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Reaction of enamines with semicarbazone-based amidoalkylating reagents: A straightforward synthesis of annulated 1-aminopyrimidin-2-one derivatives

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ABSTRACT

An efficient synthesis of 1-arylideneamino-substituted hexahydro-1*H*-cyclopenta[*d*]pyrimidin-2-ones and octahydroquinazolin-2-ones has been developed. The synthesis involves a stereo- and regioselective cascade reaction of the corresponding 4-(tosylmethyl)semicarbazones with 1-morpholinocyclopentene or 1-morpholinocyclohexene to give predominantly bicyclic pyrimidines with an exocyclic C=C double bond (80–97%). The later undergo rapid isomerization when heated in THF in the presence of TsOH to form bicyclic pyrimidines with a significant predominance of those with an endocyclic C=C double bond (90–97%).

The α-amidoalkylation reaction is a powerful tool in synthetic organic chemistry that allows the formation of carbon–carbon and carbon-heteroatom bonds at the α-position to the amide nitrogen (Scheme 1) [1]. This reaction involves the interaction between nucleophiles and electrophilic amidoalkylating reagents (e.g. **1** and **2** in Scheme 1). Despite the wide variety of C-nucleophiles used, only a few reactions with enamines have been reported including those with acylimines **2** proceeding without a catalyst [2] and those with amidoalkylating reagents **1** commonly catalyzed by a Lewis acid [3]. Since the amide components for the synthesis of **1** and **2** were carboxamides and carbamates (R = alkyl, aryl, alkoxy), the final products of these reactions after hydrolysis were the corresponding β-amido or β-carbamato ketones **3** (Scheme 1).

Recently, we have developed a general method for the synthesis of novel amidoalkylating reagents based on semicarbazones, 4-(tosylmethyl)semicarbazones **4**, and studied their reactions with *H*-, *O*-, *S*-, *P*-, *N*-nucleophiles, and anionic *C*-nucleophiles [4]. In continuation of our research on synthetic applications of these reagents, it was reasonable to explore their reactions with enamines. We hypothesized that the initial products of these reactions, iminium salts **5**, due to the presence of the nucleophilic nitrogen atom N2 in the semicarbazone fragment, could undergo spontaneous heterocyclization with the formation of 1-aminopyrimidin-2-one derivatives (Scheme 2).

It is noteworthy that 1-aminopyrimidin-2-one derivatives demonstrate a wide range of biological activities acting as competitive AMPA receptor antagonists [5] HLGPa inhibitors [6] antiallergic and antiasthmatic agents [7] and possessing antibacterial [8] antiepileptogenic [9] anxiolytic [10] schistosomicidal [11] and pesticidal properties [12].

Among the various 1-aminopyrimidin-2-ones, heterocycle annulated and benzoannulated representatives are the most studied. Their preparations involve *N*-amination [13] cyclization [14] and recyclization [15] reactions. In contrast, only a few syntheses of monocyclic and carbocycle annulated 1-aminopyrimidin-2-ones have been reported [8a,b,12a,16].

Herein we report an efficient synthesis of hydrogenated bicyclic 1-(arylideneamino)pyrimidin-2-ones based on the reaction of enamines (1-morpholinocyclopentene and 1-morpholinocyclohexene) with 4-(tosylmethyl)semicarbazones. Plausible mechanisms for the reaction as well as isomerization of the initial products are also discussed.

Sulfones **6a-d** bearing an aryl or alkyl group at the α-position to the amide nitrogen atom N4 and α-unsubstituted sulfone **6e** were used as the starting amidoalkylating reagents. Readily available 1-

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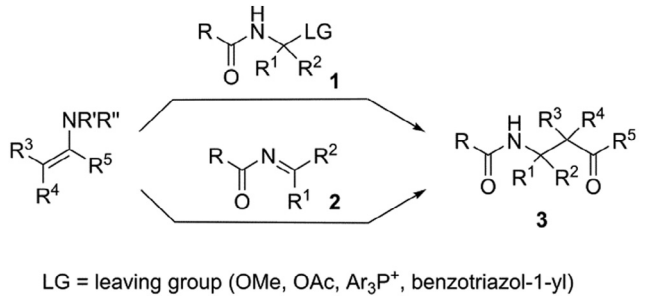
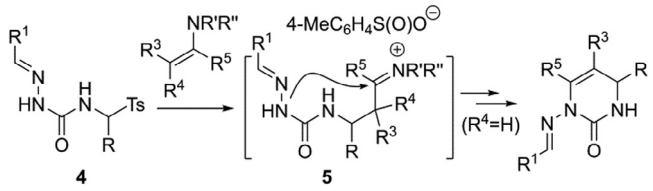


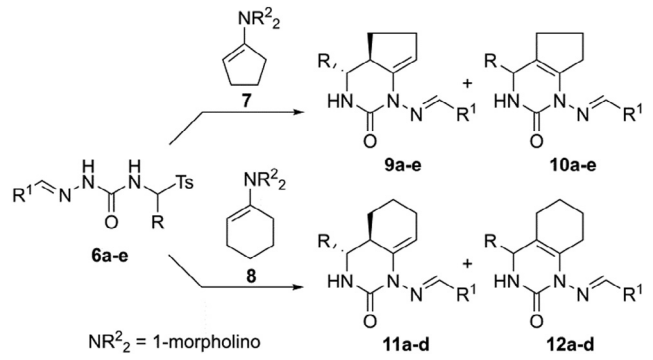
Scheme 1. Reported examples of the amidoalkylation of enamines.



Scheme 2. Proposed synthesis of 1-aminopyrimidin-2-one derivatives *via* the reaction of enamines with 4-(tosylmethyl)semicarbazones.

morpholinocyclopentene (**7**) and 1-morpholinocyclohexene (**8**) were chosen as *C*-nucleophiles. First, we studied the reaction of sulfone **6a** with enamine **7**. Taking into account the reported data on the amidoalkylation of enamines with carboxamide and carbamate-based reagents **1** (see above), we carried out the reaction between **6a** and **7** using boron trifluoride etherate as a catalyst. The reaction proceeded rapidly in CH_2Cl_2 at room temperature affording the expected heterocyclization products, which were found to be a mixture of isomeric bicyclic pyrimidines **9a** and **10a** in a 49:51 ratio, respectively (Scheme 3; entry 1 in Table 1). However, according to ^{1}H NMR spectroscopic data, the estimated purity of the isolated crude product did not exceed 72%.

We found that the reaction between **6a** and **7** proceeded in CH_2Cl_2 at room temperature for 7 h even without addition of a catalyst, resulting in a 71:29 mixture of pyrimidines **9a** and **10a** with a purity of 69% (Entry 2). However, under these conditions, the heterocyclization of the initially formed amidoalkylation products was incomplete, as evidenced by the NMR spectrum of the isolated crude material, in which two singlet signals in the range of 9.95–10.45 ppm were observed, characteristic of the N2-H proton of the semicarbazone moiety. After the reaction time was prolonged to 24 h, an 80:20 mixture of **9a** and **10a** was isolated in 77% yield with high purity (Entry 3). Use of benzene or MeCN as a solvent resulted in a decrease in the purity of the obtained pyrimidines (Entries 4 and 5).



Scheme 3. Amidoalkylation of enamines **7** and **8** with 4-(tosylmethyl)semicarbazones **6a-e**.

Under the optimized conditions (CH_2Cl_2, rt, 24 h), mixtures of pyrimidines **9b** + **10b** (80:20) and **9c** + **10c** (89:11) were prepared from sulfones **6b,c** and enamine **7** in good yields (Entries 6 and 8). Analogous to **6a**, a decrease in the reaction time with sulfone **6b** resulted in a decrease in the purity and yield of the obtained product (Entry 7).

In contrast to α-aryl substituted sulfones **6a-c**, sulfone **6d** reacted with enamine **7** to give a mixture of **9d**, **10d** and 4-methylbenzaldehyde semicarbazone in a ratio of 19:24:57, respectively (Entry 9), and α-unsubstituted sulfone **6e** did not react with **7** at all (Entry 10).

We found that sulfones **6a-c** smoothly reacted with enamine **8** in CH_2Cl_2 at room temperature for 24 h to give the corresponding mixtures of pyrimidines **11a-c** and **12a-c** in 69–77% overall yield (Entries 11, 12, and 14). Shortening the reaction time to 3 h with compound **6b** led to a decrease in the purity of the obtained pyrimidines **11b + 12b** (Entry 13). It is noteworthy that, under the optimized conditions, the reaction of compounds **6a-c** with enamine **8** proceeds more selectively than with enamine **7**. In the first case, the amount of pyrimidines with the exocyclic C=C bond is 86–97%, and in the second case, it is 80–86%.

It should be noted that the reaction between α-propyl substituted sulfone **6d** and enamine **8** (CH_2Cl_2, rt, 24 h) did not give pyrimidines **11d**, **12d**, and the only isolated reaction product was 4-methylbenzaldehyde semicarbazone (27%) (Entry 15).

Scheme 4 shows a plausible pathway for the amidoalkylation of enamines based on the experimental data. Due to their low basicity, enamines cannot participate in the amidoalkylation *via* an E1cB/Ad$_N$ mechanism. Since α-unsubstituted sulfone **6e**, in contrast to sulfones **6a-d**, did not react with enamine **7** (Entry 10 vs entries 3, 6, 8, and 9), an S_N2 mechanism can be excluded. Thus, the amidoalkylation of enamines **7** and **8** with sulfones **6a-c** proceeds *via* an S_N1 mechanism through the formation of *N*-acyliminium cations **A** stabilized by the aryl group (Scheme 4). Reaction of these cations with **7** or **8** gives intermediates **B**, which cyclize into bicyclic pyrimidines **C** followed by elimination of morpholine to afford the final products.

The regioselectivity of the amidoalkylation is determined by elimination of morpholine from intermediates **C** *via* an E1 mechanism (Scheme 4). It is noteworthy that the thermodynamically less stable pyrimidines **9a-c** and **11a-c** (see below) formed predominately in the reaction of **6a-c** with enamines **7** or **8** as a result of kinetic control involving preferential abstraction of a proton in the intermediate carbocation from the less hindered CH_2 group.

Based on ^{1}H NMR spectroscopic data, the major products (**9a-c** or **11a-c**) were formed as a single diastereomer with *trans*-diequatorial orientation of substituents at the C5 and C6 positions of the pyrimidine ring ($^3J_{5\text{-H},6\text{-H}}$ = 10.6–10.8 Hz). According to the proposed pathway, the stereochemistry of these compounds is controlled by the interaction between cations **A** and enamines.

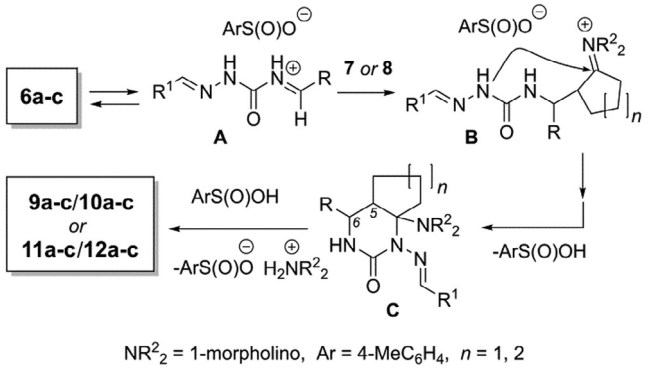
We found that heating the obtained **9a-c**/**10a-c** and **11a-c**/**12a-c** mixtures (Table 1) in various solvents (EtOH, MeCN, THF, C_6H_6) in the presence of TsOH afforded mixtures of the same compounds with a significant predominance of pyrimidines with the endocyclic C=C double bond (90–97%, according to NMR data) (Scheme 5, Table 2).

Using **9a** + **10a** mixtures we found that the purity of the isomerization reaction dramatically depended on the solvent used (Table 2, entries 2–4, 6, and 7). The best result was obtained in THF. An increase in the reaction time led to decreased purity of the isolated pyrimidines (Entries 1–3). The isomerization also proceeded in AcOH or DMF at reflux providing pyrimidine mixtures **9a** + **10a** with low purity (Entries 8 and 9). Under all tested conditions, except the reaction at room temperature (Entry 5), pyrim-

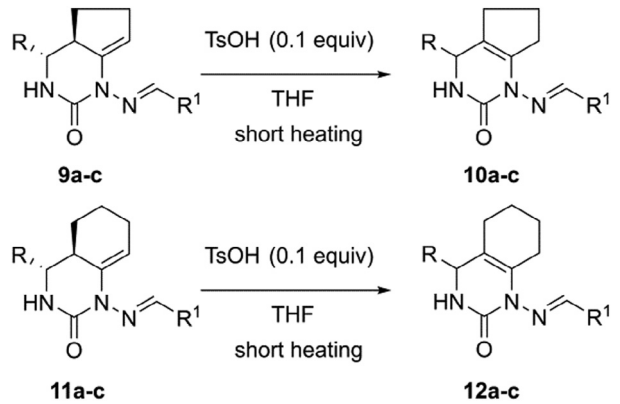
Table 1
Reactions of sulfones **6a-e** with enamines **7** and **8**.

Entry	Starting compounds[a]	R	R^1	Reaction conditions	Pyrimidine products	Pyrimidine purity[b]	Yield (%)[c]	**9**/**10** or **11**/**12** ratio[d]
1	**6a** + **7**	4-MeC_6H_4	4-MeC_6H_4	CH_2Cl_2, $BF_3{\cdot}Et_2O$ (0.90 equiv.), rt, 6 h	**9a + 10a**	72	–	49:51
2	**6a** + **7**	4-MeC_6H_4	4-MeC_6H_4	CH_2Cl_2, rt, 7 h	**9a + 10a**	69	–	71:29
3	**6a** + **7**	4-MeC_6H_4	4-MeC_6H_4	CH_2Cl_2, rt, 24 h	**9a + 10a**	96	77	80:20
4	**6a** + **7**	4-MeC_6H_4	4-MeC_6H_4	MeCN, rt, 24 h	**9a + 10a**	84	–	90:10
5	**6a** + **7**	4-MeC_6H_4	4-MeC_6H_4	C_6H_6, rt, 24 h	**9a + 10a**	76	–	87:13
6	**6b** + **7**	Ph	Ph	CH_2Cl_2, rt, 24 h	**9b + 10b**	90	74	80:20
7	**6b** + **7**	Ph	Ph	CH_2Cl_2, rt, 3 h	**9b + 10b**	81	–	91:9
8	**6c** + **7**	4-$MeOC_6H_4$	4-$MeOC_6H_4$	CH_2Cl_2,rt, 24 h	**9c + 10c**	96	62	89:11
9	**6d** + **7**	Pr	4-MeC_6H_4	CH_2Cl_2,rt, 24 h	**9d + 10d**[e]	43	–	45:55
10	**6e** + **7**	H	4-MeC_6H_4	CH_2Cl_2,rt, 24 h	no reaction[f]	–	–	–
11	**6a** + **8**	4-MeC_6H_4	4-MeC_6H_4	CH_2Cl_2, rt, 24 h	**11a + 12a**	97	75	95:5
12	**6b** + **8**	Ph	Ph	CH_2Cl_2, rt, 24 h	**11b + 12b**	97	69	86:14
13	**6b** + **8**	Ph	Ph	CH_2Cl_2, rt, 3 h	**11b + 12b**	75	–	96:4
14	**6c** + **8**	4-$MeOC_6H_4$	4-$MeOC_6H_4$	CH_2Cl_2, rt, 24 h	**11c + 12c**	98	77	97:3
15	**6d** + **8**	Pr	4-MeC_6H_4	CH_2Cl_2, rt, 24 h	–[g]	–	–	–

[a] 1.15–1.24 equiv. of enamine were used.
[b] Purity of the isolated pyrimidines was estimated as a ratio of the expected integral intensity of the NH and aromatic protons region (11*H* for **9b** + **10b** and **11b** + **12b**; 9H for **9a,c** + **10a,c** and **11a,c** + **12a,c**; 5H for **9d + 10d**) to the observed integral intensity in this region in the ^{1}H NMR spectrum of the crude product multiplied by 100.
[c] Isolated yield.
[d] According to ^{1}H NMR spectroscopy of the crude products.
[e] Obtained in a mixture with 4-methylbenzaldehyde semicarbazone (57%).
[f] 97% of starting **6e** was recovered.
[g] A 83:27 mixture of **6d** and 4-methylbenzaldehyde semicarbazone, respectively, was isolated.



Scheme 4. Plausible pathway for the amidoalkylation of enamines **7** and **8** with 4-(tosylmethyl)semicarbazones **6a-c**.



Scheme 5. Acid-catalyzed isomerization of **9a-c** into **10a-c**, and **11a-c** into **12a-c**.

idine mixtures **9a** + **10a** with similar ratios were obtained, indicating that thermodynamic equilibrium was achieved rapidly. Short heating of **9a** + **10a** in THF in the presence of TsOH (0.1 equiv.) until complete dissolution (<5 min) afforded the isomerization product with 79% purity (Entry 1). Under these optimized conditions, **9b, c**/**10b,c** and **11a-c**/**12a-c** mixtures with 56–92% purity were obtained (Entries 10–14). Isomerization of the **11c** + **12c** mixture proceeded very slowly using the weak acid AcOH (Entry 15). Crystallization of the **11a,b** + **12a,b** mixtures (Entries 12 and 13) from EtOH gave individual pyrimidines **12a,b** in 35% and 62% isolated yield, respectively.

The described isomerization proves that pyrimidines **10a-c**, **12a-c** with the endocyclic C=C double bond are thermodynamically more stable than pyrimidines **9a-c**, **11a-c** with the exocyclic one. This is also confirmed by the DFT B3LYP/6–311++G(d,p) calculations for **9b**, **10b** and **11b**, **12b** in DMSO and THF solution using the PCM solvation model. The calculations show that **10b** and **12b** (s-*cis* conformers relative to the N—N bond) are more stable than the corresponding **9b** and **11b** (ΔE = 0.88–1.26, ΔG = 1.76–1.98 kcal/mol).

In summary, the α-amidoalkylation of enamines (1-morpholinocyclopentene and -cyclohexene) with 4-(tosylmethyl)semicarbazones has been studied. It was demonstrated that with α-aryl-substituted amidoalkylating reagents, the reaction readily proceeds in CH_2Cl_2 at room temperature without any catalyst to give derivatives of 1-arylideneamino-substituted hexahydro-1*H*-cyclopenta[*d*]pyrimidin-2-ones or octahydroquinazolin-2-ones as a result of a cascade process involving spontaneous heterocyclization of the initially formed amidoalkylation products followed by elimination of morpholine. We showed that the amidoalkylation step proceeds *via* an S_N1 mechanism with complete diastereoselectivity to afford the corresponding bicyclic intermediates with *trans*-diequatorial orientation of the substituents at the C5 and C6 position of the pyrimidine ring. The morpholine elimination step is kinetically controlled and results in the predominant formation of the bicyclic pyrimidines with an exocyclic C=C double bond (80–97%). Short heating of the obtained products in THF in the presence of TsOH (0.1 equiv.) led to bicyclic pyrimidines with a significant predominance of those with an endocyclic C=C double bond (90–97%) as a result of isomerization. The DFT B3LYP/6–311++G(d,p) calculations confirm that pyrimidines with the endocyclic C=C double bond are thermodynamically more stable than those with the exocyclic bond. We believe that the developed bicyclic pyrimidine synthesis represents a flexible method to construct hydrogenated 1*H*-cyclopenta[*d*]pyrimidin-2-one and quina-

Table 2
Isomerization of **9a-c** into **10a-c**, and **11a-c** into **12a-c**.

Entry	Starting compounds	R, R[1]	Starting **9**/**10** or **11**/**12** ratio	Reaction conditions[a]	Final **9**/**10** or **11**/**12** ratio[b]	Pyrimidine purity (%)[c]
1	**9a** + **10a**	4-MeC_6H_4	86:14	TsOH (0.1 equiv.), THF, short heating	7:93	79
2	**9a** + **10a**	4-MeC_6H_4	71:29	TsOH (0.1 equiv.), THF, reflux, 0.5 h	6:94	63
3	**9a** + **10a**	4-MeC_6H_4	73:27	TsOH (0.1 equiv.), THF, reflux, 1 h	6:94	34
4	**9a** + **10a**	4-MeC_6H_4	79:21	TsOH (0.1 equiv.), EtOH, reflux, 1 h	6:94	4
5	**9a** + **10a**	4-MeC_6H_4	73:27	TsOH (0.1 equiv.), EtOH, rt, 24 h	36:64	53
6	**9a** + **10a**	4-MeC_6H_4	73:27	TsOH (0.1 equiv.), MeCN, reflux, 0.5 h	6:94	10
7	**9a** + **10a**	4-MeC_6H_4	86:14	TsOH (0.1 equiv.), C_6H_6, reflux, 0.5 h	6:94	55
8	**9a** + **10a**	4-MeC_6H_4	79:21	AcOH, reflux, 0.5 h	9:91	9
9	**9a** + **10a**	4-MeC_6H_4	78:22	DMF, reflux, 1 h	8:92	51
10	**9b** + **10b**	Ph	78:22	TsOH (0.1 equiv.), THF, short heating	4:96	80
11	**9c** + **10c**	4-$MeOC_6H_4$	89:11	TsOH (0.1 equiv.), THF, short heating	10:90	56
12	**11a** + **12a**	4-MeC_6H_4	95:5	TsOH (0.1 equiv.), THF, short heating	9:91	88
13	**11b** + **12b**	Ph	86:14	TsOH (0.1 equiv.), THF, short heating	10:90	92
14	**11c** + **12c**	4-$MeOC_6H_4$	96:4	TsOH (0.1 equiv.), THF, short heating	9:91	83
15	**11c** + **12c**	4-$MeOC_6H_4$	96:4	AcOH (1.5 equiv.), THF, reflux, 3 h	91:9	87

[a] Short heating is defined as heating on a hotplate under stirring until a solution formed (<5 min).
[b] According to ^{1}H NMR spectroscopy of the crude products.
[c] Purity of the isolated pyrimidines was estimated as described in Table 1.

zolin-2-one frameworks. The methods previously described in the literature involve the reaction of 2-(R-ylidene)cycloalkanones with urea [17] or the three-component condensation of cycloalkanones with aromatic aldehydes and urea [18] to give bicyclic 1,2,3,4-tetrahydropyrimidin-2-ones with an endocyclic C=C double bond.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data (copies of IR, ^{1}H and ^{13}C NMR spectra of the synthesized compounds, computational details) to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.152826.

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