Novel Semicarbazone-Based Amidoalkylation Reagents: Preparation and Application to the Stereoselective Synthesis of 14-Membered Hexaaza Macrocycles

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Abstract

An efficient general synthesis of hydrazones of 4-(3-oxobutyl)semicarbazones using novel semicarbazone-based amidoalkylation reagents has been developed. The prepared hydrazones were converted under acidic conditions into 14-membered cyclic bis-semicarbazones, 1,2,4,8,9,11-hexaazacyclotetradeca-7,14-diene-3,10-diones. Plausible pathway and stereochemistry of the macrocyclization are discussed.

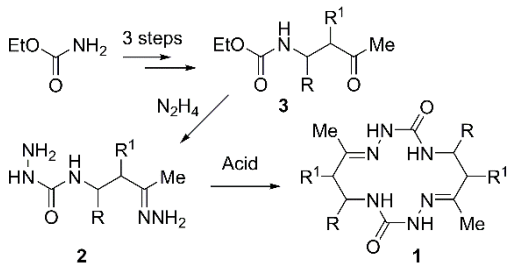
Keywords

Semicarbazones; 4-(Tosylmethyl)semicarbazones; Hydrazones; Azamacrocycles; Amidoalkylation; retro-Claisen reaction; Heterocyclization

Introduction

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]



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

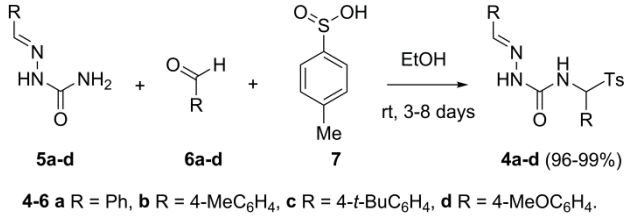
In contrast to 14-membered 1,2,4,8,9,11-hexaaza macrocycles previously described in the literature,[12] compounds **1** are conformationally more flexible because they possess only two double bonds in the heterocyclic ring. Powder X-ray diffraction analysis[13a] and DFT calculations showed that the internal 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 the substitution of the ethoxy group in β-carbamato ketones **3** on 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.

Results and discussion

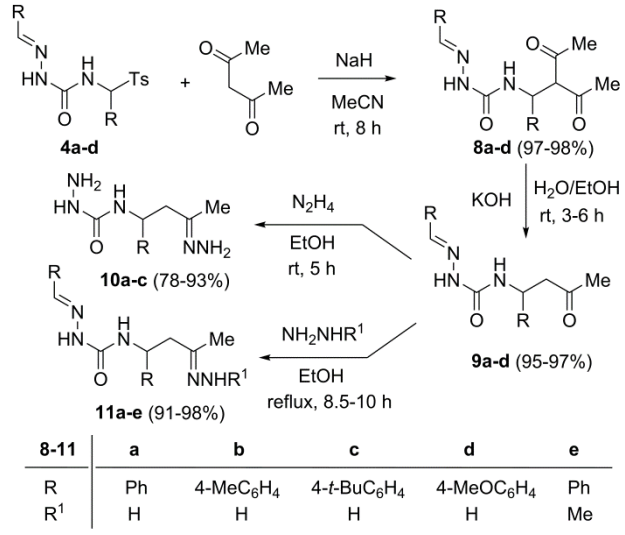
Based on previous experience,[13b,15] the amidoalkylation reagents **4a-d** were obtained by the three-component condensation of (*E*)-1-arylidenesemicarbazides **5a-d** with the corresponding aromatic aldehydes **6a-d** and *p*-toluenesulfinic acid (**7**) (Scheme 2). Under optimized reaction conditions (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 after reaction completion.



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

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.



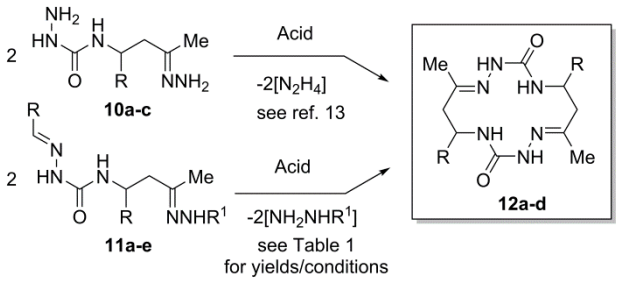
8-11	a	b	c	d	e
R	Ph	4-MeC$_6$H$_4$	4-*t*-BuC$_6$H$_4$	4-MeOC$_6$H$_4$	Ph
R^1	H	H	H	H	Me

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

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 (see Scheme 1) were only 22–32%.[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 in this isomer. 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.

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**.



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

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** (1.07 equiv. of TsOH, 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 stereoselectivity remained unchanged compared with those in MeCN (Entry 2 vs Entry 5).

Table 1. Acid-catalyzed cyclization of semicarbazones **11a-d** to give 14-membered hexaaza macrocycles **12a-d**.[a]

Entry	Starting compound	R	Conc. (mol/L)	Solvent	Acid (equiv.)	Time (h)	Product	*trans*/*cis* ratio[b]	Yield[c] (%)
1	**11a**	Ph	0.123	MeCN	$TsOH·H_2O$ (0.10)	2	**12a**	89:11	72
2	**11a**	Ph	0.217	MeCN	$TsOH·H_2O$ (0.10)	1	**12a**	93:7	70
3	**11a**	Ph	0.218	MeCN	CF_3COOH (0.10)	2	**12a**	95:5	77
4	**11a**	Ph	0.157	MeCN	AcOH (50)	9	**12a**	20:80	14[d]
5	**11a**	Ph	0.195	THF	$TsOH·H_2O$ (0.10)	4	**12a**	93:7	78
6	**11a**	Ph	0.243	MeCN	$TsOH·H_2O$ (0.20)	2	**12a**	97:3	75
7	**11a**	Ph	0.039	MeCN	$TsOH·H_2O$ (0.10)	2	**12a**	54:46	87
8	**11b**	4-MeC_6H_4	0.125	MeCN	$TsOH·H_2O$ (0.10)	2	**12b**	26:74	68
9	**11b**	4-MeC_6H_4	0.243	MeCN	$TsOH·H_2O$ (0.10)	2	**12b**	64:36	79
10	**11b**	4-MeC_6H_4	0.243	MeCN	$TsOH·H_2O$ (0.10)	1	**12b**	46:54	79
11	**11b**	4-MeC_6H_4	0.207	MeCN	CF_3COOH (0.11)	2	**12b**	63:37	80
12	**11b**	4-MeC_6H_4	0.223	MeCN	$TsOH·H_2O$ (0.10)	6	**12b**	96:4	80
13	**11b**	4-MeC_6H_4	0.216	MeCN	$TsOH·H_2O$ (0.20)	4	**12b**	98:2	78
14	**11c**	4-*t*-BuC_6H_4	0.119	MeCN	$TsOH·H_2O$ (0.09)	1	**12c**	49:51	75
15	**11c**	4-*t*-BuC_6H_4	0.118	MeCN	$TsOH·H_2O$ (0.10)	4	**12c**	59:41	70
16	**11c**	4-*t*-BuC_6H_4	0.116	MeCN	$TsOH·H_2O$ (0.20)	4	**12c**	78:22	68
17	**11c**	4-*t*-BuC_6H_4	0.119	MeCN	$TsOH·H_2O$ (0.20)	8	**12c**	100:0	92
18	**11d**	4-$MeOC_6H_4$	0.204	MeCN	$TsOH·H_2O$ (0.20)	2	**12d**	97:3	58
19	**11d**	4-$MeOC_6H_4$	0.210	MeCN	$TsOH·H_2O$ (0.10)	4	**12d**	99:1	60

[a] Reaction conditions: MeCN or THF, reflux, 1–9 h.
[b] According to ^{1}H NMR spectroscopy of the crude product.
[c] Isolated yield.
[d] NMR estimated yield.

The stereoselective transformation of **11a** into **12a** was also promoted by the strong acid TFA (Entry 3). However, only a small amount of **12a** (14% ^{1}H NMR estimated yield, *trans*/*cis* = 20:80) along with numerous side-products was obtained in the presence of the relatively weak acetic acid (50 equiv., MeCN, reflux, 9 h) (Entry 4).

Previously, we found that the macrocyclization of semicarbazide **10a** in the presence of TsOH completed in EtOH at room temperature for 4 h.[13b] In contrast, the TsOH-catalyzed conversion of **11a** into **12a** at room temperature was slow. The crude product obtained after treatment of **11a** with TsOH (0.10 equiv.) in MeCN (rt, 24 h) contained starting material (3 mol%), macrocycle **12a** (42% ^{1}H NMR estimated yield, *trans*/*cis* = 67:33) and unidentified compounds.

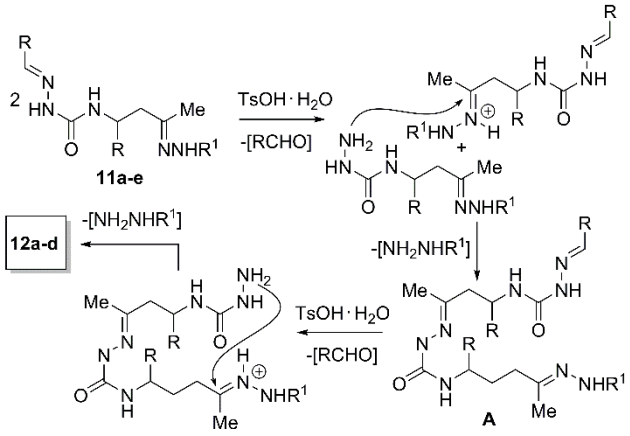
Thus, under the optimal conditions (Entry 6), macrocycle **12a** was obtained in 75% yield as a 97:3 mixture of *trans*- and *cis*-isomers. Analogously, reaction conditions were optimized for the transformation of **11b-d** into the corresponding macrocycles **12b-d** (Table 1). These compounds were prepared in good yields (60–92%) and with excellent *trans*-selectivity (up to 100%). It is noteworthy, that under the optimal conditions, the stereoselectivity for formation of macrocycles **12** from the hydrazones of semicarbazones **11** was significantly higher than that from the hydrazones of semicarbazides **10**.[13b]

Table 1 shows that the *trans*-stereoselectivity of the macrocyclization of compounds **11a-d** increases with an increase in starting material concentration, reaction time, and catalyst loading. Therefore, we propose that the reaction of **11a-d** initially proceeds rapidly with low diastereoselectivity to give mixtures of *cis*- and *trans*-**12a-d** which is then followed by a slow irreversible transformation of the *cis*-isomers into the *trans*-isomers *via* ring opening by a retro-aza-Michael reaction. Calculations performed at the DFT B3LYP/6-311++G(d,p) level of theory using the PCM solvation model showed that *trans*-**12a** was less stable than *cis*-**12a** in both MeCN and EtOH solutions (ΔG = 1.67 and 2.08 kcal/mol, respectively; 298 K and 1 atm). The predominant formation of *trans*-**12a-d** from **11a-d** can be explained by their significantly lower solubility compared with that of *cis*-isomers; therefore, *trans*-**12a-d** completely precipitates from the reaction media resulting in a gradual increase in the *trans*-selectivity of the process.

Acid-catalyzed macrocyclization of *N*-methylhydrazone **11e** could proceed via two possible pathways involving nucleophilic participation of the N1-atom to give macrocycle **12a** or the NHMe nitrogen atom to give 2,9-dimethyl derivative of **12a**. At reflux for 2.5 h or at room temperature for 96 h in MeCN in the presence of TsOH (0.10 equiv.), compound **11e** afforded macrocycle **12a** along with various side and intermediate products (^{1}H NMR). Prolonging the reaction time at reflux to 9 h led to predominant formation of **12a** (*trans:cis* = 58:42). No ^{1}H NMR signals of the 2,9-dimethyl derivative of **12a** were observed.

The presence of the hydrazone fragment in the starting semicarbazones **11** was proved to be essential for the formation of the macrocycles. Indeed, treatment of **9a** with TsOH (0.10 equiv.) in EtOH (2 h) or MeCN (4 h) at reflux resulted in partial decomposition of the starting material to give semicarbazone **5a**, benzylideneacetone, and unidentified products without any formation of macrocycle **12a** (^{1}H NMR). The starting material was completely recovered after reflux of **9a** in EtOH for 3 h in the presence of AcOH (4.06 equiv.).

Thus, the experimental data show that the macrocyclization of **11a-e** proceeds via nucleophilic attack of the N1 nitrogen atom of one molecule on the electrophilic carbon of the hydrazone moiety of the second molecule after its activation by the catalyst. However, the nucleophilicity of the N1 atom with sp^2-hybridization is not sufficient for the cyclization. We propose that under the examined reaction conditions, a more nucleophilic sp^3-hybridized nitrogen is generated by the addition of a nucleophile to the C=N double bond, for example, the water from TsOH·H_2O. A plausible pathway for the TsOH·H_2O-catalyzed macrocyclization of hydrazones **11a-e** is shown in Scheme 5.



Scheme 5. Plausible pathway for the macrocyclization of semicarbazones **11a-e**.

This pathway involves hydrolytic cleavage of the semicarbazone moiety followed by reaction of the free NH_2-group of the obtained semicarbazide with the protonated hydrazone fragment of second molecule to give acyclic intermediate **A** which cyclizes into the product **12** following the same steps.

Conclusion

In conclusion, a stereoselective five-step synthesis of novel 14-membered bis-semicarbazones based on the acid-catalyzed cyclization of hydrazones of 4-(3-oxobutyl)semicarbazides or 4-(3-oxobutyl)semicarbazones has been developed. Hydrazones were obtained by an efficient multi-gram protocol from novel amidoalkylation reagents, 1-arylidene-4-(tosylmethyl)semicarbazides, whose simple preparation was also described.

Acknowledgments

This research was financially supported by the Russian Foundation for Basic Research (Grant No. 15-03-07564) and the Ministry of Education and Science of the Russian Federation (basic part of government order, 4.9671.2017).

References and Notes

1. For selected books on polyaza macrocycles, see: (a) *Macrocyclic Chemistry: New Research Developments*; Fitzpatrick, D. W., Ulrich, H. J., Eds.; Nova Science Publishers, Inc.: New York, 2010. (b) Hermann, P.; Kotek, J. Ten-membered Rings or Larger with One or More Nitrogen Atoms, in *Comprehensive Heterocyclic Chemistry III*; Elsevier: Amsterdam, 2008; Vol. 14, pp 613–665. (c) *Macrocyclic Chemistry: Current Trends and Future Perspectives*; Gloe, K., Ed.; Springer: New York, 2005. (d) Lindoy, L. F. *The Chemistry of Macrocyclic Ligand Complexes*;

Cambridge University Press: Cambridge, 1989. (e) *Coordination Chemistry of Macrocyclic Compounds*; Melson, G., Ed.; Plenum Press: New York, 1979.

2. For some reviews on binding properties of polyaza macrocycles, see: (a) Gavey, E. L.; Pilkington, M. *Coord. Chem. Rev*. **2015**, *296*, 125–152; (b) Geduhn, J.; Walenzyk, T.; König, B. *Curr. Org. Synth*. **2007**, *4*, 390–412; (c) Radecka-Paryzek, W.; Patroniak, V.; Lisowski, J. *Coord. Chem. Rev*. **2005**, *249*, 2156–2175; (d) Reichenbach-Klinke, R.; König, B. *J. Chem. Soc., Dalton Trans*. **2002**, 121–130; (e) Aoki, S.; Kimura, E. *Rev. Mol. Biotechnol*. **2002**, *90*, 129–155; (f) McAuley, A.; Subramanian, S. *Coord. Chem. Rev*. **2000**, *200–202*, 75–103; (g) Mitewa, M.; Bontchev, P. R. *Coord. Chem. Rev*. **1994**, *135–136*, 129–163.
3. For reviews on biological activities of polyaza macrocycles, see (a) Liang, X.; Sadler, P. J. *Chem. Soc. Rev*. **2004**, *33*, 246–266; (b) Liang, F.; Wan, S.; Li, Z.; Xiong, X.; Yang, L.; Zhou, X.; Wu, C. *Curr. Med. Chem*. **2006**, *13*, 711–727.
4. (a) Cruz, C.; Cairrão, E.; Lourenço, O.; Almeida, P.; Verde, I.; Queiroz, J. A. *Chem. Biol. Drug Des*. **2013**, *81*, 517–526; (b) Sibert, J. W.; Cory, A. H.; Cory, J. G. *Chem. Commun*. **2002**, 154–155.
5. De Clercq, E. *Nat. Rev. Drug Discovery* **2003**, *2*, 581–587.
6. Sakhare, M. A.; Khillare, S. L.; Lande, M. K.; Arbad, B. R. *Adv. Appl. Sci. Res*. **2013**, *4*, 94–100.
7. (a) Aime, S.; Crich, S. G.; Gianolio, E.; Giovenzana, G. B.; Tei, L.; Terreno, E. *Coord. Chem. Rev*. **2006**, *250*, 1562–1579; (b) De León-Rodríguez, L. M.; Ortiz, A.; Weiner, A. L.; Zhang, S.; Kovacs, Z.; Kodadek, T.; Sherry, A. D. *J. Am. Chem. Soc*. **2002**, *124*, 3514–3515.
8. (a) Smith, C. J.; Volkert, W. A.; Hoffman, T. *J. Nucl. Med. Biol*. **2005**, *32*, 733–740; (b) Heppeler, A.; Froidevaux, S.; Eberle, A. N.; Maecke, H. R. *Curr. Med. Chem*. **2000**, *7*, 971–994.
9. (a) Roger, M.; Regueiro-Figueroa, M.; Azzeddine, C. B.; Patinec, V.; Bonnet, C. S.; Platas-Iglesias, C.; Tripier, R. *Eur. J. Inorg. Chem*. **2014**, 1072–1081; (b) El Majzoub, A.; Cadiou, C.; Déchamps-Olivier, I.; Chuburu, F.; Aplincourt, M. *Eur. J. Inorg. Chem*. **2007**, 5087–5097; (c) Bünzli, J.-C. G.; Piguet, C. *Chem. Soc. Rev*. **2005**, *34*, 1048–1077.
10. (a) Peters, J. A.; Huskens, J.; Raber, D. J. *Prog. Nucl. Magn. Reson. Spectrosc*. **1996**, *28*, 283–350; (b) Parker, D.; Dickins, R. S.; Puschmann, H.; Crossland, C.; Howard, J. A. K. *Chem. Rev*. **2002**, *102*, 1977–2010.
11. (a) Salavati-Niasari, M.; Najafian, H. *J. Chem. Res. (S)* **2003**, 538–539; (b) Canales, J.; Ramirez, J.; Estiu, G.; Costamagna, J. *Polyhedron* **2000**, *19*, 2373–2381; (c) Costamagna, J.; Ferraudi, G.; Canales, J.; Vargas, J. *Coord. Chem. Rev*. **1996**, *148*, 221–248.
12. (a) Arion, V. B.; Gerbeleu, N. V.; Levitsky, V. G.; Simonov, Yu. A.; Dvorkin, A. A.; Bourosh, P. N. *J. Chem. Soc., Dalton Trans*. **1994**, 1913–1916; (b) Vlasiuk, S. V.; Pavlovsky, V. I.; Andronatti, S. A.; Gdaniec, M.; Simonov, Y. A. *Chem. Heterocycl. Compd*. **2000**, *36*, 1077–1085; (c) Gradinaru, J. I.; Simonov, Yu. A.; Arion, V. B.; Bourosh, P. N.; Popovici, M. A.; Bel'skii, V. K.; Gerbeleu, N. V. *Inorg. Chimica Acta* **2001**, *313*, 30–36; (d) Chaudhary, A.; Joshi, S. C.; Singh, R. V. *Main Group*

Met. Chem. **2004**, *27*, 59–70; (e) Chandra, S.; Gupta, L. K.; Agrawal, S. *Transition Met. Chem*. **2007**, *32*, 240–245; (f) Chandra, S.; Gautam, A. *J. Serb. Chem. Soc*. **2009**, *74*, 1413–1422; (g) Dolzhenko, A. V.; Pastorin, G.; Dolzhenko, A. V.; Chui, W. K. *Tetrahedron Lett*. **2009**, *50*, 5617–5621.

13. (a) Shutalev, A. D.; Fesenko, A. A.; Kuzmina, O. M.; Volov, A. N.; Albov, D. V.; Chernyshev, V. V.; Zamilatskov, I. A. *Tetrahedron Lett*. **2014**, *55*, 5481–5485; (b) Fesenko, A. A.; Shutalev, A. D. *Tetrahedron*, **2015**, *71*, 9528–9543.
14. Volov, A. N.; Zamilatskov, I. A.; Chernyshev, V. V.; Savinkina, E. V.; Chuvaev, V. F.; Kurochkina, N. M.; Tsivadze, A. Yu. *J. Coord. Chem*. **2014**, *67*, 3121–3134.
15. (a) Shutalev, A. D.; Kishko, E. A.; Sivova, N. V.; Kuznetsov, A. Yu. *Molecules* **1998**, *3*, 100−106; (b) Shutalev, A. D.; Kurochkin, N. N. *Mendeleev Commun*. **2005**, *15*, 70−72; (c) Fesenko, A. A.; Tullberg, M. L.; Shutalev, A. D. *Tetrahedron* **2009**, *65*, 2344−2350; (d) Kurochkin, N. N.; Fesenko, A. A.; Cheshkov, D. A.; Davudi, M. M.; Shutalev, A. D. *Tetrahedron Lett*. **2011**, *52*, 88−91; (e) Fesenko, A. A.; Trafimova, L. A.; Shutalev, A. D. *Org. Biomol. Chem*. **2012**, *10*, 447−462; (f) Fesenko, A. A.; Shutalev, A. D. *J. Org. Chem*. **2013**, *78*, 1190−1207; (g) Fesenko, A. A.; Shutalev, A. D. *Tetrahedron* **2014**, *70*, 5398–5414.
16. Generally, amidoalkylation reagents are constructed by using various amides, ureas, thioureas, carbamates, and thiocarbamates as an amide backbone.[18]
17. A large variety of 4-(tosylmethyl)semicarbazones could be prepared by the reaction of *p*-toluenesulfinic acid with aliphatic and aromatic aldehydes and semicarbazones of the same or other aldehydes. The use of these reagents in organic synthesis will be the subject of forthcoming publications.
18. For selected reviews on α-amidoalkylation, see: (a) Zaugg, H. E.; Martin, W. B. *Org. Reactions* **1965**, *14*, 52–269; (b) Zaugg, H. E. *Synthesis* **1970**, 49–73; (c) Zaugg, H. E. *Synthesis* **1984**, 85–110; (d) Zaugg, H. E. *Synthesis* **1984**, 181–212; (e) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817–3856; (f) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev*. **2004**, *104*, 1431–1628; (g) Mazurkiewicz, R.; Październiok-Holewa, A.; Adamek, J.; Zielińska, K. *Adv. Heterocycl. Chem*. **2014**, *111*, 43–94.