Tetrahedron Letters 57 (2016) 5784–5787

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

An efficient and stereoselective approach to 14-membered hexaaza macrocycles using novel semicarbazone-based amidoalkylation reagents

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ARTICLE INFO

Article history:
Received 2 September 2016
Revised 1 November 2016
Accepted 8 November 2016
Available online 9 November 2016

Keywords:
Semicarbazones
Semicarbazides
Hydrazones
Amidoalkylation
retro-Claisen reaction
Azamacrocycles

ABSTRACT

An efficient synthesis of hydrazones of 4-(3-oxobutyl)semicarbazides and 4-(3-oxobutyl)semicarbazones using novel semicarbazone-based amidoalkylation reagents, 1-arylidene-4-[(aryl)(tosyl)methyl]semicarbazides, has been developed. The synthesis involved reaction of the latter with the Na-enolate of acetylacetone, followed by a base-promoted retro-Claisen reaction and treatment of the obtained 4-(3-oxobutyl)semicarbazones with hydrazine or methylhydrazine. The prepared hydrazones were converted stereoselectively into 14-membered cyclic bis-semicarbazones under acidic conditions. Especially high selectivity (*trans*/*cis* ⩾ 97:3) was observed upon the macrocyclization of 4-(3-oxobutyl)semicarbazone hydrazones. A plausible reaction pathway and the stereochemistry of this cyclization were discussed.

Polyaza macrocycles are of considerable importance in various fields of chemistry, biochemistry, medicine, and material science. The unique features of these heterocycles arise from their ability to bind to different inorganic and organic cations, anions, and neutral molecules.[1,2] Polyaza macrocycles and their metal complexes possess a wide range of biological activities[3] including anticancer,[4] anti-HIV,[5] antibacterial and antifungal properties.[6] The metal complexes also have applications as contrast agents for magnetic resonance imaging,[7] radiopharmaceuticals,[8] sensors,[9] NMR shift reagents,[10] luminescent materials,[9c,10b] and catalysis.[2d,11]

Although a large variety of polyaza macrocycles have been synthesized, the design of new members, particularly tetradentate 14-membered hexaazacycles, is a topic of great interest. Among them, 14-membered 1,2,4,8,9,11-hexaaza macrocycles remain underexploited.[12] Recently, we reported a general approach to novel 14-membered cyclic bis-semicarbazones **1** based on the acid-catalyzed cyclization of 4-(3-oxobutyl)semicarbazide hydrazones **2** (Scheme 1).[13]

In contrast to the 14-membered 1,2,4,8,9,11-hexaaza macrocycles previously described in the literature,[12] compounds **1** are conformationally more flexible because they possess only two double bonds in the heterocyclic ring. Powder X-ray diffraction analysis[13a] and DFT calculations showed that the internal cavity of macrocycles **1** is able to chelate various metal cations through the N1, N4, N8, and N11 atoms. Indeed, the neutral complex of dianion of **1** (R = Ph, R^1 = H) with Ni(II) was obtained,[14] demonstrating that hexaaza macrocycles **1** can serve as novel tetradentate ligands for metal ions. However, progress in this area was hampered by the low availability of macrocycle precursors **2** which were prepared in four steps from ethyl carbamate involving α-amidoalkylation of sodium acetylacetonates with ethyl *N*-(tosylmethyl)carbamates. The Achilles' heel of the synthesis was the low isolated yields (29–42%) for substitution of the ethoxy group in β-carbamato ketones **3** on the hydrazino fragment due to the harsh reaction conditions (N_2H_4, reflux, 20–24 h).[13b]

We hypothesized that hydrazones **2** could be readily prepared from N1-protected semicarbazides following the same strategy. Additionally, treatment of 4-(3-oxobutyl)semicarbazides with hydrazine could give access not only to N1-unprotected semicarbazide hydrazones **2**, but N1-protected analogues which could also serve as macrocycle precursors.

Herein, we describe a convenient multi-gram synthesis of hydrazones of 4-(3-oxobutyl)-substituted semicarbazides and semicarbazones from 1-arylidenesemicarbazides, and the acid-catalyzed stereoselective cyclization of these hydrazones to give 14-membered cyclic bis-semicarbazones **1**. The preparation of novel α-amidoalkylation reagents, 1-arylidene-4-(tosylmethyl) semicarbazides, is also reported.

Based on previous experience,[13b,15] the amidoalkylation reagents **4a–d** were obtained by the three-component

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http://dx.doi.org/10.1016/j.tetlet.2016.11.041
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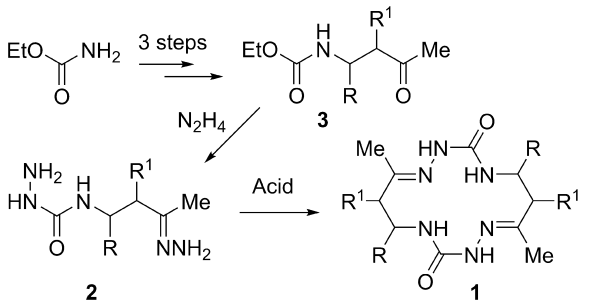
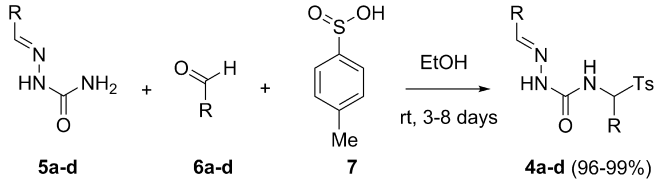


Scheme 1. Synthesis of hexaaza macrocycles **1**.[13]



4-6 a R = Ph, **b** R = 4-MeC$_6$H$_4$, **c** R = 4-*t*-BuC$_6$H$_4$, **d** R = 4-MeOC$_6$H$_4$.

Scheme 2. Synthesis of semicarbazone-based amidoalkylation reagents **4a–d**.

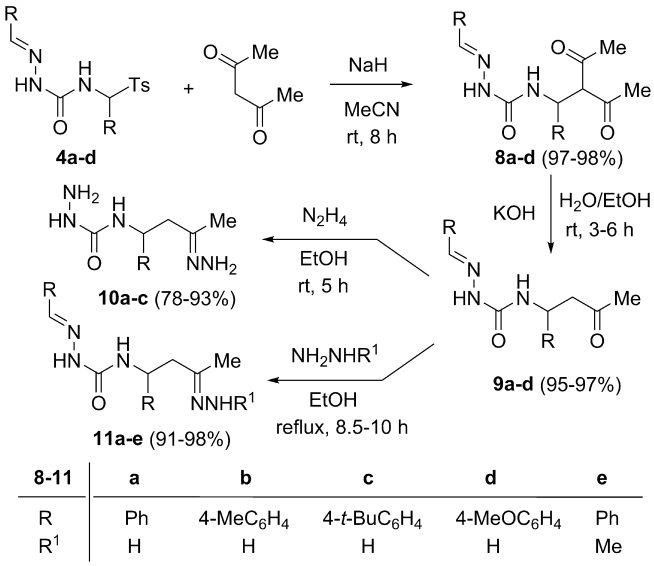
condensation of (*E*)-1-arylidenesemicarbazides **5a–d** with the corresponding aromatic aldehydes **6a–d** and *p*-toluenesulfinic acid (**7**) (Scheme 2). Under optimized reaction conditions (EtOH, rt, 3–8 days, 30–50 mol% excess of **6** and **7**), (*E*)-semicarbazones **4a–d** were isolated in 96–99% yield with >95% purity (^{1}H NMR) after filtration of the precipitate formed upon reaction completion.

It should be noted that the prepared semicarbazones **4a–d** represent novel amidoalkylation reagents[16] and can be widely used in organic synthesis.[17]

Nucleophilic substitution of the tosyl-group in sulfones **4a–d** proceeded smoothly under the action of the Na-enolate of acetylacetone in MeCN to give the corresponding (*E*)-semicarbazones **8a–d** in 97–98% yields (Scheme 3). Treatment of compounds **8a–d** with KOH (5 equiv.) in aqueous EtOH at room temperature for 3–6 h afforded (*E*)-4-(3-oxobutyl)semicarbazones **9a–d** in 95–97% yields.

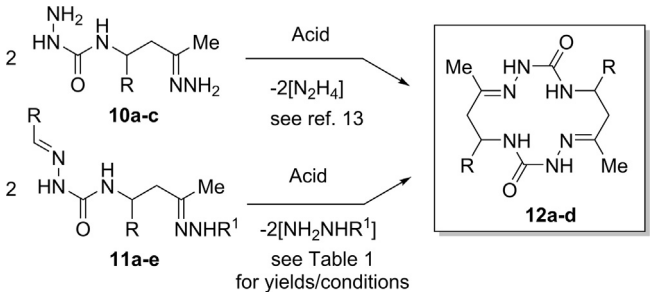
Heating compounds **9a–c** in EtOH at reflux for 8.5–10 h in the presence of $N_2H_4{\cdot}H_2O$ (30 equiv.) afforded hydrazones of semicarbazides **10a–c** (78–93%) as mixtures of (*E*)- and (*Z*)-isomers in ratios of 92:8, 94:4, and 95:5, respectively. Under all conditions tested, MeO-derivative **9d** failed to give the desired hydrazone with sufficient purity. Thus, compounds **10a–c**, the key precursors of 14-membered hexaaza macrocycles, were prepared in four steps from semicarbazones **5a–c** in 71–83% overall yield on a multi-gram scale, while the overall yields of these compounds obtained in four steps from ethyl carbamate were only 22–32% (see Scheme 1).[13b]

Treatment of semicarbazones **9a–d** with $N_2H_4{\cdot}H_2O$ (30 equiv.) in EtOH at room temperature for 5 h gave mixtures of (*E*)- and (*Z*)-hydrazones of (*E*)-semicarbazones **11a–d** in high yield (94–98%), with significant predominance of the (*E*)-isomer (91–98%). Analogously, a 92:8 mixture of (*E*)- and (*Z*)-methylhydrazones of (*E*)-semicarbazone **11e** was obtained in 91% yield from the reaction of compound **9a** with methylhydrazine. The configurations of the major and minor isomers of compounds **11a,c** were unambiguously determined using ^{1}H,^{1}H NOESY experiments in DMSO-d_6. For the major isomer of **11a,c**, a diagnostic NOE was observed between the CH_3 and C=NNH_2 protons, thus indicating the (*E*)-configuration of the C=N double bond. Since the ^{1}H and ^{13}C NMR spectra of the major isomers of **11a,c** and **11b,d,e** were similar, we concluded that the major isomers of **11b,d,e** also had the (*E*)-configuration.



8-11	**a**	**b**	**c**	**d**	**e**
R	Ph	4-MeC$_6$H$_4$	4-*t*-BuC$_6$H$_4$	4-MeOC$_6$H$_4$	Ph
R^1	H	H	H	H	Me

Scheme 3. Synthesis of macrocyclic precursors **10a–c** and **11a–e**.



Scheme 4. Syntheses of 14-membered hexaaza macrocycles **12a–d**.

Recently, we reported the TsOH-catalyzed transformation of hydrazones **10a–c** into hexaaza macrocycles **12a–c** (Scheme 4).[13] The reaction proceeded smoothly in EtOH or MeCN at room temperature or at reflux to give compounds **12a–c** in 85–93% yields as mixtures of *trans*- and *cis*-isomers whose ratio was dependent on the reaction conditions. Thus, the effective synthesis of the key precursors **10a–c** on a multi-gram scale as described herein, provides an improved access to macrocycles **12a–c**.

Having successfully prepared the hydrazones of semicarbazones **11a–e**, we took on the challenge to transform them into the corresponding macrocycles **12a–d**. Under optimal conditions for the cyclization of hydrazone **10a** (TsOH 1.07 equiv., EtOH, reflux, 2 h),[13b] compound **11a** predominantly afforded semicarbazone **5a**, and no macrocycle was detected (^{1}H NMR). The reaction of **11a** with 0.09 equivalents of TsOH (EtOH, reflux, 2 h) resulted in the formation of a complex mixture containing **12a** (24% ^{1}H NMR estimated yield of **12a**, *trans*/*cis* = 57:43).

We found that the macrocyclization of **11a** proceeded well in aprotic solvents (Table 1). In MeCN at reflux, under the action of TsOH (0.10 equiv.), a 89:11 mixture of *trans*- and *cis*-**12a** was cleanly formed from semicarbazone **11a** in 72% yield (Entry 1). Increasing the concentration of **11a** led to an increase in the cyclization stereoselectivity (Entry 2 vs Entry 1). Decreasing the concentration of **11a** resulted in a higher yield of **12a** and lower reaction stereoselectivity (Entry 7 vs Entry 1). Use of an increased amount of TsOH improved both the selectivity and yield of the cyclization (Entry 2 vs Entry 6). When the reaction of **11a** with TsOH was performed in THF, the yield of **12a** increased while the