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Tetrahedron Letters 46 (2005) 8997–8999
Tetrahedron Letters

Synthesis of 7,8-benzo-9-aza-4-oxabicyclo[3.3.1]nonan-3-ones by sequential 'condensation–iodolactonization' reactions of 1,1-bis(trimethylsilyloxy)ketene acetals with isoquinolines

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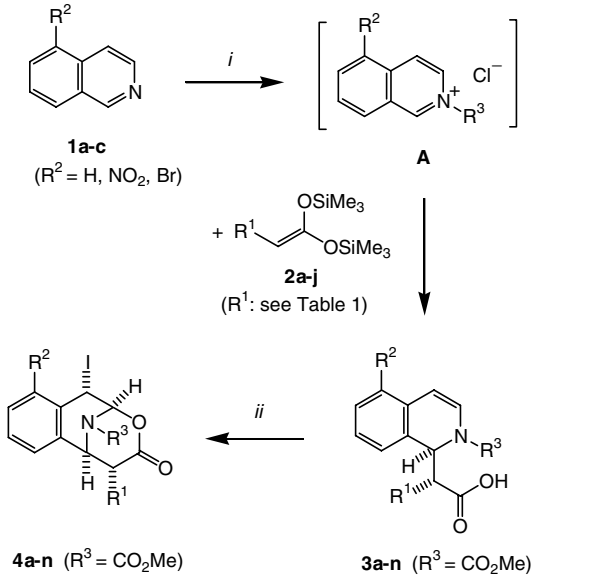
Received 16 September 2005; revised 19 October 2005; accepted 21 October 2005
Available online 9 November 2005

Abstract—Functionalized 7,8-benzo-9-aza-4-oxabicyclo[3.3.1]nonan-3-ones were prepared by regio- and diastereoselective condensation of 1,1-bis(silyloxy)ketene acetals with isoquinolinium salts and subsequent regioselective and stereospecific iodolactonization.

Quinolinium- and isoquinolinium salts represent important synthetic building blocks.[1] They are readily generated by alkylation or acylation of quinolines and isoquinolines and have been used in a number of reactions, for example, with Grignard reagents, cyanide (Reissert reaction),[2] trimethylsilylacetonitrile, allylsilanes, silyl enol ethers[3,4] or diazoesters.[5] We have studied the synthesis of 7,8-benzo-3-hydroxy-9-azabicyclo-[3.3.1]non-3-enes based on cyclocondensations of 1,3-bis-silyl enol ethers with isoquinolinium salts.[6] Very recently, Rudler et al. have reported the two-step cyclocondensation of silyl ketene acetals with pyridinium salts.[7] The publication of this work prompted us to disclose our own findings in this field: herein, we report what are, to the best of our knowledge, the first cyclocondensations of 1,1-bis(trimethylsilyloxy)ketene acetals with isoquinolinium salts. These reactions allow a convenient synthesis of densely functionalized 7,8-benzo-9-aza-4-oxabicyclo[3.3.1]nonan-3-ones. Notably, bicyclic N/O-acetals are present in a number of natural products, such as quinocarcin, tetrazomine and the bioxalomycins, showing good antitumour or antimicrobial activity.[8]

1,1-Bis(trimethylsilyloxy)ketene acetal **2a** ($R^1 = Me$) was prepared by deprotonation of trimethylsilyl propionic acid using lithio-1,1,1,3,3,3-hexamethyldisilazane (LiHMDS) and subsequent addition of trimethylchlorosilane.[9] The reaction of **2a** with isoquinoline (**1a**,



Scheme 1. Cyclization of silyl enol ethers **2a–j** with **1a–c**: (i), **1** (1.0 equiv), **2** (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, 20 °C, 12 h.

Keywords: Cyclizations; Heterocycles; Iminium salts; Isoquinoline; Silyl ketene acetals.
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doi:10.1016/j.tetlet.2005.10.108

$R^2 = H$) in the presence of methyl chloroformate afforded the condensation product **3a** (Scheme 1).[†] Treatment of **3a** with iodine in the presence of sodium bicarbonate afforded 7,8-benzo-9-aza-4-oxabicyclo-[3.3.1]nonan-3-one **4a**.[‡] In contrast, the reaction of **3a** with TFA resulted in decomposition. During the optimization of the cyclocondensation, the activating agent, temperature and concentration played an important role.

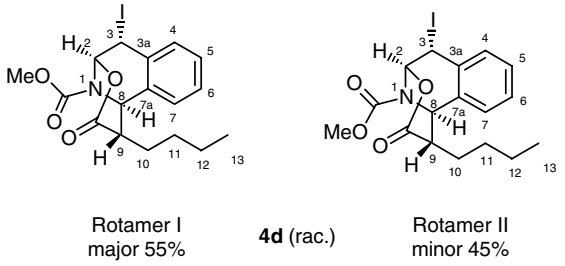
The preparative scope of our methodology was studied (Scheme 1 and Table 1). The reaction of **1a** ($R^2 = H$) with 1,1-bis(silylyloxy)ketene acetals **2a–e** ($R^1 =$ Me, Et, *n*Pr, *n*Bu, *n*Oct), prepared from the corresponding alkanoic acids, afforded the condensation products **3a–e**, which were transformed into the alkyl-substituted 7,8-benzo-9-aza-4-oxabicyclo[3.3.1]nonan-3-ones **4a–e**. The reaction of **1a** with **2f–h** ($R^1 =$ Ph, 4-MeC_6H_4, 4-ClC_6H_4), prepared from the corresponding arylacetic acids, afforded the condensation products **3f–h**, which were transformed into **4f–h**. The transformation of **3i** into **4i** ($R^1 =$ 4-(MeO)C_6H_4) was not successful. Starting with 5-nitroisoquinoline (**1b**, $R^2 = NO_2$) and 5-bromoisoquinoline (**1c**, $R^2 =$ Br) the 7,8-benzo-9-aza-4-oxabicyclo[3.3.1]nonan-3-ones **4j–n** were prepared.

Table 1. Products and yields

3, 4	R^1	R^2	% (3)[a]	% (4)[a]
a	Me	H	56	46
b	Et	H	62	61
c	*n*Pr	H	60	48
d	*n*Bu	H	65	70
e	*n*Oct	H	60	67
f	Ph	H	47	65
g	4-MeC_6H_4	H	54	64
h	4-ClC_6H_4	H	83	72
i	4-(MeO)C_6H_4	H	75	0
j	*n*Oct	NO_2	30	71
k	OPh	Br	70	50
l	*n*Bu	Br	36	73
m	*n*Oct	Br	54	67
n	Ph	Br	36	53

[a] Yields of isolated products.

The condensation of 1,1-bis(trimethylsilyloxy)ketene acetals **2** with isoquinolines **1** afforded the carboxylic acids **3** with very good regio- and diastereoselectivity (step 1). The formation of 7,8-benzo-9-aza-4-oxabicyclo[3.3.1]nonan-3-ones **4a–n** can be explained by regioselective formation of an iminium salt from **3** and subsequent trans-stereospecific iodolactonization (step 2). The formation of regioisomeric products, by generation of benzylic rather than iminium cations, was not observed. The configuration of all products was established by spectroscopic methods. For example, the NMR signals of **4d** were assigned by DEPT and two-dimensional ^{1}H,^{1}H COSY, ^{1}H,^{1}H NOESY and ^{1}H,^{13}C correlation spectra (HSQC, HMBC). In the NOESY spectrum of **4d** cross peaks were found for protons H-2 with H-3, H-3 with H-4, and H-7 with H-8,9. Besides the relevant NOESY signals, EXSY signals have been found between the signals of protons H-$2_{(I)}$ and H-$2_{(II)}$ as well as H-$8_{(I)}$ and H-$8_{(II)}$, which confirm the presence of two exchanging isomers (rotamers I and II). In the HMBC spectrum cross peaks were found for C-3 with H-4, C-8 with H-7, and for COO with H-2,8,9,10, which confirm the given structures (Scheme 2). The two rotamers were observed owing to the rigidity of the urethane



Scheme 2. Relative configuration and rotamers of **4d**.

[†] *Typical procedure:* To a CH_2Cl_2 solution (20 ml) of isoquinoline (0.250 g, 1.9 mmol) were added the 1,1-bis(trimethylsilyloxy)hex-1-ene (1.0 g 3.8 mmol) and methyl chloroformate (0.218 g, 2.3 mmol) at 0 °C. The solution was stirred for 2 h at 0 °C and for 12 h at 20 °C. A saturated aqueous solution of ammonium chloride (20 ml) was added and the organic and the aqueous layers were separated. The latter was extracted with CH_2Cl_2 (3×100 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, *n*-heptane → *n*-heptane/EtOAc = 2:1) to give **3d** as a slightly brownish solid (0.384 g, 65%), mp 82 °C.

[‡] *Typical procedure*: To a CH_2Cl_2 solution (6 ml) of **3d** (0.1 g, 0.35 mmol) and I_2 (0.17 g 0.70 mmol) was added a saturated solution of $NaHCO_3$ (3.5 ml) and the solution was stirred for 12 h at 20 °C. The excess of iodine was removed by addition of a saturated aqueous solution of sodium sulfite (20 ml). The organic and the aqueous layers were separated. The latter was extracted with CH_2Cl_2 (3×30 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, *n*-heptane → *n*-heptane/EtOAc = 2:1) to give **4d** as a yellow oil (0.10 g, 70%). Due to the amide resonance and formation of *E*/*Z*-isomers, doubling of some signals was observed. ^{1}H NMR (500.13 MHz, $CDCl_3$) $\delta = 7.40–7.35$ (m, $1H_{(I)}$, $1H_{(II)}$, H-$4_{(I)}$, H-$4_{(II)}$); 7.30–7.24 (m, $2H_{(I)}$, $2H_{(II)}$, H-$5,6_{(I)}$, H-$5,6_{(II)}$); 7.02–6.97 (m, $1H_{(I)}$, $1H_{(II)}$, H-$7_{(I)}$, H-$7_{(II)}$); 6.82 ('t', 1H, $^3J_{2,3} = 1.8$ Hz, $^4J_{2,8} = 1.5$ Hz, H-$2_{(II)}$); 6.68 ('t', 1H, $^3J_{2,3} = 1.8$ Hz, $^4J_{2,8} = 1.5$ Hz, H-$2_{(I)}$); 5.69 (d, 1H, $^3J_{2,3} = 1.8$ Hz, H-$3_{(II)}$); 5.68 (d, 1H, $^3J_{2,3} = 1.8$ Hz, H-$3_{(I)}$); 5.50 (br s, 1H, $^4J_{2,8} = 1.5$ Hz, $^3J_{8,9} = 1.0$ Hz, H-$8_{(I)}$); 5.36 (br s, 1H, $^4J_{2,8} = 1.5$ Hz, $^3J_{8,9} = 1.0$ Hz, H-$8_{(II)}$); 3.89 (s, 3H, $MeO_{(I)}$); 3.88 (s, 3H, $MeO_{(II)}$); 2.56–2.50 (m, $1H_{(I)}$, $1H_{(II)}$, H-$9_{(I)}$, H-$9_{(II)}$); 1.75–1.35 (m, $6H_{(I)}$, $6H_{(II)}$, H-$10,11,12_{(a,b),(I)}$, H-$10,11,12_{(a,b),(II)}$); 0.944 (t, 3H, $J = 7.2$ Hz, H-$13_{(II)}$); 0.936 (t, 3H, $J = 7.2$ Hz, H-$13_{(I)}$). ^{13}C NMR (125.8 MHz, $CDCl_3$) $\delta = 169.3$ ($COO_{(I)}$); 169.0 ($COO_{(II)}$); 153.8 ($NCO_{(I)}$); 154.3 ($NCO_{(II)}$); 132.2, 132.2 (C-$3a_{(II)}$, C-$7a_{(II)}$); 131.9, 132.2 (C-$3a_{(I)}$, C-$7a_{(I)}$); 131.6 (C-$4_{(II)}$); 131.5 (C-$4_{(I)}$); 129.5, 128.9 (C-$5,6_{(I)}$); 129.4, 129.1 (C-$5,6_{(II)}$); 126.6 (C-$7_{(I)}$); 126.4 (C-$7_{(II)}$); 85.4 (C-$2_{(I)}$); 84.8 (C-$2_{(II)}$); 53.8 ($OMe_{(I)}$); 53.6 ($OMe_{(II)}$); 52.2 (C-$9_{(I)}$); 51.9 (C-$9_{(II)}$); 51.8 (C-$8_{(II)}$); 50.6 (C-$8_{(I)}$); 30.7 (C-$10_{(I)}$); 30.5 (C-$10_{(II)}$); 29.4 (C-$11_{(I)}$); 29.3 (C-$11_{(II)}$); 23.5 (C-$3_{(I)}$); 23.0 (C-$3_{(II)}$); 22.2 (C-$12_{(I)}$); 22.3 (C-$12_{(II)}$); 13.8 (C-$13_{(I)}$); 13.8 (C-$13_{(II)}$). IR (KBr): $\tilde{\nu} = 772$(m), 1109 (w), 1231 (s), 1450 (s), 1780 (s), 3430 (br) cm^{-1}; MS (EI, 70 eV): *m*/*z* (%) = 429 (M^+, 2), 302 (7), 204 (19), 188 (100), 144 (25), 129 (36). All products were prepared as racemic material. All new compounds gave satisfactory spectroscopic and analytical and/or high resolution mass data.

moiety, which possesses a considerable double bond character and, thus, a high rotation barrier.

Our current studies are directed towards extension of the preparative scope, development of an enantioselective version and towards synthetic applications of our methodology.

Acknowledgements

Financial support from the state of Mecklenburg-Vorpommern (Landesforschungsschwerpunkt 'Neue Wirkstoffe und Screeningverfahren' and Landesgraduiertenstipendium for A.S.), from Boehringer-Ingelheim Pharma GmbH, BASF AG and from the Deutsche Forschungsgemeinschaft is gratefully acknowledged.

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