Journal of Sulfur Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713926081

Chemoselective insertion of dimethoxycarbene into the N - H bond of thiolactams with diverse ring size

Grzegorz Mloston[a]; Karolina Kania[a]; Heinz Heimgartner[a]
[a] Department of Organic and Applied Chemistry, University of Lodz, Lodz, Poland

To cite this Article Mloston, Grzegorz , Kania, Karolina and Heimgartner, Heinz(2009) 'Chemoselective insertion of dimethoxycarbene into the N - H bond of thiolactams with diverse ring size', Journal of Sulfur Chemistry, 30: 3, 278 — 286
To link to this Article: DOI: 10.1080/17415990902870935
URL: http://dx.doi.org/10.1080/17415990902870935

Journal of Sulfur Chemistry
Vol. 30, Nos. 3–4, June–August 2009, 278–286

Taylor & Francis
Taylor & Francis Group

Chemoselective insertion of dimethoxycarbene into the N−H bond of thiolactams with diverse ring size

Grzegorz Mloston[a]*, Karolina Kania[a†] and Heinz Heimgartner[b]

[a]*Department of Organic and Applied Chemistry, University of Lodz, Narutowicza 68, PL-90-136 Lodz, Poland;* [b]*Institute of Organic Chemistry, University of Zurich, Winterthurerst. 190, CH-8057 Zurich, Switzerland*

(*Received 29 January 2009; final version received 28 February 2009*)

This paper is dedicated to Professor Juzo Nakayama on the occasion of his 65th birthday and retirement, and for his outstanding contributions to the organic chemistry of sulfur.

Thermal decomposition of 2,5-dihydro-1,3,4-oxadiazole **4** in toluene solution in the presence of thiolactams **7** or corresponding lactams **11** result in the chemoselective formation of the *N*-(dimethoxy)methyl derivatives **8** and **12**, respectively. The products of both types are formed via insertion of dimethoxycarbene **2a** into the N−H bonds. A reaction mechanism via the intermediate ion pair **14**/**15** or a complex of type **13** is postulated to explain the formation of the products.

Keywords: thiolactams; lactams; dimethoxycarbene; insertion reactions; acetals

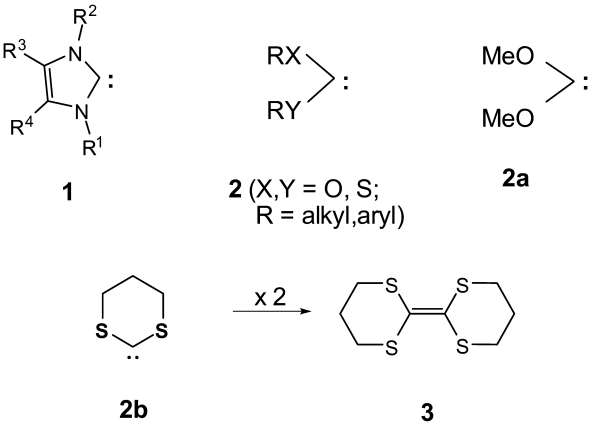
1. Introduction

In the last decade, the rapid development of the chemistry of nucleophilic carbenes is evidenced by a large number of books (*1*), review articles (*2*), and original papers (*3*). Without doubt, the main attention is focused on the nitrogen-stabilized heterocyclic carbenes with the general formula **1**, which are abbreviated as "NHC" species (*2a, b*). Nevertheless, sulfur- and/or oxygen-stabilized carbenes **2**, which are less stable than the NHC analogs (*4*), attract considerable attention from the point of view of both fundamental questions relating to their structure (*4*, *5*) and the possible exploration for purposes of organic synthesis. As to the first question, a plausible explanation of the reaction leading to the "Seebach carbene dimer" **3** via the *in situ* dimerization of 1,3-dithian-2-ylidene (**2b**) can be cited as a very recent example (*4*). On the other hand, dimethoxycarbene (DMC, **2a**), which has been known for more than four decades (*6*), can be stressed as a reactive nucleophilic carbene with significant importance for preparative organic chemistry (*3*).

*Corresponding author. Email: gmloston@uni.lodz.pl
†Part of the Diploma thesis of *K.K.*, University of Lodz, 2009.

ISSN 1741-5993 print/ISSN 1741-6000 online

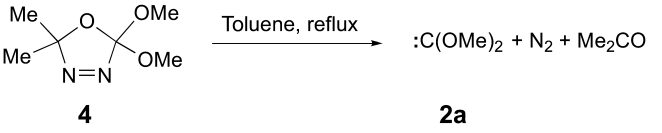
DOI: 10.1080/17415990902870935
http://www.informaworld.com



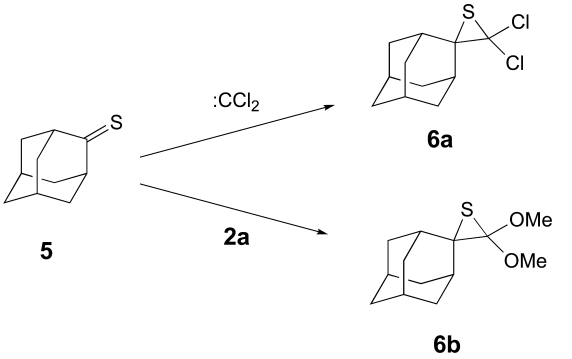
In the case of **2a**, a decisive factor is the straightforward method of its generation based on the thermal decomposition of the relatively easily available 4,5-dihydro-1,3,4-oxadiazole derivative **4**, elaborated some time ago by Warkentin and coworkers (*7*) (Scheme 1).

In a series of very recent papers, reactions of **2a** with, among others, thiocarbonyl compounds such as thioketones (*8*), dithioesters (*9*), and enolizable imidazole-2(3*H*)-thiones (*10*) were reported. Interestingly enough, the reaction of adamantanethione (**5**) with both the electrophilic dichlorocarbene (*11*) and the nucleophilic **2a** (*8a*) resulted in the formation of thiiranes **6a** and **6b**, respectively, in high yields (Scheme 2).

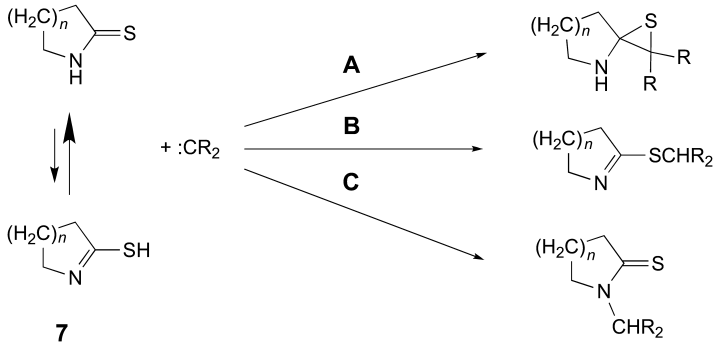
Cyclic thioamides (thiolactams) **7** are important starting materials for synthetic applications (*12*), and some of them display biological activity (*13*). A well-known example of their exploration is the reaction with α-bromoacetates leading to the corresponding vinylogous urethanes via a thiirane carboxylate and desulfurization, a sequence which is known as "Eschenmoser coupling reaction" (*14*). This conversion can also be achieved by starting with a thiolactam and a carbene/carbenoide, which potentially can form the desired thiirane via an intermediate



Scheme 1. Thermal generation of DMC (**2a**).



Scheme 2. Reactions of adamantanethione (**5**) with the electrophilic dichlorocarbene and the nucleophilic **2a**.



Scheme 3. Three possible reaction pathways for the reaction of enolizable thiolactams with a carbene.

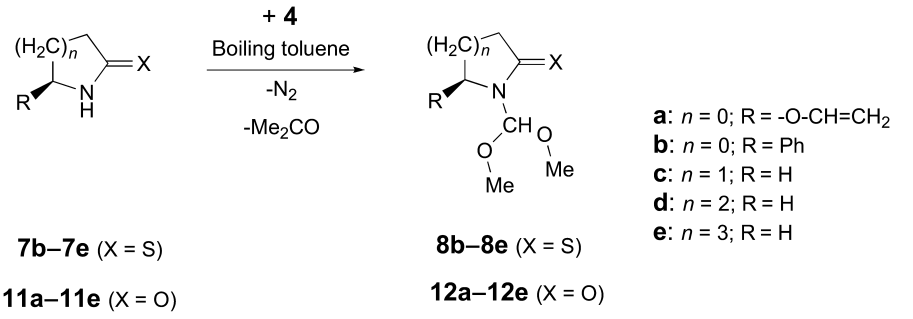
thiocarbonyl ylide (*15*). In the case of the N-unsubstituted thiolactams, the insertion reaction into either the S−H (path **B**) or N−H bond (path **C**) can compete with the formation of a thiirane (path **A**) (Scheme 3).

To the best of our knowledge, there are no reports on reactions of NH thiolactams of type **7** with carbenes or carbenoids available. On the other hand, reactions of N-substituted thiolactams with methyl bromozincacetate (Reformatsky reagent), which also lead to the vinylogous urethanes, occur differently and the result depends on the size of the thiolactam ring (*16*).

The goal of the present study was to investigate if the nucleophilic carbene **2a** is able to react with the NH thiolactams **7b**–**7e** and to establish the structure of the obtained products. In addition, the reactivity of thiolactams **7** towards **2a** should be compared with that of the corresponding lactams **11** and with a linear N-monosubstituted thioamide. For this purpose, *N*-methyl thiobenzamide (**9**) was selected.

2. Results and discussion

Thiolactams **7**, easily available from the corresponding lactams **11** by using a typical thionation protocol (Lawesson's reagent) (*17*), are well soluble in typical hydrocarbons and, therefore, reactions with the DMC precursor **4** in boiling toluene could be performed at quite high concentration of the starting material.[1] In a typical experiment, a thiolactam **7** and **4** were used in a ratio of 1:1.3, and the toluene solution was heated under reflux for ca. 8 h. Under these conditions, the ^{1}H-NMR spectrum of the crude reaction mixture evidenced complete conversion of thiolactam **7** in each case. The newly formed products were characterized by the presence of two new singlets with intensities in a ratio 1:6. For example, the reaction of azepane-2-thione (**7e**) yielded a product with the less intense singlet localized at δ 7.18 (1H) and the more intense one at δ 3.42 (6H). The isolation of pure products was achieved on preparative plates coated with silica. During the development and separation from the stationary phase, no decomposition of the products was observed. The additional purification by vacuum micro-distillation was also performed smoothly, without decomposition of the products. The analysis of the spectroscopic data collected for the purified products allowed the elucidation of their structures. On the one hand, the ^{1}H-NMR spectra did not reveal the characteristic, broad signals of the NH group, which was always present in the starting material **7** at δ 10.50–11.00. This fact, in combination with the presence of a new, less intense signal localized between δ 5.85 and 7.20 and a signal for two MeO groups at δ 3.21–3.43, indicate the formation of an insertion product into the N−H bond. In addition, the ^{13}C-NMR spectra of all new products showed the characteristic absorption of the C=S group at δ 203–210. Taking into account all these facts, the structure of the *N*-dimethoxymethyl-substituted thiolactams **8** is



Scheme 4. Reactions of thiolactams **7** and lactams **11** with DMC (**2a**).

proved without doubt (Scheme 4). It is worth mentioning that, in all experiments, the insertion products were isolated in nearly quantitative yields, and the size of the thiolactam ring did not influence the course of the reaction.

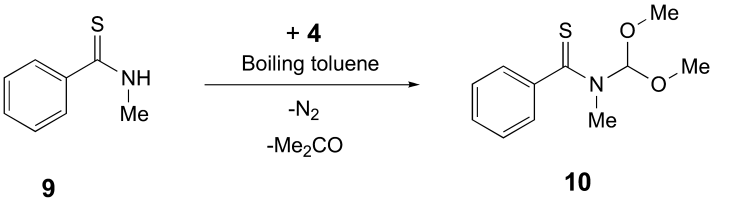
An analogous reaction was observed with *N*-methyl thiobenzamide (**9**, Scheme 5). Also in this case, the expected product **10** of the insertion of DMC into the N−H bond was formed in high yield and its purification was performed with preparative layer chromatography followed by micro-distillation.

On the other hand, the attempted reaction of **2a** with *N*-methyl pyrrolidine-2-thione was in vain, and the thiocarbonyl substrate was recovered unchanged from the reaction mixture. Thus, N-substituted thiolactams, in contrast to dithioesters (*9*) or non-enolizable thioketones (*8*), do not react with **2a**.

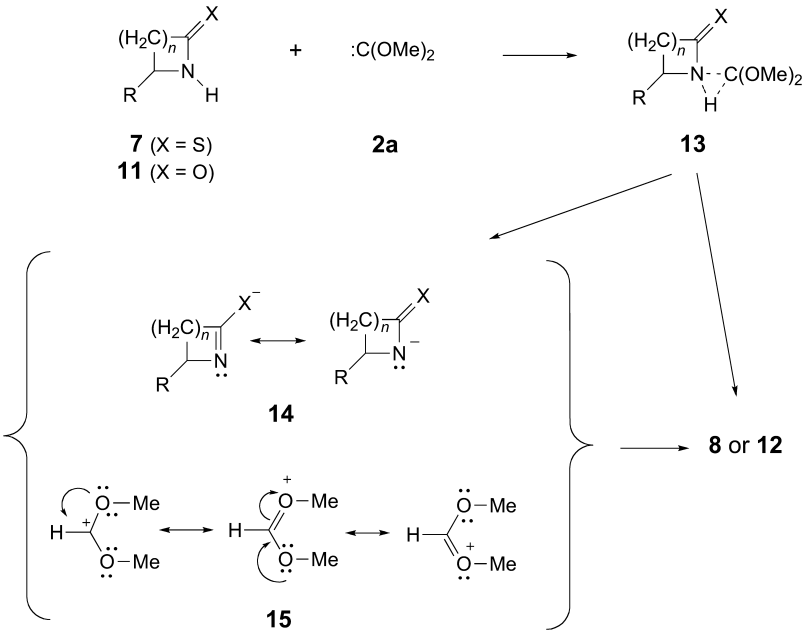
In extension of the presented study and for comparison purposes, a series of lactams **11** was tested in the reaction with DMC (**2a**) under analogous conditions as applied for thiolactams **7**. A slight excess of the precursor **4** (0.3 mol-equiv.) secured complete conversion of the corresponding lactam **11** in each case. The collected spectroscopic data proved unambiguously the structure of the N−H insertion products **12a**–**12e**. The smooth and selective formation of the four-membered derivatives **12a** and **12b** (β-lactams) is worth emphasizing, as the reaction of DMC with strained cyclobutanones was reported to yield the ring-enlarged cyclopentanone derivatives, albeit in rather poor yield (*18*). The high yield of both **12a** and **12b** shows that **2a** does not attack the C=O group, but another mechanism, which will be discussed below, is involved.

In contrast to the insertion products of type **8**, the N-functionalized lactams **12** easily decomposed, not only during chromatographic work up but also during attempted distillative purification. For this reason, they could not be obtained in analytically pure form. The easy hydrolytic decomposition resulted in the splitting of the newly formed N−C bond and the isolated material contained significant amounts of starting lactames **11**. Qualitatively, the fastest decomposition was observed in the case of the six-membered product **12d**.

The mechanism of the insertion process of **2a** into an X−H bond in compounds **7** or **11** has not been proved yet, but the formation of stabilized anions of type **14** and the cation **15** seems



Scheme 5. Reaction of *N*-methyl thiobenzamide **9** with **2a**.



Scheme 6. Proposed mechanism of the insertion of **2a** into the N−H bond of thiolactams **7** and lactams **11**.

likely (Scheme 6). Favorable delocalization of the negative charge between nitrogen and sulfur (oxygen) atoms enhances the stability of the intermediates of this type. The weak point of the mechanism via the intermediate ion pair **14**/**15** is that a preferred attack of the sulfur atom of **14** (X = S) at the cation **15** is expected. Another likely intermediate is the three-center complex **13**, which could lead to **8**/**12** or the ion pair **14**/**15**. The direct reaction **13** → **8** could explain the selectivity of the insertion reaction (*cf.* (*10*)).

In summary, the presented study showed that both N-unsubstituted thiolactams **7** and lactams **11**, irrespective of the ring size (four to seven membered), react efficiently with **2a**, which was generated thermally from the precursor **4** in a toluene solution. In both cases, the reactions occurred with complete chemoselectivity, yielding the corresponding, hitherto unknown, products of the insertion of **2a** into the N−H bond. The N-substituted products **8** obtained from thiolactams **7** showed enhanced stability in comparison with the analogous compounds **12** formed from the corresponding lactams **11**. The relatively simple access to both classes of *N*-dimethoxymethyl derivatives, **8** and **12**, enables their further exploration in organic synthesis. In the case of products of type **12**, some analogous *N*-diethoxymethyl derivatives have already been synthesized, however, by a completely different reaction, and utilized for the generation of a new type of carbenoids (*19*). Our approach offers an alternative, efficient method for the preparation of this type of synthetically useful compounds.

3. Experimental

3.1. *General*

Melting points were determined in capillary using a Meltemp 2 apparatus and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were registered with a Tesla BS 687 (80 and 20 MHz, respectively) or a Bruker 300 (300 and 75 MHz, respectively) spectrometer using TMS ($\delta_{TMS} = 0$) as an internal

standard. The multiplicity of the signals was elucidated by distortionless enhancement of polarization transfer (DEPT) experiments. IR spectra were registered with a Nexus spectrophotometer. EI-MS and HR-EIMS (70 eV) were recorded on a Finnigan MAT95 instrument, and ESI-MS (MeOH/NaI) was on a Bruker Esquire-LC instrument.

3.2. *Starting materials*

2,2-Dimethoxy-5,5-dimethyl-2,5-dihydro-1,3,4-oxadiazole (**4**), used as the precursor of DMC (**2a**), was synthesized by following Warkentin's protocol (*7*). The lactam **11a** (*20a*) originated from the collection of Prof. M. Chmielewski (Warsaw), and **11b** was prepared according to a known protocol from styrene and chlorosulfonyl isocyanate (*20b*); lactams **11c**–**d** were available as commercial reagents and **11e** was obtained from cyclohexanone oxime via a well-known procedure based on the Beckmann rearrangement (*21*). Thiolactams (**7b**–**e**) were prepared via a slightly modified thionation protocol with Lawesson's reagent in tetrahydrofuran (THF) solution (*17*). Instead of the recommended overnight heating, only 30 min reflux turned out to be sufficient to achieve complete conversion of the starting lactam **12**.

3.3. *Reactions of thiolactams 7 and lactams 11 with the* in situ *generated DMC (2a): general procedure*

A toluene solution containing 2.6 mmol (352 mg) of the DMC precursor **4** and 2.0 mmol of **7**, **9**, or **11** was heated under reflux for 8 h. After that time, the decomposition of **4** was complete, and after evaporation of the solvent, the crude product was analyzed by ^{1}H-NMR spectroscopy. In all cases, only products **8**, **10**, and **12**, respectively, were observed in the mixture. The products were purified by chromatography on preparative plates coated with silica (PLC, CH_2Cl_2 was used as the eluent in all cases) and by vacuum micro-distillation. Yields refer to isolated products. In all cases of the insertion products **12**, the isolated material contained various amounts of the corresponding lactam **11**.

3.3.1. *1-Dimethoxymethyl-4-phenylazetidine-2-thione (**8b**)*

Yield: 351 mg (78%). Isolated chromatographically (PLC, SiO_2). Colorless, thick oil; additionally purified by micro-distillation at 70 °C (oil bath)/0.08 Torr. IR (neat): ν (cm^{-1}): 2939s, 2838m, 1446s, 1402s, 1272s, 1190s, 1108vs, 1070vs, 1024m, 991m, 912w, 824m, 758m, 699s. ^{1}H-NMR (80 MHz, $CDCl_3$): $\delta = 3.01$ (dd, *cis*-$J_{H,H} = 2.6$ Hz, *gem*-$J_{H,H} = 15.8$ Hz, 1H, HC(3)), 3.40 (dd, *trans*-$J_{H,H} = 4.9$ Hz, *gem*-$J_{H,H} = 15.8$ Hz, 1H, H'C(3)), 3.23, 3.44 (2s, 2MeO), 5.25 (dd, *trans*-$J_{H,H} = 4.9$ Hz, *cis*-$J_{H,H} = 2.6$ Hz, 1H, HC(4)), 5.87 (s, 1H, CH(OMe)$_2$), 7.36 (br s, 5H, 5 arom. CH). ^{13}C-NMR (50 MHz, $CDCl_3$): $\delta = 48.6$ (t, CH_2), 54.0, 54.7 (2q, 2MeO), 60.9 (d, HC(4)), 102.2 (d, CH(OMe)$_2$), 126.6, 128.6, 128.7 (3t, 5 arom. CH), 137.5 (s, 1 arom. C), 203.9 (s, C=S). ESI-MS: 260 (100, $[M + Na]^+$), 149 (12), 102 (30).

3.3.2. *1-(Dimethoxymethyl)pyrrolidine-2-thione (**8c**)*

Yield: 224 mg (64%). Isolated chromatographically (PLC, SiO_2). Colorless, thick oil; additionally purified by micro-distillation at 70 °C (oil bath)/0.08 Torr. IR (neat): ν (cm^{-1}): 2940s, 2838m, 1490s, 1460s, 1421s, 1366m, 1324s, 1309s, 1224s, 1112vs, 1070vs, 990s, 940m, 782m. ^{1}H-NMR (80 MHz, $CDCl_3$): $\delta = 1.70$–2.35 (m, 2H), 3.05 (t, $J_{H,H} = 6.5$ Hz, 2H), 3.43 (s, 6H, 2MeO), 3.70 (t, $J_{H,H} = 6.5$ Hz, 2H), 6.45 (s, 1H, CH(OMe)$_2$). ^{13}C-NMR (50 MHz, $CDCl_3$): $\delta = 19.8$, 45.6, 47.5 (3t, 3CH_2), 54.4 (q, 2MeO), 103.2 (d, CH(OMe)$_2$), 204.7 (s, C=S). EI-MS: 175 (24, M^+),

160 (51), 144 (41), 129 (10), 112 (14), 101 (18), 85 (38), 75 (100). HR-EIMS: 175.0667 (calcd for $C_7H_{13}NO_2S$: 175.0667).

3.3.3. *1-(Dimethoxymethyl)piperidine-2-thione (**8d**)*

Yield: 231 mg (61%). Isolated chromatographically (PLC, SiO_2). Colorless, thick oil; additionally purified by micro-distillation at 70 °C (oil bath)/0.08 Torr. IR (neat): ν (cm^{-1}): 2946s, 2839m, 1490s, 1464s, 1443s, 1348s, 1320s, 1194vs, 1107vs, 1074vs, 1024s, 991s, 959m, 889w, 872w, 752m. ^{1}H-NMR (80 MHz, $CDCl_3$): $\delta = 1.60$–2.00 (m, 4H), 3.01, 3.40 (2t, $J_{H,H} = 6.5$ Hz, 4H), 3.42 (s, 6H, 2MeO), 7.20 (s, 1H, C*H*$(OMe)_2$). ^{13}C-NMR (50 MHz, $CDCl_3$): $\delta = 19.7, 21.8, 41.9, 42.7$ (4t, 4 CH_2), 54.8 (q, 2MeO), 105.4 (d, *C*H$(OMe)_2$), 204.8 (s, C=S). EI-MS: 189 (32, M^+), 174 (32), 158 (37), 114 (10), 82 (51), 75 (100). HR-EIMS: 189.0825 (calcd for $C_8H_{15}NO_2S$: 189.0823).

3.3.4. *1-(Dimethoxymethyl)azepane-2-thione (**8e**)*

Yield: 203 mg (50%). Isolated chromatographically (PLC, SiO_2). Colorless, thick oil; additionally purified by micro-distillation at 85 °C (oil bath)/0.08 Torr. IR (neat): ν (cm^{-1}): 2934s, 2855m, 1485s, 1443s, 1424s, 1367s, 1342s, 1255m, 1210s, 1104vs, 1075vs, 1003s, 973s, 889w, 825w, 726m. ^{1}H-NMR (80 MHz, $CDCl_3$): $\delta = 1.50$–2.05 (m, 6H), 3.05–3.30, 3.50–3.75 (2m, 4H), 3.42 (s, 6H, 2MeO), 7.18 (s, 1H, C*H*$(OMe)_2$). ^{13}C-NMR (50 MHz, $CDCl_3$): $\delta = 24.3, 27.2, 28.6, 44.6, 47.6$ (5t, 5CH_2), 54.1 (q, 2MeO), 106.0 (d, *C*H$(OMe)_2$), 209.9 (s, C=S). EI-MS: 203 (26, M^+), 188 (25), 172 (10), 96 (71), 75 (100). HR-EIMS: 203.0980 (calcd for $C_9H_{17}NO_2S$: 203.0980).

3.3.5. *N-Dimethoxymethyl-N-methylthiobenzamide (**10**)*

Yield: 320 mg (71%). Isolated chromatographically (PLC, SiO_2). Colorless, thick oil; additionally purified by micro-distillation at 120 °C (oil bath)/0.07 Torr; decomposes slowly in the $CDCl_3$ solution at room temperature. IR (neat): ν (cm^{-1}): 2933vs, 2858m, 1473s, 1443s, 1351s, 1333s, 1263vs, 1186vs, 1104vs, 1085vs, 970s, 901m, 842w, 872w, 752m. ^{1}H-NMR (80 MHz, $CDCl_3$): $\delta = 3.25$ (s, 6H, 2 MeO), 3.35 (s, 3H, MeN), 5.35 (s, 1H, C*H*$(OMe)_2$), 7.36 (br s, 5H, 5 arom. CH). ^{13}C-NMR (50 MHz, $CDCl_3$): $\delta = 32.9$ (q, MeN), 54.0 (q, 2MeO), 108.1 (d, *C*H$(OMe)_2$), 126.2, 128.4, 129.1 (3d, 5 arom. CH), 141.7 (s, 1 arom. C), 200.1 (s, C=S). EI-MS: 225 (21, M^+), 151 (44), 150 (36), 122 (11), 121 (95), 118 (50), 117 (10), 77 (38), 75 (100). HR-EIMS: 225.0825 (calcd for $C_{11}H_{15}NO_2S$: 225.0823).

3.3.6. *1-Dimethoxymethyl-4-(vinyloxy)azetidin-2-one (**12a**)*

Yield: 255 mg (68%). Isolated and purified by micro-distillation at 60 °C (oil bath)/0.08 Torr. Colorless, viscous oil. IR (neat): ν (cm^{-1}): 2945s, 2842m, 1781vs (C=O), 1643m, 1446w, 1360 br s, 1248w, 1197vs, 1108vs, 1072vs, 991w, 965m, 946w, 849br m. ^{1}H-NMR (80 MHz, $CDCl_3$): $\delta = 2.83$ (dd, $J_{H,H} = 15.5$ Hz, $J_{H,H} = 2.0$ Hz, 1H, HC(3)), 3.42 (dd, $J_{H,H} = 15.5$ Hz, $J_{H,H} = 3.9$ Hz, 1H, H'C(3)), 3.36, 3.42 (2s, 2MeO), 4.20 (dd, *cis*-$J_{H,H} = 6.6$ Hz, *gem*-$J_{H,H} = 2.0$ Hz, 1H, CH=CH_2), 4.42 (dd, *trans*-$J_{H,H} = 14.0$ Hz, *gem*-$J_{H,H} = 2.0$ Hz, 1H, CH=CH_2), 5.41 (dd, $J_{H,H} = 2.0$ Hz, $J_{H,H} = 3.9$ Hz, 1H, HC(4)), 5.43 (s, 1H, C*H*$(OMe)_2$), 6.43 (dd, *cis*-$J_{H,H} = 6.6$ Hz, *trans*-$J_{H,H} = 14.0$ Hz, 1H, C*H*=CH_2). ^{13}C-NMR (50 MHz, $CDCl_3$): $\delta = 44.1$ (t, C(3)), 52.3, 54.2 (2q, 2MeO), 78.2 (d, C(4)), 91.2 (t, CH=*C*H_2), 99.5 (d, *C*H$(OMe)_2$), 148.7 (d, *C*H=CH_2), 165.2 (s, C=O). EI-MS: 186 (<1), 144 (8), 86 (19), 75 (100). ESI-MS: 210 (100, $[M + Na]^+$), 140 (20). HR-ESIMS: 210.0744 (calcd for $C_8H_{13}NO_4Na$: 210.0980).

3.3.7. *1-Dimethoxymethyl-4-phenylazetidin-2-one (**12b**)*

Yield: 252 mg. Isolated by micro-distillation at 102–105 °C/0.08 Torr; according to ^{13}C-NMR contaminated with ca. 15% of **11b**. Colorless, thick oil. IR (neat): ν (cm^{-1}): 2940s, 2839m, 1767vs (C=O), 1366vs, 1325vs, 1194vs, 1109vs, 1070vs. ^{1}H-NMR (80 MHz, $CDCl_3$): $\delta = 2.85$ (dd, *cis*-$J_{H,H} = 3.8$ Hz, *gem*-$J_{H,H} = 15.1$ Hz, 1H, HC(3)), 3.36 (dd, *trans*-$J_{H,H} = 5.6$ Hz, *gem*-$J_{H,H} = 15.1$ Hz, 1H, H'C(3)), 3.20, 3.40 (2s, 2MeO), 4.76 (dd, *trans*-$J_{H,H} = 5.6$ Hz, *cis*-$J_{H,H} = 3.8$ Hz, 1H, HC(4)), 5.40 (s, 1H, C*H*(OMe)$_2$), 7.38 (br s, 5H, 5 arom. CH). ^{13}C-NMR (50 MHz, $CDCl_3$): $\delta = 45.3$ (t, CH_2), 51.9 (d, HC(4)), 52.8, 53.8 (2q, 2MeO), 100.6 (d, *C*H(OMe)$_2$), 126.1, 127.9, 128.4 (3t, 5 arom. CH), 138.8 (s, 1 arom. C), 167.5 (s, C=O).

3.3.8. *1-(Dimethoxymethyl)pyrrolidin-2-one (**12c**)*

Yield: 217 mg. Isolated by micro-distillation at 65–70 °C/0.08 Torr; according to ^{13}C-NMR contaminated with ca. 20% of **11c**. Decomposes completely upon PLC on silica. Colorless, thick oil. IR (neat): ν (cm^{-1}): 2945s, 2838m, 1698vs (C=O), 1463m, 1445s, 1357w, 1285s, 1269s, 1196s, 1105vs, 1069vs, 992m, 960m, 800w. ^{1}H-NMR (80 MHz, $CDCl_3$): $\delta = 1.80$–2.25 (m, 2H, CH_2), 2.30–2.60 (m, 2H, CH_2), 2.35 (s, 6H, 2MeO), 3.30–3.60 (m, 2H, CH_2CO), 5.72 (s, 1H, C*H*(OMe)$_2$). ^{13}C-NMR (50 MHz, $CDCl_3$): $\delta = 17.9$, 31.4, 40.5 (3t, 3CH_2), 53.9 (q, 2MeO), 101.3 (d, *C*H(OMe)$_2$), 176.0 (s, C=O) (*cf*. NMR data for the Et-analog in (*19*)).

3.3.9. *1-(Dimethoxymethyl)piperidin-2-one (**12d**)*

Yield: 156 mg. Isolated by micro-distillation at 65–70 °C/0.08 Torr; according to ^{13}C-NMR contaminated with ca. 25% of **11d**. Decomposes completely upon PLC on silica. Colorless, thick oil. IR (neat): ν (cm^{-1}): 2945s, 2838m, 1698vs (C=O), 1463m, 1445s, 1357w, 1285s, 1269s, 1196s, 1105vs, 1069vs, 992m, 960m, 800w. ^{1}H-NMR (80 MHz, $CDCl_3$): $\delta = 1.65$–2.20 (m, 4H, 2CH_2), 2.25–2.60 (m, 2H, CH_2), 3.15–3.45 (m, 2H, CH_2CO), 3.35 (s, 6H, 2MeO), 6.20 (s, 1H, C*H*(OMe)$_2$). ^{13}C-NMR (50 MHz, $CDCl_3$): $\delta = 20.3, 21.8, 31.1, 41.8$ (4*t*, 4CH_2), 53.9 (*q*, 2MeO), 101.4 (*d*, *C*H(OMe)$_2$), 171.0 (*s*, C=O).

3.3.10. *1-(Dimethoxymethyl)azepan-2-one (**12e**)*

Yield: 281 mg. Isolated by micro-distillation at 70–80 °C/0.08 Torr; according to ^{13}C-NMR contaminated with ca. 10% of **11e**. Decomposes completely upon PLC on silica. Colorless, thick oil. IR (neat): ν (cm^{-1}): 2933vs, 2857m, 1662vs (C=O), 1473s, 1443s, 1415s, 1364m, 1313m, 1259m, 1188vs, 1151m, 1104vs, 1069vs, 997m, 973s, 900m, 839m, 744m, 712m. ^{1}H-NMR (80 MHz, $CDCl_3$): $\delta = 1.45$–1.85 (m, 6H, 3CH_2), 2.20–2.65 (m, 2H, CH_2), 3.10–3.50 (m, 2H, CH_2CO), 3.35 (s, 6H, 2MeO), 6.15 (s, 1H, C*H*(OMe)$_2$). ^{13}C-NMR (50 MHz, $CDCl_3$): $\delta = 22.8$, 29.3, 29.6, 36.3, 40.7 (5t, 5CH_2), 53.9 (q, 2MeO), 102.3 (d, *C*H(OMe)$_2$), 177.0 (s, C=O). EI-MS: 172 (25), 156 (14), 113 (16), 96 (19), 84 (10), 75 (100). ESI-MS: 210 (100, $[M + Na]^+$), 194 (10), 178 (6). HR-ESIMS: 210.1108 (calcd for $C_9H_{17}NO_3Na$: 210.1106).

Acknowledgements

The authors thank the Rector of the University of Lodz for a Grant (#505/0712, G. M., K. K.) and the Institute of Organic Chemistry of the University of Zurich for mass spectra. Prof. M. Chmielewski (Polish Academy of Sciences, Warsaw) provided us generously with a sample of the lactam **11a** (*20a*).

Note

1. Low solubility of the starting material in reactions with DMC often leads to the formation of significant amounts of tetramethoxyethene, the DMC dimer (see comments in (*10*)).

References

(1) Werner, H. *Metal Carbenes and Carbynes: The Taming of "Non-existing" Molecules*; Profiles in Inorganic Chemistry; Springer: New York, 2009; Chapter 8; pp. 235–297.
(2) (a) Mata, J.A.; Poyatos, M.; Peris, E. *Coordin. Chem. Rev*. **2007,** *251,* 841–859; (b) Lin, I.J.B.; Vasam, C.S. *Coordin. Chem. Rev.* **2007,** *251,* 642–670; (c) Enders, D.; Balensifer, T. *Acc. Chem. Res.* **2004,** *37,* 534–541; (d) Nair, V.; Menon, R.S.; Sreekumar, V. *Pure Appl. Chem.* **2005,** *77,* 1191–1198; (e) Warkentin, J. *Acc. Chem. Res.* **2009,** *42,* 205–212.
(3) (a) Rigby, J.H.; Laurent, S.; Dong, W.T.; Danca, M.D. *Tetrahedron* **2000,** *56,* 10101–10111; (b) Zhou, H.; Mloston, G.; Warkentin, J. *Org. Lett.* **2005,** *7,* 487–489; (c) Rigby, J.H.; Burke, P.J. *Heterocycles* **2006,** *67,* 643–653; (d) Nair, V.; Deepthi, A.; Poonoth, M.; Santhamma, B.; Vellalath, S.; Babu, B.P.; Mohan, R.; Suresh, E. *J. Org. Chem*. **2006,** *71,* 2313–2319; (e) Sliwinska, A.; Czardybon, W.; Warkentin, J. *Org. Lett.* **2007,** *9,* 695–698; (f) Mloston, G.; Heimgartner, H. *Helv. Chim. Acta* **2007,** *90,* 1758–1764; (g) Mloston, G.; Warkentin, J.; Linden, A.; Heimgartner, H. *Helv. Chim. Acta* **2007,** *90,* 2024–2036; (h) Cheng, Y.; Ma, Y.-G.; Wang, X.-R.; Mo, J.-M. *J. Org. Chem.* **2009,** *74,* 850–855.
(4) Schreiner, P.R.; Reisenauer, H.P.; Romanski, J.; Mloston, G. *Angew. Chem. Int. Ed*., **2006,** *45,* 3989–3992.
(5) (a) Moss, R.A.; Wlostowski, M.; Terpinski, J.; Kmiecik-Lawrynowicz, G.; Krogh-Jespersen, K. *J. Am. Chem. Soc*. **1987,** *109,* 3811–3812; (b) Reisenauer, H.P.; Romanski, J.; Mloston, G.; Schreiner, P.R. *Eur. J. Org. Chem.* **2006,** 4813–4818.
(6) (a) Hoffmann, R.W.; Häuser, H. *Tetrahedron Lett*. **1964,** *5,* 197–201; (b) Lemal, D.M.; Gosselink, E.P.; Ault, A. *Tetrahedron Lett*. **1964,** *5,* 579–585.
(7) El-Saidi, M.; Kassam, K.; Pole, D.L.; Tadey, T.; Warkentin, J. *J. Am. Chem. Soc*. **1992,** *114,* 8751–8752.
(8) (a) Dawid, M.; Młostoń, G.; Warkentin, J. *Org. Lett.* **2001,** *3,* 2455–2456; (b) Dawid, M.; Mloston, G.; Warkentin, J. *Chem. Eur. J.* **2002,** *8,* 2184–2187.
(9) Dawid, M.; Mloston, G.; Reid, D.L.; Warkentin, J. *Can. J. Chem.* **2003,** *81,* 1025–1028.
(10) Mloston, G.; Heimgartner, H. *Phosphorus, Sulfur, Silicon* **2009,** in press.
(11) Mloston, G.; Romanski, J.; Swiatek, A.; Heimgartner, H. *Helv. Chim. Acta* **1999,** *82,* 946–956.
(12) (a) Smith, D.C.; Lee, S.W.; Fuchs, P.L. *J. Org. Chem.* **1994,** *59,* 348–354; (b) Jagodziński, T.S. *Chem. Rev.* **2003,** *103,* 197–228.
(13) (a) Krstić, N.M.; Bjelaković, M.S.; Žižak, Ž.; Pavlović, M.D.; Juranić, Z.D.; Pavlović V.D. *Steroids* **2007,** *72,* 406–414; (b) Chicharro, R.; Alonso, M.; Arán, V.J.; Herradón, B. *Tetrahedron Lett*. **2008,** *49,* 2275–2279.
(14) (a) Roth, M.; Dubs, P.; Götschi, E.; Eschenmoser, A. *Helv. Chim. Acta* **1971,** *54,* 710–734; (b) Shiosaki, K. In *Comprehensive Organic Synthesis*, Vol. 2, Section 3.7.: Trost, B.M., Fleming, I., Eds.; *The Eschenmoser Coupling Reaction*; Pergamon Press: Oxford, 1991; pp. 865–892.
(15) Mloston, G.; Heimgartner, H. In *"The Chemistry of Heterocyclic Compounds"*, Vol 59: Padwa, A., Pearson, W.H., Eds.; *Synthetic Application of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; J. Wiley & Sons: New York, 2002; pp. 315–360.
(16) Lee, H.K.; Kim, J.; Pak, Ch.S. *Tetrahedron Lett.* **1999,** *40,* 2173–2174.
(17) Lacroix, S.; Rixhon, V.; Marchand-Brynaert, J. *Synthesis* **2006,** 2327–2334.
(18) Venneri, P.C.; Warkentin, J. *Can. J. Chem.* **2000,** *78,* 1194–1203.
(19) Motherwell, W.B.; Bégis, G.; Cladingboel, D.E.; Jerome, L.; Sheppard, T.D. *Tetrahedron* **2007,** *63,* 6462–6476.
(20) (a) Kałuża, Z.; Park, H.-S. *Synlett* **1996,** 895–896; (b) Forró, E.; Fülöp, F. *Tetrahedron: Asymmetry* **2001,** *12,* 2351–2358.
(21) Vogel, A.I. "*Preparatyka organiczna*" (translated version of "Vogel's textbook of practical organic chemistry", Longmann Group UK Limited 1989); Wydawnictwa Naukowo-Techniczne: Warszawa, 2006; p. 1011.