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Synthesis of Bridged and Nonbridged N-Heterocycles by Cyclocondensation of Bis(silyl enol ethers) with Iminium Salts

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Keywords: Cyclizations / Iminium salts / N-Heterocycles / Silyl enol ethers

Cyclization reactions of iminium salts with bis(silyl enol ethers) – such as 1,3-bis(silyloxy)-1,3-butadienes and 1,1-bis(silyloxy)ketene acetals – allow a convenient synthesis of various bridged and nonbridged N-heterocycles. The iminium salts were generated in situ from pyridines, quinolines, isoquinolines, quinoxalines, pyrazines, quinazolines, and 2,5-dimethoxypyrrolidines. The products include 4-oxa-9-aza-7,8-benzobicyclo[3.3.1]nonan-3-ones, 7-oxa-1,4-diaza-2,3-benzobicyclo[4.3.0]non-2-en-6-ones, 7-oxa-1,4-diazabicyclo[4.3.0]non-2-en-6-ones, 3-hydroxy-9-aza-7,8-benzobicyclo[3.3.1]non-3-enes, 4-hydroxy-1,9-diaza-7,8-benzobicyclo[3.3.1]non-4-enes, alkylidene-7-oxa-1,4-diaza-2,3-benzobicyclo[4.3.0]non-2-enes, and tropinones.

1. Introduction

One-pot cyclizations and domino reactions provide versatile tools for the assembly of complex molecules from simple starting materials.[1,2] Bis(silyl enol ethers) can be regarded as electroneutral equivalents of dianions (masked dianions) and represent important synthetic building blocks in one-pot cyclizations. 1,1-Bis(silyloxy)ketene acetal **A**, 1,3-bis(silyloxy)-1,3-butadiene **B**, 2,3-bis(silyloxy)-1,3-butadiene **C**, 2-(silyloxy)allyl-trimethylsilane **D**, 1,4-bis(silyloxy)-1,3-butadiene **E**, and 1,5-bis(silyloxy)-1,4-pentadiene **F**, can be regarded as equivalents of the dianions of acetic acid, methyl acetoacetate, butane-2,3-dione, acetone, dimethyl succinate, and dimethyl adipate, respectively. The chemistry of silyl enol ethers,[3] Danishefsky's diene,[4] and of 1,3-bis(silyloxy)-1,3-butadienes[5] has been reviewed. Recent reviews cover one-pot cyclizations of silyl enol ethers with oxalyl chloride[6] and [3+3] cyclizations of 1,3-bis(silyloxy)-1,3-butadienes with 1,3-dielectrophiles.[7] The present microreview is focussed on cyclization reactions of bis(silyl enol ethers) with iminium salts (Scheme 1). These reactions allow an efficient approach to a variety of bridged and nonbridged nitrogen heterocycles which are of considerable pharmacological relevance.

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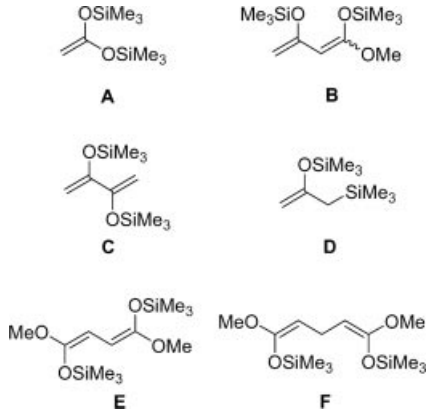
2. 1,1-Bis(trimethylsiloxy)ketene Acetals

1,1-Bis(trimethylsilyloxy)ketene acetals – masked carboxylic acid dianions – are available in one or two steps from the corresponding carboxylic acids.[8]

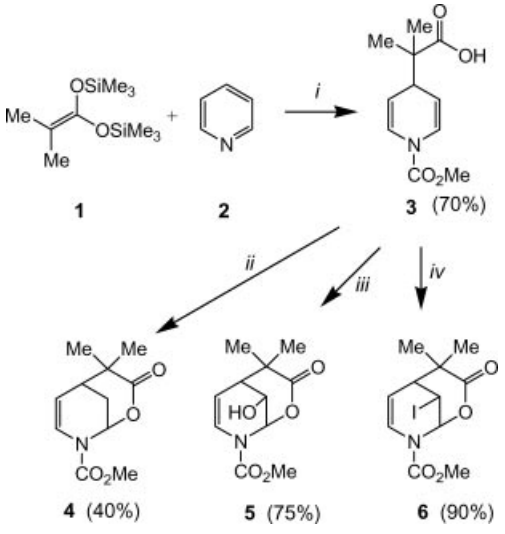
Peter Langer was born in Hannover (Germany) in 1969. He studied chemistry at the University of Hannover and at the Massachusetts Institute of Technology (MIT) and received his Diploma under the guidance of Prof. Dietmar Seyferth in March 1994. In February 1997 he obtained his Ph. D. for a synthetic work (summa cum laude) on Cinchona alkaloids under the supervision of Prof. H. Martin R. Hoffmann at the University of Hannover. During a postdoctoral period with Prof. Steven V. Ley, FRS (Cambridge, UK) he worked on the synthesis of oligosaccharides. In 1998 he moved to the University of Göttingen where he started his independent research (related to cyclization reactions of dianions) associated to Prof. Armin de Meijere. He completed his habilitation in July 2001 and was appointed Privatdozent. In April 2002 he took a permanent position as a full professor (C4) at the University of Greifswald. In December 2004, Peter Langer moved to a new position as a full professor (C4) at the University of Rostock which is located in the North-East of Germany at the Baltic Sea. Since July 2005 he is associated to the Leibniz-Institute of Catalysis e. V. Rostock. Prof. Langer is co-author of currently 184 research papers (July 2006). His research is focussed on the development of new synthetic methods and their application to the synthesis of biologically relevant ring systems and natural products. This includes one-pot cyclizations, domino reactions, catalysis, azide and isothiocyanate chemistry, arene and heterocyclic chemistry, carbohydrate chemistry, and medicinal chemistry. Awards and scholarships: Studienstiftung des deutschen Volkes (1992–1994), Fonds der Chemischen Industrie (1995–1996), Feodor Lynen scholarship (1997–1998), Liebig scholarship (1999–2001), Heisenberg scholarship (2001).



Scheme 1. Bis(silyl enol ethers).

Pyridine

Pyridinium salts, generated by alkylation or acylation of pyridine,[9,10] have been reacted with various nucleophiles, such as organometallic reagents, cyanide (Reissert reaction), trimethylsilylacetonitrile, allylsilanes, and diazoesters.[11] In their pioneering work, Wenkert et al. studied the twofold functionalization of pyridinium salts by sequential double nucleophilic addition reactions.[12] Lavilla studied the synthesis of polycyclic frameworks starting with pyridines.[13,14] Rudler et al. reported the synthesis of (dihydropyrid-4-yl)-acetic acid **3** by MeOC(O)Cl-mediated condensation of 2,2-dimethyl-1,1-bis(trimethylsilyloxy)ethene (**1**) with pyridine (**2**).[15,16] Treatment of **3** with silica gel afforded lactone **4** (Scheme 2).[15,16] The reaction of **3** with *m*CPBA gave **5** (Scheme 2). Treatment of **3** with iodine and sodium hydrogen carbonate (iodolactonization) afforded the iodinated lactone **6** with very good *trans*-stereospecificity (Scheme 2).[15,16] A number of related transformations, starting with substituted pyridines and related 1,1-bis(trimethylsilyloxy)ketene acetals, were reported.[15,16] Notably,

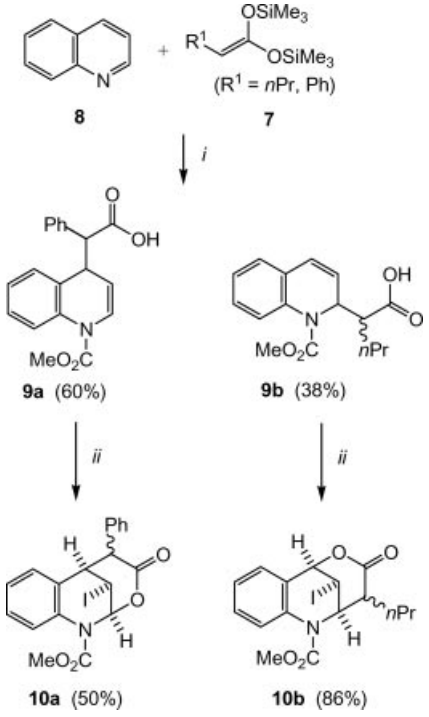


Scheme 2. Synthesis of lactones **4**–**6**; conditions: *i.* **1** (1.4 equiv.), **2** (1.0 equiv.), CH_2Cl_2, $ClCO_2Me$ (2.0 equiv.), 2 h; *ii.* SiO_2; *iii.* **3** (1.0 equiv.), *m*CPBA (1.4 equiv.), 2 h, NaOH, H_2O; *iv.* I_2 (1.1 equiv.), CH_2Cl_2, $NaHCO_3$, H_2O, 20 °C, 12 h.

(dihydropyrid-2-yl)carboxylic acids[17] and dihydropyridines[18] are of considerable pharmacological relevance.

Quinoline

The MeOC(O)Cl-mediated condensation of quinoline (**8**) with 2-phenyl-1,1-bis(trimethylsilyloxy)ethene afforded (quinolin-4-yl)acetic acid **9a** by attack of the silyl enol ether onto carbon atom C-4.[19] In contrast, the reaction of **6** with 2-propyl-1,1-bis(trimethylsilyloxy)ethene mediated by methyl chloroformate resulted in attack on C-2 to give (quinolin-2-yl)acetic acid **9b** (Scheme 3). Treatment of **9a** and **9b** with iodine in the presence of sodium hydrogen carbonate afforded 4-oxa-9-aza-7,8-benzobicyclo[3.3.1]nonan-3-ones **10a** and **10b**, respectively.

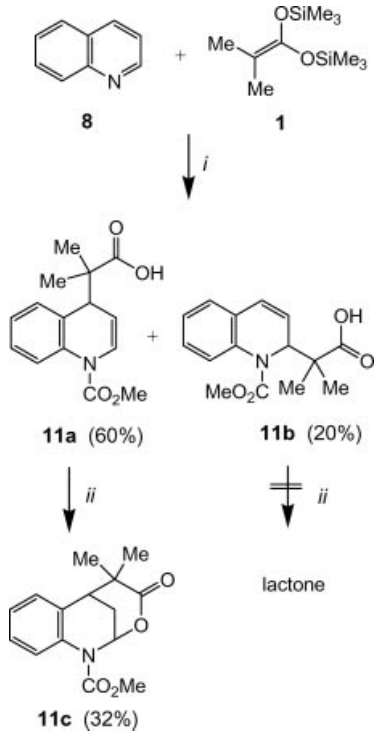


Scheme 3. Synthesis of 4-oxa-9-aza-7,8-benzobicyclo[3.3.1]nonan-3-ones **10a** and **10b**: *i.* **8** (1.0 equiv.), **7** (2.0 equiv.), $ClCO_2Me$ (1.2 equiv.), CH_2Cl_2, 0 °C, 2 h, 20 °C, 12 h; *ii.* I_2 (2.0 equiv.), CH_2Cl_2, $NaHCO_3$, H_2O, 20 °C, 12 h.

The reaction of quinoline with 1,1-bis(trimethylsiloxy)-ketene acetal **1** mediated by methyl chloroformate afforded a separable mixture of (quinolin-2-yl)acetic acids **11a** and **11b**. Treatment of a CH_2Cl_2 solution of **11a** with silica gel afforded 4-oxa-9-aza-7,8-benzobicyclo[3.3.1]nonan-3-one **11c** (Scheme 4).[16] In contrast, no lactone could be obtained from **11b**.

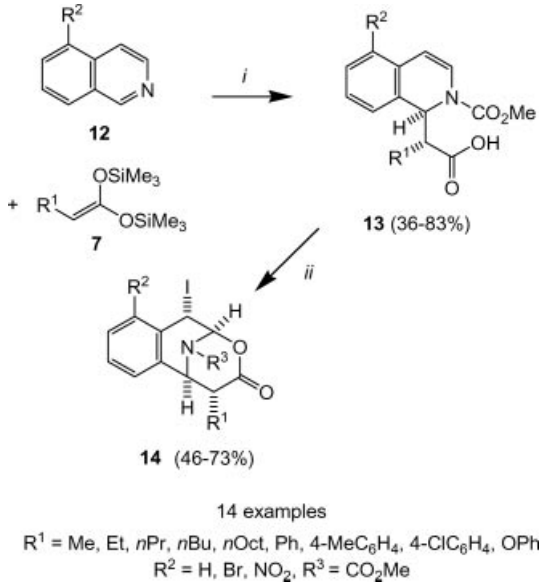
Isoquinolines

The MeOC(O)Cl-mediated reaction of isoquinolines **12** with 1,1-bis(trimethylsilyloxy)ketene acetals **7** afforded (isoquinolin-1-yl)acetic acids **13** which were transformed, by iodolactonization, into 4-oxa-9-aza-7,8-benzobicyclo[3.3.1]-



Scheme 4. Synthesis of 4-oxa-9-aza-7,8-benzobicyclo[3.3.1]nonan-3-one **11c**: *i.* **1** (1.4 equiv.), **8** (1.0 equiv.), $ClCO_2Me$ (2.0 equiv.), 2 h; *ii.* SiO_2 (10.0 equiv.), CH_2Cl_2, reflux, 2 h.

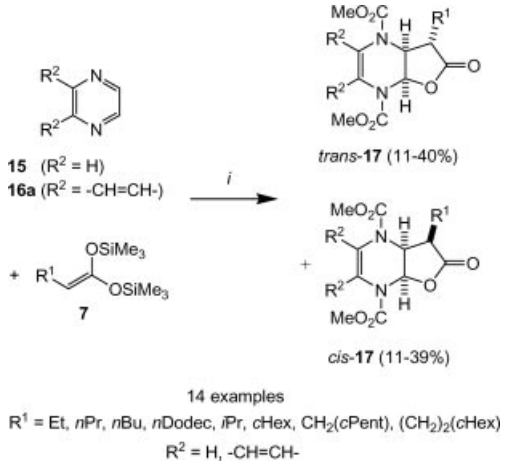
nonan-3-ones **14** (Scheme 5).[20] Products **13** were formed with very good regio- and diastereoselectivity. The iodolactonization proceeded with very good regioselectivity and *trans* stereospecificity.



Scheme 5. Cyclization of 1,1-bis(trimethylsilyloxy)ketene acetals **7** with isoquinolines **12**: *i.* **7** (1.0 equiv.), **12** (2.0 equiv.), $ClCO_2Me$ (1.2 equiv.), CH_2Cl_2, 0 °C, 2 h, 20 °C, 12 h; *ii.* I_2 (2.0 equiv.), CH_2Cl_2, $NaHCO_3$, H_2O, 20 °C, 12 h.

Quinoxaline and Pyrazine

The reaction of 1,1-bis(trimethylsiloxy)ketene acetals **7** with pyrazine (**15**) and quinoxaline (**16a**) mediated by methyl chloroformate afforded 1,4-diaza-7-oxabicyclo[4.3.0]-non-2-en-6-ones **17** (Scheme 6).[16,21,22] The formation of these products can be explained by generation of an iminium ion, attack of **7**, generation of a second iminium ion, and subsequent cyclization. In contrast to the reaction of 1,1-bis(trimethylsilyloxy)ketene acetals with isoquinoline (vide supra), the reactions of quinoxaline and pyrazine proceeded with low 1,2-diastereoselectivity. However, the isomers could be separated by chromatography.



Scheme 6. Synthesis of 7-oxa-1,4-diaza-2,3-benzobicyclo[4.3.0]non-2-en-6-ones **17**: *i.* **15**,**16a** (1.0 equiv.), **7** (1.4 equiv.), $ClCO_2Me$ (4.0 equiv.), CH_2Cl_2, 20 °C, 12 h.

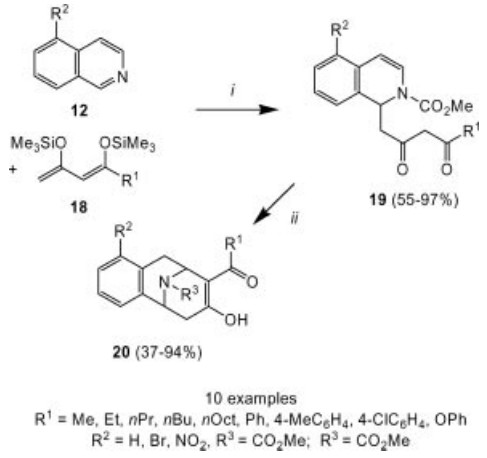
3. 1,3-Bis(silyloxy)-1,3-butadienes

1,3-Bis(silyloxy)-1,3-butadienes – also termed as 1,3-bis(silyl enol ethers) – are available in two steps from β-keto esters and in one or two steps from 1,3-diketones.[23] They can be regarded as masked 1,3-dicarbonyl dianions and a variety of cyclization reactions have been reported.[5–7]

Isoquinolines

The reaction of 1,3-bis(silyl enol ethers) **18** with isoquinolines **12** mediated by methyl chloroformate afforded products **19** (Scheme 7).[24] Treatment of **19** with trifluoroacetic acid (TFA) regioselectively afforded he 3-hydroxy-9-aza-7,8-benzobicyclo[3.3.1]non-3-enes **20** by acid-mediated generation of an iminium ion and subsequent cyclization by attack of the enol onto the iminium ion. The regioselectivity can be explained by the higher stability of the iminium compared to the benzylic ion. Parent 9-aza-7,8-benzobicyclo[3.3.1]non-3-ones were successfully prepared by decarboxylation (LiCl, DMSO, H_2O). The related 9-aza-3,4;7,8-dibenzobicyclo[3.3.1]nonanes, containing an isoquinoline substructure, occur in a number of pavin alkaloids (isolated from *Papaver* plant sources).[25,26] Notably, the MeOC(O)-

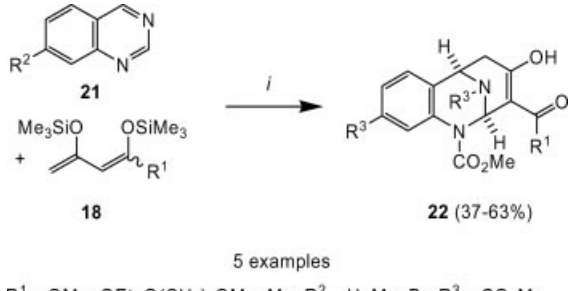
Cl-mediated condensation of 1,3-bis(silyl enol ethers) with quinoline and pyridine afforded the corresponding open-chain products in good yields. However, the acid-mediated cyclization failed.



Scheme 7. Cyclization of 1,3-bis(silyl enol ethers) **18** with isoquinolines **12**: *i*. **12** (1.0 equiv.), **18** (2.0 equiv.), $ClCO_2Me$ (1.2 equiv.), CH_2Cl_2, 0 °C, 2 h, 20 °C, 12 h; *ii*. TFA (2.0 equiv.), CH_2Cl_2, 20 °C, 12 h.

Quinazolines

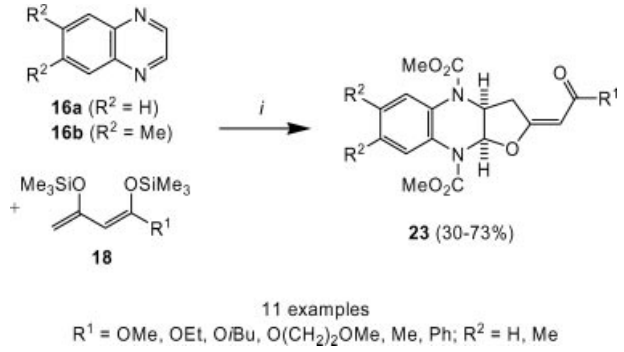
The reaction of 1,3-bis(silyl enol ethers) **18** with quinazolines **21**, in the presence of methyl chloroformate, afforded the 7,8-benzo-4-hydroxy-1,9-diazabicyclo[3.3.1]non-4-enes **22** (Scheme 8).[27] The one-pot cyclization presumably proceeds by reaction of **21** with methyl chloroformate to give an iminium salt, regioselective attack of the terminal carbon atom of **18** onto carbon atom C-4 of the quinazoline moiety, generation of a second iminium ion, and subsequent cyclization via the central carbon of **18**.



Scheme 8. Cyclization of 1,3-bis(silyl enol ethers) **18** with quinazolines **21**: *i*. **21** (1.0 equiv.), **18** (1.4 equiv.), $ClCO_2Me$ (4.0 equiv.), CH_2Cl_2, 0 °C, 2 h, 20 °C, 12 h.

Quinoxalines

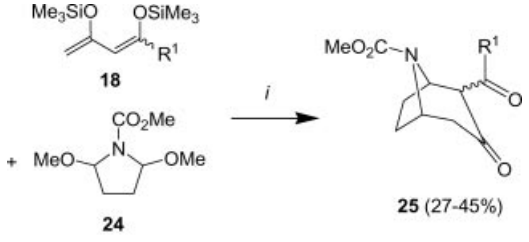
The MeOC(O)Cl-mediated reaction of 1,3-bis(silyl enol ethers) **18** with quinoxalines **16** afforded the alkylidene-7-oxa-1,4-diaza-2,3-benzobicyclo[4.3.0]non-2-enes **23** (Scheme 9).[28] The formation of the products can be explained by generation of an iminium salt, attack of the terminal carbon atom of **18**, formation of a second iminium ion, and cyclization via the oxygen atom. The crude material generally contains a mixture of **23** and of the product derived from hydration of the exocyclic double bond of **23**. Treatment of the mixture with TFA resulted in transformation of the side product into the desired product **23** (by elimination of water) which could thus be isolated in moderate to good yields. The exocyclic double bond was formed with very good *E* diastereoselectivity, due to the higher stability of the *E*- compared to the *Z*-configured exocyclic double bond.



Scheme 9. Cyclization of 1,3-bis(silyl enol ethers) **18** with quinoxalines **16a**,**b**: *i*. **16** (1.0 equiv.), **18** (1.4 equiv.), $ClCO_2Me$ (4.0 equiv.), CH_2Cl_2, 20 °C, 14 h; then: TFA (1.0 equiv.), CH_2Cl_2, reflux, 4 h.

2,5-Dimethoxypyrrolidine

The Me_3SiOTf-mediated cyclization of 1,3-bis(silyl enol ethers) **18** with 2,5-dimethoxypyrrolidine **24** afforded the tropinones **25** (Scheme 10).[29] The tropinone substructure is present in pharmacologically relevant tropane alkaloids.[30]

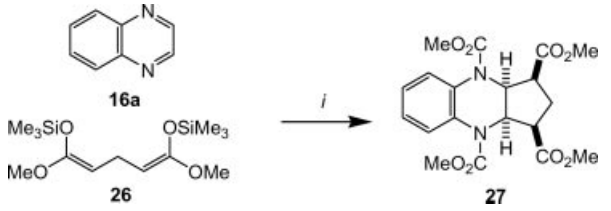


Scheme 10. Cyclization of 1,3-bis(silyl enol ethers) **18** with 2,5-dimethoxypyrrolidine **24**, *i*. Me_3SiOTf (0.3 equiv.), CH_2Cl_2, –78 → 20 °C.

4. 1,5-Dimethoxy-1,5-bis(trimethylsilyloxy)-1,4-pentadiene

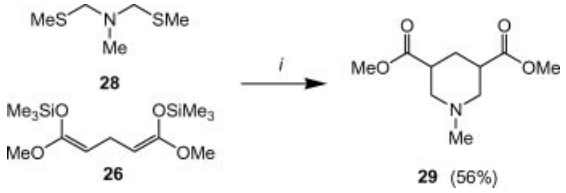
1,5-Bis(silyloxy)-1,4-pentadiene **26** can be regarded as an electroneutral equivalent of the dianion of dimethyl propanedioate and can be readily prepared by silylation of the latter.[31] The MeOC(O)Cl-mediated cyclization of **26** with

quinoxaline (**16a**) afforded the 1,4-diaza-2,3-benzobicyclo[4.3.0]nonane **27** (Scheme 11).[32] The cyclization of **27** with quinazoline (**22**) resulted in the formation of the corresponding bridged bicyclic product.[32]



Scheme 11. Cyclization of 1,3-bis(silyl enol ether) **26** with **16a**: *i.* **16a** (1.0 equiv.), **26** (1.4 equiv.), $ClCO_2Me$ (4.0 equiv.), CH_2Cl_2, 20 °C, 14 h; *ii.* TFA (1.0 equiv.), CH_2Cl_2, reflux, 4 h.

The Me_3SiOTf-mediated cyclization of bis(silyl enol ether) **26** with bis(sulfide) **28** afforded the piperidine **29** (Scheme 12).[33] The same product was obtained when 1,3,5-trimethyl-1,3,5-tetrahydrotriazine, rather than **28**, was employed.



Scheme 12. Cyclization of 1,3-bis(silyl enol ether) **26** with bis(sulfide) **28**: *i.* Me_3SiOTf, CH_2Cl_2, 20 °C, 5 h.

5. Conclusions

The cyclization of iminium salts with bis(silyl enol ethers) allows an efficient synthesis of bridged and nonbridged N-heterocycles. The MeOC(O)Cl-mediated reaction of 1,3-bis(silyloxy)-1,3-butadienes and 1,1-bis(siloxy)ketene acetals with pyridines, quinolines, isoquinolines, quinazolines, pyrazines, quinoxalines, and 2,5-dimethoxypyrrolidines affords 4-oxa-9-aza-7,8-benzobicyclo[3.3.1]nonan-3-ones, 7-oxa-1,4-diaza-2,3-benzobicyclo[4.3.0]non-2-en-6-ones, 7-oxa-1,4-diazabicyclo[4.3.0]non-2-en-6-ones, 3-hydroxy-9-aza-7,8-benzobicyclo[3.3.1]non-3-enes, 4-hydroxy-1,9-diaza-7,8-benzobicyclo[3.3.1]non-4-enes, alkylidene-7-oxa-1,4-diaza-2,3-benzobicyclo[4.3.0]non-2-enes, and tropinones. In general, the cyclization of bis(silyl enol ethers) with heterocycles containing *one* nitrogen atom (pyridine, quinoline, isoquinoline) has to be carried out in two steps. In the first step, an open-chain product is formed which subsequently is transformed into a bridged bicyclic product. The cyclization of bis(silyl enol ethers) with heterocycles containing *two* nitrogen atoms (pyrazine, quinoxaline, quinazoline) proceeds in one step and results in direct formation of the final product.

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[1] a) L. F. Tietze, U. Beifuss, *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 131; *Angew. Chem.* **1993**, *105*, 137; b) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115.
[2] For a review of one-pot cyclizations of dianions with dielectrophiles, see: a) P. Langer, W. Freiberg, *Chem. Rev.* **2004**, *104*, 4125. See also: b) P. Langer, *Chem. Eur. J.* **2001**, *7*, 3858.
[3] P. Brownbridge, *Synthesis* **1983**, 85.
[4] a) K. A. Jorgensen, *Angew. Chem.* **2000**, *112*, 3702; *Angew. Chem. Int. Ed.* **2000**, *39*, 3558; b) S. J. Danishefsky, M. T. Bilodeau, *Angew. Chem.* **1996**, *108*, 1482; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1380; c) M. D. Bednarski, J. P. Lyssikatos, *Comprehensive Organic Synthesis: Selectivity, Strategy and Efficiency in Modern Organic Chemistry* (Ed.: B. M. Trost), **1991**, *2*, 661.
[5] Review: P. Langer, *Synthesis* **2002**, 441.
[6] Review: P. Langer, *Synlett* **2006**, 3369.
[7] Review: P. Langer, *Synthesis* **2007**, 327.
[8] a) C. Ainsworth, Y.-N. Kuo, *J. Organomet. Chem.* **1972**, *46*, 73; b) A. Wissner, *J. Org. Chem.* **1979**, *44*, 4617; c) K. Takai, C. H. Heathcock, *J. Org. Chem.* **1985**, *50*, 3247.
[9] F. V. Scriven, *Pyridines and their Benzo Derivatives: (ii) Reactivity at Ring Atoms*, vol. 2, part 2A, chapter 2.05 (Eds.: A. J. Boulton, A. McKillop), in *Comprehensive Heterocyclic Chemistry* (Eds.: A. R. Katritzky, C. W. Rees), Elsevier Science, Oxford, **1984**, p. 165.
[10] a) D. M. Stout, A. I. Meyers, *Chem. Rev.* **1982**, *82*, 223; b) R. Kumar, R. Chandra, *Adv. Heterocycl. Chem.* **2001**, *78*, 269; c) A. Sausins, G. Duburs, *Heterocycles* **1988**, *27*, 291; d) J. P. Kutney, *Heterocycles* **1977**, *7*, 593; e) D. L. Comins, S. O'Connor, *Adv. Heterocycl. Chem.* **1988**, *44*, 199; f) J. Bosch, M.-L. Bennasar, M. Amat, *Pure Appl. Chem.* **1996**, *68*, 557.
[11] a) W. Bradley, S. Jeffrey, *J. Chem. Soc.* **1954**, 2770; b) F. Diaba, C. Le Houerou, M. Grignon-Dubios, P. Gerval, *J. Org. Chem.* **2000**, *65*, 907; c) R. Yamaguchi, B. Hatano, T. Nakaysau, S. Kozima, *Tetrahedron Lett.* **1997**, *38*, 403; d) K. Akiba, Y. Nishihara, M. Wada, *Tetrahedron Lett.* **1983**, *24*, 5269; e) F. Diaba, C. Le Houerou, M. Grignon-Dubois, B. Rezzonico, P. Gerval, *Eur. J. Org. Chem.* **2000**, 2915; f) T. Itoh, K. Nagata, M. Miyazaki, K. Kameoka, A. Ohsawa, *Tetrahedron* **2001**, *57*, 8827; g) A. R. Katritzky, S. Zhang, T. Kurz, M. Wang, *Org. Lett.* **2001**, *3*, 2807; h) D. L. Comins, M. J. Sandelier, T. A. Grillo, *J. Org. Chem.* **2001**, *66*, 6829; i) J. S. Yadav, B. V. S. Reddy, M. K. Gupta, A. Prabhakar, B. Jagadeesh, *Chem. Commun.* **2004**, 2124.
[12] E. Wenkert, C.-J. Chang, H. P. S. Chawla, D. W. Cochran, E. W. Hagaman, J. C. King, K. Orito, *J. Am. Chem. Soc.* **1976**, *98*, 3645.
[13] Review: R. Lavilla, *J. Chem. Soc., Perkin Trans. 1* **2002**, 1141.
[14] R. Lavilla, A. Spada, I. Carranco, J. Bosch, *J. Org. Chem.* **2001**, *66*, 1487.
[15] H. Rudler, B. Denise, A. Parlier, J.-C. Daran, *Chem. Commun.* **2002**, 940.
[16] H. Rudler, B. Denise, A. Parlier, J.-C. Daran, *Eur. J. Org. Chem.* **2005**, 3724.
[17] A. Krauze, S. Germane, O. Eberlins, I. Sturms, V. Klusa, G. Duburs, *Eur. J. Med. Chem.* **1999**, *34*, 301.
[18] a) R. Peri, S. Padmanabhan, A. Rutledge, S. Singh, D. J. Triggle, *J. Med. Chem.* **2000**, *43*, 2906; b) M. J. Kukla, H. J. Breslin, A. Gill, *J. Med. Chem.* **1990**, *33*, 223; c) A. Sobolev, M. C. R. Franssen, B. Vigante, B. Cekavicus, R. Zhalubovskis, H. Kooijman, A. L. Spek, G. Duburs, A. de Groot, *J. Org. Chem.* **2002**, *67*, 401.
[19] A. Schmidt, E. Ullah, H. Reinke, P. Langer, unpublished results.

[20] E. Ullah, S. Rotzoll, A. Schmidt, D. Michalik, P. Langer, *Tetrahedron Lett.* **2005**, *46*, 8997.
[21] H. Rudler, B. Denise, Y. Xu, J. Vaissermann, *Tetrahedron Lett.* **2005**, *46*, 3449.
[22] S. Rotzoll, E. Ullah, C. Fischer, D. Michalik, A. Spannenberg, P. Langer, *Tetrahedron* **2006**, *62*, 12084.
[23] a) T.-H. Chan, P. Brownbridge, *J. Am. Chem. Soc.* **1980**, *102*, 3534; b) K. Krägeloh, G. Simchen, *Synthesis* **1981**, 30; c) G. A. Molander, K. O. Cameron, *J. Am. Chem. Soc.* **1993**, *115*, 830.
[24] A. Schmidt, J.-P. Gütlein, A. Preuss, U. Albrecht, H. Reinke, P. Langer, *Synlett* **2005**, 2489.
[25] B. Fugmann (Ed.) *Römpp-Lexikon Naturstoffe* **1997**, Georg Thieme Verlag, Stuttgart, New York, p. 468.
[26] W.-T. Chang, S.-S. Lee, F.-S. Chueh, K. C. S. Liu, *Phytochemistry* **1998**, *48*, 119.
[27] A. Schmidt, J.-P. Gütlein, H. Reinke, P. Langer, *Synlett* **2007**, accepted.
[28] A. Schmidt, J.-P. Gütlein, P. Langer, *Tetrahedron Lett.* **2007**, in print.
[29] P. Langer, U. Albrecht, H. Ambrust, *Synlett* **2004**, 143.
[30] a) S. Isomura, T. Z. Hofman, P. Wirsching, K. D. Janda, *J. Am. Chem. Soc.* **1981**, *103*, 1172, and references cited therein; b) M. Lounasmaa, T. Tamminen, *Alkaloids* **1993**, *44*, 1; c) R. Dharanipragada, G. Fodor, *Nat. Prod. Rep.* **1991**, *8*, 603. For an early synthesis, see: d) R. Willstätter, *Ber. Dtsch. Chem. Ges.* **1901**, *34*, 129.
[31] I. H. M. Wallace, T. H. Chan, *Tetrahedron* **1983**, *39*, 847.
[32] J.-P. Gütlein, P. Langer, unpublished results.
[33] S. Miyazawa, I. Shuhei, K. Ikeda, K. Achiwa, M. Sekiya, *Chem. Lett.* **1984**, 785.

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