Novel 14-Membered Hexaaza Macrocycles

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Abstract

An efficient method for the stereoselective synthesis of novel 14-membered cyclic bis-semicarbazones based on acid-catalyzed cyclization of the hydrazones of 3-(3-oxobutyl)semicarbazides has been developed. The starting semicarbazides were prepared according to a four-step strategy involving amidoalkylation of the sodium enolate of acetylacetone with *N*-(α-tosylbenzyl)carbamates followed by base-promoted retro-Claisen reaction and treatment of the obtained *N*-(3-oxobutyl)carbamates with hydrazine.

Keywords

Amidoalkylation; retro-Claisen reaction; Semicarbazides; Azamacrocycles

Introduction

Monocyclic semicarbazones (**A**, Figure 1), particularly 5- and 6-membered representatives, are of current interest due to their multifaceted biological properties. For example, 2,4-dihydro-3*H*-1,2,4-triazol-3-ones **1** are antagonists of the angiotensin AII receptor[1] and human-type neurokinin1 receptor.[2] These compounds possess antimicrobial,[3] anticonvulsant,[4] anticancer,[5] antifungal,[6] and herbicidal[7] activities. A wide range of biological effects of 2,3,4,5-tetrahydro-1,2,4-triazin-3-ones **2** have been reported.[8] The high synthetic accessibility of compounds **1**[9] and **2**[10] is crucial for their versatile applications in medicine and agriculture. In contrast, the biological activities of seven-membered monocyclic semicarbazones, 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepin-3-ones **3**, and monocyclic semicarbazones with larger ring sizes, remain unknown due to a lack of simple general approaches to these compounds.

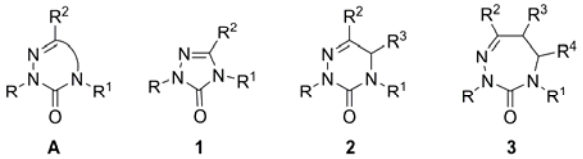
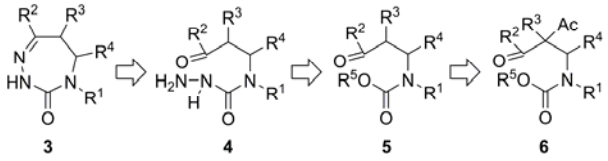


Figure 1. General formula of heterocyclic semicarbazones **A** and their five-seven membered representatives **1-3**.

In continuation of our research on the synthesis of 1,3-diazepin-2-ones,[11] we were interested in the preparation of their aza-analogs, cyclic semicarbazones **3**. To date, only a few compounds of type **3** have been synthesized according to the reported procedures based on the reaction of 4-isocyanato-4-methylpent-2-one with methylhydrazine,[12] oxidation of 5,5,7-trimethyl-2,4,5,6-tetrahydro-3*H*-1,2,4-triazepin-3-thione,[13] or cyclizations of two semicarbazones.[14] Thus, the development of a new and general approach to compounds **3** is desirable for both synthetic and medicinal chemistry.

We hypothesized that 2-unsubstituted triazepinones **3** could be obtained by intramolecular cyclization of (γ-oxoalkyl)semicarbazides **4**, prepared by substitution of the alkoxy group in carbamates **5** by treatment with hydrazine (Scheme 1).



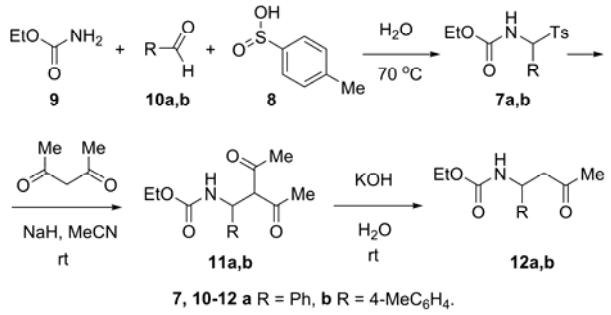
Scheme 1. Retrosynthesis of seven-membered cyclic semicarbazones **3**.

Compounds **5** can be synthesized by aza-Michael addition of carbamates to enones,[15] Mannich condensation of aldehydes with methyl ketones and carbamates,[16] reactions of *N*-alkoxycarbonylimines with ketones,[17] etc. The main drawbacks of the reported syntheses that strongly reduce their preparative value are small-scale preparations and the use of chromatography for isolation of the target products. We supposed that compounds **5** could be obtained by retro-Claisen reaction of carbamates **6**, which could be readily synthesized following our previousely reported approach based on amidoalkylation reactions.[18]

Here we report the three-step synthesis of two examples of carbamates **5** on multigram scale via the preparation of carbamates **6** followed by retro-Claisen condensation, and the reaction of compounds **5** with hydrazine to provide the hydrazones of semicarbazides **4**. The results of the acid-catalyzed heterocyclizations of **4**, which unexpectedly gave 14-membered cyclic bis-semicarbazones instead of seven-membered cyclic semicarbazones **3**, are described.

Results and discussion

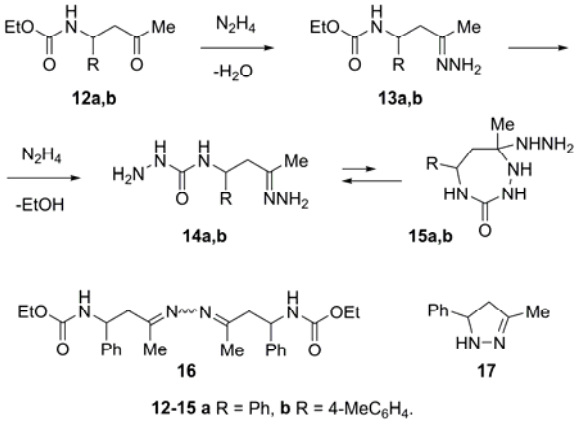
The starting amidoalkylation reagents, ethyl *N*-(α-tosylbenzyl)carbamates **7a,b**, were obtained by our convenient modification[18] of Engberts method[19] using *p*-toluenesulfinic acid (**8**) instead of sodium *p*-toluenesulfinate in the presence of formic acid. The three-component condensation of ethyl carbamate (**9**) with aldehydes **10a,b** and sulfinic acid **8** proceeded in water at 70 °C for 1-1.35 h to give the corresponding sulfones **7a,b** in 88% and 71% yield, respectively (Scheme 2).



Scheme 2. Synthesis of ethyl *N*-(oxoalkyl)carbamates **12a,b**.

Reaction of sulfones **7a,b** with the sodium enolate of acetylacetone proceeded readily in dry MeCN at room temperature for eight hours to afford the products of nucleophilic substitution of the tosyl group, i.e., carbamates **11a,b**, in 93% and 91% yield, respectively (Scheme 2). Ethyl *N*-(3-oxobutyl)-carbamates **12a,b** were prepared in high yields from **11a,b** by retro-Claisen reaction using an aqueous solution of KOH (5 equiv) at room temperature for three hours.

Next, we studied the reaction of carbamate **12a** with hydrazine under various conditions using ^{1}H NMR spectroscopy. This reaction was found to proceed in two sequential steps involving a relatively fast formation of hydrazone **13a** followed by slow substitution of the ethoxy group resulting in the target hydrazone of semicarbazide **14a** (Scheme 3, Table 1). The latter could be readily isolated from the reaction mixtures after evaporation of all the volatiles under reduced pressure and treatment of the residues with ether in which compound **14a** was poorly soluble.



Scheme 3. Synthesis of the hydrazones of *N*-(3-oxobutyl)semicarbazides **14a,b**.

Table 1. Product distribution upon reaction of carbamate **12a** with hydrazine.[a]

Entry	Reagent	Equiv. of N_2H_4	Solvent	Conc of **12a** (mmol/mL)	Reaction conditions	Product distribution[b] (%)			
						13a (*E*/*Z*)[c]	**14a** (*E*/*Z*)[c]	**16**[d]	**17**
1	$N_2H_4 \cdot H_2O$	3	EtOH	0.40	reflux, 5 h	76 (86/14)	0	24	0
2	$N_2H_4 \cdot H_2O$	3	EtOH	0.40	reflux, 10 h	85 (87/13)	0	15	0
3	$N_2H_4 \cdot H_2O$	10	EtOH	0.36	rt, 11 h	90 (88/12)	0	10	0
4	$N_2H_4 \cdot H_2O$	10	EtOH	0.36	reflux, 5.37 h	86 (88/12)	0	14	0
5	$N_2H_4 \cdot H_2O$	10	EtOH	0.36	reflux, 10.78 h	87 (85/15)	0	13	0
6	$N_2H_4 \cdot H_2O$	10	*n*-BuOH	0.33	reflux, 5.23 h	90 (87/13)	0	10	0
7[e]	$N_2H_4 \cdot H_2O$	41	-	0.50	reflux, 10.67 h	39 (87/13)	46 (84/16)	0	15
8	$N_2H_4 \cdot H_2O$	105	-	0.20	reflux, 10.32 h	32 (84/16)	55 (84/16)	0	13
9[f]	$N_2H_4 \cdot H_2O$	105	-	0.20	reflux, 24 h	trace	87 (84/16)	0	13
10	$N_2H_4 \cdot H_2O$	103	-	0.20	reflux, 36.42 h	0	39 (81/19)	0	61
11	N_2H_4	11	pyridine	0.30	reflux, 2.58 h	87 (87/13)	0	13	0
12	N_2H_4	11	pyridine	0.30	reflux, 12 h	37 (86/14)	0	63	0
13[g]	N_2H_4	88	-	0.36	reflux, 20 h	13 (85/15)	81 (84/16)	0	6

[a] In all cases the starting material was completely consumed.
[b] According to the ^{1}H NMR spectra of the crude products obtained after evaporation of the reaction mixtures in vacuo to dryness, co-evaporation of the residues with toluene (2-4 times) and drying in vacuo. The amounts of azine **16** in mixtures with **13a** were determined by comparision of the integral intensities of the NH_2 signals for **13a** with those of the OCH_2 or CH_3 signals for **13a** plus **16**.
[c] *E*/*Z* isomer ratios are given in parentheses.
[d] Mixtures of stereoisomers.
[e] Compound **14a** was isolated in a 31% yield after evaporation of the reaction mixture in vacuo to dryness followed by treatment with Et_2O and filtration.
[f] Unidentified products were observed in the ^{1}H NMR spectrum along with **14a** and **17**.
[g] Compound **14a** was isolated in a 52% yield after evaporation of the reaction mixture in vacuo to dryness followed by treatment with Et_2O and filtration.

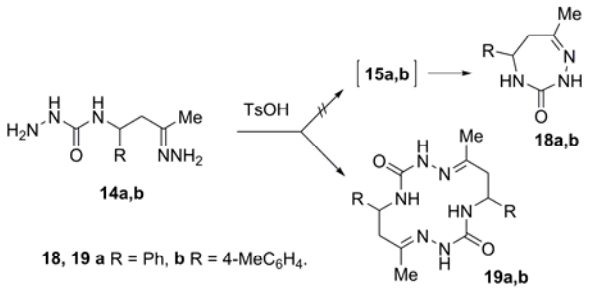
The reaction of **12a** with hydrazine hydrate or hydrazine in different solvents (EtOH, *n*-BuOH, Py) at room temperature or at reflux gave mixtures of hydrazone **13a** and azine **16** (Table 1; entries 1-6, 11 and 12). The amount of azine **16** decreased with an increase in the reaction time (entry 1 vs entry 2), the use of an excess of N_2H_4 (entry 2 vs entry 3), and when alcohols were used as solvents instead of pyridine (entries 3-6 vs entry 12). According to ^{1}H NMR spectroscopic data, hydrazone **13a** was formed as a mixture of *E*- and *Z*-isomers, and azine **16** was a mixture of stereoisomers (up to 8) with significant predominance of two of them (Table 1).

Since the formation of semicarbazide **14a** in the reaction of **12a** with hydrazine in EtOH, *n*-BuOH and Py did not proceed, refluxing hydrazine or hydrazine hydrate was used as the solvent and reagent to induce the substitution of the ethoxy group. Under these conditions formation of azine **16** was completely suppressed, and gradual transformation of the intermediate hydrazone **13a** into semicarbazide **14a** (a mixture of *E*- and *Z*-isomers) was observed (Table 1; entries 7-9, 13). This transformation was practically complete in 24 hours. Dihydropyrazole **17** resulting from elimination of semicarbazide in **13a** followed by ring closure was the major by-product formed in the reaction with hydrazine hydrate. Refluxing hydrazine gave the best results. Only 6% of dihydropyrazole **17** was observed after 20 hours (entry 13), and semicarbazide **14a** was isolated in 52% yield. Under optimal

conditions (N_2H_4, reflux, 23.5 h), compound **14a** was obtained in 60% yield. Similarly, compound **14b** was prepared in 65% yield from carbamate **12b**.

The crude semicarbazides **14a,b** were isolated as mixtures of *E*- and *Z*-isomers with significant predominance of one of them (up to 90%). Their configuration could not be determined unambiguously using a ^{1}H-^{1}H NOESY experiment in DMSO-d_6. However, comparison of the experimental carbon chemical shifts for the CH_2 and CH_3 groups of the $CH_2C(=NNH_2)CH_3$ moiety in **14a** with those calculated by the GIAO method at the RHF/6-311+G(2d,p) level using the DFT-B3LYP/6-31+G(d,p) optimized geometries for both (*E*)-**14a** and (*Z*)-**14a** clearly demonstrated that the major isomer of **14a** had the (*E*)-configuration. The DFT calculations at the B3LYP/6-31+G(d,p) level also showed that the (*E*)-isomer of **14a** was more stable (1.91 kcal/mol in DMSO) than the (*Z*)-isomer. Since the ^{1}H and ^{13}C NMR spectra of the major isomers of **14a** and **14b** were similar, we concluded that the major isomer of **14b** also had the (*E*)-configuration.

Finally, we studied the heterocyclization of **14a,b** under acidic conditions expecting the formation of triazepinones **18a,b** via **15a,b** (Scheme 4). Surprisingly, reflux of **14a,b** in EtOH in the presence of TsOH (1.2 equiv) gave 14-membered cyclic bis-semicarbazones **19a,b** in 71% and 80% yields, respectively, instead of triazepinones **18a,b**. Compound **19a** was also prepared in 70% yield in refluxing MeCN.



Scheme 4. Acid-catalyzed transformation of semicarbazides **14a,b** into 14-membered macrocyclic bis-semicarbazones **19a,b**.

Compounds **19a,b** were formed as white solids which were practically insoluble (especially **19b**) in common solvents including DMSO, DMF, etc. The structure of **19a** was established by IR, ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry, and powder X-ray diffraction. It was difficult to record satisfactory NMR spectra of **19b** due to its extremely low solubility. Therefore, solid-state ^{15}N and ^{13}C NMR spectra were acquired. This compound was also characterized by IR spectroscopy, mass spectrometry, and powder X-ray diffraction. The crystal structures of **19a,b** are shown in Figure 2 and Figure 3.

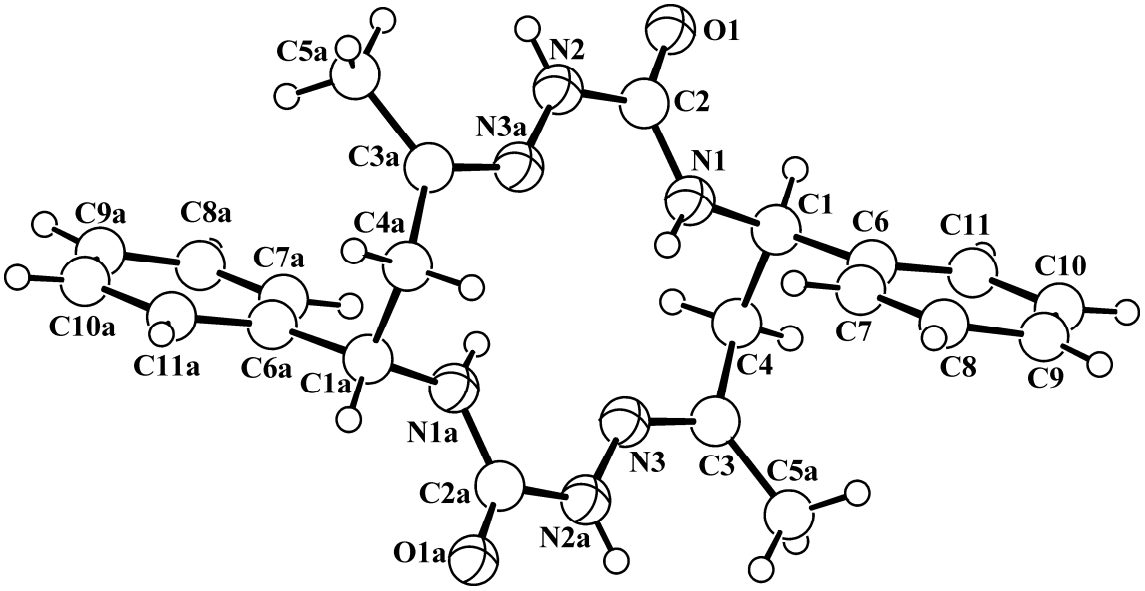


Figure 2. Molecular structure of **19a** showing the atomic numbering and 50% probability displacement spheres [symmetry code: (a) 1-*x*, 1-*y*, 1-*z*].

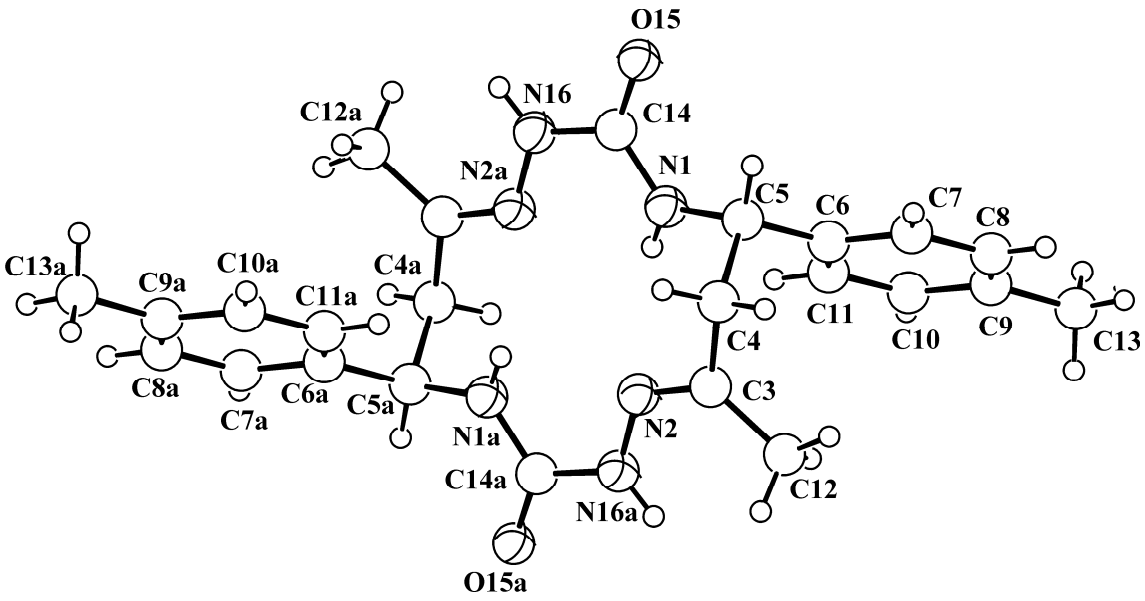
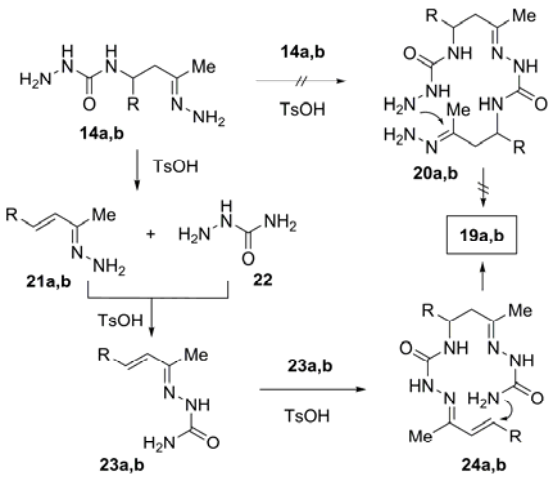


Figure 3. Molecular structure of **19b** showing the atomic numbering and 50% probability displacement spheres [symmetry code: (a) 2-*x*, 1-*y*, 1-*z*].

Since macrocycle **19a** has two distant chiral centers, we expected it to form as a mixture of two diastereomers in approximately equal amounts. However, according to NMR spectra and X-ray analysis, only a single diastereomer of **19a** with *trans*-orientation of the phenyl groups was obtained. Thus, formation of **19a** via intermediate **20a** could be excluded (Scheme 5).



Scheme 5. A plausible pathway for the transformation of **14a,b** into macrocycles **19a,b**.

Scheme 5 shows a plausible pathway for the transformation of **14a** into macrocycle **19a**, including acid-catalyzed elimination of semicarbazide **22** resulting in unsaturated hydrazone **21a** followed by formation of semicarbazone **23a**. Dimerization of compound **23a** via intramolecular aza-Michael addition affords intermediate **24a** which cyclizes through an intermolecular aza-Michael reaction to give the final product **19a**. Most probably, cyclization of **24a** is controlled by the presence of the phenyl group at the chiral center to give exclusively the *trans*-isomer of **19a**.

According to powder X-ray analysis, the crystallized macrocycle **19b** was also a single diastereomer with *trans*-orientation of the aryl groups. Because of the extremely low solubility of analytically pure **19b**, attempts to record its NMR spectra in solutions failed. However, the ^{1}H NMR spectrum (8489 scans) of a saturated solution of crude **19b** in DMSO-d_6 showed two sets of signals of *trans*- and *cis*-isomers in a ratio of 91:9. Therefore, we suppose that compound **19b** was similarly formed with high stereoselectivity according to the pathway shown in Scheme 5.

Conclusion

We have demonstrated that the acid-catalyzed cyclization of the hydrazones of 3-(3-oxobutyl)-semicarbazides involving two molecules of the starting material provides an efficient stereoselective access to novel 14-membered cyclic bis-semicarbazones. The starting semicarbazides were readily prepared according to our original four-step approach involving amidoalkylation of the sodium enolate of acetylacetone with *N*-(α-tosylbenzyl)carbamates followed by base-promoted retro-Claisen reaction and treatment of the obtained *N*-(3-oxobutyl)carbamates with hydrazine. We hope that the obtained class of heterocycles could be of interest from various viewpoints, in particular, as new polyaza macrocyclic ligands for metal complexes.

Acknowledgments

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