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N2-Alkylation of semicarbazones. A general and efficient protocol for the synthesis of 2-alkylsemicarbazides from semicarbazide

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Dedicated to Professor Lorenzo Testaferri in the occasion of his 75th birthday

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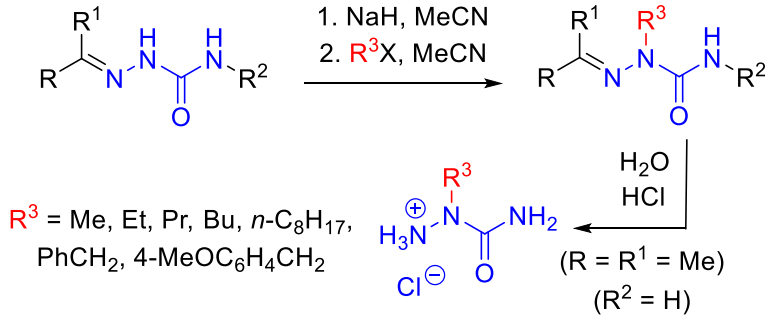
Abstract

Synthesis of 2-alkylsemicarbazones based on selective N2-alkylation of semicarbazones has been described. The synthesis involves deprotonation of semicarbazones with sodium hydride in MeCN followed by treatment with alkylating reagents. The developed alkylation method was applied to the preparation of hardly available 2-alkylsemicarbazides and their hydrochlorides from semicarbazide hydrochloride. This general and efficient protocol is based on preparation of acetone semicarbazone, its alkylation, and hydrolysis under mild conditions.



Keywords: Semicarbazides, semicarbazones, alkylation, hydrolysis

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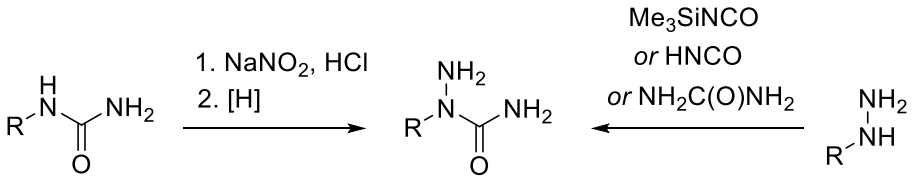
Introduction

Acyclic semicarbazides are versatile reagents commonly utilized for preparation of various acyclic and heterocyclic nitrogen-containing compounds, e.g. semicarbazones, azapeptides, hydantoines, pyrazoles, 1,2,4-triazoles, 1,2,4-triazines, 1,2,4-triazepines, pyrimidines, 1,3,4-oxadiazoles, azamacrocycles, etc.[1] Semicarbazides are also used for synthesis of various semicarbazide-containing substances with remarkable biological properties, particularly, analogs of antimicrobial nitrofurazone and nitrofurantoin,[2] selective peroxisome proliferator-activated receptor hPPARα agonist,[3] inhibitors of MALT1 protease,[4] azapeptide activators of apoptosis mediated by caspase-9 in cancer cells,[5] etc.

Semicarbazide hydrochloride is commercially available and, as a rule, many other acyclic semicarbazides can be readily prepared. However, no general and convenient approaches to 2-alkylsemicarbazides have been developed. Scheme 1 shows two commonly used methods of 2-alkylsemicarbazide synthesis. The first is based on nitrosonation of *N*-alkylureas with nitrous acid or its anhydride followed by reduction of nitroso group in the obtained *N*-alkyl-*N*-nitrosoureas with Zn in aqueous AcOH,[6-8] H_2 over Pd/C,[9] or using electrochemical method.[10] The second approach involves carbamoylation of the corresponding monosubstituted hydrazines with trimethylsilyl isocyanate,[4,11-13] urea,[14] or cyanic acid generated by reaction of Brønsted acid and metal cyanate.[15-18]



Scheme 1. Commonly used approaches to 2-alkylsemicarbazides.

In addition, there are some particular syntheses of 2-alkylsemicarbazides. For example, 2-methylsemicarbazide was prepared by the reaction of benzaldehyde methylhydrazone with phosgene and NH_3 followed by acid-catalyzed hydrolytic cleavage of benzylidene group.[19] A derivative of 2-benzylsemicarbazide was synthesized by *N*-alkylation of *tert*-butoxycarbonyl hydrazine followed by successive reactions with triphosgene, NH_3, HCl in MeOH, and aqueous $NaHCO_3$.[20] Synthesis of the hydromethanesulfonate salt of 2-(4-methylbenzyl)semicarbazide involved reaction of *tert*-butoxycarbonyl hydrazine with 4-methylbenzaldehyde to give the corresponding Boc-protected hydrazone which was reduced with H_2/Pd into 1,2-disubstituted hydrazine followed by treatment with trimethylsilyl isocyanate, and then with $MeSO_2OH$.[21]

All the above approaches to 2-alkylsemicarbazides are based on construction of semicarbazide fragment by N-N or C-N bond formation and have such drawbacks as multistep procedures, laborious isolation of products, low yields, use of highly toxic reagents, poor scalability, etc.

We hypothesized that general and preparative synthesis of 2-alkylsemicarbazides could be developed starting from commercially available unsubstituted semicarbazide. However, higher basicity and nucleophilicity of the nitrogen N1 in semicarbazide compared with the amide nitrogens N2 and N4 (e.g., pK_a = 3.86[22] and pK_a = 0.053[23] for protonated semicarbazide and urea, respectively, in water at 25 °C) inhibits direct alkylation at the nitrogen N2. Therefore, N(1)H_2-group should be protected with an electron-withdrawing alkylidene or arylidene group which result in decrease in nucleophilicity of the nitrogen N1 and significant increase in acidity of the N(2)H group. Deprotonation of N(2)H-group with appropriate base followed by

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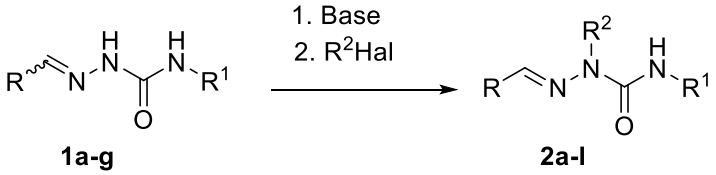
alkylation and deprotection would provide the target products. To our knowledge, there is the only report describing the application of this approach.[24] Namely, 2-{3-[4-(3-chlorophenyl)piperazin-1-yl]prop-1-yl}semicarbazide was prepared by deprotonation of benzaldehyde semicarbazone with $NaNH_2$ (1,4-dioxane, reflux, 1 h) followed by alkylation with 3-[4-(3-chlorophenyl)piperazin-1-yl]propyl chloride (reflux, 18 h) and hydrolysis (water, $H_2C_2O_4$, reflux) with removal of benzaldehyde formed by steam distillation. However, reaction time of the last step and isolation and purification of the target semicarbazide as well as yields in the alkylation and hydrolysis steps were not described. Since the acid-catalyzed hydrolysis of semicarbazones of aromatic aldehydes is known to proceed under drastic conditions along with the formation of side products, e.g. hydrazines from initially formed semicarbazides,[18] we supposed that hydrolytically labile semicarbazones of aliphatic ketones would be the best starting materials.

Herein we report a reliable method for selective N2-alkylation of semicarbazones to give 2-alkylsemicarbazones. A general three-step synthesis of 2-alkylsemicarbazides from semicarbazide hydrochloride involving preparation of acetone semicarbazone followed by its alkylation and mild hydrolysis is also described.

Results and Discussion

The first step of our approach to 2-alkylsemicarbazides was the development of selective alkylation of semicarbazones at the N2-nitrogen. Clearly, this alkylation can proceed only via formation of a conjugate base of the starting material. Various base/solvent combinations for deprotonation of semicarbazones (e.g. MeONa/DMF,[25,26] Et_4NOH/THF,[27-29] NaOH/EtOH-H_2O,[30] *t*-BuOK/THF,[5,31-33] NaH/DMF,[34] K_2CO_3/DMF,[35-37] Cs_2CO_3/MeCN,[38] *tert*-butylimino-tri(pyrrolidino)phosphorane/THF[39]) followed by treatment with alkylating reagents were reported. We tested some base/solvent combinations for the alkylation of semicarbazones of aromatic aldehydes (*E*)-**1a-c** as model compounds. Treatment of (*E*)-**1a** with BuBr in the presence of K_2CO_3 under the described contitions[37] (DMF, rt, 12h) failed to give *N*-butyl derivative **2a** (NMR data) (Scheme 2; Table 1, entry 1), while the yield of **2a** was reported to be 60%. Prolongation of the reaction time (15 h and 23 h) also did not result in product formation.



Scheme 2. Synthesis of 2-alkylsemicarbazones by alkylation of 2-unsubstituted semicarbazones.

Next, we reacted (*E*)-**1b** with significantly more active alkylating reagent MeI under the above conditions (K_2CO_3/DMF, rt, 17 h) and again no expected *N*-methylated product **2b** was formed (NMR data) (Table 1, entry 2). Thus, the conditions described in ref. 37 are inapplicable for N2-alkylation of semicarbazones.

We suppose that basicity of K_2CO_3 in DMF is not sufficient to generate essential concentrations of semicarbazone conjugated bases. It is noteworthy that the nature of semicarbazones, in particular their solubility in reaction media, may also play a role in the alkylation. Indeed, 4-substituted semicarbazone (*E*)-

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1c,[40] which is more soluble in organic solvents than (*E*)-**1a,b**, was found to react with MeI in the presence of K_2CO_3 in DMF at room temperature to give the expected *N*-methylated product **2c**, although the rate of this reaction is very low. According to NMR spectroscopic data, conversion of (*E*)-**1c** into **2c** was 39% after 22 h, and 50% after 5 days (entry 4). The rate of methylation of (*E*)-**1c** with MeI in the presence of DBU (DMF, rt, 24 h) was also low and only 14% conversion of the starting material into **2c** was observed (NMR data) (entry 5). Use of MeONa in MeOH failed to give compound **2c**.

Table 1. Synthesis of 2-alkylsemicarbazones **2b-l** by alkylation of semicarbazones **1b-g**[a]

Entry	**1**	R	R^2Hal	Base	Reaction conditions	Product	Yield,[b] %
1	(*E*)-**1a**	4-$MeOC_6H_4$	BuBr	K_2CO_3	DMF, rt, 12 h	**2a**	0
2	(*E*)-**1b**	4-MeC_6H_4	MeI	K_2CO_3	DMF, rt, 17 h	**2b**	0
3	(*E*)-**1b**	4-MeC_6H_4	MeI	NaH	MeCN, rt, 5.3 h	**2b**	95
4	(*E*)-**1c**	4-MeC_6H_4	MeI	K_2CO_3	DMF, rt, 120 h	**2c**	-[c]
5	(*E*)-**1c**	4-MeC_6H_4	MeI	DBU	DMF, rt, 24 h	**2c**	-[d]
6	(*E*)-**1c**	4-MeC_6H_4	MeI	NaH	MeCN, rt, 2 h	**2c**	97
7	(*E*)-**1d**	Ph	MeI	NaH	MeCN, rt, 1.5 h	**2d**	72
8	(*E*)-**1d**	Ph	EtI	NaH	MeCN, rt, 26 h	**2e**	90
9	(*E*)-**1d**	Ph	BuI	NaH	MeCN, reflux, 26 h	**2f**	88
10	(*E*)-**1d**	Ph	$PhCH_2Br$	NaH	MeCN, rt, 19 h	**2g**	96
11	**1e**[e]	Et	$PhCH_2Br$	NaH	MeCN, rt, 72 h	**2h**	70
12	**1f**[f]	Pr	$PhCH_2Cl$	NaH	MeCN, reflux, 4 h	**2i**	70
13	**1f**[f]	Pr	4-$MeOC_6H_4CH_2Cl$	NaH	MeCN, reflux, 4 h	**2j**	66
14	(*E*)-**1g**	*i*-Pr	$PhCH_2Cl$	NaH	MeCN, reflux, 4 h	**2k**	72
15	(*E*)-**1g**	*i*-Pr	4-$MeOC_6H_4CH_2Cl$	NaH	MeCN, reflux, 4 h	**2l**	78

[a] R^1 = $CH(C_6H_4Me\text{-}4)CH_2Ac$ for (*E*)-**1c** and **2c**, R^1 = H for other compounds. [b] Isolated yield at complete conversion of the starting material (NMR data). [c] (*E*)-**1c**/**2c** = 50:50. [d] (*E*)-**1c**/**2c** = 86:14. [e] (*E*)-**1e**/(*Z*)-**1e** = 86:14. [f] (*E*)-**1f**/(*Z*)-**1f** = 74:26.

We found that NaH in MeCN is the best choice for complete and selective N2-deprotonation of various semicarbazones. Treatment of (*E*)-**1c** with NaH (1.1 equiv.) in MeCN at room temperature smoothly gave the corresponding conjugated base which was reacted with excess of MeI (MeCN, rt, 2 h) to provide semicarbazone **2c** in 97% yield (entry 6). Analogously, after deprotonation with NaH in MeCN semicarbazone (*E*)-**1b** was alkylated with MeI (rt, 5.3 h) to afford compound **2b** in 95% yield (entry 3), and semicarbazone (*E*)-**1d** was alkylated with MeI, EtI, BuI, or $PhCH_2Br$ to give the corresponding compounds **2d-g** in 72-96% yields (entries 7-10). According to the ^1H NMR spectroscopic data, semicarbazones **2b-g** were obtained as a single stereoisomer with (*E*)-configuration, the same as in the starting materials **1b-d**.

Similarly, 2-benzyl- **2h**,**i**,**k** and 2-(4-methoxybenzyl)-substituted semicarbazones of aliphatic aldehydes **2j**,**l** were prepared in 66-78% yields by alkylation of semicarbazones of propanal, butanal, or 2-methylpropanal **1e**,**f**, (*E*)-**1g** after their deprotonation with NaH in MeCN (entries 11-15). Only a single stereoisomer of **2h-l** presumably with (*E*)-configuration was obtained in each case. Interestingly, while semicarbazones of propanal (**1e**) and butanal (**1f**) used for the alkylation were mixtures of (*E*)- and (*Z*)-isomers in a ratio of 86:14 and 74:26, respectively (NMR data), the corresponding alkylated products **2h-g** were isolated as (*E*)-isomers. It could be

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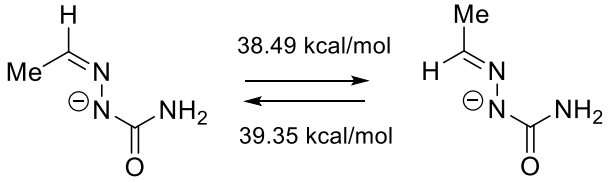
explained either by *Z*/*E*-isomerization in the course of the alkylation or by the fact that the minor (*Z*)-isomers were not alkylated and were lost during work up of reaction mixtures.

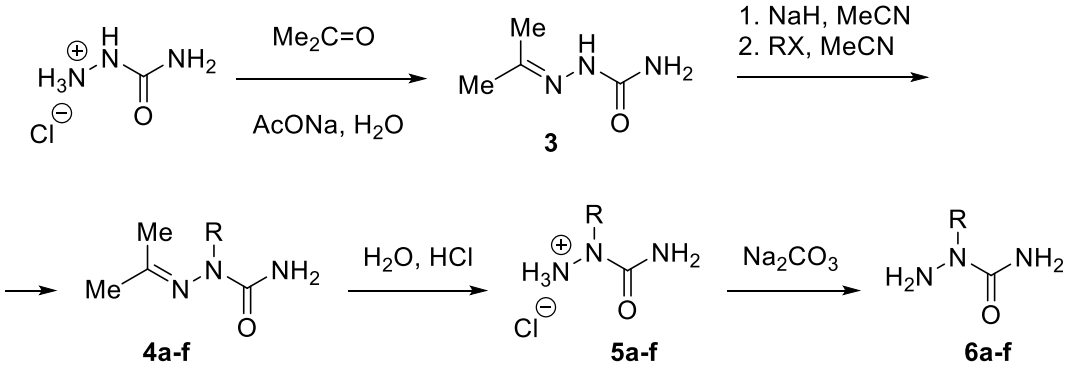
The most plausible *Z*/*E*-isomerization pathway in semicarbazones involves inversion at the N1 nitrogen atom.[41] We estimated energy barrier for the inversion in the conjugated base of ethanal semicarbazone using the DFT B3LYP/6-311++G(d,p) calculations. The IRC analysis demonstrated that the found transition state connect the desired minima. The data obtained show that energy barrier for the conversion of (*Z*)-isomer into (*E*)-isomer (Scheme 3) is relatively high (38.49 kcal/mol).



Scheme 3. Transformation of the (*Z*)-isomer of the conjugated base of ethanal semicarbazone into the (*E*)-isomer via inversion pathway.

Since the alkylation of the conjugated base of **1e** with $PhCH_2Br$ proceeds at room temperature (Table 1, entry 11), *Z*/*E*-isomerization can be excluded. Thus, we suppose that the isolation of only (*E*)-isomers of **2h-j** is due to the fact that (Z)-isomers of the starting materials **1e,f** were not alkylated, presumably due to steric hindrance.

Next we applied the above conditions to the N2-alkylation of hydrolytically labile acetone semicarbazone (**3**). Starting compound **3** was readily prepared from semicarbazide hydrochloride and acetone in the presence of sodium acetate (H_2O, rt) according to routine procedure in excellent yield (Scheme 4).



4-6 a R = Me, **b** R = Et, **c** R = Pr, **d** R = Bu, **e** R = CH_2Ph, **f** R = *n*-C_8H_{17}.

Scheme 4. Synthesis of 2-alkylsemicarbazides **6a-f** and their hydrochlorides **5a-f** from semicarbazide hydrochloride.

Compounds **4a-f** were synthesized by the treatment of **3** with NaH (1.05–1.07 equiv.) in MeCN at room tempetature for 40–60 min followed by the reaction of the generated conjugated base with excess of appropriate alkylating reagent. The degree of conversion of **3** into **4a-f** was determined by ^{1}H NMR spectroscopic data for crude products isolated after removal of all volatiles under reduced pressure.

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Reaction of the conjugated base of **3** with methyl iodide (10 equiv.) completed in MeCN at room temperature for 4 h. The resulting solution was evaporated to dryness under vacuum, the residue was dissolved in H_2O, the solution was heated at 60 °C for 10–15 min, and the solvent was removed under vacuum. The obtained oily residue was triturated with Et_2O/EtOH mixture (1:1) to give a solid product. ^{1}H NMR spectroscopic data showed that the isolated product was 2-methylsemicarbazide (**6a**) resulted from hydrolysis of **4a** upon water treatment. According to the data of elemental analysis the crystallized from EtOH or MeCN **6a** contained 33mol% of NaI. Therefore, we supposed that compound **6a** formed a stable complex with NaI. Since 2-methylsemicarbazide is highly soluble in water, aqueous work up of crude product to remove NaI became inacceptable in contrast to **2b-d**. Treatment of water solution of crude **6a** with lead nitrate for the same purpose was inefficient.

Next we used dimethyl sulfate as methylating reagent instead of MeI. The reaction of the conjugated base of **3** with dimethyl sulfate (1.06 equiv) smoothly proceeded at room temperature for 17 h to give semicarbazone **4a**. After removal of the solvent under reduced pressure, compound **4a** was readily hydrolyzed with excess of hydrochloric acid followed by evaporation of the solution formed under vacuum. Treatment of the obtained residue with cold *i*-PrOH afforded easy to handle crystalline 2-methylsemicarbazide hydrochloride (**5a**) in 72% yield (based on **3**) (Table 2, entry 1).

Table 2. Synthesis of 2-alkylsemicarbazides hydrochlorides **5a-f** by alkylation of the conjugated base of acetone semicarbazone (**3**) in MeCN followed by treatment with excess of hydrochloric acid (60 °C)

Entry	Alkylating reagent (equiv.)	Reaction conditions	Product	Yield,[a] %
1	$(MeO)_2SO_2$ (1.06)	rt, 17 h	**5a**	72
2	EtBr (10.3)	reflux, 9 h	**5b**	71
3	PrBr (5.0)	reflux, 9 h	**5c**	71
4	BuBr (10.0)	reflux, 9 h	**5d**	59
5	$PhCH_2Br$ (1.06)	reflux, 6.5 h	**5e**	60
6	*n*-$C_8H_{17}Br$ (5.0)	reflux, 9 h	**6f**[b]	58

[a] Isolated yield based on acetone semicarbazone (**3**). [b] After treatment with aq. Na_2CO_3.

Analogously, hydrochlorides of 2-ethyl- (**5b**), 2-propyl- (**5c**), and 2-butylsemicarbazides (**5d**) were prepared in 59-71% yields by the treatment of conjugated base of **3** with excess (5-10 equiv.) of the corresponding alkyl bromides (MeCN, reflux, 9 h) followed by the acidic workup (Table 2, entries 2-4).

Alkylation with benzyl bromide (1.06 equiv.) with the subsequent acidic treatment gave hydrochloride of 2-benzylsemicarbazide (**5e**) in 60% yield (entry 5).

It should be noted that the 2-alkylated semicarbazides can be also isolated as free bases **6a-e**[42] by treatment of reaction mixtures after their evaporation with aqueous Na_2CO_3 followed by extraction with EtOAc. However, it was more difficult to handle and purify free bases **6a-e** compared with hydrochlorides **5a-e**. In contrast, our attempts to obtain the analytically pure sample of hydrochloride 2-octylsemicarbazide (**5f**)[43] prepared by the alkylation of **3** with octyl bromide (5.0 equiv.) (MeCN, reflux, 6.5 h) failed, while free base **6f** was isolated in 58% yield (based on **3**) (Table, entry 6) and readily purified.

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Conclusions

An effective method for selective N2-alkylation of semicarbazones to give 2-alkylsemicarbazones has been developed. It involves deprotonation of semicarbazones with sodium hydride in MeCN followed by treatment with alkylating reagents. This method was applied to general and convenient synthesis of 2-alkylsemicarbazides and their hydrochlorides starting from commercially available semicarbazide hydrochloride. It is based on selective N2-alkylation of acetone semicarbazone under the action of sodium hydride and dimethyl sulfate or alkyl bromides. The resulting acetone 2-alkylsemicarbazones were hydrolyzed by brief heating (60 °C) with 17-36% hydrochloric acid to give the target products in 58-72% yields. Alkylation and hydrolytic steps were conveniently performed in one reaction flask making the described approach very simple and preparative.

Experimental Section

General. All solvents and liquid reagents purchased from commercial sources were distilled prior to use. Petroleum ether had a distillation range 40-70 °C. Anhydrous MeCN and petroleum ether were obtained according to the standard procedures. Sodium hydride (60% suspension in mineral oil) was washed thoroughly with anhydrous petroleum ether and dried in vacuum before use. All other reagents were purchased from commercial sources and used without additional purification. FTIR spectra were recorded using a Bruker Vector 22 spectrophotometer in Nujol or Bruker Alpha-T spectrophotometer in KBr. Band characteristics in the IR spectra are defined as very strong (vs), strong (s), medium (m), weak (w), shoulder (sh), and broad (br). NMR spectra (solutions in DMSO-d_6) were acquired using a Bruker DPX-300 spectrometer at 300.13 (^{1}H) and 75.48 (^{13}C) MHz. ^{1}H NMR chemical shifts are referenced to the residual proton signal in DMSO-d_6 (2.50 ppm). In ^{13}C NMR spectra, central signal of DMSO-d_6 (39.50 ppm) was used as a reference. Multiplicities are reported as singlet (s), doublet (d), triplet (t), quartet (q), and some combinations of these, multiplet (m). Selective ^{1}H–^{1}H decoupling and DEPT-135 experiments were used to aid in the assignment of ^{1}H and ^{13}C NMR signals. Elemental analyses (CHN) were performed using a Thermo Finnigan Flash EA1112 apparatus. Thin-layer chromatography was performed on silica gel plates Kieselgel 60 F_{254} (Merck) in $CHCl_3$/MeOH (9:1, v/v). Spots were visualized with UV light.

(*E*)-2-Methylsemicarbazone of 4-methylbenzaldehyde (2b). To a stirred suspension of NaH (0.109 g, 4.54 mmol) in dry MeCN (15 mL) was added semicarbazone (*E*)-**1b** (0.792 g, 4.47 mmol) and the obtained mixture was stirred at room temperature for 20 min. To the resulting light yellow suspension was added a solution of methyl iodide (3.200 g, 22.54 mmol) in dry MeCN (2 mL) and the reaction mixture was stirred at room temperature for 5 h 20 min. After 20 min from the beginning of the reaction a clear light yellow solution was formed. The solvent was removed under vacuum. To the solid residue was added H_2O (8 mL) and the obtained suspension was cooled. The precipitate was filtered, washed with ice-cold H_2O, petroleum ether, and dried to give compound **2b** (0.808 g, 95%) as a white solid. Mp 179-179.5 °C (EtOH) [Mp liter[44] 178-179 °C (EtOH)]. IR (Nujol) ν, cm^{-1}: 3472 (s), 3344 (br m), 3265 (br s), 3197 (br s), 3124 (br m) (ν NH), 3060 (w) (ν CH_{arom}), 1682 (vs) (amide-I), 1608 (s) (ν C=N), 1573 (s) (δ_s NH_2), 1510 (w) (ν CC_{arom}), 819 (s) (δ CH_{arom}). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 7.70-7.76 (2H, m, ArH), 7.64 (1H, s, CH=N), 7.17-7.23 (2H, m, ArH), 6.89 (1H, br s, NH), 6.64 (1H, br s, NH), 3.22 (3H, s, NCH_3), 2.32 (3H, s, CH_3 in 4-$CH_3C_6H_4$). ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 156.4 (C=O),

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138.4 (C), 136.7 (CH=N), 132.5 (C), 129.1 (2CH), 126.9 (2CH), 27.7 (NCH_3), 21.0 (CH_3 in 4-$CH_3C_6H_4$). Anal. Calcd for $C_{10}H_{13}N_3O$: C, 62.81; H, 6.85; N, 21.97. Found: C, 62.67; H, 6.92; N, 21.80.

(*E*)-2-Methyl-4-{[1-(4-methylphenyl)-3-oxo]but-1-yl}semicarbazone of 4-methylbenzaldehyde (2c). Compound **2c** (2.231 g, 98%) as a light yellow solid was prepared from semicarbazone (*E*)-**1c**[40] (2.192 g, 6.50 mmol), NaH (0.172 g, 7.17 mmol) and methyl iodide (9.308 g, 65.58 mmol) in dry MeCN (20 mL) (rt, 2 h) as described for **2b**. Analytically pure sample (white solid) was obtained after crystallization from EtOH. Mp 143.5-146.5 °C (EtOH). IR (KBr) ν, cm^{-1}: 3344 (br s), 3020 (br s) (ν NH), 1720 (s) (ν C=O in Ac), 1653 (vs) (amide-I), 1611 (m) (ν CC_{arom}), 1599 (s) (ν C=N), 1508 (vs) (amide-II), 817 (s) (δ CH_{arom}). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 7.71-7.76 (2H, m, ArH), 7.72 (1H, d, ^3J 8.8 Hz, NH), 7.69 (1H, s, CH=N), 7.22-7.28 (4H, m, ArH), 7.08-7.14 (2H, m, ArH), 5.22 (1H, ddd, ^3J 8.8, ^3J 7.6, ^3J 5.7 Hz, CH-N), 3.23 (3H, s, NCH_3), 3.21 (1H, dd, ^2J 16.5, ^3J 7.6 Hz, H_A in CH_2), 2.98 (1H, dd, ^2J 16.5, ^3J 5.7 Hz, H_B in CH_2), 2.34 (3H, s, CH_3 in $CH_3C_6H_4$), 2.25 (3H, s, CH_3 in $CH_3C_6H_4$), 2.09 (3H, s, CH_3 in Ac). ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 207.1 (C=O in Ac), 154.5 (NHC=O), 140.3 (C), 138.6 (C), 137.2 (CH=N), 135.7 (C), 132.3 (C), 129.2 (2CH), 128.7 (2CH), 126.8 (2CH), 126.2 (2CH), 49.7 (CH-N), 48.7 (CH_2), 30.4 (CH_3 in Ac), 28.3 (NCH_3), 20.9 (CH_3 in $CH_3C_6H_4$), 20.6 (CH_3 in $CH_3C_6H_4$). Anal. Calcd for $C_{21}H_{25}N_3O_2$: C, 71.77; H, 7.17; N, 11.96. Found: C, 71.63; H, 7.17; N, 11.70.

(*E*)-2-Methylsemicarbazone of benzaldehyde (2d). Compound **2d** (0.209 g, 72%) as a white solid was obtained from semicarbazone (*E*)-**1d** (0.269 g, 1.65 mmol), NaH (0.040 g, 1.67 mmol) and methyl iodide (2.340 g, 16.49 mmol) in dry MeCN (10 mL) (rt, 1.5 h) as described for **2b**. Mp 163.5-164 °C (EtOH) [Mp liter[45] 163-164 °C (EtOH)]. IR (Nujol) ν, cm^{-1}: 3446 (s), 3431 (s), 3281 (br s), 3212 (br s) (ν NH), 3059 (w) (ν CH_{arom}), 1656 (vs) (amide-I), 1600 (s) (ν C=N), 1579 (s) (δ_s NH_2), 755 (s), 692 (s) (δ CH_{arom}). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 7.81-7.87 (2H, m, ArH), 7.68 (1H, s, CH=N), 7.30-7.43 (3H, m, ArH), 6.91 (1H, br s, NH), 6.69 (1H, br s, NH), 3.24 (3H, s, CH_3). ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 156.4 (C=O), 136.6 (CH=N), 135.2 (C), 128.8 (CH), 128.5 (2CH), 126.9 (2CH), 27.8 (CH_3). Anal. Calcd for $C_9H_{11}N_3O$: C, 61.00; H, 6.26; N, 23.71. Found: C, 60.88; H, 6.24; N, 23.77.

(*E*)-2-Ethylsemicarbazone of benzaldehyde (2e). Compound **2e** (1.493 g, 90%) as a white solid was obtained from semicarbazone (*E*)-**1d** (1.423 g, 8.72 mmol), NaH (0.213 g, 8.88 mmol) and ethyl iodide (6.800 g, 43.60 mmol) in dry MeCN (22 mL) (rt, 26 h) as described for **2b**. Mp 138-140 °C (AcOEt) [Mp liter[46] 137.5-139 °C (EtOH-H_2O)]. IR (KBr) ν, cm^{-1}: 3482 (s), 3290 (br s), 3226 (s), 3130 (br m) (ν NH), 3065 (w), 3028 (w) (ν CH_{arom}), 1704 (vs), 1658 (s) (amide-I), 1601 (s) (ν C=N), 1578 (s) (δ_s NH_2), 763 (s), 697 (s) (δ CH_{arom}). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 7.82-7.87 (2H, m, ArH), 7.75 (1H, s, CH=N), 7.30-7.42 (3H, m, ArH), 6.82 (1H, br s, NH), 6.64 (1H, br s, NH), 3.94 (2H, q, ^3J 7.0 Hz, CH_2), 1.03 (3H, t, ^3J 7.0 Hz, CH_3). ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 156.2 (C=O), 136.0 (CH=N), 135.3 (C), 128.8 (CH), 128.5 (2CH), 126.9 (2CH), 34.2 (CH_2), 11.0 (CH_3). Anal. Calcd for $C_{10}H_{13}N_3O$: C, 62.81; H, 6.85; N, 21.97. Found: C, 62.78; H, 7.01; N, 21.98.

(*E*)-2-Butylsemicarbazone of benzaldehyde (2f). Compound **2f** (1.736 g, 88%) as a white solid was obtained from semicarbazone (*E*)-**1d** (1.462 g, 8.96 mmol), NaH (0.262 g, 10.92 mmol) and butyl iodide (4.946 g, 26.88 mmol) in dry MeCN (44 mL) (reflux, 7 h) as described for **2b**. Mp 91.5-92 °C (EtOH-H_2O, 1:1 v/v) [Mp liter[47] 89-90 °C (C_6H_6-petroleum ether)]. IR (KBr) ν, cm^{-1}: 3455 (s), 3290 (br s), 3226 (br s) (ν NH), 3061 (w), 3024 (w) (ν CH_{arom}), 1672 (vs) (amide-I), 1594 (s) (ν C=N), 1581 (s) (δ_s NH_2), 1509 (w) (ν CC_{arom}), 756 (s), 692 (s) (δ CH_{arom}). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 7.81-7.87 (2H, m, ArH), 7.72 (1H, s, CH=N), 7.30-7.42 (3H, m, ArH), 6.83 (1H, br s, NH), 6.62 (1H, br s, NH), 3.89 (2H, t, ^3J 7.2 Hz, NCH_2), 1.22-1.50 (4H, m, CH_2CH_2), 0.90 (3H, t, ^3J 7.2 Hz, CH_3). ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 156.5 (C=O), 136.0 (CH=N), 135.3 (C), 128.8 (CH), 128.5 (2CH), 126.9 (2CH), 39.1 (NCH_2), 27.3 (CH_2), 19.6 (CH_2), 13.8 (CH_3). Anal. Calcd for $C_{12}H_{17}N_3O$: C, 65.73; H, 7.81; N, 19.16. Found: C, 65.80; H, 7.91; N, 19.18.

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(*E*)-2-Benzylsemicarbazone of benzaldehyde (2g). Compound **2g** (0.979 g, 96%) as a white solid was obtained from semicarbazone (*E*)-**1d** (0.657 g, 4.03 mmol), NaH (0.098 g, 4.08 mmol) and benzyl bromide (0.823 g, 4.81 mmol) in dry MeCN (13 mL) (rt, 19 h) as described for **2b**. Mp 154-155 °C (EtOH) [Mp liter[48] 153-154 °C (EtOH)]. IR (KBr) ν, cm^{-1}: 3488 (s), 3349 (m), 3264 (br s), 3199 (br s), 3125 (br m) (ν NH), 3086 (w), 3027 (m) (ν CH_{arom}), 1693 (vs) (amide-I), 1601 (m) (ν C=N), 1575 (s) (δ_s NH_2), 1494 (m) (ν CC_{arom}), 757 (s), 734 (s), 692 (s) (δ CH_{arom}). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 7.69-7.75 (2H, m, ArH), 7.59 (1H, s, CH=N), 7.19-7.38 (8H, m, ArH), 7.09 (1H, br s, NH), 6.85 (1H, br s, NH), 5.18 (2H, s, CH_2). ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 156.8 (C=O), 137.0 (CH=N), 136.5 (C), 134.8 (C), 129.0 (CH), 128.6 (2CH), 128.5 (2CH), 126.9 (CH), 126.9 (2CH), 126.6 (2CH), 43.2 (CH_2). Anal. Calcd for $C_{15}H_{15}N_3O$: C, 71.13; H, 5.97; N, 16.59. Found: C, 70.87; H, 6.13; N, 16.47.

(*E*)-2-Benzylsemicarbazone of propanal (2h). Compound **2h** (1.202 g, 70%) as a white solid was obtained from semicarbazone **1e** (0.962 g, 8.36 mmol) [a mixture of (*E*)- and (*Z*)-isomers in a ratio of 86:14, respectively], NaH (0.221 g, 9.21 mmol) and benzyl bromide (1.575 g, 9.21 mmol) in dry MeCN (18 mL) (rt, 72 h) as described for **2b**. Mp 92.5-94 °C (petroleum ether - AcOEt, 6:1 v/v). IR (KBr) ν, cm^{-1}: 3485 (s), 3337 (m), 3267 (br s), 3208 (s), 3187 (s) (ν NH), 3084 (m), 3031 (m), 3005 (w) (ν CH_{arom}), 1681 (vs) (amide-I), 1631 (s) (ν C=N), 1605 (w) (ν CC_{arom}), 1562 (s) (δ_s NH_2), 1525 (w), 1495 (m) (ν CC_{arom}), 736 (s), 697 (s) (δ CH_{arom}). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 7.27-7.34 (2H, m, ArH), 7.18-7.25 (1H, m, ArH), 7.11-7.16 (2H, m, ArH), 6.85 (1H, t, ^3J 4.8 Hz, CH=N), 6.61 (2H, br s, NH_2), 4.98 (2H, s, NCH_2), 2.14 (2H, dt, ^3J 7.5, ^3J 4.8 Hz, CH_2 in Et), 0.92 (3H, t, ^3J 7.5 Hz, CH_3). ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 156.9 (C=O), 141.6 (CH=N), 136.6 (C), 128.4 (2CH), 126.7 (CH), 126.4 (2CH), 43.0 (NCH_2), 25.4 (CH_2 in Et), 10.7 (CH_3). Anal. Calcd for $C_{11}H_{15}N_3O$: C, 64.37; H, 7.37; N, 20.47. Found: C, 64.51; H, 7.57; N, 20.27.

(*E*)-2-Benzylsemicarbazone of butanal (2i). Compound **2i** (2.588 g, 70%) as a white solid was obtained from semicarbazone **1f** (2.165 g, 16.76 mmol) [a mixture of (*E*)- and (*Z*)-isomers in a ratio of 74:26, respectively], NaH (0.462 g, 19.25 mmol) and benzyl chloride (2.318 g, 18.31 mmol) in dry MeCN (35 mL) (reflux, 4 h) as described for **2b**. Mp 63.5-64 °C (petroleum ether - AcOEt, 15:1 v/v). IR (Nujol) ν, cm^{-1}: 3484 (s), 3335 (m), 3266 (br s), 3209 (s), 3184 (s) (ν NH), 3084 (w), 3030 (m), 3002 (w) (ν CH_{arom}), 1682 (amide-I), 1631 (m) (ν C=N), 1567 (s) (δ_s NH_2), 1524 (w), 1495 (m) (ν CC_{arom}), 742 (s), 699 (m) (δ CH_{arom}). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 7.27-7.34 (2H, m, ArH), 7.17-7.24 (1H, m, ArH), 7.10-7.16 (2H, m, ArH), 6.80 (1H, t, ^3J 5.3 Hz, CH=N), 6.60 (2H, br s, NH_2), 4.99 (2H, s, NCH_2), 2.10 (2H, dt, ^3J 7.3, ^3J 5.3 Hz, CH_2 in Pr), 1.35 (2H, qt, ^3J 7.4, ^3J 7.3 Hz, CH_2 in Pr), 0.74 (3H, t, ^3J 7.4 Hz, CH_3). ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 156.8 (C=O), 140.8 (CH=N), 136.5 (C), 128.4 (2CH), 126.7 (CH), 126.4 (2CH), 42.9 (NCH_2), 34.0 (CH_2), 19.6 (CH_2), 13.2 (CH_3). Anal. Calcd for $C_{12}H_{17}N_3O$: C, 65.73; H, 7.81; N, 19.16. Found: C, 65.82; H, 7.81; N, 19.06.

(*E*)-2-(4-Methoxybenzyl)semicarbazone of butanal (2j). Compound **2j** (2.734 g, 66%) as a white solid was obtained from semicarbazone **1f** (2.161 g, 16.73 mmol) [a mixture of (*E*)- and (*Z*)-isomers in a ratio of 74:26, respectively], NaH (0.443 g, 18.46 mmol) and 4-methoxybenzyl chloride (2.879 g, 18.38 mmol) in dry MeCN (25 mL) (reflux, 4 h) as described for **2b**. Mp 89.5-90 °C (petroleum ether - AcOEt, 10:3 v/v). IR (KBr) ν, cm^{-1}: 3490 (s), 3352 (m), 3268 (br s), 3188 (br s), 3140 (m) (ν NH), 3070 (w), 3036 (w) (ν CH_{arom}), 1696 (vs) (amide-I), 1625 (m) (ν C=N), 1615 (m) (ν CC_{arom}), 1581 (s) (δ_s NH_2), 1513 (s) (ν CC_{arom}), 1239 (s), 1036 (ν C-O), 801 (m) (δ CH_{arom}). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 7.04-7.10 (2H, m, ArH), 6.84-6.89 (2H, m, ArH), 6.83 (1H, t, ^3J 5.3 Hz, CH=N), 6.56 (2H, br s, NH_2), 4.91 (2H, s, NCH_2), 3.71 (3H, s, OCH_3), 2.10 (2H, dt, ^3J 7.3, ^3J 5.3 Hz, CH_2 in Pr), 1.37 (2H, qt, ^3J 7.4, ^3J 7.3 Hz, CH_2 in Pr), 0.76 (3H, t, ^3J 7.4 Hz, CH_3). ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 158.1 (C), 156.8 (C=O), 140.7 (CH=N), 128.3 (C), 127.7 (2CH), 113.9 (2CH), 55.0 (OCH_3), 42.3 (NCH_2), 34.0 (CH_2), 19.6 (CH_2), 13.2 (CH_3). Anal. Calcd for $C_{13}H_{19}N_3O_2$: C, 62.63; H, 7.68; N, 16.85. Found: C, 62.71; H, 7.71; N, 16.75.

(*E*)-2-Benzylsemicarbazone of 2-methylpropanal (2k). Compound **2k** (3.936 g, 72%) as a white solid was obtained from semicarbazone (*E*)-**1g** (3.236 g, 25.05 mmol), NaH (0.691 g, 28.79 mmol) and benzyl chloride

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(3.495 g, 27.61 mmol) in dry MeCN (72 mL) (reflux, 4 h) as described for **2b**. Mp 93-93.5 °C (EtOH-H_2O, 5:8 v/v). IR (Nujol) ν, cm^{-1}: 3477 (s), 3345 (m), 3265 (br s), 3185 (br s) (ν NH), 3065 (w), 3029 (w) (ν CH_{arom}), 1686 (s) (amide-I), 1629 (m) (ν C=N), 1574 (s) (δ_s NH_2), 1525 (w), 1495 (w) (ν CC_{arom}), 733 (s), 697 (m) (δ CH_{arom}). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 7.27-7.34 (2H, m, ArH), 7.17-7.24 (1H, m, ArH), 7.10-7.16 (2H, m, ArH), 6.78 (1H, d, ^3J 4.8 Hz, CH=N), 6.58 (2H, br s, NH_2), 4.99 (2H, s, NCH_2), 2.38 (1H, doublet of septet, ^3J 6.9, ^3J 4.8 Hz, CH in *i*-Pr), 0.92 (6H, d, ^3J 6.9 Hz, two CH_3). ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 156.9 (C=O), 145.6 (CH=N), 136.5 (C), 128.4 (2CH), 126.7 (CH), 126.4 (2CH), 42.9 (NCH_2), 30.9 (CH in *i*-Pr), 19.8 ($2CH_3$). Anal. Calcd for $C_{12}H_{17}N_3O$: C, 65.73; H, 7.81; N, 19.16. Found: C, 65.70; H, 7.77; N, 19.31.

(*E*)-2-(4-Methoxybenzyl)semicarbazone of 2-methylpropanal (2l). Compound **2l** (2.288 g, 78%) as a white solid was obtained from semicarbazone (*E*)-**1g** (1.522 g, 11.78 mmol), NaH (0.311 g, 12.96 mmol) and 4-methoxybenzyl chloride (2.016 g, 12.87 mmol) in dry MeCN (35 mL) (reflux, 4 h) as described for **2b**. Mp 105.5-106 °C (petroleum ether - AcOEt, 10:3 v/v). IR (KBr) ν, cm^{-1}: 3482 (s), 3346 (m), 3276 (br s), 3210 (br s), 3128 (br m) (ν NH), 3072 (w), 3054 (w), 3012 (m) (ν CH_{arom}), 1684 (vs) (amide-I), 1628 (m) (ν C=N), 1614 (m) (ν CC_{arom}), 1572 (s) (δ_s NH_2), 1510 (s) (ν CC_{arom}), 1241 (s), 1032 (s) (ν C-O), 810 (m) (δ CH_{arom}). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 7.04-7.10 (2H, m, ArH), 6.84-6.89 (2H, m, ArH), 6.82 (1H, d, ^3J 4.8 Hz, CH=N), 6.54 (2H, br s, NH_2), 4.90 (2H, s, NCH_2), 3.71 (3H, s, OCH_3), 2.38 (1H, doublet of septet, ^3J 6.8, ^3J 4.8 Hz, CH in *i*-Pr), 0.93 (6H, d, ^3J 6.8 Hz, two CH_3). ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 158.0 (C), 156.9 (C=O), 145.5 (CH=N), 128.3 (C), 127.8 (2CH), 113.8 (2CH), 55.0 (OCH_3), 42.3 (NCH_2), 30.9 (CH in *i*-Pr), 19.8 ($2CH_3$). Anal. Calcd for $C_{13}H_{19}N_3O_2$: C, 62.63; H, 7.68; N, 16.85. Found: C, 62.65; H, 7.68; N, 16.94.

2-Methylsemicarbazide hydrochloride (5a). To a suspension of NaH (0.319 g, 13.28 mmol) in dry MeCN (10 mL) was added acetone semicarbazone (1.458 g, 12.67 mmol), the obtained mixture was stirred at room temperature for 40 min, then the solution of dimethyl sulfate (1.692 g, 13.41 mmol) in dry MeCN (10 mL) was added. The reaction mixture was stirred at room temperature for 17 h, and filtered. The filtrate was concentrated under vacuum, to the residue was added conc. HCl (8 mL), and the resulting solution was concentrated under vacuum at 60 °C (temperature of bath). The obtained residue was triturated with *i*-PrOH until crystallization, and cooled. The precipitate was filtered, washed with cold *i*-PrOH, petroleum ether, and dried to give compound **5a** (1.150 g, 72%). Mp 135.5-136 °C (decomp., *i*-PrOH-EtOH, 2:1 v/v) [Mp liter[49] 145 °C (decomp., EtOH)]. IR (Nujol) ν, cm^{-1}: 3354 (br s), 3196 (br s), 3174 (br s), 2717 (br s), 2654 (br s), 2625 (br s), 1975 (br m) (NH_2, NH_3^+), 1685 (br s) (amide-I), 1611 (br s), 1590 (m), 1572 (m), 1531 (s), 1510 (s) (NH_3^+). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 10.26 (3H, br s, NH_3^+), 6.95 (2H, br s, NH_2), 3.13 (3H, s, CH_3). ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 158.7 (C=O), 36.6 (CH_3). Anal. Calcd for $C_2H_8ClN_3O$: C, 19.13; H, 6.42; N, 33.47. Found: C, 19.41; H, 6.69; N, 33.72.

2-Ethylsemicarbazide hydrochloride (5b). To a suspension of NaH (0.092 g, 3.84 mmol) in dry MeCN (10 mL) was added acetone semicarbazone (0.421 g, 3.66 mmol), the obtained mixture was stirred at room temperature for 1 h, then the solution of ethyl bromide (4.100 g, 37.63 mmol) in dry MeCN (5 mL) was added. The reaction mixture was stirred under reflux for 9 h, and filtered. The filtrate was concentrated under vacuum, to the residue was added 17% aqueous HCl (3 mL), and the resulting solution was concentrated under vacuum at 60 °C (temperature of bath). The obtained residue was triturated with mixture of *i*-PrOH and diethyl ether until crystallization, and cooled. The precipitate was filtered, washed with cold *i*-PrOH, cold ether, petroleum ether, and dried to give compound **5b** (0.326 g, 71%). Mp 127-127.5 °C (decomp., *i*-PrOH-EtOH, 2:1 v/v) [Mp liter[49] 131-133 °C (decomp., EtOH)]. IR (Nujol) ν, cm^{-1}: 3357 (br s), 3173 (br s), 2712 (br s), 2676 (br s), 2618 (br s), 1989 (br m) (NH_2, NH_3^+), 1681 (s) (amide-I), 1621 (m), 1592 (s), 1550 (m), 1530 (s) (NH_3^+). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 10.21 (3H, br s, NH_3^+), 6.92 (2H, br s, NH_2), 3.61 (2H, q, ^3J 7.0 Hz,

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CH_2), 1.10 (3H, t, ^3J 7.0 Hz, CH_3). ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 157.6 (C=O), 43.7 (CH_2), 11.5 (CH_3). Anal. Calcd for $C_3H_{10}ClN_3O$: C, 25.81; H, 7.22; N, 30.10. Found: C, 25.57; H, 7.25; N, 30.12.

2-Propylsemicarbazide hydrochloride (5c). Compound **5c** (0.382 g, 71%) was obtained from NaH (0.093 g, 3.88 mmol), acetone semicarbazone (0.407 g, 3.53 mmol) and propyl bromide (2.171 g, 17.65 mmol) in dry MeCN (15 mL) (reflux, 9 h), then 17% aqueous HCl (2.9 mL) as described for **5b**. Mp 129-129.5 °C (decomp., *i*-PrOH-EtOH, 2:1 v/v). IR (Nujol) ν, cm^{-1}: 3322 (br s), 3200 (br s), 3104 (br m), 2696 (br m), 2649 (br m), 2604 (br m), 2565 (br s), 1923 (br m) (NH_2, NH_3^+), 1701 (s) (amide-I), 1613 (s), 1556 (s), 1525 (s) (NH_3^+). ^1H NMR (300.13 MHz, DMSO-d_6) δ: 10.24 (3H, br s, NH_3^+), 6.89 (2H, br s, NH_2), 3.45-3.52 (2H, m, NCH_2), 1.50-1.62 (2H, m, CH_2), 0.82 (3H, t, ^3J 7.3 Hz, CH_3). ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 157.5 (C=O), 50.1 (NCH_2), 19.4 (CH_2), 10.5 (CH_3). Anal. Calcd for $C_4H_{12}ClN_3O$: C, 31.28; H, 7.87; N, 27.36. Found: C, 31.34; H, 8.14; N, 27.29.

2-Butylsemicarbazide hydrochloride (5d). Compound **5d** (0.398 g, 59%) was obtained from NaH (0.101 g, 4.21 mmol), acetone semicarbazone (0.463 g, 4.02 mmol) and butyl bromide (5.506 g, 40.18 mmol) in dry MeCN (20 mL) (reflux, 9 h), then 17% aqueous HCl (3.2 mL) as described for **5b**. Mp 133.5-134 °C (decomp., *i*-PrOH). IR (Nujol) ν, cm^{-1}: 3340 (br s), 3180 (br s), 2725 (br s), 2597 (br s), 2008 (br m) (NH_2, NH_3^+), 1666 (s) (amide-I), 1626 (s), 1596 (s), 1558 (s) (NH_3^+). ^1H NMR (300.13 MHz, DMSO-d_6) δ: 10.20 (3H, br s, NH_3^+), 6.88 (2H, br s, NH_2), 3.50-3.57 (2H, m, NCH_2), 1.47-1.58 (2H, m, CH_2), 1.18-1.30 (2H, m, CH_2), 0.87 (3H, t, ^3J 7.3 Hz, CH_3). ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 157.6 (C=O), 48.4 (NCH_2), 28.1 (CH_2), 19.0 (CH_2), 13.7 (CH_3). Anal. Calcd for $C_5H_{14}ClN_3O$: C, 35.82; H, 8.42; N, 25.07. Found: C, 35.84; H, 8.31; N, 25.11.

2-Benzylsemicarbazide hydrochloride (5e). Compound **5f** (1.816 g, 60%) was obtained from NaH (0.380 g, 15.84 mmol), acetone semicarbazone (1.740 g, 15.11 mmol) and benzyl bromide (2.730 g, 15.96 mmol) in dry MeCN (25 mL) (reflux, 6.5 h), then conc. HCl (14.5 mL) as described for **5b**. Mp 139-139.5 °C (decomp., EtOH). IR (Nujol) ν, cm^{-1}: 3330 (br s), 3312 (br s), 3161 (br s), 2682 (br s), 2572 (br s), 1963 (br m) (NH_2, NH_3^+), 1674 (s) (amide-I), 1616 (s), 1587 (s), 1551 (s) (NH_3^+), 1494 (w) (CC_{arom}), 747 (s), 700 (s) (CH_{arom}). ^1H NMR (300.13 MHz, DMSO-d_6) δ: 9.88 (3H, br s, NH_3^+), 7.29-7.43 (5H, m, Ph), 7.05 (2H, br s, NH_2), 4.84 (2H, s, NCH_2). ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 157.6 (C=O), 135.4 (C), 128.6 (2CH), 128.1 (2CH), 127.9 (CH), 51.7 (NCH_2). Anal. Calcd for $C_8H_{12}ClN_3O$: C, 47.65; H, 6.00; N, 20.84. Found: C, 47.63; H, 6.14; N, 20.88.

2-Octylsemicarbazide (6f). To a suspension of NaH (0.098 g, 4.06 mmol) in dry MeCN (13 mL) was added acetone semicarbazone (0.446 g, 3.87 mmol), the obtained mixture was stirred at room temperature for 1 h, then the solution of octyl bromide (3.741 g, 19.37 mmol) in dry MeCN (7 mL) was added. The reaction mixture was stirred under reflux for 9 h, and filtered. The filtrate was concentrated under vacuum, to the residue was added 17% aqueous HCl (3.2 mL), and the resulting solution was concentrated under vacuum at 60 °C (temperature of bath). To the obtained residue were added H_2O (5 mL) and Na_2CO_3 (1.789 g, 21.29 mmol), and the resulting mixture was extracted with ethyl acetate (4 × 3 mL). Combined extract was concentrated under vacuum, the residue was triturated with petroleum ether until suspension formed, and cooled. The precipitate was filtered, washed with petroleum ether, cold ether (2 × 3 mL), and dried to give compound **5b** (0.421 g, 58%). Mp 72-72.5 °C (EtOH-H_2O, 1:3 v/v). IR (Nujol) ν, cm^{-1}: 3472 (br vs), 3322 (br vs), 3211 (br s) (NH_2), 1649 (br vs), 1615 (s), 1569 (s) (amide-I, NH_2). ^1H NMR (300.13 MHz, DMSO-d_6) δ: 5.89 (2H, br s, NH_2C=O), 4.33 (2H, s, NH_2-N), 3.26-3.32 (2H, m, NCH_2, partly overlapped with HOD signal), 1.42-1.52 (2H, m, CH_2), 1.13-1.35 (10H, m, $CH_2CH_2CH_2CH_2CH_2$), 0.86 (3H, t, ^3J 6.7 Hz, CH_3). ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 159.9 (C=O), 48.2 (NCH_2), 31.2 (CH_2), 28.8 (CH_2), 28.7 (CH_2), 26.2 (CH_2), 26.1 (CH_2), 22.0 (CH_2), 13.9 (CH_3). Anal. Calcd for $C_9H_{21}N_3O$: C, 57.72; H, 11.30; N, 22.44. Found: C, 57.73; H, 11.47; N, 22.55.

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Supplementary Material

Supplementary data (copies of IR, ^{1}H and ^{13}C NMR spectra of all the synthesized compounds, computational details) associated with this article are provided.

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42. ^{1}H NMR spectra (300.13 MHz, DMSO-d_6) of **6a**: δ 5.94 (2H, br s, NH_2C=O), 4.50 (2H, s, NH_2-N), 2.91 (3H, s, CH_3); **6b**: δ ^{1}H NMR (300.13 MHz, DMSO-d_6) δ 5.95 (2H, br s, NH_2C=O), 4.38 (2H, s, NH_2-N), 3.33 (2H, q, ^{3}J 7.1 Hz, NCH_2), 1.00 (3H, t, ^{3}J 7.1 Hz, CH_3); **6c**: δ ^{1}H NMR (300.13 MHz, DMSO-d_6) δ 5.93 (2H, br s, NH_2C=O), 4.37 (2H, s, NH_2-N), 3.22–3.29 (2H, m, NCH_2), 1.42–1.55 (2H, m, CH_2), 0.79 (3H, t, ^{3}J 7.4 Hz, CH_3); **6d**: δ ^{1}H NMR (300.13 MHz, DMSO-d_6) δ 5.93 (2H, br s, NH_2C=O), 4.36 (2H, s, NH_2-N), 3.26–3.33 (2H, m, NCH_2), 1.40–1.51 (2H, m, CH_2), 1.15–1.28 (2H, m, CH_2), 0.87 (3H, t, ^{3}J 7.3 Hz, CH_3); **6e**: δ ^{1}H NMR (300.13 MHz, DMSO-d_6) δ 7.19–7.38 (5H, m, Ph), 6.13 (2H, br s, NH_2C=O), 4.54 (2H, s, NCH_2), 4.28 (2H, s, NH_2-N).
43. ^{1}H NMR of compound **5f** (300.13 MHz, DMSO-d_6) δ 10.20 (3H, br s, NH_3^+), 6.88 (2H, br s, NH_2), 3.48–3.55 (2H, m, NCH_2), 1.46–1.60 (2H, m, CH_2), 1.17–1.31 (10H, m, $CH_2CH_2CH_2CH_2CH_2$), 0.85 (3H, t, ^{3}J 6.7 Hz, CH_3).
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