Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 2067–2069

Synthesis of 6-alkylidene-2,3-benzo-1,4-diaza-7-oxabicyclo-[4.3.0]non-2-enes by cyclization of 1,3-bis(silyl enol ethers) with quinoxalines

Andreas Schmidt,[a] Jörg-Peter Gütlein[a] and Peter Langer[a,b,*]

[a]*Institut für Chemie, Universität Rostock, Albert-Einstein-Str. 3a, D-18059 Rostock, Germany*
[b]*Leibniz-Institut für Katalyse e. V. an der Universität Rostock, Albert-Einstein-Str. 29a, D-18059 Rostock, Germany*

Received 14 December 2006; revised 24 January 2007; accepted 26 January 2007
Available online 31 January 2007

Abstract—6-Alkylidene-2,3-benzo-1,4-diaza-7-oxabicyclo[4.3.0]non-2-enes were prepared by cyclization of 1,3-bis(silyl enol ethers) with quinoxaline.

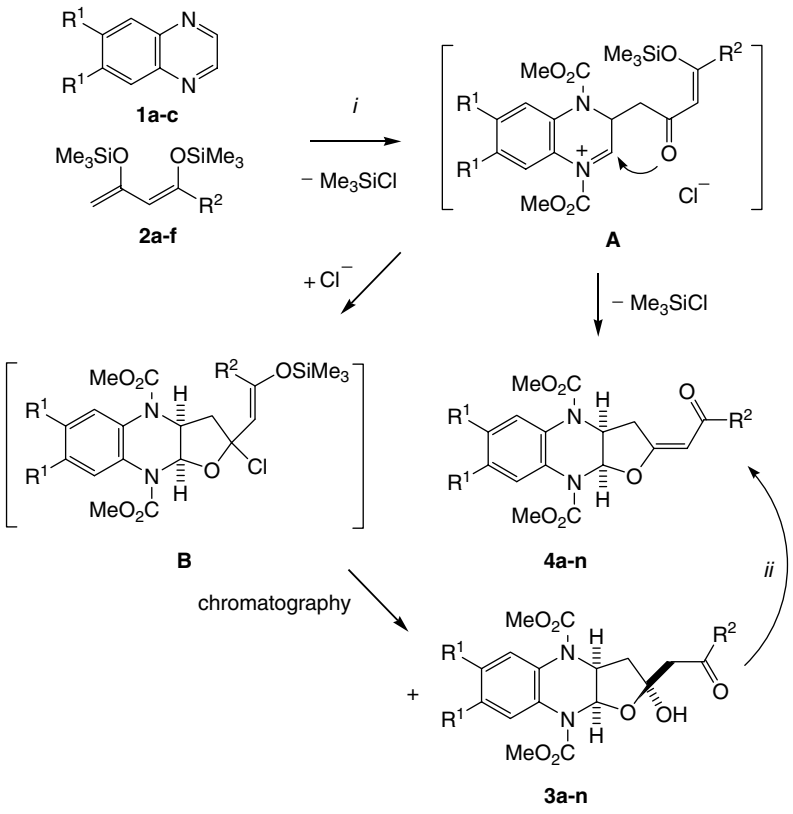
1,3-Bis(silyl enol ethers), which can be regarded as electroneutral equivalents of 1,3-dicarbonyl dianions (masked dianions), represent versatile building blocks in one-pot cyclizations with various electrophiles, such as oxalyl chloride, epoxides, 3-siloxy-2-en-1-ones, 1,4-diketones, or benzopyrylium triflates.[1] Recently, we started a program to study the cyclization of 1,3-bis(silyl enol ethers) with iminium salts. The cyclization of 1,3-bis(silyl enol ethers) with *N*-methoxycarbonyl-2,5-dimethoxypyrrolidine and isoquinoline afforded tropinones[2] and 7,8-benzo-3-hydroxy-9-azabicyclo-[3.3.1]non-3-enes,[3] respectively. Herein, we report what are, to the best of our knowledge, the first cyclizations of 1,3-bis(silyl enol ethers) with quinoxaline. These reactions allow a convenient synthesis of 6-alkylidene-2,3-benzo-1,4-diaza-7-oxabicyclo[4.3.0]non-2-enes. Recently, the cyclization of 1,1-bis(silyloxy)ketene acetals with pyrazine and quinoxaline has been reported.[4,5] The products are of potential biological relevance as they represent analogues of clofazimine, riboflavin (vitamin B_2) and lumiflavin. Clofazimine represents an important drug against leprosy and diseases related to the autoimmune system.[6] Due to serious problems, such as bacterial resistance,[6] the development of suitable clofazimine analogues is of pharmacological relevance.

1,3-Bis(silyl enol ether) **2a** is readily available from methyl acetoacetate in two steps.[7] The reaction of **2a** (1.4 equiv) with quinoxaline (**1a**) (1.0 equiv), in the presence of methyl chloroformate (4.0 equiv), afforded a separable mixture of 6-(methoxycarbonyl)methyl-6-hydroxy-2,3-benzo-1,4-diaza-7-oxabicyclo[4.3.0]non-2-ene **3a** (35%) and 6-(methoxycarbonyl)methylidene-2,3-benzo-1,4-diaza-7-oxabicyclo[4.3.0]non-2-ene **4a** (31%). The formation of **4a** can be explained by generation of an iminium salt, attack of the terminal carbon atom of **2a**, generation of a second iminium salt (intermediate **A**), and cyclization by attack of the oxygen atom. The formation of by-product **3a** can be explained by attack of a chloride ion after cyclization (intermediate **B**) and subsequent hydrolysis upon chromatography. Alcohol **3a** could be transformed into the desired product **4a** by treatment of the crude material with trifluoroacetic acid (TFA, CH_2Cl_2, reflux). Therefore, our final protocol for the synthesis of **4a** relies on the chloroformate-mediated cyclization of **2a** with **1a**, removal of the solvent and subsequent refluxing of a CH_2Cl_2 solution of the crude product mixture in the presence of TFA (1.0 equiv).[8] Using this procedure, **4a** could be isolated in 53% yield (Scheme 1, Table 1). A cis-annulation was observed for **4a**. 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.

The reaction of **1a** with 1,3-bis(silyl enol ethers) **2a–d**, prepared in two steps from the corresponding β-ketoesters,

Keywords: Cyclizations; Heterocycles; Iminium salts; Quinoxaline; Silyl enol ethers.
* Corresponding author. Tel.: +49 381 4986410; fax: +49 381 4986412; e-mail: peter.langer@uni-rostock.de

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.01.147



Scheme 1. Cyclization of 1,3-bis(silyl enol ethers) **2a–f** with quinoxalines **1a–c**: (i) **1a–c** (1.0 equiv), **2a–f** (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.

Table 1. Products and yields

1	2	4	R^1	R^2	% (**4**)[a]
a	**a**	**a**	H	OMe	53
a	**b**	**b**	H	OEt	67
a	**c**	**c**	H	O*i*Bu	65
a	**d**	**d**	H	$O(CH_2)_2OMe$	58
a	**e**	**e**	H	Me	30
a	**f**	**f**	H	Ph	35
b	**a**	**g**	Me	OMe	73
b	**b**	**h**	Me	OEt	70
b	**d**	**i**	Me	$O(CH_2)_2OMe$	51
b	**e**	**j**	Me	Me	40
b	**f**	**k**	Me	Ph	40
c	**b**	**l**	–CH=CH–	OEt	36
c	**d**	**m**	–CH=CH–	$O(CH_2)_2OMe$	50
c	**f**	**n**	–CH=CH–	Ph	50

[a] Yields of isolated products (based on **1a–c**).

afforded the ester-substituted 6-alkylidene-2,3-benzo-1,4-diaza-7-oxabicyclo[4.3.0]non-2-enes **4a–d** (Scheme 1, Table 1). The cyclization of **1a** with 1,3-bis(silyl enol ethers) **2e** and **2f**, derived from acetylacetone and benzoylacetone, gave acetyl and benzoyl-substituted products **4e** and **4f**. 6-Alkylidene-2,3-benzo-1,4-diaza-7-oxabicyclo[4.3.0]non-2-enes **4g–k** were prepared from 6,7-dimethylquinoxaline (**1b**). The cyclization of 6,7-benzoquinoxaline (**1c**) with 1,3-bis(silyl enol ethers) **2b**, **2d** and **2f** resulted in the formation of 6-alkylidene-2,3-naphtho-1,4-diaza-7-oxabicyclo[4.3.0]non-2-enes **4l–n**. In all cases, a mixture of compounds **3** and **4** was initially formed. Treatment of the crude material with TFA (CH_2Cl_2, reflux) gave products **4** in moderate to good yields.

Acknowledgments

We thank Ms. Satenik Mkrtchyan and Mr. Vahuni Karapetyan for experimental contributions. Financial support from the State of Mecklenburg-Vorpommern (Landesgraduiertenstipendium for A.S.) is gratefully acknowledged.

References and notes

1. Langer, P. *Synthesis* **2002**, *4*, 441.
2. Langer, P.; Albrecht, U.; Ambrust, H. *Synlett* **2004**, 143.
3. Schmidt, A.; Gütlein, J.-P.; Preuss, A.; Albrecht, U.; Reinke, H.; Langer, P. *Synlett* **2005**, 2489.
4. (a) Rudler, H.; Denise, B.; Parlier, A.; Daran, J.-C. *Eur. J. Org. Chem.* **2005**, 3724; (b) Rudler, H.; Denise, B.; Xu, Y.; Vaissermann, J. *Tetrahedron Lett.* **2005**, *46*, 3449.
5. Rotzoll, S.; Ullah, E.; Fischer, C.; Michalik, D.; Spannenberg, A.; Langer, P. *Tetrahedron* **2006**, *62*, 12084.
6. (a) Rychlewska, U.; Broom, M. B. H.; Eggleston, D. S.; Hodgson, D. J. *J. Am. Chem. Soc.* **1985**, *107*, 4768; (b) Patel, T. V. B.; Misra, A. N.; Manfatia, Y. S. *Pharmazie* **1999**, *54*, 448, and references cited therein; See also: (c) Fugmann, B. (Hrsg.) *Römpp-Lexikon Naturstoffe*; Georg Thieme Verlag: Stuttgart, New York, 1997; p 468.

7. (a) Chan, T.-H.; Brownbridge, P. *J. Chem. Soc., Chem. Commun.* **1979**, 578; (b) Molander, G. A.; Cameron, K. O. *J. Am. Chem. Soc.* **1993**, *115*, 830.

8. *General procedure*: To a CH_2Cl_2 solution (40 mL) of quinoxaline (4.0 mmol) was added 1,3-bis(silyl enol ether) (5.6 mmol) and methyl chloroformate (1.512 g, 16.0 mmol) at 20 °C. The solution was stirred for 14 h at 20 °C, concentrated in vacuo and dissolved in CH_2Cl_2 (40 mL). To the solution was added TFA (0.456 g, 4.0 mmol) and the solution was refluxed for 4 h. A saturated aqueous solution of sodium bicarbonate (20 mL) was added and the organic and the aqueous layers were separated. The latter was extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, heptane → heptane/EtOAc = 2:1). Synthesis of **4d**: Starting with **1a** (0.521 g, 4.0 mmol), **2d** (1.705 g, 5.6 mmol) and methyl chloroformate (1.512 g, 16.0 mmol), **4d** was prepared as a viscous yellow oil (0.943 g, 58%). ^{1}H NMR (500.13 MHz, $CDCl_3$): $\delta = 2.87$ (br d, $^2J = 19.5$ Hz, 1H, CH_2), 3.32 (s, 3H, OCH_3), 3.48 (ddd, $^2J = 19.5$ Hz, $^3J = 10.0$ Hz, $^4J = 1.9$ Hz, 1H, CH_2), 3.51 (m, 2H, CH_2OCH_3), 3.78, 3.83 (2s, 6H, $COOCH_3$), 4.13 (m, 2H, $COOCH_2$), 5.24 (t, $^4J = 1.9$ Hz, 1H, CHCO), 5.63 (br, 1H, NCH), 6.71 (br d, $^3J = 8.5$ Hz, 1H, NCHO), 7.14–7.18 (m, 2H, CH, Ar), 7.36 (br, 1H, CH, Ar), 7.42 (br, 1H, CH, Ar); ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 34.3$ (br, $NCHCH_2$), 53.5, 53.7 ($COOCH_3$), 56.0 ($NCHCH_2$), 58.9 (OCH_3), 62.5 ($COOCH_2$), 70.5 (CH_2), 90.2 (NCH), 91.3 (CHCO), 125.5, 125.9 (br), 126.0, 126.1 (br) (CH, Ar), 130.3, 130.5 (C, Ar), 153.9 (br, $2 \times$ NCO), 167.6 (COO), 171.3 (CO); IR (KBr, cm^{-1}): $\tilde{\nu} = 3432$ (br, w), 2956 (w), 1715 (s), 1647 (m), 1507 (m), 1442 (s), 1398 (m), 1330 (s), 1298 (m), 1220 (m), 1200 (m), 1110 (s), 1049 (m), 1015 (m), 761 (w); MS (EI, 70 eV): m/z (%) = 406 (M^+, 100), 330 (22), 303 (15), 271 (37), 227 (10), 189 (13), 145 (16); Anal. Calcd for $C_{19}H_{22}N_2O_8$ (406.39): C, 56.15; H, 5.46; N, 6.89. Found: C, 56.10; H, 5.57; N, 6.59. All new compounds gave satisfactory spectroscopic and analytical and/or high resolution mass data.