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Novel Semicarbazone-Based α-Amidoalkylating Reagents: General Synthesis and Reactions with *H*-, *O*-, *S*-, *N*- and *P*-Nucleophiles †

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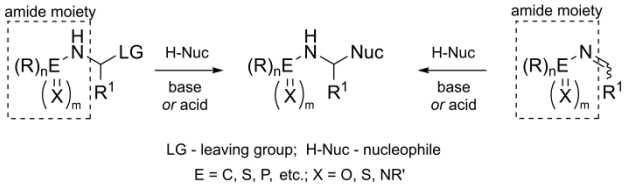
Abstract: A general synthesis of previously unknown semicarbazone-based α-amidoalkylating reagents, 4-(tosylmethyl)semicarbazones, has been developed. The synthesis involved three-component condensation of semicarbazones of aliphatic or aromatic aldehydes with the same or other aldehydes and *p*-toluenesulfinic acid. The scope and limitations of this reaction were investigated. The compounds obtained were demonstrated to be an efficient α-4-semicarbazono)alkylating agents. They were reacted with *H*- (sodium borohydride), *O*- (sodium methylate), *S*- (sodium phenylthiolate), *N*- (pyrrolidine, sodium succinimide), and *P*-nucleophiles (trialkyl phosphites) to give the corresponding products of the tosyl group substitution, 4-substituted semicarbazones.

Keywords: semicarbazones; three-component condensation; sulfones; α-amidoalkylation; nucleophiles

1. Introduction

α-Amidoalkylation reaction is a powerful tool of modern organic synthesis for carbon-carbon or carbon-heteroatom bond formation (Scheme 1) [1–3]. The distinguishing features of amidoalkylating reagents are higher electrophilicity and wider structural diversity compared with those of reagents involved in aminoalkylation reactions (the Mannich reaction, the Pictet-Spengler reaction, etc.). Therefore, amidoalkylation has been extensively applied in the synthesis of various nitrogen-containing acyclic and heterocyclic compounds including bioactive natural products (e.g., alkaloids [4–7], antibiotics [8–11], toxins [12–14], vitamins [15,16]) and pharmaceuticals [17–20]. Recently, some enantioselective variants of this reaction employing catalytic amounts of chiral auxiliaries has also been described [21–23].



Scheme 1. Some α-amidoalkylating reagents and their reactions with nucleophiles.

Commonly, electrophilic amidoalkylating reagents are based on carboxamides and carbamates [1–3]. Their preparation from other amides, e.g., ureas [24–27], thioureas [28–30], guanidines [31–33], thio- and dithiocarbamates [34–36], amides of various oxoacids of sulfur [37,38] and phosphorus [39,40] has been much less studied. To the best of our knowledge, there are no reports on preparation and application of semicarbazide-based amidoalkylating reagents. Synthesis of these reagents would significantly extend scope of the amidoalkylation reaction and give unique access to various semicarbazide-containing compounds which are of great interest due to their different valuable properties [41–43]. For example, they exhibit anticonvulsant, antihypertensive, antitumor, antitrypanosomal activity, serve as effective ligands in coordination chemistry, and are used in the synthesis of azapeptides.

Synthesis of the desired amidoalkylating reagents directly from semicarbazides can not be performed since the basicity and nucleophilicity of the nitrogen N1 are significantly higher than those of the amide nitrogen N4 (e.g., pK_a = 3.86 and pK_a = 0.053 for protonated semicarbazide and urea, respectively, in water at 25 °C). Therefore, the nitrogen N1 of semicarbazide should be initially protected with an electron-withdrawing group (e.g., alkylidene, arylidene, or acyl group). In a preliminary report, we described the first synthesis of semicabazide-based amidoalkylating reagents, 4-(tosylmethyl)semicarbazones (4 examples), involving the condensation of aromatic aldehydes with semicarbazones of the same aldehydes and *p*-toluenesulfinic acid in EtOH [44]. It would be highly desirable to examine the scope and limitations of this three-component condensation depending on structure of starting compounds and reaction conditions, prepare a representative number of 4-(tosylmethyl)semicarbazones, and study in detail their reactivity towards a large variety of nucleophiles.

Herein we describe preparative synthesis of various 4-(tosylmethyl)semicarbazones and their application for the amidoalkylation of some *H*-, *O*-, *S*-, *N*-, and *P*-nucleophiles to afford the corresponding 4-substituted semicarbazones including analogues of 5-nitro-2-furancarboxaldehyde semicarbazone (nitrofurazone) with potential antimicrobial activity. Results of antibacterial, antifungal, cytotoxicity, and haemolytic tests of some synthesized compounds are also reported.

2. Results and Discussion

The starting compounds, semicarbazones of aromatic aldehydes **1a–g** or aliphatic aldehydes **1h–j**, were prepared according to a known procedure using the reaction of semicarbazide hydrochloride with the corresponding aldehyde in the presence of AcONa in water or aqueous ethanol (Scheme 2).

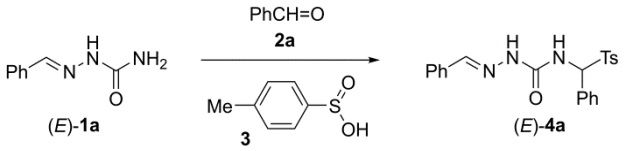
1-2 a R = Ph, **b** R = 4-MeC_6H_4, **c** R = 4-$MeOC_6H_4$, **d** R = 4-EtC_6H_4, **e** R = 4-*i*-PrC_6H_4, **f** R = 4-*t*-BuC_6H_4, **g** R = 5-nitrofur-2-yl, **h** R = Et, **i** R = Pr, **j** R = *i*-Pr.

Scheme 2. Synthesis of aldehyde semicarbazones **1a–j**.

According to NMR data, semicarbazones of aromatic aldehydes **1a–g** and semicarbazone of isobutyric aldehyde (**1j**) were isolated as a single stereoisomer with (*E*)-configuration, which was assigned based on previously reported single-crystal X-ray structural analyses of analogous semicarbazones. In contrast, depending on the reaction conditions and isolation procedure semicarbazones of propionic and butyric aldehyde (**1h** and **1i**) were obtained as mixtures of two stereoisomers in various ratio. To the best of our knowledge, stereochemistry of these compounds has not been previously described. Therefore, we assigned configuration of both stereoisomers by the comparison of their ^{1}H NMR spectra with those of (*E*)-**1j** in DMSO-d_6. Chemical shifts of the NH and NH_2 protons (9.76 and 6.11 ppm, respectively) in (*E*)-**1j** are close to those in the major isomers of compounds **1h,i** (9.80 and 6.12–6.13 ppm) and strongly differ from those in the minor isomers (9.29

and 6.28–6.29 ppm). Thus, the major isomers of **1h,i** have (*E*)- and minor isomers have (*Z*)-configuration. The additional evidence of (*E*)-configuration in the major isomers of compounds **1h,i** is a long-range coupling ^{4}J between the NH and CH protons (0.6–0.7 Hz), which was also observed for (*E*)-**1j** (0.7 Hz), while the spectra of the minor isomers of semicarbazones **1h,i** did not show this coupling.

4-(Tosylmethyl)semicarbazones **4** were synthesized using the three-component condensation of aldehyde semicarbazones **1** with aldehydes **2** and *p*-toluenesulfinic acid (**3**). First, based on our previous experience [45], we attempted to prepare sulfone (*E*)-**4a** by the reaction of semicarbazone of benzaldehyde [(*E*)-**1a**] with equimolar amounts of benzaldehyde (**2a**) and acid **3** in H_2O at room temperature (Scheme 3).



Scheme 3. Synthesis of sulfone (*E*)-**4a** by the reaction of semicarbazone (*E*)-**1a.**with benzaldehyde and sulfinic acid **3**.

However, under the above conditions, the reaction proceeded very slowly, and after 6 days, the conversion of (*E*)-**1a** into (*E*)-**4a** was only 15% (^{1}H NMR data for isolated crude material) (Table 1, entry 1). A slow reaction rate can be explained by the extremely poor solubility of (*E*)-**1a** in water.

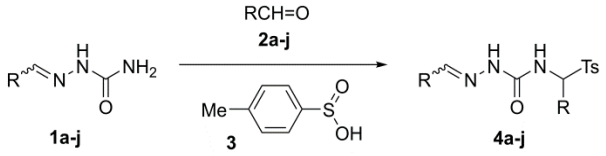
Table 1. Synthesis of sulfone (*E*)-**4a** by the reaction of benzaldehyde semicarbazone [(*E*)-**1a**] with benzaldehyde (**2a**) and *p*-toluenesulfinic acid (**3**).

Entry	1a:2a:3 Ratio	Solvent	Reaction Conditions	4a:1a Ratio [a]
1	1:1:1	H_2O	rt, 6 days	15:85
2	1:1:1	H_2O	58 °C, 1.5 h	69:31
3	1:1.1:1.1	H_2O	rt, 7 days	73:27
4	1:1.1:1.1	H_2O	70 °C, 7 h	67:33
5	1:1.5:1.5	H_2O	rt, 8 days	82:18
6	1:1:1	H_2O-EtOH, 1:1	rt, 6 days	30:70
7	1:1:1	H_2O-EtOH, 1:1	47 °C, 6.5 h	24:76
8	1:1.5:1.5	H_2O-EtOH, 1:2	rt, 5 days	89:11
9	1:1.5:1.5	H_2O-EtOH, 5:95	rt, 8 days	100:0 [b]
10	1:1.1:1.1	H_2O-HCOOH, 20:80	rt, 24 h	100:0 [c]

[a] According to ^{1}H NMR spectroscopic data of the crude product isolated by filtration after cooling the reaction mixture to 0 °C. [b] 96% isolated yield. [c] 74% isolated yield.

Elevated temperature (entry 1 vs entry 2; entry 6 vs entry 7), use of excess of **2a** and **3** (entry 1 vs entry 3 vs entry 5), and change of the solvent from water (entry 5) to aqueous ethanol (entries 6, 8, 9) or 80% aqueous formic acid (entry 10) resulted in an increase in the level of conversion of (*E*)-**1a**. Under optimal conditions, the reaction proceeded with 100% conversion at room temperature in 95% aq EtOH for 8 days (Method A) or in 80% aq HCOOH for 24 h (Method B) to give sulfone (*E*)-**4a** in 96 or 74% yield, respectively. In both cases, the crude product was isolated by filtration of the precipitate formed after completion of the reaction with >95% purity (^{1}H NMR data) and was used for amidoalkylation without additional purification.

Methods A and B were applied for the preparation of other 4-(tosylmethyl)semicarbazones **4b-g** by the condensation of aromatic aldehydes **2b-g** with semicarbazones of the same aldehydes **1b-g** and sulfinic acid **3** (Scheme 4).



Scheme 4. Synthesis of sulfones **4a–j** by the reaction of semicarbazones (*E*)-**1a–j**, with aldehydes **2a–j** and sulfinic acid **3**.

All sulfones **4b-g** precipitated from the reaction mixture and were isolated by filtration in good yields (83–99%) and excellent purity (>95%) (Table 2, entries 3–13). Generally, the product yields were higher according to Method A (EtOH, rt, 3–6 days) compared with Method B (80% aq HCOOH, rt, 24 h). Since nitrofurazone [(*E*)-**1g**] appeared to be practically insoluble in EtOH its condensation with 5-nitrofurfural (**2g**) and sulfinic acid **3** under Method A conditions failed to give the target sulfone **4g**. When a EtOH–DMF mixture (2:1 v/v) was used for this reaction (rt, 7 days), the only isolated material was starting (*E*)-**1g**. However, sulfone **4g** was prepared according to Method B in 83% yield (entry 13).

Table 2. Synthesis of sulfones **4a–j** by the reaction of semicarbazones **1a–j** with aldehydes **1a-j** and *p*-toluenesulfinic acid.

Entry	1	2	R	Method [a]	Time (d)	Product	Yield (%) [b]
1	(*E*)-**1a**	**2a**	Ph	A	8	(*E*)-**4a**	96
2 [c]	(*E*)-**1a**	**2a**	Ph	B	1	(*E*)-**4a**	74
3	(*E*)-**1b**	**2b**	4-MeC$_6$H$_4$	A	6	(*E*)-**4b**	98
4	(*E*)-**1b**	**2b**	4-MeC$_6$H$_4$	B	1	(*E*)-**4b**	91
5	(*E*)-**1c**	**2c**	4-MeOC$_6$H$_4$	A	6	(*E*)-**4c**	99
6	(*E*)-**1c**	**2c**	4-MeOC$_6$H$_4$	B	1	(*E*)-**4c**	89
7	(*E*)-**1d**	**2d**	4-EtC$_6$H$_4$	A	5	(*E*)-**4d**	94
8	(*E*)-**1d**	**2d**	4-EtC$_6$H$_4$	B	1	(*E*)-**4d**	92
9	(*E*)-**1e**	**2e**	4-*i*-PrC$_6$H$_4$	A	5	(*E*)-**4e**	94
10	(*E*)-**1e**	**2e**	4-*i*-PrC$_6$H$_4$	B	1	(*E*)-**4e**	88
11 [d]	(*E*)-**1f**	**2f**	4-*t*-BuC$_6$H$_4$	A	3	(*E*)-**4f**	96
12	(*E*)-**1f**	**2f**	4-*t*-BuC$_6$H$_4$	B	1	(*E*)-**4f**	96
13	(*E*)-**1g**	**2g**	4-*t*-BuC$_6$H$_4$	B	1	(*E*)-**4g**	83
14	**1h** [e]	**2h**	Et	C	1	**4h** [g]	95
15	**1i** [f]	**2i**	Pr	C	1	**4i** [h]	94
16	(*E*)-**1j**	**2j**	*i*-Pr	C	1	**4j** [i]	87

[a] Method A: 95% aq EtOH, **1**:**2**:**3** molar ratio = 1:1.5:1.5, rt, 3-8 days; Method B: 80% aq HCOOH, **1**:**2**:**3** molar ratio = 1:1.25:1.25, rt, 1 day; Method C: H$_2$O, **1**:**2**:**3** molar ratio = 1.1:1:1, rt, 1 day. [b] Isolated yield. [c] **1a**:**2a**:**3** molar ratio = 1:1.1:1.1. [d] **1f**:**2f**:**3** molar ratio = 1:1.25:1.25. [e] (*E*)-**1h**/(*Z*)-**1h** = 59:41. [f] (*E*)-**1i**/(*Z*)-**1i** = 72:28. [g] (*E*)-**4h**/(*Z*)-**4h** = 90:10. [h] (*E*)-**4i**/(*Z*)-**4i** = 90:10. [i] (*E*)-**4j**/(*Z*)-**4j** = 97:3.

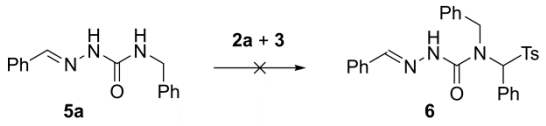
Sulfones **4a–g** were formed as a single geometrical isomer (^{1}H NMR spectroscopic data) with (*E*)-configuration of the C=N double bond, which was proved by close chemical shifts of the CH=N proton in starting semicarbazones (*E*)-**1a–g** (7.79–7.84 ppm) and in sulfones **4a–g** (7.84–7.90 ppm) in DMSO-*d*$_6$.

Aliphatic aldehydes **2h–j** also reacted with semicarbazones of the same aldehydes **1h–j** and sulfinic acid **3** to give the corresponding sulfones **4h–j** (Table 2). Under optimized conditions, the condensation completed in H$_2$O with 10% molar excess of **1h–j** at room temperature for 24 h (Method C) to afford compounds **4h–j** in 90–95% yields (Table 2, entries 14–16). Unexpectedly, a partial *cis*/*trans* isomerization around the C=N double bond proceeded during the reaction. Condensation of (*E*)-**1j** with **2j** and **3** gave mixture of (*E*)- and (*Z*)-isomers of **4j** in a ratio of 97:3 (entry 16), reactions of **1h** (*E*/*Z* = 59:41) or **1i** (*E*/*Z* = 72:28) with the corresponding aldehydes **2h,i** and sulfinic acid **3** resulted

in mixtures of (*E*)- and (*Z*)-**4h,i** in ratio of 90:10 and 89:11, respectively. We suppose that these products are formed under thermodynamic control conditions, since an increase in the reaction time up to 48 h had no effect on isomeric ratio. Presumably, the *cis*/*trans* isomerization proceeded via addition of sulfinic acid **3** to the C=N double bond of **4h–j** followed by fast elimination.

Configuration of both stereoisomers of compounds **4h–j** was assigned by the comparison of their ^{1}H and ^{13}C NMR spectra with those of semicarbazones **1h–j** in DMSO-d_6. Chemical shifts of the CH=N proton in the major isomers of **4h–j** (7.14–7.18 ppm) are close to those of (*E*)-**1h–j** (7.08–7.16 ppm) and in minor isomers of **4h–j** (6.33–6.48 ppm) are close to those of (*Z*)-**1h,i** (6.34–6.37 ppm). A long-range coupling ^{4}J between the NH and CH protons was observed in the spectra of the major isomers of **4h–j** (0.6–0.7 Hz) and (*E*)-**1h–j** (0.6–0.7 Hz), while the spectra of the minor isomers of **4h–j** and (*Z*)-**1h,i** did not show this coupling. Close values of carbon chemical shifts of the α-CH_2 group were observed for (*E*)-**1h,i** (25.0 and 33.6 ppm) and the major isomer of **4h,i** (25.0 and 33.5 ppm), and for (*Z*)-**1h,i** (20.1 and 28.5 ppm) and the minor isomer of **4h,i** (20.3 and 28.6 ppm). Thus, the major isomers of **4h–j** have (*E*)-configuration, and minor isomers of **4h–j** have (*Z*)-configuration.

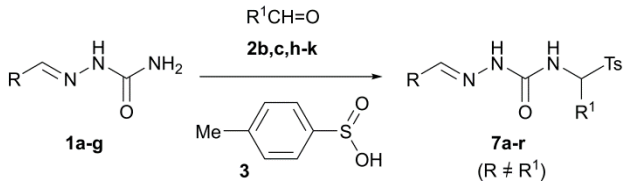
We also tried to perform the three-component condensation using 4-substituted semicarbazones. However, all attempts to prepare of sulfone **6** by the reaction of semicarbazone **5a** with benzaldehyde (**2a**) and sulfinic acid **3** under various conditions failed, and only starting **5a** was recovered. Therefore, substitution at the N4 nitrogen of semicarbazones hampers the condensation presumably due to steric hindrance.



Scheme 5. Attempt to synthesize sulfone **6** from 4-substituted semicarbazone **5a**.

Next, we studied the condensation of various aldehydes with semicarbazones of other aldehydes and *p*-toluenesulfinic acid. It should be noted that this reaction could be complicated by the formation of trans-semicarbazonation products.

We found that the condensation proceeds smoothly with aliphatic aldehydes and semicarbazones of aromatic aldehydes (Scheme 6). The transformation of 1-arylidene-semicarbazides into 1-alkylidene-derivatives does not take place under reaction conditions. It can be explained by a higher thermodynamic stability of semicarbazones of aromatic aldehydes compared with semicarbazones of aliphatic aldehydes due to conjugation effect in the former ones.



Scheme 6. Synthesis of "mixed" sulfones **7a–r** by the reaction of semicarbazones **1a–g**, with aldehydes **2b,c,h–k** and sulfinic acid **3**.

Thus, semicarbazones of aromatic aldehydes **1a,b,d–g** reacted with aliphatic aldehydes **2h–j** (1.25 equiv) and sulfinic acid **3** (1.25 equiv) in 80% aq HCOOH at room temperature for 24 h (Method B) to give the corresponding sulfones **7a–e,g–o** in high yields (71–96%) (Table 3). Reaction of semicarbazone **1b** with butanal (**2i**) and sulfinic acid **3** also proceeded in 95% aq EtOH (Method A) affording sulfone **7d** in 96% yield, however, the reaction rate was lower than in 80% aq HCOOH (Method B) (entry 4 vs entry 5). According to Method B, sulfone **7f** was prepared from semicarbazone **1b**, formaldehyde (1.05 equiv) and sulfinic acid (1.05 equiv) in 69% yield (Table 3, entry 7)

Table 3. Synthesis of sulfones **7a–r** by the reaction of semicarbazones of aromatic aldehydes **1a–g** with aldehydes **2b,c,h–k** and *p*-toluenesulfinic acid.

Entry	1	2	R	R^1	Method [a]	Product	Yield (%) [b]
1	**1a**	**2h**	Ph	Et	B	**7a**	77
2	**1a**	**2i**	Ph	Pr	B	**7b**	88
3	**1b**	**2h**	4-MeC_6H_4	Et	B	**7c**	82
4	**1b**	**2i**	4-MeC_6H_4	Pr	A	**7d**	96
5	**1b**	**2i**	4-MeC_6H_4	Pr	B	**7d**	86
6	**1b**	**2j**	4-MeC_6H_4	*i*-Pr	B	**7e**	71
7 [c]	**1b**	**2k**	4-MeC_6H_4	H	B	**7f**	69
8	**1d**	**2h**	4-EtC_6H_4	Et	B	**7g**	81
9	**1d**	**2i**	4-EtC_6H_4	Pr	B	**7h**	84
10	**1e**	**2h**	4-*i*-PrC_6H_4	Et	B	**7i**	86
11	**1e**	**2i**	4-*i*-PrC_6H_4	Pr	B	**7j**	83
12	**1f**	**2h**	4-*t*-BuC_6H_4	Et	B	**7k**	83
13	**1f**	**2i**	4-*t*-BuC_6H_4	Pr	B	**7l**	84
14	**1g**	**2h**	5-NO_2-2-furyl	Et	B	**7m**	91
15	**1g**	**2i**	5-NO_2-2-furyl	Pr	B	**7n**	92
16	**1g**	**2j**	5-NO_2-2-furyl	*i*-Pr	B	**7o**	89
17	**1b**	**2c**	4-MeC_6H_4	4-$MeOC_6H_4$	A	**7p**	95 [d]
18	**1c**	**2b**	4-$MeOC_6H_4$	4-MeC_6H_4	A	**7r**	96 [e]

[a] Method A: 95% aq EtOH, **1**:**2**:**3** molar ratio = 1:1.5:1.5, rt, 7 days; Method B: 80% aq HCOOH, **1**:**2**:**3** molar ratio = 1:1.25:1.25, rt, 1 day. [b] Isolated yield. [c] **1b**:**2k**:**3** molar ratio = 1:1.05:1.05. [d] The crude product contained 5mol% of (*E*)-**4c**. [e] The crude product contained 5mol% of (*E*)-**4b**.

According to ^{1}H NMR spectroscopic data, sulfones **7a–o** were formed as a single geometric isomer with (*E*)-configuration of the C=N double bond.

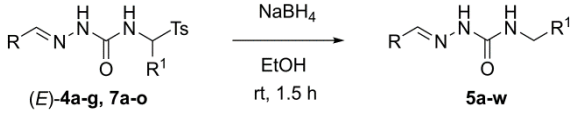
The condensation of aromatic aldehydes with semicarbazones of other aromatic aldehydes and sulfinic acid **3** gave the expected 4-(tosylmethyl)semicarbazones **7** along with a small amount of trans-semicarbazonation products. When semicarbazone of *p*-methylbenzaldehyde (**1b**) was reacted with *p*-methoxybenzaldehyde (**2c**) and acid **3** in EtOH for 7 days (Method A) a mixture of sulfones **7p** and (*E*)-**4c** in a ratio of 95:5 was isolated (Table 3, entry 17). Analogously, the condensation of semicarbazone of *p*-methoxybenzaldehyde (**1c**) with *p*-methybenzaldehyde (**2b**) and acid **3** under Method A conditions gave a 95:5 mixture of **7r** and (*E*)-**4b** (entry 18).

We found that alkylidene group in semicarbazones of aliphatic aldehydes or ketones was readily replaced by arylidene group when these semicarbazones were reacted with aromatic aldehydes and sulfinic acid **3** under various conditions. The treatment of propanal semicarbazone (**1h**) (1.1 equiv) with benzaldehyde (**2a**) (1.0 equiv) and acid **3** (1.0 equiv) in H_2O at room temperature for 24 h gave a mixture of benzaldehyde semicarbazone [(*E*)-**1a**], two "symmetrical" sulfones—(*E*)-**4a** and **4h** (E/Z = 89:11), and "mixed" sulfone - (*E*)-1-propylidene-4-[(phenyl)(tosyl)methyl]- semicarbazide in a ratio of 29:5:21:45, respectively (^{1}H NMR spectroscopic data). Equimolar amounts of acetone semicarbazone, benzaldehyde (**2a**) and acid **3** reacted in EtOH at room temperature for 7 h 20 min to afford a 80:20 mixture of benzaldehyde semicarbazone [(*E*)-**1a**] and sulfone (*E*)-**4a**.

We found that the obtained 4-(tosylmethyl)semicarbazones **4a–j** and **7a–r** are efficient reagents for amidoalkylation of various nucleophiles. We started with the hydride reduction affording 4-substituted semicarbazones. These compounds are of current interest due to their various biological activities such as antimicrobial, anticonvulsant, anti-HIV, antitrypanosomal, antihypertensive, and herbicidal effects. The reported syntheses of 4-substituted semicarbazones include condensation of carbonyl compounds or their derivatives with 4-substituted semicarbazides, *N*-carbamoylation of hydrazones, and substitution of group X in $RR^1CH{=}NR^2NHC(O)X$ (where X = NH_2, OR', Cl, etc.) under the action of amines. The drawbacks of these methods are low availability of some starting

compounds, multistep syntheses, harsh reaction conditions, laborious procedures, use of hazardous reagents, etc.

We showed that sulfones (*E*)-**4a–g** and **7a–o** were smoothly reduced with $NaBH_4$ (1.1–2.0 equiv.) in EtOH at room temperature for 1.5 h to give the corresponding 4-substituted semicarbazones **5a–w** in good to excellent yields (Scheme 7, Table 4).



Scheme 7. Synthesis of 4-substituted semicarbazones **5a-w** by the reduction of sulfones (*E*)-**4a–g** and **7a–o** with $NaBH_4$.

Table 4. Synthesis of 4-substituted semicarbazones **5a-w** by the reduction of sulfones (*E*)-**4a–g** and **7a–o** with $NaBH_4$ (EtOH, rt, 1.5 h).

Entry	Sulfone	R	R^1	Equiv. of $NaBH_4$	Product	Yield (%) [a]
1	(*E*)-**4a**	Ph	Ph	1.1	**5a**	93
2	**7a**	Ph	Et	2.0	**5b**	91
3	**7b**	Ph	Pr	2.0	**5c**	93
4	(*E*)-**4b**	4-MeC_6H_4	4-MeC_6H_4	1.1	**5d**	94
5	**7c**	4-MeC_6H_4	Et	2.0	**5e**	89
6	**7d**	4-MeC_6H_4	Pr	2.0	**5f**	89
7	**7e**	4-MeC_6H_4	*i*-Pr	2.0	**5g**	95
8	**7f**	4-MeC_6H_4	H	2.0	**5h**	96
9	(*E*)-**4c**	4-$MeOC_6H_4$	4-$MeOC_6H_4$	2.0	**5i**	94
10	(*E*)-**4d**	4-EtC_6H_4	4-EtC_6H_4	1.1	**5j**	82
11	**7g**	4-EtC_6H_4	Et	2.0	**5k**	91
12	**7h**	4-EtC_6H_4	Pr	2.0	**5l**	88
13	(*E*)-**4e**	4-*i*-PrC_6H_4	4-*i*-PrC_6H_4	1.1	**5m**	60
14	**7i**	4-*i*-PrC_6H_4	Et	2.0	**5n**	92
15	**7j**	4-*i*-PrC_6H_4	Pr	2.0	**5o**	81
16	(*E*)-**4f**	4-*t*-BuC_6H_4	4-*t*-BuC_6H_4	1.1	**5p**	88
17	**7k**	4-*t*-BuC_6H_4	Et	2.0	**5r**	99
18	**7l**	4-*t*-BuC_6H_4	Pr	2.0	**5s**	100
19	(*E*)-**4g**	5-NO_2-2-furyl	5-NO_2-2-furyl	1.5	**5t**	89
20	**7m**	5-NO_2-2-furyl	Et	1.5	**5u**	85
21	**7n**	5-NO_2-2-furyl	Pr	1.5	**5v**	84
22	**7o**	5-NO_2-2-furyl	*i*-Pr	1.5	**5w**	85

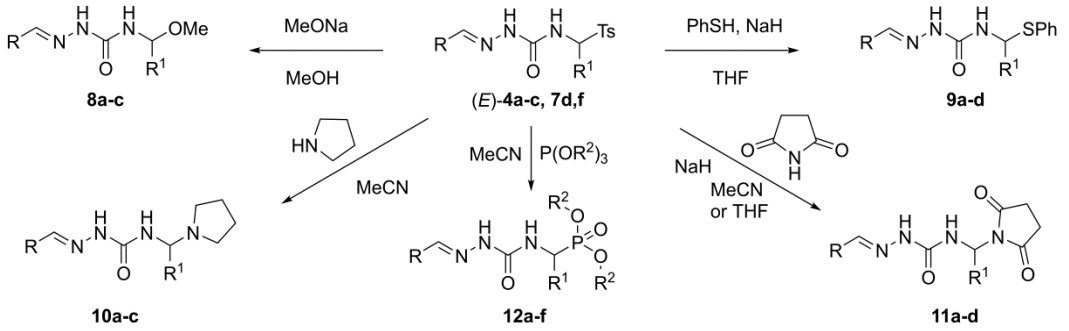
[a] Isolated yield.

According to ^{1}H NMR spectroscopic data, semicarbazones **5a–w** were obtained as a single geometric isomer. Since the starting compounds had (*E*)-configuration, the same configuration was assigned to **5a-w**.

Thus, we developed a novel general two-step approach to 4-substituted semicarbazones starting from semicarbazones (e.g., **1a-j**) based on preparation of 4-(tosylmethyl)semicarbazones (e.g., **4a–j** and **7a–r**) followed by their reduction with $NaBH_4$. This approach has various advantages over classic syntheses of 4-substituted semicarbazones. For example, following our method 4-propyl-, 4-butyl-, and 4-isobutylsemicarbazones of 5-nitrofurfural (**5u–w**) were obtained from readily available 5-nitrofurfural semicarbazone (**1g**) in 75–77% overall yields (see, Tables 2–4), while previously reported synthesis of these compounds included condensation (51–65% yields) of 5-nitrofurfural with the

corresponding 4-substituted semicarbazides, which were prepared in 4 steps starting from nitrourea [45].

Next, 4-(tosylmethyl)semicarbazones **4** and **7** were reacted with typical *O*- and *S*-nucleophiles such as methylate-anion and phenylthiolate-anion. The reaction of sulfones (*E*)-**4b,c** and **7d** with MeONa (1.09–1.10 equiv) smoothly proceeded in MeOH at room temperature for 3 h to give the corresponding products of the tosyl group substitution, ethers **8a–c**, in excellent yields (Scheme 8, Table 5, entries 1–3). Similarly, the treatment of sulfones (*E*)-**4b,c** and **7d,f** with PhSNa (1.09–1.10 equiv), generated by reaction of PhSH with NaH, in THF (rt, 3 h) afforded phenylthio derivatives **9a–d** in good to excellent yields (entries 4–7).



Scheme 8. Reactions of (*E*)-**4a–c** and **7d,f** with *O*-, *S*-, *N*-, and *P*-nucleophiles.

Compounds **8a–c** and **9a–d** are the first representatives of previously unknown types of 4-substituted semicarbazones. They can be considered as novel amidoalkylating reagents for organic synthesis, and also as potentially biological active substances. For example, 4-(hydroxymethyl)nitrofurazone (a close analog of compounds **8**) was found to exhibit remarkable trypanocidal activity [46].

Pyrrolidine and sodium succinimide were chosen as *N*-nucleophiles for amidoalkylation reaction with 4-(tosylmethyl)semicarbazones. We found that the treatment of α-aryl sulfones (*E*)-**4b,c** with excess of pyrrolidine (2.17–2.21 equiv) in MeCN at room temperature for 1.5 h gave the expected aminals **10a,b** in 92–95% yields (Table 5, entries 8 and 10). In contrast, the reaction of α-alkyl sulfone **7d** with pyrrolidine (2.96 equiv) in MeCN (rt, 6h) afforded a mixture of aminal **10c** and semicarbazone (*E*)-**1b** in a ratio of 15:85 (entry 11). We suppose that the initially formed **10c** further reacted with excess of pyrrolidine to give (*E*)-**1b** as a product of nucleophilic substitution via an S_N1-type pathway. It is noteworthy that under the same conditions sulfone (*E*)-**4b** afforded only aminal **10a** in 86% yield (entry 9).

Similarly to **10c**, compounds **10a,b** have a strong tendency to cleavage of the N4-C bond to produce the corresponding semicarbazones (*E*)-**1b,c**. For example, these compounds partly decomposed during crystallization from boiling MeCN to give mixtures of **10a**/(*E*)-**1b** and **10b**/(*E*)-**1c** in ratio of 83:17 and 72:28, respectively. Slow formation of (*E*)-**1b,c** was also observed upon storage of solid samples of **10a,b** in closed vessels at room temperature (2mol% for 4 days according to ^{1}H

Table 5. Amidoalkylation of *O*-, *S*-, *N*-, and *P*-nucleophiles with sulfones (*E*)-**4a–c** and **7d,f**.

Entry	Sulfone	R	R^1	R^2	Reaction Conditions	Product	Yield (%)[a]
1	(*E*)-**4b**	4-MeC_6H_4	4-MeC_6H_4	-	MeONa (1.10 equiv), MeOH, rt, 3 h	**8a**	98
2	(*E*)-**4c**	4-$MeOC_6H_4$	4-$MeOC_6H_4$	-	MeONa (1.10 equiv), MeOH, rt, 3 h	**8b**	97
3	**7d**	4-MeC_6H_4	Pr	-	MeONa (1.09 equiv), MeOH, rt, 3 h	**8c**	96

4	(*E*)-**4b**	4-MeC_6H_4	4-MeC_6H_4	-	PhSH (1.15 equiv), NaH (1.10 equiv), THF, rt, 3 h	**9a**	99
5	(*E*)-**4c**	4-$MeOC_6H_4$	4-$MeOC_6H_4$	-	PhSH (1.13 equiv), NaH (1.09 equiv), THF, rt, 3 h	**9b**	96
6	**7d**	4-MeC_6H_4	Pr	-	PhSH (1.15 equiv), NaH (1.10 equiv), THF, rt, 3 h	**9c**	89
7	**7f**	4-MeC_6H_4	H	-	PhSH (1.12 equiv), NaH (1.10 equiv), THF, rt, 3 h	**9d**	83
8	(*E*)-**4b**	4-MeC_6H_4	4-MeC_6H_4	-	Pyrrolidine (2.21 equiv), MeCN, rt, 1.5 h	**10a**	95
9	(*E*)-**4b**	4-MeC_6H_4	4-MeC_6H_4	-	Pyrrolidine (3.01 equiv), MeCN, rt, 6 h	**10a**	86
10	(*E*)-**4c**	4-$MeOC_6H_4$	4-$MeOC_6H_4$	-	Pyrrolidine (2.17 equiv), MeCN, rt, 1.5 h	**10b**	92
11	**7d**	4-MeC_6H_4	4-MeC_6H_4	-	Pyrrolidine (2.96 equiv), MeCN, rt, 6 h	**10c**[b]	-
12	(*E*)-**4b**	4-MeC_6H_4	4-MeC_6H_4	-	Succinimide (1.56 equiv), NaH (1.50 equiv), THF, rt, 3.5 h	**11a**	84
13	(*E*)-**4c**	4-$MeOC_6H_4$	4-$MeOC_6H_4$	-	Succinimide (1.56 equiv), NaH (1.49 equiv), THF, rt, 3.5 h	**11b**	75
14	**7d**	4-MeC_6H_4	Pr	-	Succinimide (1.56 equiv), NaH (1.49 equiv), THF, rt, 3.5 h	**11c**	75
15	**7f**	4-MeC_6H_4	H	-	Succinimide (1.56 equiv), NaH (1.51 equiv), THF, rt, 3.5 h	**11d**	-
16	**7f**	4-MeC_6H_4	H	-	Succinimide (1.53 equiv), NaH (1.51 equiv), MeCN, rt, 3.5 h	**11d**	56
17	(*E*)-**4a**	Ph	Ph	OMe	$P(OMe)_3$ (2.99 equiv), MeCN, reflux, 1 h	**12a**	98
18	(*E*)-**4a**	Ph	Ph	OEt	$P(OEt)_3$ (2.96 equiv), MeCN, reflux, 1 h	**12b**	87
19	(*E*)-**4b**	4-MeC_6H_4	4-MeC_6H_4	OMe	$P(OMe)_3$ (2.91 equiv), MeCN, reflux, 1 h	**12c**	98
20	(*E*)-**4b**	4-MeC_6H_4	4-MeC_6H_4	OEt	$P(OEt)_3$ (2.99 equiv), MeCN, reflux, 1 h	**12d**	96
21	(*E*)-**4c**	4-$MeOC_6H_4$	4-$MeOC_6H_4$	OMe	$P(OMe)_3$ (3.00 equiv), MeCN, reflux, 1 h	**12e**	95
22	**7d**	4-MeC_6H_4	Pr	OMe	$P(OMe)_3$ (4.96 equiv), MeCN, reflux, 6 h	**12f**	94
23	**7f**	4-MeC_6H_4	H	OMe	$P(OMe)_3$ (2.90 equiv), MeCN, reflux, 1 h	NR[c]	-

[a] Isolated yield. [b] Obtained in a mixture with semicarbazone (*E*)-**1b**, **10c**/(*E*)-**1b** = 15:85. [c] No reaction.

NMR data). The above tendency can be explained by a high stability of the iminium cations arising from the heterolytic cleavage of the N4-C bond.

Sulfones (*E*)-**4b,c**, **7d,f** reacted with sodium succinimide (1.49–1.51 equiv) generated by treatment of succinimide with NaH in THF at room temperature for 3.5 h to give the corresponding succinimido-derivatives **11a–d** along with some unidentified side products (ca. 7–14% according to

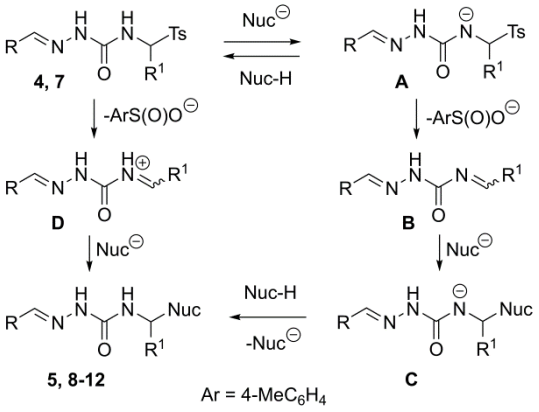
^{1}H NMR data) (entry 12–15). In MeCN the reaction between sulfone **7f** and sodium succinimide (1.51 equiv) also proceeded (rt, 3.5 h) to afford compound **11d**, however, the amount of unidentified side products under these conditions increased compared with THF (ca. 13% in MeCN vs ca. 7% in THF) (entry 16). Crude **11a–d** were purified using silica gel column chromatography to give the pure compounds in 56–84% yields.

Thus, the amidoalkylation of *N*-nucleophiles with 4-(tosylmethyl)semicarbazones provides a convenient general access to various semicarbazone aminals. To the best of our knowledge, the only reported synthesis of these compounds is based on the reaction of some semicarbazones with formaldehyde and secondary amines affording products in moderate (44–48%) or not specified yields. Some of the obtained aminals demonstrated pronounced antibacterial activity [47].

Amidoalkylation of *P*-nucleophiles (trimethyl phosphite or triethyl phosphite) with sulfones (*E*)-**4a-c** gave the corresponding products of the Arbuzov transformation, phosphonates **12a–e**, in excellent yields (87–98%) (Table 5, entries 17–21). However, in contrast to other nucleophiles, the phosphites reacted with sulfones (*E*)-**4a–c** under more drastic conditions (2.91–3.00 equiv of phosphite, refluxing MeCN, 1 h). The rate of the reaction between α-alkyl sulfone **7d** and $P(OMe)_3$ (2.88 equiv) in refluxing MeCN significantly decreased compared with α-aryl sulfones (*E*)-**4a–c**. Thus, after 2.5 h, a mixture of starting material **7d** and phosphonate **12f** in a ratio of 21:79 was isolated. After 6 h with 4.96 equivalents of $P(OMe)_3$ in refluxing MeCN reaction was complete to provide phosphonate **12f** in 94% yield (entry 22). It is noteworthy that sulfone **7f** being treated with $P(OMe)_3$ (MeCN, reflux) remained intact (entry 23).

Compounds **12a–f** represent a novel type of derivatives of α-aminophoshonic acids which are currently of great interest due to their pronounced biological activities [48], e.g., antibacterial, anticancer, and enzyme inhibition properties.

We suppose that the pathway of the reaction of 4-(tosylmethyl)semicarbazones **4** and **7** with nucleophiles with relatively strong basicity ($NaBH_4$, MeONa, PhSNa, sodium succinimide, and pyrrolidine) differs from that with weakly basic phosphites. In the first case, we suppose that the reaction proceeds through an E1cB-type elimination of *p*-toluenesulfinic acid to give *N*-acylimines **B** followed by addition of nucleophile to the C=N double bond (Scheme 9).



Scheme 9. Plausible pathways for amidoalkylation of anionic nucleophiles, with 4-(tosylmethyl)semicarbazones **4** and **7**.

Because of low basicity phosphites can not participate in the amidoalkylation via the E1cB-Ad_N pathway. If the transformation proceeded via S_N2 mechanism the rate of the reaction between $P(OMe)_3$ and α-unsubstituted sulfone **7f** would be much higher compared with α-alkyl sulfone **7d** (Table 5, entry 22 vs entry 23). However, α-unsubstituted sulfone **7f** did not react with $P(OMe)_3$, therefore, S_N2 mechanism can be excluded. We suppose that the amidoalkylation of phosphites proceeds via S_N1 mechanism with the formation of *N*-acyliminium cations **D**, which is supported by a higher rate of the reaction between phosphites and α-aryl sulfones (*E*)-**4a–c** compared with α-alkyl sulfone **7d** (entries 17–21 vs entry 22).

3. Conclusions

A general synthesis of 4-(tosylmethyl)semicarbazones of aliphatic and aromatic aldehydes based on three-component condensation of the corresponding semicarbazones with various aldehydes and *p*-toluenesulfinic acid has been developed. The scope and limitations of this condensation were investigated. Under optimal conditions, the target compounds can be obtained in high yields from aliphatic or aromatic aldehydes and semicarbazones of aromatic aldehydes, and from aliphatic aldehydes and semicarbazones of aliphatic aldehydes. The obtained compounds represent a novel type of α-amidoalkylating reagents, which makes it possible to easily introduce a (4-semicarbazono)methyl moiety into various nucleophilic substrates. The synthetic utility of these reagents has been demonstrated by their reactions with *H*- (sodium borohydride), *O*- (sodium methylate), *S*- (sodium phenylthiolate), *N*- (pyrrolidine, sodium succinimide), and *P*-nucleophiles (trialkyl phosphites) affording the corresponding products of the tosyl group substitution, 4-substituted semicarbazones, in particular, α-functionalized ones. We believe that this research provides a valuable extension of the classic α-amidoalkylation reaction.

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References

1. Maryanoff, B.E.; Zhang, H.-C.; Cohen, J.H.; Turchi, I.J.; Maryanoff, C.A. Cyclizations of N-acyliminium ions. *Chem. Rev*. **2004**, *104*, 1431–1628.
2. Mazurkiewicz, R.; Październiok-Holewa, A.; Adamek, J.; Zielińska, K. α-Amidoalkylating agents: Structure, synthesis, reactivity and application. *Adv. Heterocycl. Chem*. **2014**, *111*, 43–94.
3. Wu, P.; Nielsen, T.E. Scaffold diversity from N-acyliminium ions. *Chem. Rev*. **2017**, *117*, 7811–7856.
4. Alujas-Burgos, S.; Oliveras-González, C.; Álvarez-Larena, Á.; Bayón, P.; Figueredo, M.J. Iterative Synthetic Strategy for Azaphenalene Alkaloids. Total Synthesis of (−)-9aepi-Hippocasine. *Org. Chem*. **2018**, *83*, 5052–5057.
5. Anderson, B.K.; Livinghouse, T.J. Divergent Stereocontrolled Synthesis of the Enantiopure Tetracyclic Cores of Asparagamine A and Stemofoline via an Intramolecular 2-Propylidine-1, 3-(bis) silane Bicyclization. *Org. Chem*. **2015**, *80*, 9847–9855.
6. Plas, A.; Marchand, F.; Eschalier, A.; Troin, Y.; Chalard, P. Stereoselective synthesis and in vivo evaluation of the analgesic activity of polysubstituted bispidines. *Eur. J. Org. Chem.* **2012**, *2012*, 6070–6079.
7. Han, G.; LaPorte, M.G.; Folmer, J.J.; Werner, K.M.; Weinreb, S.M.J. Total Syntheses of the Securinega Alkaloids (+)-14,15-Dihydronorsecurinine, (−)-Norsecurinine, and Phyllanthine. *Org. Chem.* **2000**, *65*, 6293–6306.
8. Lee, Y.-S; Jung, J.-W.; Kim, S.-H.; Jung, J.-K.; Paek, S.-M.; Kim, N.-J.; Chang, D.-J.; Lee, J.; Suh, Y.-G. First total synthesis and structural confirmation of fluvirucinine A2 via an iterative ring expansion strategy. *Org. Lett.* **2010**, *12*, 2040–2043.
9. Coleman, R.S.; Felpin, F.-X.; Chen, W.J. Mitomycin Synthetic Studies: Stereocontrolled and Convergent Synthesis of a Fully Elaborated Aziridinomitosane. *Org. Chem.* **2004**, *69*, 7309–7316.
10. Metais, E.; Overman, L.E.; Rodriguez, M.I.; Stearns, B.A.J. Halide-Terminated N-Acyliminium Ion−Alkyne Cyclizations: A New Construction of Carbacephem Antibiotics. *Org. Chem.* **1997**, *62*, 9210–9216.
11. Flann, C.J.; Overman, L.E.J. Enantioselective total synthesis of streptazolin. The tandem use of iminium ion vinylsilane cyclizations and intramolecular acylations. *Am. Chem. Soc.* **1987**, *109*, 6115–6118.
12. Wang, X.; Li, J.; Saporito, R.A.; Toyooka, N. Enantiodivergent synthesis of the quinolizidine poison frog alkaloid 195C. *Tetrahedron* **2013**, *69*, 10311–10315.
13. Vlahov, I.R.; Wang, Y.; Vetzel, M.; Hahn, S.; Kleindl, P.J.; Reddy, J.A.; Leamon, C.P. Acid mediated formation of an N-acyliminium ion from tubulysins: A new methodology for the synthesis of natural tubulysins and their analogs. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 6778–6781.
14. Hjelmgaard, T.; Søtofte, I.; Tanner, D.J. Total synthesis of pinnamine and anatoxin-a via a common intermediate. A caveat on the anatoxin-a endgame. *Org. Chem.* **2005**, *70*, 5688–5697.
15. Chavan, S.P.; Chittiboyina, A.G.; Ravindranathan, T.; Kamat, S.K.; Kalkote, U.R.J. Diastereoselective Amidoalkylation of (3S,7aR)-6-Benzyl-7-hydroxy-3-phenyltetra- hydro-5H-imidazo[1,5-c][1,3]thiazol-5-one: A Short and Highly Efficient Synthesis of (+)-Biotin. *Org. Chem*. **2005**, *70*, 1901–1903.

16. Moolenaar, M.J.; Speckamp, W.N.; Hiemstra, H.; Poetsch, E.; Casutt, M. Synthesis of D-(+)-Biotin through Selective Ring Closure of N-Acyliminium Silyl Enol Ethers. *Angew. Chem. Int. Ed.* **1995**, 34, 2391–2393.
17. Pomplun, S.; Wang, Y.; Kirschner, A.; Kozany, C.; Bracher, A.; Hausch, F. Rational Design and Asymmetric Synthesis of Potent and Neurotrophic Ligands for FK506-Binding Proteins (FKBPs). *Angew. Chem. Int. Ed*. **2015**, *54*, 345–348.
18. Lorenz, J.C.; Busacca, C.A.; Feng, X.W.; Grinberg, N.; Haddad, N.; Johnson, J.; Kapadia, S.; Lee, H.; Saha, A.; Sarvestani, M.; Spinelli, E.M.; Varsolona, R.; Wei, X.; Zeng, X.; Senanayake, C.H.J. Large-Scale Asymmetric Synthesis of a Cathepsin S Inhibitor. *Org. Chem*. **2010**, *75*, 1155–1161.
19. McDermott, T.S.; Bhagavatula, L.; Borchardt, T.B.; Engstrom, K.M.; Gandarilla, J.; Kotecki, B.J.; Kruger, A.W.; Rozema, M.J.; Sheikh, A.Y.; Wagaw, S.H.; Wittenberger, S.J. Development of a Scalable Synthesis of Dipeptidyl Peptidase-4 Inhibitor ABT-279. *Org. Process Res. Dev.* **2009**, *13,* 1145–1155.
20. Joossens, J.; Van der Veken, P.; Lambeir, A.-M.; Augustyns, K.; Haemers, A.J. Development of Irreversible Diphenyl Phosphonate Inhibitors for Urokinase Plasminogen Activator. *Med. Chem.* **2004**, *47,* 2411–2413.
21. Vinogradov, M.G.; Turova, O.V.; Zlotin, S.G. The progress in the chemistry of N-acyliminium ions and their use in stereoselective organic synthesis. *Russian Chem. Rev*. **2017**, *86*, 1–17.
22. Marcantoni, E.; Petrini, M. Recent Developments in the Stereoselective Synthesis of Nitrogen-Containing Heterocycles using N-Acylimines as Reactive Substrates. *Adv. Synth. Catal*. **2016**, *358*, 3657–3682.
23. Royer, J.; Bonin, M.; Micouin, L. Chiral heterocycles by iminium ion cyclization. *Chem. Rev.* **2004**, *104,* 2311–2352.
24. Fesenko, A.A.; Grigoriev, M.S.; Shutalev, A.D.J. Nucleophile-Mediated Ring Expansion of 5-Acyl-substituted 4-Mesyloxymethyl-1,2,3,4-tetrahydropyrimidin-2-ones in the Synthesis of 7-Membered Analogues of Biginelli Compounds and Related Heterocycles. *Org. Chem*. **2017**, *82*, 8085–8110.
25. Antropow, A.H.; Xu, K.; Buchsbaum, R.J.; Movassaghi, M.J. Synthesis and Evaluation of Agelastatin Derivatives as Potent Modulators for Cancer Invasion and Metastasis. *Org. Chem*. **2017**, *82*, 7720–7731.
26. Lillo, V.J.; Saá, J.M. Towards Enzyme-like, Sustainable Catalysis: Switchable, Highly Efficient Asymmetric Synthesis of Enantiopure Biginelli Dihydropyrimidinones or Hexahydropyrimidinones. *Chem. Eur. J.* **2016**, *22*, 17182–17186.
27. Fesenko, A.A.; Shutalev, A.D.J. Synthesis of γ-Azido-β-ureido Ketones and Their Transformation into Functionalized Pyrrolines and Pyrroles via Staudinger/aza-Wittig Reaction. *Org. Chem*. **2013**, *78*, 1190–1207.
28. Martinovich, Yu. A.; Ramsh, S.M.; Hamoud, F.; Fundamenskii, V.S.; Gurzhii, V.V.; Zakharov, V.I.; Khrabrova, E.S. Aminomethylation of Thiourea with Formaldehyde and Cyclic Amines. *Russ. J. Org. Chem*. **2018**, *54*, 878–885.
29. Khairullina, R.R.; Geniyatova, A.R.; Tyumkina, T.V.; Karamzina, D.S.; Ibragimov, A.G.; Dzhemilev, U.M. Synthesis of a new class of heterocycles 1, 7-dithia-3, 5-diazacycloalkan (e)-4-(thi) ones using Cs-and Rb-containing catalysts. *Tetrahedron* **2017**, *73*, 7079–7084.
30. Shutalev, A.D. Reaction of α-(thio) amidoalkylation in the synthesis of α-cyano-substituted cyclic (thio) ureas and dithiocarbamates. *Chem. Heterocycl. Compd*. **1993**, 29, 1192–1199.
31. Shutalev, A.D.; Fesenko, A.A. 4-Hydroxy-4-methyl-5-tosylhexahydropyrimidin-2-imines: synthesis and different dehydration pathways. *Tetrahedron* **2011**, *67*, 6883–6888.
32. Solovyev, P.A.; Shutalev, A.D. Synthesis and oxidative aromatization of 5-acetyl-2-cyanoimino-6-methyl-4-phenyl-1, 2, 3, 4-tetrahydropyrimidine with manganese dioxide. *Chem. Heterocycl. Compd*. **2009**, *45*, 809–814.
33. Takimoto, M.; Ebisuno, T.; Shiba, R. The Reaction of Cyanoguanidine with Formaldehyde. I. Hydroxymethylation and Methoxymethylation of Cyanoguanidine. *Bull. Chem. Soc. Jpn*. **1983**, *56*, 3319–3322.
34. Trafimova, L.A.; Zimin, M.O.; Shutalev, A.D.J. *Chem. Res.* **2017**, *41*, 149–156.
35. Stalling, T.; Saak, W.; Martens, J. Synthesis of Bicyclic Thiazolidinethiones and Oxazolidinones by Water-Mediated Multicomponent Reactions (MCR) and Ring-Closing Metathesis (RCM). *Eur. J. Org. Chem*. **2013**, 8022–8032.
36. Hamersma, J.A.M.; Nossin, P.M.M.; Speckamp, W.N. Thia-acyliminium cyclisations: Synthesis of five-membered rings and macrocycles. *Tetrahedron* **1985**, *41*, 1999–2005.
37. Shikora, J.M.; Chemler, S.R. Synthesis of Benzyl Amines via Copper-Catalyzed Enantioselective Aza-Friedel–Crafts Addition of Phenols to N-Sulfonyl Aldimines. *Org. Lett*. **2018**, *20*, 2133–2137.

38. Boultwood, T.; Affron, D.P.; Bull, J.A. Studies on the synthesis of α-iodoaziridines and improved conditions for the synthesis of alkyl-α-iodoaziridines using ClMgCHI2. *Tetrahedron* **2015**, *71*, 4949–4957.
39. Skarbek, C.; Lesueur, L.L.; Chapuis, H.; Deroussent, A.; Pioche-Durieu, C.; Daville, A.; Caron, J.; Rivard, M.; Martens, T.; Bertrand, J.-R.; Cam, E.; Vassal, G.; Couvreur, P.; Desmaele, D.; Paci, A.J. Preactivated oxazaphosphorines designed for isophosphoramide mustard delivery as bulk form or nanoassemblies: Synthesis and proof of concept. *Med. Chem*. **2015**, *58*, 705–717.
40. Sierecki, E.; Errasti, G.; Martens, T.; Royer, J. Diastereoselective α-allylation of secondary amines. *Tetrahedron* **2010**, *66*, 10002–10007.
41. Scarim, C.B.; Jornada, D.H.; Machado, M.G.M.; Ferreira, C.M.R.; dos Santos, J.L.; Chung, M.C. Thiazole, thio and semicarbazone derivatives against tropical infective diseases: Chagas disease, human African trypanosomiasis (HAT), leishmaniasis, and malaria. *Eur. J. Med. Chem*. **2019**, *162*, 378−395.
42. Chingle, R.; Proulx, C.; Lubell, W.D. Azapeptide synthesis methods for expanding side-chain diversity for biomedical applications. *Acc. Chem. Res*. **2017**, *50*, 1541−1556.
43. Garg, B.S.; Jain, V.K. Analytical applications of thiosemicarbazones and semicarbazones. *Microchem. J.* **1988**, *38*, 144–169.
44. Fesenko, A.A.; Yankov, A.N.; Shutalev, A.D. An efficient and stereoselective approach to 14-membered hexaaza macrocycles using novel semicarbazone-based amidoalkylation reagents. *Tetrahedron Lett.* **2016**, *57*, 5784–5787.
45. Kawabe, K.; Suzui, T.; Iguchi, M. *Yakugaku Zasshi* **1960**, *80*, 65−68; *Chem. Abs.* **1960**, *54*, 62648.
46. Chung, M.-C.; Güido, R.V.C.; Martinelli, T.F.; Gonçalves, M.F.; Polli, M.C.; Botelho, K.C.A.; Varanda, E.A.; Colli, W.; Miranda, M.T.M.; Ferreira, E.I. Synthesis and in vitro evaluation of potential antichagasic hydroxymethylnitrofurazone (NFOH-121): A new nitrofurazone prodrug. *Bioorg. Med. Chem*. **2003**, *11*, 4779–4783.
47. Joshi, S; Manikpuri, A.D.; Tiwari, P. *Int. J. Chem. Sci*. **2009**, *7*, 869–877.
48. *Aminophosphonic and Aminophosphinic Acids: Chemistry and Biological Activity*; Kukhar, V.P., Hudson, H.R., Eds.; John Wiley & Sons: New York, NY, USA, 2000.