). ^1H NMR (300 MHz) δ : 2.27 (s, 3H, CH₃), 3.81 (s, 2H, CH₂), 7.15–7.27 (m, 8H, NH₂, and Ar), 7.49 (m, 2H, Ar), 8.09 (m, 2H, Ar). ^{13}C NMR (125 MHz) δ : 23.0 (CH₃), 29.9 (CH₂), 109.7 (C-6), 118.8, 125.2, 125.8, 128.0, 128.3, 129.0, 137.3, 140.4 (carbons of phenyls), 144.4, 146.1 (carbons of triazole), 159.2 (CO), 164.0 (C-7). MS (EI, 70 eV), m/z (%): 331 (M^+ , 69), 254 (36), 226 (23), 128 (26), 115 (13), 105 (14), 103 (17), 91 (91), 77 (100), 67 (19), 65 (26), 51 (55), 42 (12), 39 (23). Anal. Calcd for $\text{C}_{19}\text{H}_{17}\text{N}_5\text{O}$: C, 68.87; H, 5.17; N, 21.13. Found: C, 69.09; H, 5.29; N, 20.87.

4.6.13. 3-Amino-7-methyl-6-(4-methylbenzyl)-1-phenyl-[1,2,4]triazolo[4,3-*a*]pyrimidin-5(1H)-one (11d). Yield 226 mg (23%) of yellowish needles, mp 221–222 °C; $R_f=0.89$. IR (ATR) ν (cm^{-1}): 3432, 3309, 1667, 1577, 1503, 1479. UV, λ_{max} , nm ($\epsilon \cdot 10^{-3}$): 220 sh (18.4), 276 (7.5), and 348 (18.1). ^1H NMR (300 MHz) δ : 2.23 (s, 3H, CH₃), 2.52 (s, 3H, CH₃), 3.75 (s, 2H, CH₂), 7.03–7.12 (m, 4H, Ar), 7.19 (s, 2H, NH₂), 7.24 (m, 1H, Ph), 7.49 (m, 2H, Ph), 8.09 (m, 2H, Ph). ^{13}C NMR (75 MHz) δ : 20.5 (CH₃), 22.8 (CH₃), 29.4 (CH₂), 109.8 (C-6), 118.7, 125.0, 127.8, 128.7, 128.9, 134.6, 137.11, 137.14 (carbons of benzene rings), 144.3, 146.0 (carbons of triazole), 159.0 (CO), 163.8 (C-7). MS (EI, 70 eV), m/z (%): 345 (M^+ , 80), 330 (20), 275 (10), 254 (39), 241 (19), 226 (34), 200 (12), 143 (20), 128 (38), 115 (31), 105 (61), 91 (66), 77 (100), 67 (28), 51

(61), 43 (18), 39 (36). Anal. Calcd for $C_{20}H_{19}N_5O$: C, 69.55; H, 5.54; N, 20.28. Found: C, 69.39; H, 5.69; N, 20.36.

4.6.14. 3-Amino-6-chloro-7-methyl-1-phenyl-[1,2,4]triazolo[4,3-*a*]pyrimidin-5(1*H*)-one (**11e**). Yield 102 mg (13%) of yellowish needles, mp 164–165 °C; $R_f=0.82$. IR (ATR) ν (cm^{-1}): 3426, 3412, 3284, 1705, 1685, 1674, 1653, 1580, 1502, 1481. UV, λ_{max} , nm ($\epsilon \cdot 10^{-3}$): 231 (10.8), 274 (5.9), and 347 (14.6). 1H NMR (300 MHz) δ : 2.41 (s, 3H, CH₃), 7.18 (s, 2H, NH₂), 7.28 (m, 1H, Ph), 7.51 (m, 2H, Ph), 8.05 (m, 2H, Ph). ^{13}C NMR (125 MHz) δ : 23.3 (CH₃), 105.2 (C-6), 119.0, 125.6, 129.0, 136.7 (carbons of Ph), 143.8, 145.7 (carbons of triazole), 154.3 (CO), 162.6 (C-7). MS (EI, 70 eV), m/z (%): 275 (M^+ , 59), 170 (14), 128 (11), 103 (10), 91 (28), 77 (100), 73 (12), 68 (25), 64 (24), 51 (74), 42 (19), 39 (49). Anal. Calcd for $C_{12}H_{10}ClN_5O$: C, 52.28; H, 3.66; N, 25.40. Found: C, 52.01; H, 3.61; N, 25.65.

4.6.15. 3-Amino-1-phenyl-7-propyl-[1,2,4]triazolo[4,3-*a*]pyrimidin-5(1*H*)-one (**11f**). Yield 161 mg (21%) of colorless needles, mp 118–120 °C; $R_f=0.76$. IR (ATR) ν (cm^{-1}): 3421, 3262, 3196, 3143, 2960, 1711, 1687, 1583, 1496. UV, λ_{max} , nm ($\epsilon \cdot 10^{-3}$): 227 (12.4), 270 (4.8), and 337 (14.8). 1H NMR (300 MHz) δ : 0.91 (t, $J=7.4$ Hz, 3H, CH₃), 1.67 (m, 2H, CH₂), 2.45 (m, 2H, CH₂), 5.72 (s, 1H, CH), 7.13 (s, 2H, NH₂), 7.24 (m, 1H, Ph), 7.49 (m, 2H, Ph), 8.08 (m, 2H, Ph). ^{13}C NMR (125 MHz) δ : 13.5 (CH₃), 21.0 (CH₂), 39.2 (CH₂), 98.7 (C-6), 118.9, 125.2, 128.9, 137.0 (carbons of Ph), 146.16, 146.22 (carbons of triazole), 158.9 (CO), 170.7 (C-7). MS (EI, 70 eV), m/z (%): 269 (M^+ , 77), 254 (31), 241 (100), 137 (13), 91 (45), 77 (79), 67 (33), 51 (48), 39 (62). Anal. Calcd for $C_{14}H_{15}N_5O$: C, 62.44; H, 5.61; N, 26.01. Found: C, 62.18; H, 5.50; N, 26.18.

4.6.16. 3-Amino-7-isopropyl-1-phenyl-[1,2,4]triazolo[4,3-*a*]pyrimidin-5(1*H*)-one (**11g**). Yield 292 mg (38%) of colorless plates, mp 143–144 °C; $R_f=0.75$. IR (ATR) ν (cm^{-1}): 3419, 3363, 3294, 2962, 1698, 1650, 1578, 1497. UV, λ_{max} , nm ($\epsilon \cdot 10^{-3}$): 226 (10.1), 270 (4.1), and 336 (11.8). 1H NMR (300 MHz) δ : 1.20 (d, $J=6.9$ Hz, 6H, 2CH₃), 2.77 (m, 1H, CH), 5.75 (s, 1H, CH), 7.14 (s, 2H, NH₂), 7.25 (m, 1H, Ph), 7.51 (m, 2H, Ph), 8.11 (m, 2H, Ph). ^{13}C NMR (125 MHz) δ : 21.3 (2CH₃), 35.4 (CH of *i*-Pr), 96.7 (C-6), 118.7, 125.1, 128.9, 137.1 (carbons of Ph), 146.12, 146.27 (carbons of triazole), 159.1 (CO), 175.7 (C-7). MS (EI, 70 eV), m/z (%): 269 (M^+ , 79), 254 (38), 241 (46), 91 (44), 77 (100), 67 (41), 41 (45), 39 (43). Anal. Calcd for $C_{14}H_{15}N_5O$: C, 62.44; H, 5.61; N, 26.01. Found: C, 62.22; H, 5.74; N, 25.78.

4.6.17. 3-Amino-1-benzyl-7-methyl-[1,2,4]triazolo[4,3-*a*]pyrimidin-5(1*H*)-one (**11h**). Yield 146 mg (20%) of colorless plates, mp 188–188.5 °C; $R_f=0.50$. IR (ATR) ν (cm^{-1}): 3391, 3293, 1673, 1648, 1579, 1506. UV, λ_{max} , nm ($\epsilon \cdot 10^{-3}$): 229 (12.6), 257 (4.8), and 325 (11.1). 1H NMR (300 MHz) δ : 2.19 (s, 3H, CH₃), 5.11 (s, 2H, CH₂), 5.56 (s, 1H, CH), 6.86 (s, 2H, NH₂), 7.29–7.34 (m, 5H, Ph). ^{13}C NMR (125 MHz) δ : 24.2 (CH₃), 48.8 (CH₂), 96.8 (C-6), 127.8 (3C of Ph), 128.6 (2C of Ph), 135.9 (1C of Ph), 146.0 (C-3), 147.7 (C-8a), 158.8 (CO), 167.8 (C-7). MS (EI, 70 eV), m/z (%): 255 (M^+ , 19), 94 (14), 91 (100), 65 (10), 39 (17). Anal. Calcd for $C_{13}H_{13}N_5O$: C, 61.17; H, 5.13; N, 27.43. Found: C, 61.34; H, 5.24; N, 27.09.

4.6.18. 3-Amino-1-benzyl-7-propyl-[1,2,4]triazolo[4,3-*a*]pyrimidin-5(1*H*)-one (**11i**). Yield 226 mg (28%) of yellowish plates, mp 181–182 °C; $R_f=0.56$. IR (ATR) ν (cm^{-1}): 3355, 3267, 3224, 2961, 1662, 1596, 1499. UV, λ_{max} , nm ($\epsilon \cdot 10^{-3}$): 230 (12.0), 258 (4.2), and 327 (9.2). 1H NMR (600 MHz) δ : 0.89 (t, $J=7.4$ Hz, 3H, CH₃), 1.60–1.66 (m, 2H, CH₂), 2.41 (t, $J=7.4$ Hz, 2H, CH₂), 5.12 (s, 2H, CH₂), 5.54 (s, 1H, CH), 6.84 (s, 2H, NH₂), 7.27–7.34 (m, 5H, Ph). ^{13}C NMR (150 MHz) δ : 13.5 (CH₃), 21.1 (CH₂), 39.3 (CH₂), 48.8 (CH₂), 96.3 (C-6), 127.75, 127.78, 128.5, 135.9 (carbons of Ph), 145.9 (C-3), 147.8 (C-8a), 158.9 (CO), 171.2 (C-7). MS (EI, 70 eV), m/z (%): 283 (M^+ , 31), 255 (46), 91

(100), 65 (16), 39 (14). Anal. Calcd for $C_{15}H_{17}N_5O$: C, 63.59; H, 6.05; N, 24.72. Found: C, 63.59; H, 6.10; N, 24.59.

4.6.19. 3-Amino-1-phenyl-7-(trifluoromethyl)-[1,2,4]triazolo[4,3-*a*]pyrimidin-5(1*H*)-one (**11j**). Yield 118 mg (14%) of colorless needles, mp 176–177 °C; $R_f=0.85$. IR (ATR) ν (cm^{-1}): 3449, 3347, 3068, 1709, 1654, 1595, 1577, 1513. UV, λ_{max} , nm ($\epsilon \cdot 10^{-3}$): 233 (10.6), 272 (4.9), and 353 (10.8). 1H NMR (300 MHz) δ : 6.28 (s, 1H, CH), 7.24 (s, 2H, NH₂), 7.33 (m, 1H, Ph), 7.55 (m, 2H, Ph), 8.01 (m, 2H, Ph). ^{13}C NMR (125 MHz) δ : 98.0 (C-6), 119.6 (carbon of Ph), 121.9 (CF₃), 126.2, 129.2, 136.4 (carbons of Ph), 146.5, 152.6, 152.9, 158.8. MS (EI, 70 eV), m/z (%): 295 (M^+ , 49), 91 (51), 77 (93), 69 (38), 64 (35), 51 (100), 42 (16), 39 (28). Anal. Calcd for $C_{12}H_8F_3N_5O$: C, 48.82; H, 2.73; N, 23.72. Found: C, 49.12; H, 2.91; N, 24.04.

4.7. HPLC monitoring of the thermal decomposition of compound (8a)

An open glass vial containing the compound **8a** (200 mg, 0.696 mmol) was heated to 115–120 °C for complete melting of **8a** and then immediately placed in a thermostat, which maintained temperature at 100–101 °C. After heating during the necessary time (Table 2) the content of the vial was dissolved in DMF (10 mL). Then, 1 mL of the resulted solution was diluted with acetonitrile to 20 mL and analyzed by HPLC (Table 2).

4.8. Decomposition of compound (11a)

A magnetically stirred mixture of compound **11a** (200 mg, 0.83 mmol) and acetic acid (0.2 mL) in a glass ampoule placed in the oil bath was heated at 150–160 °C for 10 h. After cooling to room temperature the ampoule was unsealed (caution: excessive pressure!) and the reaction mixture was diluted with DMF to a volume of 5 mL. According to HPLC analysis, the conversion of compound **11a** was amounted to 12% and small peaks of unidentified compounds were observed. The DMF solution (4 mL) was evaporated to dryness at reduced pressure and the residue was extracted with hot chloroform (5 mL). The extract was subjected to a column chromatography (Al₂O₃, CHCl₃) to give 150 mg (75%) of starting compound **11a**. Its melting point and 1H NMR spectrum were identical with those prepared by method A.

4.9. (Z)-Ethyl 3-(7-methyl-5-oxo-1-phenyl-1,5-dihydro-[1,2,4]triazolo[4,3-*a*]pyrimidin-3-ylamino)but-2-enoate (14)

Compound **4a** (1.0 g, 2.50 mmol) was added to a solution of sodium (0.173 g, 7.5 mmol) in absolute ethanol (30 mL) and the resulted mixture was heated to reflux for 30 min, then neutralized by acetic acid. The solution was evaporated to a volume of about 10 mL and diluted with water (15 mL). The precipitate formed was isolated by filtration and recrystallized from acetonitrile to give 0.73 g of white needles (yield 82%), mp 177–177.5 °C, lit.^{6b} mp 172–173 °C. IR (ATR) ν (cm^{-1}): 3070, 2973, 1686, 1616, 1530, 1500. 1H NMR (500 MHz) δ : 1.22 (t, $J=7.1$ Hz, 3H, OCH₂CH₃), 2.28 (s, 3H, CH₃), 2.46 (s, 3H, C⁴H₃), 4.11 (q, $J=7.1$ Hz, 2H, OCH₂CH₃), 5.06 (s, 1H, H-2), 5.81 (s, 1H, H-6'), 7.30 (m, 1H, Ph), 7.52 (m, 2H, Ph), 8.08 (m, 2H, Ph), 12.20 (s, 1H, NH). ^{13}C NMR (125 MHz) δ : 14.3 (OCH₂CH₃), 22.2 (CH₃), 24.3 (CH₃), 59.1 (OCH₂CH₃), 94.5 (C-2), 99.7 (C-6'), 119.4, 126.1, 129.2, 136.8 (carbons of Ph), 141.2, 145.9 (carbons of triazole), 152.6 (C-3), 158.2 (C-5'), 167.4 (CO+C-7'). MS (EI, 70 eV), m/z (%): 353 (M^+ , 51), 307 (77), 279 (19), 266 (19), 240 (20), 200 (15), 185 (11), 134 (18), 118 (10), 109 (25), 91 (29), 77 (100), 67 (37), 51 (14), 39 (27). Anal. Calcd for $C_{18}H_{19}N_5O_3$: C, 61.18; H, 5.42; N, 19.82. Found: C, 59.87; H, 5.49; N, 20.05.

4.10. X-ray diffraction data

Single crystal X-ray diffraction experiments for compounds **10a** and **11d** (both crystallized from acetonitrile) were carried out with a Bruker APEX II CCD area detector, using graphite monochromated Mo K_{α} radiation ($\lambda=0.71073$ Å, ω -scans with a 0.3° step in ω and 10 s per frame exposure) at 100 K. The structures were solved by direct method and refined by the full-matrix least-squares against F^2 in anisotropic (for no-hydrogen atoms) approximation. All hydrogen H(N) atoms were located from the difference Fourier syntheses, the H(C) atoms were placed in geometrically calculated positions. All hydrogen H(N) atom positions were refined in isotropic approximation in riding model with the $U_{iso}(H)$ parameters equal to 1.2 $U_{eq}(N_i)$, where $U(N_i)$ are, respectively, the equivalent thermal parameters of the atoms to which corresponding H atoms are bonded.

Table 5
Crystallographic data and refinement parameters for **10a** and **11d**

	10a	11d
Molecular formula	C ₁₂ H ₁₁ N ₅ O	C ₂₀ H ₁₉ N ₅ O
Formula weight	241.26	345.40
Color, shape	Colorless, plate	Colorless, needle
Crystal size [mm]	0.21 × 0.20 × 0.14	0.42 × 0.30 × 0.25
Crystal system	Orthorhombic	Rhombohedral
Space group	<i>Pbca</i>	<i>R</i> -3
<i>a</i> [Å]	14.0320(6)	32.6055(15)
<i>b</i> [Å]	7.5793(3)	32.6055(15)
<i>c</i> [Å]	20.6559(9)	8.3815(7)
α [°]	90	90
β [°]	90	90
γ [°]	90	120
V [Å ³]	2196.8(2)	7716.7(8)
<i>Z</i>	8	18
<i>F</i> (000)	1008	3276
ρ_{calcd} [g cm ^{−3}]	1.459	1.338
Linear absorption, μ [cm ^{−1}]	1.00	0.87
θ range [°]	1.97–29.99	2.16–29.98
Completeness of dataset [%]	97.7	98.2
Diffn reflns	26,796	18,308
Unique reflns	3,189 [<i>R</i> (int)=0.0487]	4,923 [<i>R</i> (int)=0.0613]
Reflns with $ I > 2\sigma(I)$	2,441	2,985
ls. parameters	164	239
Final <i>R</i> (<i>F</i> _{hkl}): <i>R</i> ₁	0.0403	0.0480
<i>wR</i> ₂	0.1086	0.1046
Goodness of fit	0.965	1.116
$\rho_{\text{max}}/\rho_{\text{min}}$ (eÅ ^{−3})	0.402/−0.238	0.207/−0.246

Crystallographic data and refinement parameters for compounds are presented in Table 5. Atomic coordinates, bond lengths, bond angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC), deposition numbers 753133 (compound **10a**), and 753134 (compound **11d**). These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ; fax: +44 1223 335 033; or deposit@ccdc.cam.ac.uk). Any request to the CCDC for data should quote the full literature citation and CCDC reference numbers.

Acknowledgements

Authors thank the Federal Agency for Education of Russia for the financial support of this work through the Federal Target Program 'Research and Educational Personnel of Innovative Russia at 2009–2013 Years', State contract P302, project NK-109P/2.

Supplementary data

Copies of IR, NOESY, HSQC, HMBC, proton, and carbon spectra of some synthesized compounds are provided. Supplementary data

associated with this article can be found in online version at doi:10.1016/j.tet.2010.03.009.

References and notes

- (a) Yamashkin, S. A.; Kucherenko, N. Y.; Yurovskaya, M. A. *Chem. Heterocycl. Compd. (Engl. Transl.)* **1997**, 33, 499–514; (b) Hajós, G.; Riedl, Z. In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Eds.; Elsevier: Oxford, 2008; Vol. 11, pp 671–763; (c) Riggs, R. L.; Smith, D. M. In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Eds.; Elsevier: Oxford, 2008; Vol. 12, pp 857–973; (d) Metwally, M. A.; Abdel-Latif, E.; Amer, F. A.; Kaupp, G. *J. Sulfur Chem.* **2004**, 25, 63–85; (e) Awadallah, F. M. *Sci. Pharm.* **2008**, 76, 415–438; (f) Nam, N. L.; Grandberg, I. I.; Sorokin, V. I. *Chem. Heterocycl. Compd. (Engl. Transl.)* **2003**, 39, 1210–1212; (g) Shiota, T.; Yamamori, T.; Sakai, K.; Kiyokawa, M.; Honma, T.; Ogawa, M.; Hayashi, K.; Ishizuka, N.; Matsumura, K.; Hara, M.; Fujimoto, M.; Kawabata, T.; Nakajima, S. *Chem. Pharm. Bull.* **1999**, 47, 928–938; (h) Mukaiyama, H.; Nishimura, T.; Shiohara, H.; Kobayashi, S.; Komatsu, Y.; Kikuchi, S.; Tsuji, E.; Kamada, N.; Ohnata, H.; Kusama, H. *Chem. Pharm. Bull.* **2007**, 55, 881–889.
- (a) Fischer, G. *Adv. Heterocycl. Chem.* **2007**, 95, 143–219; (b) Reiter, J.; Pongó, L.; Dvortsák, P. *Tetrahedron* **1987**, 43, 2497–2504; (c) Esses-Reiter, K.; Reiter, J. *J. Heterocycl. Chem.* **1987**, 24, 1503–1508; (d) Reiter, J.; Rivó, E. *J. Heterocycl. Chem.* **1988**, 25, 1497–1502; (e) Reiter, J.; Pongó, L.; Somorai, T.; Pallagi, I. *Monatsh. Chem.* **1990**, 121, 173–187; (f) Fischer, G. *Adv. Heterocycl. Chem.* **1993**, 57, 81–138.
- (a) Revankar, G. R.; Robins, R. K. In *Chemistry of Nucleosides and Nucleotides*; Townsend, L. B., Ed.; Plenum: New York, NY, 1988; Vol. 2, pp 161–398; (b) Shaban, M. A. E. *Adv. Heterocycl. Chem.* **1997**, 70, 163–337; (c) Revankar, G. R.; Robins, R. K.; Tolman, R. L. *J. Org. Chem.* **1974**, 39, 1256–1262.
- (a) Akhondzadeh, S.; Malek-Hosseini, M.; Ghoreishi, A.; Raznahan, M.; Rezazadeh, S.-A. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2008**, 32, 1879–1883; (b) Hafez, H. N.; Abbas, H. A. S.; El-Gazzar, A.-R. B. A. *Acta Pharm.* **2008**, 58, 359–378; (c) El-Gazzar, A.-R. B. A.; Hussein, H. A. R.; Hafez, H. N. *Acta Pharm.* **2007**, 57, 395–411; (d) El-Gazzar, A.-R. B. A.; Hafez, H. N. *Acta Chim. Slov.* **2008**, 55, 359–371; (e) Soliman, F. S. G.; Shafik, R. M.; Darwish, M. *J. Pharm. Sci.* **1982**, 71, 178–182; (f) Ravindra, K. C.; Vagdevi, H. M.; Vaidya, V. P. *ARKIVOC* **2008**, xi, 1–10; (g) Suiko, M.; Hayashida, S.; Nakatsu, S. *Agric. Biol. Chem.* **1982**, 46, 2691–2695; (h) Magán, R.; Marín, C.; Salas, J. M.; Barrera-Pérez, M.; Rosales, M. J.; Sánchez-Moreno, M. *Mem. Inst. Oswaldo Cruz* **2004**, 99, 651–656; (i) Łakomska, I. *Inorg. Chim. Acta* **2009**, 362, 669–681.
- (a) Zhai, X.; Zhao, Y.-F.; Liu, Y.-J.; Zhang, Y.; Hun, F.-Q.; Liu, J.; Gong, P. *Chem. Pharm. Bull.* **2008**, 56, 941–945; (b) Phillips, M. A.; Gujjar, R.; Malmquist, N. A.; White, J.; El Mazouni, F.; Baldwin, J.; Rathod, P. K. *J. Med. Chem.* **2008**, 51, 3649–3653; (c) Cavallaro, C. L.; Hari Krishnan, L. S.; Chi, F.; Dodd, D.; Purandare, A. *J. Comb. Chem.* **2008**, 10, 28–30.
- (a) Papini, P. *Gazz. Chim. Ital.* **1950**, 80, 100–106; (b) Papini, P.; Checchi, S. *Gazz. Chim. Ital.* **1950**, 80, 850–854; (c) Papini, P. *Gazz. Chim. Ital.* **1952**, 82, 735–745.
- Bavley, A. U.S. Patent 2,406,654, 1946; *Chem. Abstr.* 1947, 41, 42h.
- (a) Shaban, M. A. E.; Morgaan, A. E. *Adv. Heterocycl. Chem.* **1999**, 73, 131–176; (b) Golubushina, G. M.; Poshtaruk, G. N.; Chuiguk, V. A. *Chem. Heterocycl. Compd. (Engl. Transl.)* **1974**, 10, 491–494; (c) Bratulescu, G. *Synthesis* **2005**, 2833–2834.
- (a) Chernyshev, V. M.; Rakitov, V. A.; Taranushich, V. A.; Blinov, V. V. *Chem. Heterocycl. Compd. (Engl. Transl.)* **2005**, 41, 1139–1146; (b) Chernyshev, V. M.; Kosov, A. E.; Gladkov, E. S.; Shishkina, S. V.; Taranushich, V. A.; Desenko, S. M.; Shishkin, O. V. *Russ. Chem. Bull. (Engl. Transl.)* **2006**, 55, 338–344; (c) Chernyshev, V. M.; Rakitov, V. A.; Astakhov, A. V.; Sokolov, A. N.; Zemlyakov, N. D.; Taranushich, V. A. *Russ. J. Appl. Chem. (Engl. Transl.)* **2006**, 79, 624–630; (d) Chernyshev, V. M.; Rakitov, V. A.; Taranushich, V. A.; Starikova, Z. A. *Chem. Heterocycl. Compd. (Engl. Transl.)* **2007**, 43, 776–780.
- (a) Minkin, V. I.; Garnovskii, A. D.; Elguero, J.; Katritzky, A. R.; Denisko, O. V. *Adv. heterocycl. Chem.* **2000**, 76, 157–323; (b) Reiter, J.; Pongó, L.; Lukovits, I. *Monatsh. Chem.* **1988**, 119, 341–348.
- Reiter, J.; Pongó, L.; Dvortsák, P. *J. Heterocycl. Chem.* **1987**, 24, 1149–1154.
- (a) Reiter, J.; Somorai, T.; Jerkovich, G.; Dvortsák, P. *J. Heterocycl. Chem.* **1982**, 19, 1157–1164; (b) Reiter, J.; Somorai, T.; Dvortsák, P.; Bujtás, G. *J. Heterocycl. Chem.* **1985**, 22, 385–394; (c) Reiter, J.; Pongó, L.; Somorai, T.; Dvortsák, P. *J. Heterocycl. Chem.* **1986**, 23, 401–408.
- (a) Chiara, J. L.; Gómez-Sánchez, A. In *The Chemistry of Enamines*; Rappoport, Z., Ed.; Wiley: Chichester, 1994; pp 279–404; (b) Vainiotalo, P.; Savolainen, P.-L.; Ahlgrén, M.; Mäklönen, P. J.; Vepsäläinen, J. *J. Chem. Soc., Perkin Trans. 2* **1991**, 735–741; (c) Bartoli, G.; Cimarelli, C.; Dalpozzo, R.; Palmieri, G. *Tetrahedron* **1995**, 51, 8613–8622; (d) Kumar, R.; Maulik, P. R.; Misra, A. K. *J. Carbohydr. Chem.* **2007**, 26, 83–90; (e) Kascheres, C. M. *J. Braz. Chem. Soc.* **2003**, 14, 945–969.
- (a) El Ashry, E. S. H.; El Kilany, Y.; Rashed, N.; Assafir, H. *Adv. Heterocycl. Chem.* **1999**, 75, 79–165; (b) El Ashry, E. S. H.; Rashed, N. *Adv. Heterocycl. Chem.* **1998**, 72, 127–224; (c) Gizatullina, E. M.; Kartsev, V. G. *Chem. Heterocycl. Compd. (Engl. Transl.)* **1993**, 29, 1369–1392; (d) Danagulyan, G. G. *Chem. Heterocycl. Compd. (Engl. Transl.)* **2005**, 41, 1205–1236.
- (a) Van der Plas, H. C. *Acc. Chem. Res.* **1978**, 11, 462–468; (b) Van der Plas, H. C. *Adv. Heterocycl. Chem.* **1999**, 74, 1–253; (c) Van der Plas, H. C. *J. Heterocycl. Chem.* **2000**, 37, 427–438.
- Maiboroda, D. A.; Babaev, E. V. *Chem. Heterocycl. Compd. (Engl. Transl.)* **1995**, 31, 1251–1279.

17. (a) Babaev, E. V.; Zefirov, N. S. *Chem. Heterocycl. Compd. (Engl. Transl.)* **1992**, *28*, 671–689; (b) Babaev, E. V.; Zefirov, N. S. *J. Math. Chem.* **1992**, *11*, 65–78; (c) Babaev, E. V.; Lushnikov, D. E.; Zefirov, N. S. *J. Am. Chem. Soc.* **1993**, *115*, 2416–2427.
18. Iyer, R. N.; Venkataraman, K. *Proc. Indian Acad. Sci.* **1953**, *37*, 629–642.
19. Butler, R. N. *Can. J. Chem.* **1973**, *51*, 2315–2322.
20. (a) Berecz, G.; Reiter, J. *J. Heterocycl. Chem.* **2001**, *38*, 237–252; (b) Berecz, G.; Reiter, J.; Argay, G.; Kálmán, A. *J. Heterocycl. Chem.* **2002**, *39*, 319–325.
21. (a) Vas'kevich, R. I.; Savitskii, P. V.; Zborovskii, Y. L.; Staninets, V. I.; Rusanov, E. B.; Chernega, A. N. *Russ. J. Org. Chem.* **2006**, *42*, 1403–1408; (b) Hassaneen, H. M.; Abdelhadi, H. A.; Abdallah, T. A. *Tetrahedron* **2001**, *57*, 10133–10138; (c) Elwan, N. M.; Awad, E. M.; Hassaneen, H. M.; Linden, A.; Heimgartner, H. *Helv. Chim. Acta* **2003**, *86*, 739–749; (d) Oganisyan, A. S.; Noravyan, A. S.; Karapetyan, A. A.; Aleksanyan, M. S.; Struchkov, Y. T. *Chem. Heterocycl. Compd. (Engl. Transl.)* **2004**, *40*, 79–83; (e) Markosyan, A. I.; Kuroyan, R. A.; Dilanyan, S. V.; Aleksanyan, M. S.; Karapetyan, A. A.; Struchkov, Y. T. *Chem. Heterocycl. Compd. (Engl. Transl.)* **2000**, *36*, 574–578; (f) Shawali, A. S.; Ali, N. A. H.; Ali, A. S.; Osman, D. A. *J. Chem. Res.* **2006**, 327–332.
22. (a) Burke-Laing, M.; Laing, M. *Acta Crystallogr., Sect. B* **1976**, *32*, 3216–3224; (b) Allen, F. H.; Kennard, O.; Watson, D. G.; Brammer, L.; Orpen, A. G.; Taylor, R. *J. Chem. Soc., Perkin Trans. 2* **1987**, S1–S19.
23. (a) Dunstan, A. R.; Weber, H.-P.; Rihs, G.; Widmer, H.; Dziadulewicz, E. K. *Tetrahedron Lett.* **1998**, *39*, 7983–7986; (b) Chernyshev, V. M.; Rakitov, V. A.; Blinov, V. V.; Taranushich, V. A.; Starikova, Z. A. *Chem. Heterocycl. Compd. (Engl. Transl.)* **2009**, *45*, 436–444.
24. Sato, Y.; Shimoji, Y.; Fujita, H.; Nishino, H.; Mizuno, H.; Kobayashi, S.; Kumakura, S. *J. Med. Chem.* **1980**, *23*, 927–937.
25. Steck, E. A.; Brundage, R. P.; Fletcher, L. T. *J. Am. Chem. Soc.* **1958**, *80*, 3929–3931.
26. Fuentes, J. J.; Lenoir, J. A. *Can. J. Chem.* **1976**, *54*, 3620–3625.
27. Güzel, Ö.; Innocenti, A.; Scozzafava, A.; Salman, A.; Parkkila, S.; Hilvo, M.; Supuran, C. T. *Bioorg. Med. Chem.* **2008**, *16*, 9113–9120.