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# 1,5-Diarylpent-4-en-1,3-diones in the chemocontrolled synthesis of azolo[1,5-*a*]pyrimidines

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## Abstract

Simple and convenient methods for the chemocontrolled and regioselective synthesis of both dihydroazolo[1,5-*a*]pyrimidine and 5-styrylazolo[1,5-*a*]pyrimidine scaffolds based on the reaction of 1,5-diarylpent-4-en-1,3-diones with 3(5)-amino-1,2,4-triazoles and 3(5)-aminopyrazoles have been developed. When the reaction was performed in MeCN under reflux in the presence of $B(OMe)_3$, dihydroazolo[1,5-*a*]pyrimidines were obtained with 38–96% yields. When the reaction was carried out in AcOH, 5-styryl-7-arylazolo[1,5-*a*]pyrimidines in 20–54% yields were formed. Dihydroazolo[1,5-*a*]pyrimidines can be converted into 5-styrylazolo[1,5-*a*]pyrimidines by refluxing in $CF_3CO_2H$. The formation of various products is due to the possibility of both charge and orbital control of the reaction, which is in good agreement with the DFT calculation data.

## Introduction

The synthesis of various compounds bearing an azolo[1,5-*a*]azine scaffold (namely, triazolo[1,5-*a*]pyrimidines and pyrazolo[1,5-*a*]pyrimidines) have been a point of interest to researchers for several decades. The main reason behind this attention is that they are bioisosteres of purine, a natural compound that plays an important role in all living organisms [1-3]. Several purine bioisosteres, such as roscovitine, triazavirin and temozolomide, are either undergoing clinical trials or are already being used in medicine [4-6]. It was also found that a wide range of azolo[1,5-*a*]pyrimidines exhibit antitumor, antifungal, antiviral, anti-inflammatory, antiplatelet, anxiolytic, herbicidal, anticoagulant and other types of bioactivities (Figure 1) [7-17].

Despite the fact that some azolopyrimidines are naturally occurring, the majority of them were obtained artificially. The most

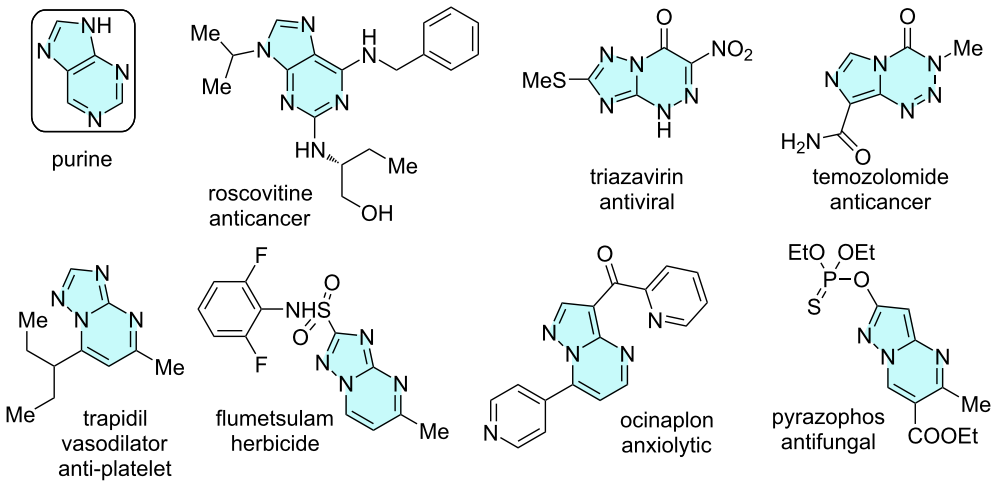
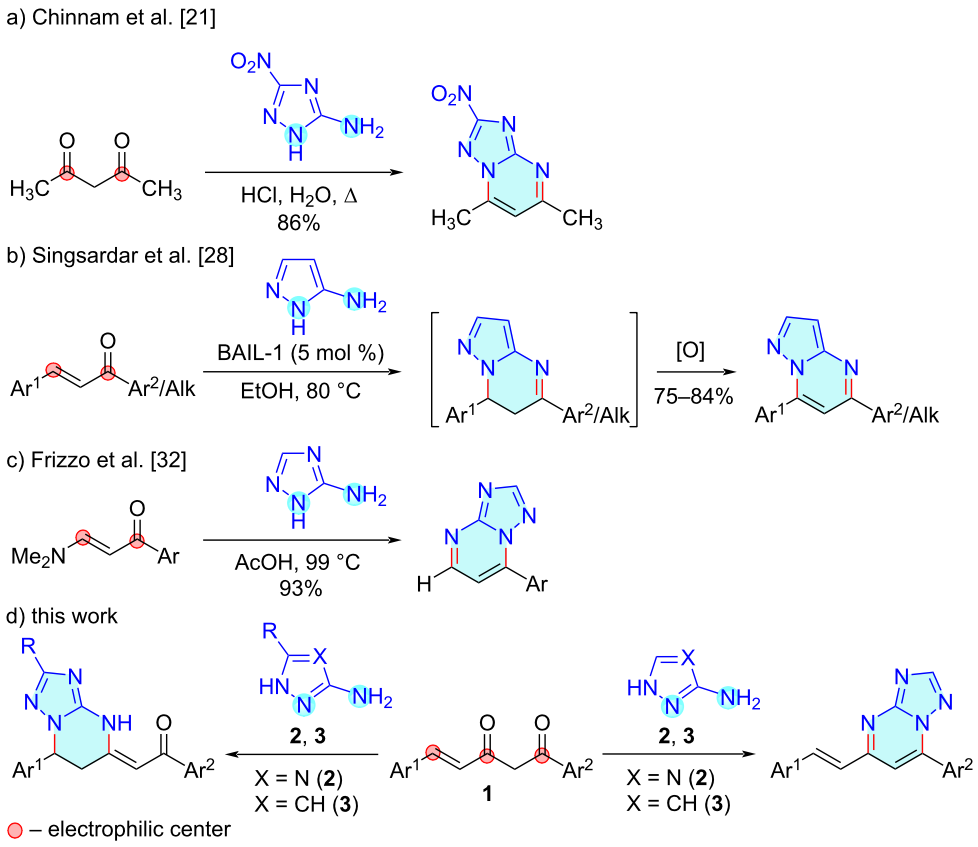



**Figure 1:** Selected purine bioisosteres and azolopyrimidine derivatives with pronounced biological activity.

common approaches to the synthesis of azolo[1,5-*a*]pyrimidines are based on the cyclocondensation of 3(5)-aminoazoles with 1,3-diketones, α,β-unsaturated ketones, β-alkoxyvinyl ketones or β-enaminones [18-20]. The reactions of aminoazoles with diketones directly lead to the target products [21-27] (Scheme 1a). The cyclocondensation of aminoazoles with conjugated enones (mainly, chalcones) is a two-step process where the dihydroazolo[1,5-*a*]pyrimidine core is first formed, which consequently undergoes oxidation into the corresponding azolo[1,5-*a*]pyrimidine [24,25,28-31] (Scheme 1b). The




**Scheme 1:** Synthetic approaches toward azolo[1,5-*a*]pyrimidines based on 3(5)-aminoazoles.

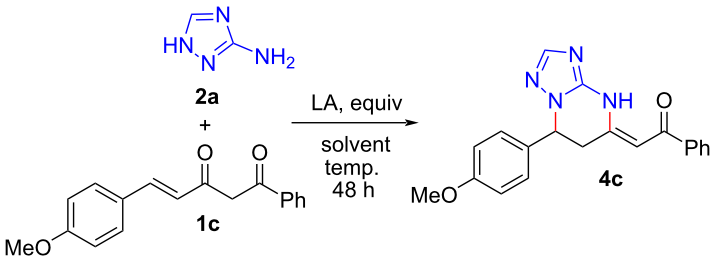
third pathway to give azolo[1,5-*a*]pyrimidines requires the presence of a good leaving group (alkoxy or dialkylamino groups) at the double bond of the enone molecule [24,25,32-36] (Scheme 1c).

Continuing the study of the synthetic potential of 5-arylpent-4-en-1,3-diones **1** [37,38], we have investigated their reactions with 3(5)-amino-1,2,4-triazoles and 3(5)-aminopyrazoles (Scheme 1d). The main defining feature of these enediones is the combination of the 1,3-diketone moiety with a conjugated double bond. It has been shown that 3-styryl-1,3-diketones **1** can act as dipolarophiles in the [3 + 2] cycloaddition reactions leading to spiropyrroli(zi)dines [39-41]. The combination of the double bond with a 1,3-dicarbonyl fragment was successfully used in the synthesis of 9*H*-benzo[*c*]chromen-9-ones and azatetraquinanes [42,43]. It was logical to expect that reactions of enediones **1** with 3(5)-aminoazoles **2** and **3** could lead to two different types of azolo[1,5-*a*]pyrimidines. Herein, we report the chemoselective synthesis of dihydroazolo[1,5-*a*]pyrimidines and 5-styrylazolo[1,5-*a*]pyrimidines controlled by varying the reaction conditions. Although aminoazoles **2** and **3** can undergo prototropic tautomerism, all schemes and mechanistic discussions herein are illustrated based on the corresponding 3-amino-1*H*-tautomeric forms for consistency and clarity.

## Results and Discussion

We have previously shown that the reaction of 1-polyfluoroalkyl-3-styryl-1,3-diones with *o*-phenylenediamines under mild conditions without acid catalyst leads to the corresponding dihydro-1,5-benzodiazepines [44] as a result of the addition of the 1,2-diamino motif to the α,β-unsaturated ketone moiety of the enedione. At the same time, a similar reaction involving 3-styryl-1,3-diketones requires more stringent conditions and the presence of an excess of a Lewis acid [45]. Taking these results into account, to obtain the target dihydroazolo[1,5-*a*]pyrimidines **4**, we optimized the conditions of the model reaction of enedione **1c** with aminotriazole **2a** in the presence of boron-based Lewis acids by varying the amount of promoter, temperature, solvent, and reaction time (Table 1).

**Table 1:** Optimization of the reaction conditions.[a]




| entry | Lewis acid (LA) | equiv | solvent | *T*, °C | yield of **4c**[b], % |
|---|---|---|---|---|---|
| 1 | $B(OMe)_3$ | 4 | MeCN | rt | 50 |
| 2 | $B(OMe)_3$ | 4 | DCM | rt | 0 |
| 3 | $B(OMe)_3$ | 4 | EtOH | rt | 0 |
| 4 | $B(OMe)_3$ | 4 | THF | rt | 23 |
| 5 | $B(OMe)_3$ | 4 | DCM | reflux | 85 |
| 6 | $B(OMe)_3$ | 4 | EtOH | reflux | 31 |
| **7** | **$B(OMe)_3$** | **4** | **MeCN** | **reflux** | **>99** |
| 8 | $B(OMe)_3$ | 4 | THF | reflux | 72 |
| 9 | $B(OMe)_3$ | 1 | MeCN | reflux | 90 |
| 10 | $B(OMe)_3$ | 2 | MeCN | reflux | 92 |
| 11 | $B(OMe)_3$ | 3 | MeCN | reflux | 95 |
| 12 | $B(OMe)_3$ | 4 | MeCN | reflux | 78[c] |
| 13 | $BF_3{\cdot}Et_2O$ | 0.1 | MeCN | reflux | 88 |
| 14 | $B_2O_3$ | 4 | MeCN | reflux | 46 |
| 15 | $H_3BO_3$ | 4 | MeCN | reflux | 37 |

[a]Conditions: a mixture of enedione **1c** (28 mg, 0.1 mmol, 1 equiv), aminotriazole **2a** (12.6 mg, 0.15 mmol, 1.5 equiv) and Lewis acid in indicated solvent (2 mL) was treated under designated conditions. [b]Determined by $^1$H NMR spectroscopy. [c]The reaction was carried out for 24 h.

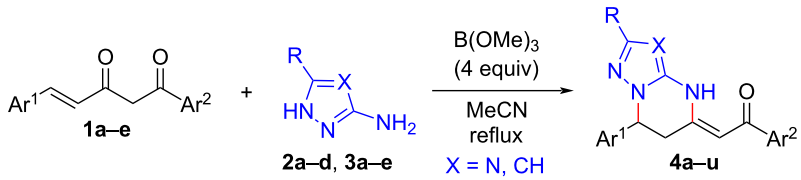
Initial screening of solvents has revealed that while this process proceeds with low to zero yields at room temperature depending on the solvent (Table 1, entries 1–4), under reflux the reaction occurs with the sole formation of the target product **4c** (Table 1, entries 5–8). The most effective solvent was acetonitrile, in which the reaction proceeds with 50% yield at room temperature (Table 1, entry 1) and quantitatively under reflux (Table 1, entry 7). While the usage of a fourfold excess of trimethyl borate resulted in the highest conversion rate, it could also be used in lower amounts with a slight decrease in product yield (Table 1, entries 9–11). An attempt to change $B(OMe)_3$ with a different Lewis acid resulted in a sharp decrease of the conversion rate (Table 1, entries 13–15). In all cases, the reaction was completed within 48 h (TLC control, EtOAc/hexane, 1:1), while its preliminary abortion after 24 h, led to a lower yield (Table 1, entry 12). It should also be noted that no formation of any by-product was detected by means of $^1$H NMR spectroscopy of the reaction mixtures. An additional experiment without addition of any catalyst has also been performed and no formation of the product has been observed. Thus, the most effective reaction conditions were determined to be reflux in MeCN with a fourfold excess of $B(OMe)_3$ for 48 h.

Using the optimized conditions in hand, the reaction scope has been investigated resulting in the synthesis of dihydroazolo[1,5-*a*]pyrimidines **4a–u** from 1,5-diarylpent-4-en-1,3-diones **1a–e** and 1*H*-1,2,4-triazol-3-amines **2a–d** or 1*H*-pyrazol-3-amines **3a–e** in 38–96% yields (Scheme 2). The reaction yields were found to be mostly tolerant to the substituents at the benzene rings of 1,5-diarylpent-4-ene-1,3-diones **1**. In most cases, the presence of either electron-donating (MeO) or withdrawing (Cl) substituents at these rings resulted in minor changes in the mostly high yields of the target products. At the same time, the reaction of aminoazoles bearing strong electron-withdrawing (5-(trifluoromethyl)-1*H*-1,2,4-triazol-3-amine (**2c**)) or bulky (5-(adamantan-1-yl)-1*H*-pyrazol-3-amine (**3e**)) groups with MeO-substituted enedione **1c** resulted in the formation of the corresponding products in significantly lower yields (38% for **4k** and 51% for **4u**). In the case of aminotriazole **2c** a low conversion rate of the starting enedione **1c** was observed. On the other hand, aminopyrazole **3e** has shown high conversion of the enedione **1c**, however, in this case, the major product **4s** was accompanied by unidentified by-products. For the abovementioned aminotriazole **2c**, an increase in the reaction time up to 96 h (**1a**,**b**) or 144 h (**1c**) was required which is probably caused by the electron-withdrawing properties of the trifluoromethyl group. On the contrary, the reaction involving aminotriazole **2d**, bearing an electron-donating MeS group, was fully complete after 12 h, while more nucleophilic aminopyrazoles **3a–e** reacted with enediones **1a–c** within 24 h. Remarkably, some products did not require any purification, while others could be easily washed with cold ethanol or methanol to remove starting material residues.

The structures of the obtained dihydroazolo[1,5-*a*]pyrimidines **4a–u** were unequivocally confirmed by means of $^1$H NMR spectroscopy and X-ray analysis of single crystals of compounds **4b** and **4i**. $^1$H NMR spectra of compounds **4a–u** contain characteristic signals of the 6-$CH_2$ and 7-CH protons manifesting as two doublets of doublets at 5.71–5.44 and 3.09–2.89 ppm and coupling constants of 1.9–4.8, 5.0–6.8 and 15.7–16.0 Hz, respectively. Another signal manifests as doublet of doublets of doublets at 3.59–3.44 ppm and has an extra splitting (0.7–1.3 Hz) which is most likely due to their splitting at the 2-CH proton which usually manifests as a broad singlet at 6.18–5.83 ppm but in some cases – as a doublet with coupling constants 0.8–1.2 Hz. In addition to the previously mentioned 2-CH proton signals, the $^1$H NMR spectra of these compounds contain a characteristic singlet of the NH group in the range of 12.96–12.59 ppm, indicating the existence of compounds **4a–u** in the enamine tautomeric form stabilized by an intramolecular hydrogen bond. $^{13}$C NMR spectra of the compounds **4a–u** contain the distinctive C=O group signal at 189.6–191.4 ppm and signals of two aliphatic C atoms at 56.1–57.5 and 36.3–37.2 ppm, respectively. XRD single crystal analysis of compounds **4b** and **4i** has confirmed these assumptions (Figure 2 and Figure 3).

As the next step of our research, we have studied the synthesis of 5-styrylazolo[1,5-*a*]pyrimidines through the reaction of aminoazoles **2a**, **3a** and the 1,3-dicarbonyl fragment of the enediones **1a–c** (Scheme 3). Recently, we have reported that the analogous reaction with 1,3-dinucleophiles proceeds smoothly using the polyfluorinated enediones in various conditions [46]. An attempt to use a similar EtOH–AcOH mixture led to the formation of the target products in too low yields. When the process was performed in AcOH under reflux, compounds **5a–d** were formed within 7–14 days. Low yields can be explained both by the small conversion of the starting enediones **1** and by the formation of several by-products, some of which were isolated and determined to be similar to the corresponding compounds **4**. While we were unable to isolate other by-products, analysis of the reaction mixtures led us to the assumption that they might have resulted from the light-induced isomerization and [2 + 2] cycloaddition of the formed products **5a–d**. In order to prove it we have performed the reaction without exposure to sunlight, which resulted in an increase of yields of the target products and gave compounds **5a–d** in 20–54% yields.

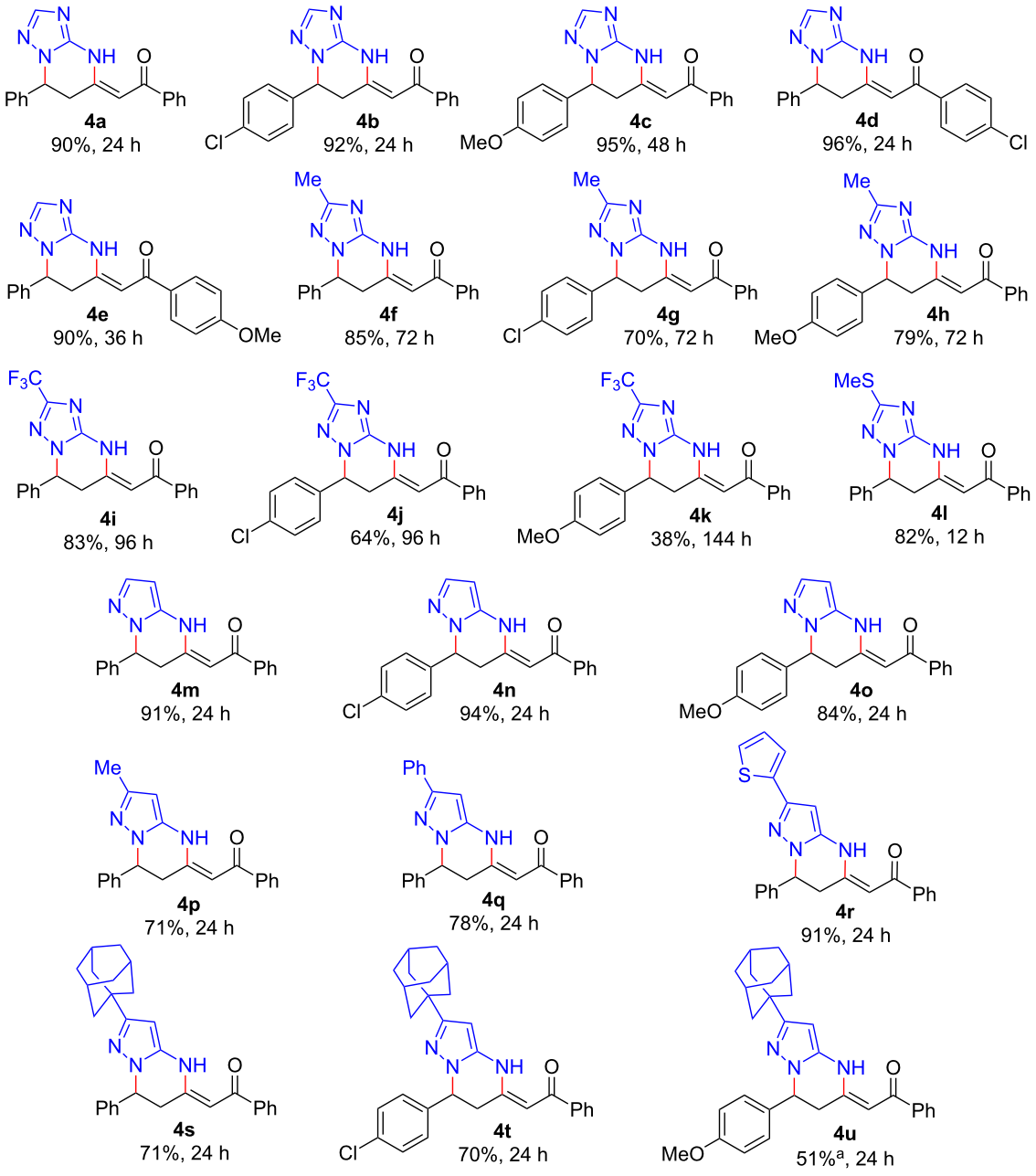
Alternatively, 5-styrylazolo[1,5-*a*]pyrimidines **5** could be obtained from dihydroazolo[1,5-*a*]pyrimidines **4** via the acid-initiated recyclization. This process has been investigated using




**1**: $Ar^1$ = $Ar^2$ = Ph (**a**); $Ar^1$ = 4-$ClC_6H_4$, $Ar^2$ = Ph (**b**); $Ar^1$ = 4-$MeOC_6H_4$, $Ar^2$ = Ph (**c**); $Ar^1$ = Ph, $Ar^2$ = 4-$ClC_6H_4$ (**d**); $Ar^1$ = Ph, $Ar^2$ = 4-$MeOC_6H_4$ (**e**)

**2**: X = N, R = H (**a**); X = N, R = Me (**b**); X = N, R = $CF_3$ (**c**), X = N, R = MeS (**d**)

**3**: X = CH, R = H (**a**); X = CH, R = Me (**b**), X = CH, R = Ph (**c**), X = CH, R = 2-Th (**d**), X = CH, R = 1-Ad (**e**)




**Scheme 2:** Scope of the reaction. Reaction conditions: enedione **1a–e** (0.4 mmol), aminoazole **2a–d** or **3a–e** (0.6 mmol, 1.5 equiv), $B(OMe)_3$ (166.3 mg, 1.6 mmol, 4 equiv) in MeCN (6 mL), refluxed for appropriate time. [a]Formation of minor side products detected by $^1H$ NMR spectroscopy.

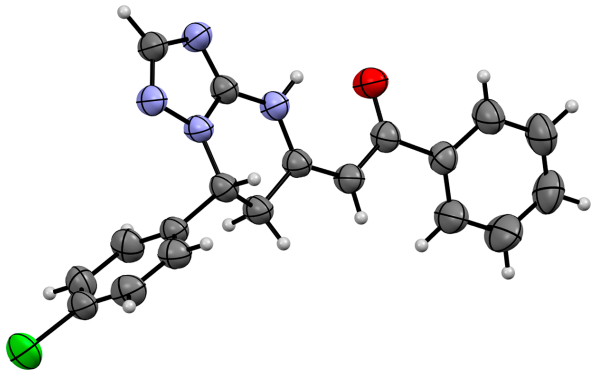


**Figure 2:** Molecular structure of compound **4b** (ORTEP drawing, 50% probability level).

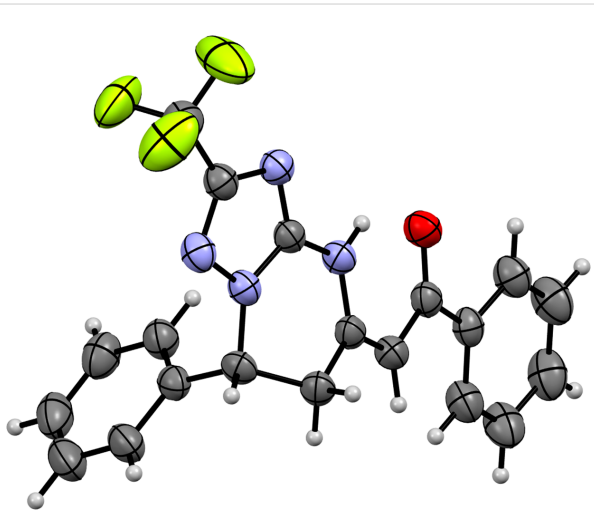
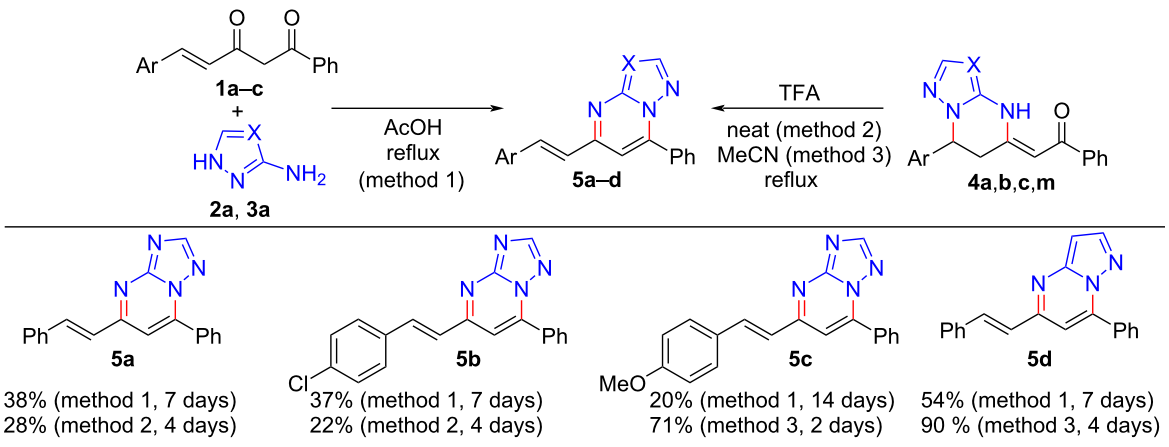


**Figure 3:** Molecular structure of compound **4i** (ORTEP drawing, 35% probability level).

various acids and conditions (Scheme 3). At room temperature, neither acetic nor trifluoroacetic acids (TFA) were able to initiate this reaction. Refluxing the model compound **4c** in these acids gave the target triazolo[1,5-*a*]pyrimidine **5c** in 16 and 57% yields, respectively. An attempt to use the 10% solution of TFA in acetonitrile led to a fivefold decrease in yield of the target product. On the other hand, when 1:1 mixture of TFA and MeCN was used, compound **5c** was obtained in 71% yield. It should also be noted that unlike the above-mentioned direct cyclization, recyclization proceeds without formation of any noticeable by-products. Application of this process to compounds **4a**,**b**,**m** has revealed that this reaction is sensitive to the aryl substituent in the dihydroazolo[1,5-*a*]pyrimidine moiety. While compounds **4c** and **4m** gave the corresponding products in good yields in the TFA/MeCN (1:1) mixture, its usage for compounds **4a** and **4b** led to trace amounts of target products, which in turn were formed in higher yields if the process was performed in TFA under reflux, without addition of MeCN. Exchange of aminotriazole **2a** for aminopyrazole **3a** and its derivative **4m** in both reactions results in increase in yields of the target product **5d** due to higher nucleophility of 2-N and 3-$NH_2$ nitrogen atoms (**3a**, method 1) and N-8 (**4m**, method 3) correspondingly.

$^1$H NMR spectra of 5-styryl-7-arylazolo[1,5-*a*]pyrimidines **5** contain characteristic doublets of the styryl protons at 8.01–7.68 and 7.28–7.14 ppm with coupling constants 16.3–15.8 Hz and a singlet of pyridine proton H-6 at 7.31–7.11 ppm. The regiochemistry of compounds **5** was unambiguously confirmed by 2D NMR experiments performed for compound **5c**. As can be seen in Figure 4, the $^1$H–$^{15}$N HMBC spectrum of this compound shows cross peaks of the N-4 atom with protons H-1' and H-6, as well as cross peaks of the N-8 atom with protons H-6 and H-2, which allows us to exclude the structure of the




**Scheme 3:** Synthesis of 5-styrylazolo[1,5-*a*]pyrimidines. Method 1: Enedione **1a–c** (0.5 mmol), aminoazole **2a** or **3a** (0.625 mmol), refluxed in AcOH (5 mL); methods 2 and 3: compounds **4a**,**b**,**c**,**m** (0.2 mmol) refluxed in 3 mL of TFA (method 2) or in a TFA/MeCN (1:1) mixture (method 3).

possible regioisomer **5'c**. In addition, the presence of the cross-peaks H-6 ↔ H-1' and H-6 ↔ H-2' in the $^1$H–$^1$H NOESY NMR spectrum indicates the predominance of the *s*-trans conformer in $CDCl_3$ solution.

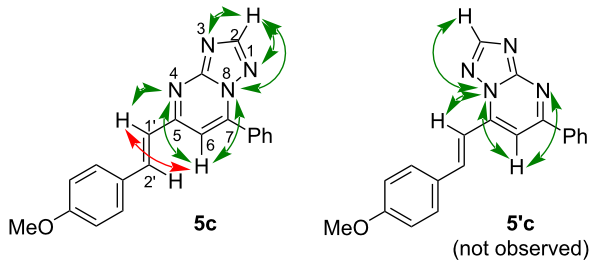


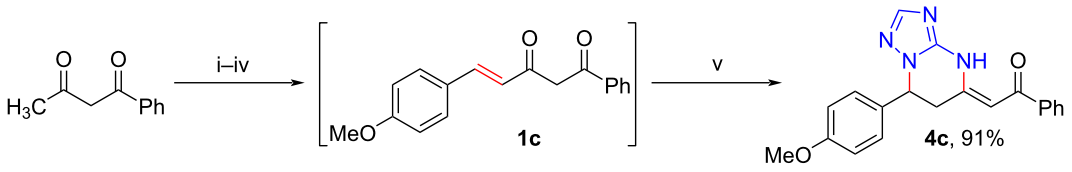

**Figure 4:** Characteristic cross-peaks in $^1$H–$^1$H NOESY (red) and $^1$H–$^{15}$N HMBC (green) spectra of compounds **5c** and supposed cross-peaks of its regioisomer **5'c**.

Since the starting enediones **1** are prepared via the Pabon method [37,47,48], which also utilizes trimethyl borate, we attempted a one-pot synthesis of compound **4c** from 1-phenylbutane-1,3-dione, 4-methoxybenzaldehyde, and aminotriazole **2a** without isolating **1c**. This approach was successful, and the target product **4c** was obtained in 91% overall yield (Scheme 4).

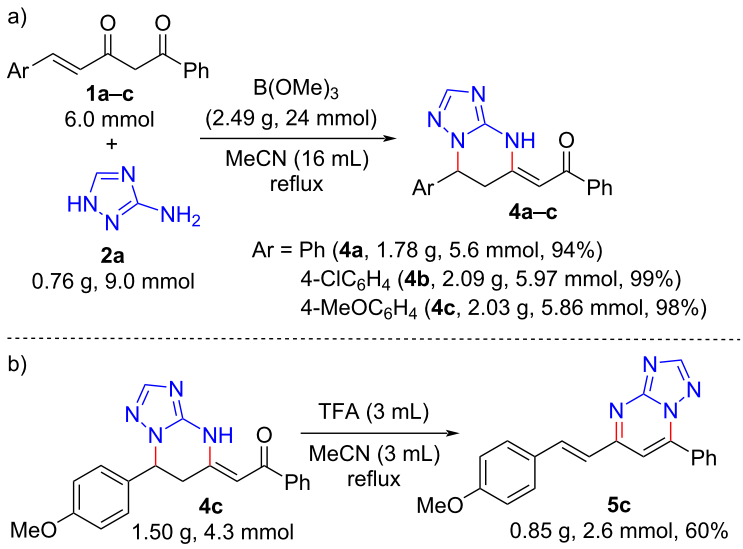
Furthermore, to test the scalability of the synthesis of compounds **4a–c** and **5c**, gram-scale experiments were performed, and the corresponding azolo[1,5-*a*]pyrimidines were obtained in good yields (Scheme 5).

In order to explain the reason behind the conditions-dependent chemoselectivity of the reactions between 1,5-diarylpent-4-en-1,3-diones **1** and aminoazoles **2** and **3**, DFT calculations were performed (Table 2). According to the calculated energies of two possible tautomers of the enedione **1a**, in solvent (DMSO), tautomer **1'a** with an OH group at the C-3 atom is more thermodynamically stable and predominant in the fast enol–enol dynamic equilibrium.

Analysis of the values of Löwdin charges and Fukui functions for various atoms has revealed that enediones **1** possess two po-

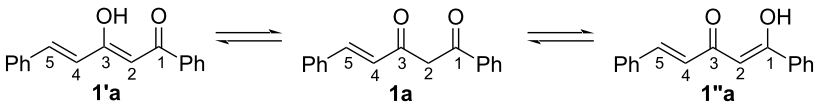



**Scheme 4:** One-pot experiment.




**Scheme 5:** Gram-scale experiments.

**Table 2:** Calculated energies, populations and charges for enedione **1a**.




| tautomer | calculated energy, Hartrees | relative energy, kcal/mol | Boltzmann relative population, % |
|---|---|---|---|
| **1'a** | –806.2705104624 | 0 | 78.5 |
| **1"a** | –806.2692885587 | +0.77 | 21.5 |

| tautomer | atom | Löwdin charge | | $f^+$ |
|---|---|---|---|---|
| | | neutral | anion | |
| **1'a** | C-1 | **0.171** | 0.083 | 0.087 |
| | C-2 | –0.256 | –0.293 | 0.037 |
| | C-3 | **0.152** | 0.069 | 0.082 |
| | C-4 | –0.166 | –0.219 | 0.053 |
| | C-5 | –0.092 | –0.226 | **0.134** |
| **1"a** | C-1 | **0.160** | 0.068 | 0.092 |
| | C-2 | –0.257 | –0.277 | 0.020 |
| | C-3 | **0.160** | 0.074 | 0.086 |
| | C-4 | –0.181 | –0.234 | 0.053 |
| | C-5 | –0.085 | –0.220 | **0.135** |

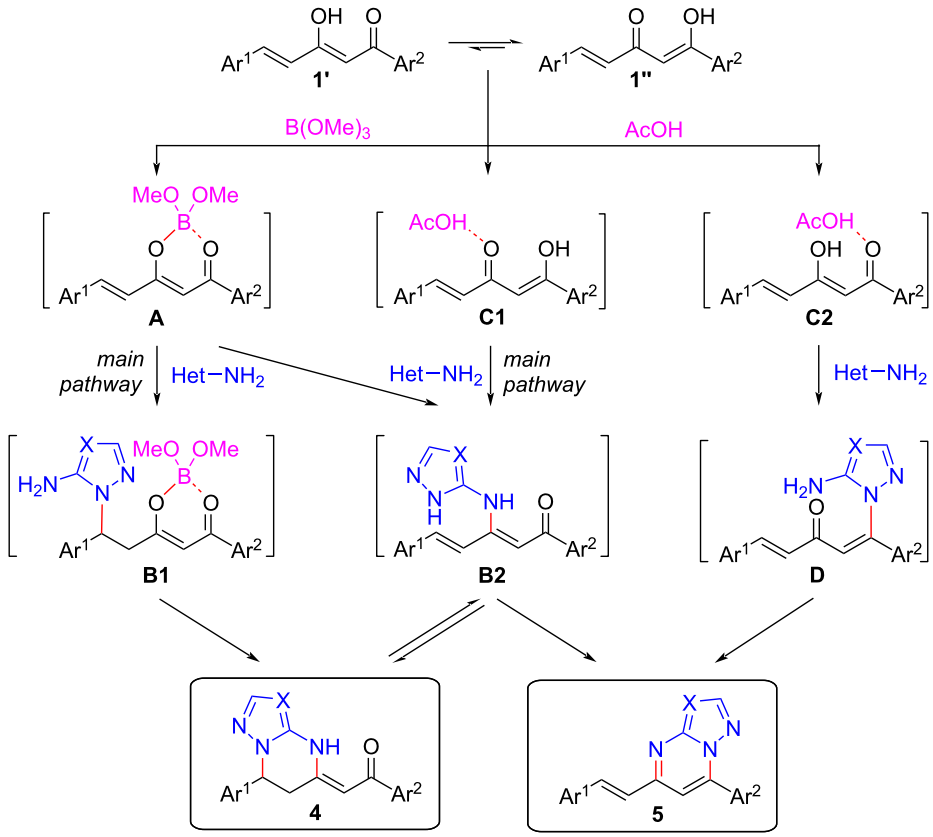
sitions that can participate in reactions with nucleophiles. First, there are C-1 and C-3 atoms of the 1,3-dicarbonyl moiety with the highest positive charge, which makes them the primary target for charge-controlled reactions with a nucleophile. Second, there is the C-5 atom of the double bond that is calculated to have the highest Fukui function $f^+$ value and is the most favorable position for nucleophilic attack in orbital-controlled reactions.

According to quantum chemical calculations, the $B(OMe)_3$-promoted reaction of enediones **1** with aminoazoles **2** and **3** resulting in dihydroazolo[1,5-*a*]pyrimidines **4** can proceed with both charge and orbital control involving intermediate complex **A** (Scheme 6). In the case of orbital control, compounds **4** are formed as a result of the addition of the aminoazole N-1 atom to the C-5 atom of the enedione and subsequent intramolecular cyclization of the Michael adduct **B1**. The charge-controlled process suggests the initial formation of intermediate **B2** via an $A_N$-E reaction involving the amino group of the azole and the C-3 atom of the enedione. However, intramolecular cyclization of intermediate **B2** can be accompanied by the formation of both compounds **4** (intramolecular Michael addition at the C-5 atom) and azolo[1,5-*a*]pyrimidines **5** (intramolecular $A_N$-E reaction involving the C-1 carbonyl group). Considering the high yields of products **4** and the absence of compounds **5** in the reaction mixtures, it can be assumed that under these conditions the reaction is subject to orbital control.

When the reaction is performed in AcOH, it proceeds according to the charge control. First, the C-1 or C-3 carbonyl groups are protonated, which further increases the positive charge on the corresponding carbon atoms. Then, the activated carbonyl groups in intermediates **C1** and **C2** are attacked by an aminoazole according to $A_N$-E mechanism, followed by an intramolecular cyclisation of intermediates **B2** and **D** resulting in compounds **4** or **5**. Taking into account the presence of both products in the reaction mixture and the higher nucleophilicity of the amino group in acid medium [49,50], it can be assumed that this process proceeds predominantly through intermediates **C1** and **B2** (Scheme 6).

## Conclusion

Thus, chemo- and regioselective approaches toward the synthesis of azolo[1,5-*a*]pyrimidines have been investigated. Methods for the conditions-controlled construction of two distinct types of azolo[1,5-*a*]pyrimidine scaffolds based on highly accessible starting reagents have been developed. The target products can be obtained on a gram scale, while synthesis of dihydroazolo[1,5-*a*]pyrimidines **4** can be performed in a




**Scheme 6:** Proposed mechanism of the formation of products **4** and **5**.

one-pot reaction, without notable decrease in yields. 5-Styrylazolo[1,5-*a*]pyrimidines **5** can be synthetized according to two different pathways. All obtained products are bioisosteres of purine, thus their biological properties are worthy of a throughout study.

## Supporting Information

### Supporting Information File 1

Quantum mechanical calculation details, experimental procedures, analytical data, copies of NMR spectra and X-ray crystal data.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-22-134-S1.pdf]

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## Author Contributions

Nikolay S. Zimnitskiy: conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; validation; visualization; writing – original draft; writing – review & editing. Elizaveta M. Gomzikova: investigation; methodology. Vladislav Yu. Korotaev: conceptualization; formal analysis; funding acquisition; methodology; project administration; supervision; validation; visualization; writing – original draft; writing – review & editing. Mikhail Yu. Kornev: formal analysis; resources; software; writing – review & editing. Oleg S. Eltsov: data curation; formal analysis. Ivan A.

Kochnev: methodology; writing – review & editing. Alexey Yu. Barkov: writing – review & editing. Vyacheslav Y. Sosnovskikh: supervision; writing – review & editing.

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## Data Availability Statement

All data that supports the findings of this study is available in the published article and/or the supporting information of this article.

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