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Stereoselective Amine Addition to Six-Membered Cyclic Nitronates Promoted by Silyl Triflate

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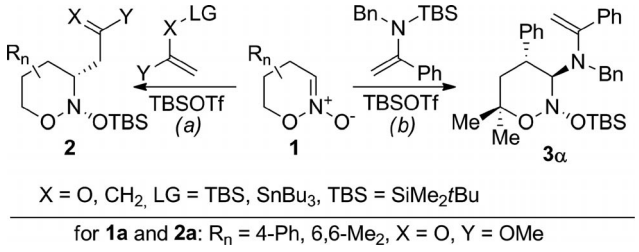
Six-membered cyclic nitronates couple with amines or their *N*-silyl derivatives in a diastereoselective fashion to give 3-amino-substituted nitroso acetals in 53–89% yield through silyl triflate electrophilic catalysis. Stereodifferentiation of this process is determined by thermodynamic control, which is realized due to reversibility of amine addition and a decreased nitrogen inversion barrier in the resulting nitroso acetals. Selected chemical transformations of nitroso acetals were examined.

Introduction

The chemistry of six-membered cyclic nitronates **1** is currently an object of systematic investigations.[1] Enhanced interest in this class of organic derivatives has been provoked not only by the diversity of their chemical transformations,[1] but also by their applications in the syntheses of natural products and medical substances.[2,3]

Coupling of nitronates **1** with π-nucleophiles mediated by *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) gives rise to nitroso acetals **2** [Scheme 1, Path (a)].[4] This reaction is a powerful method of creating C–C bonds, as well as an effective mode of standard reactivity inversion of aliphatic nitro compounds.[4a,4d,5] In contrast, analogous coupling of nitronates **1** with N-nucleophiles is limited to a single example:[4a,6] nitronate **1a** interacts with *N*-silylenamine to form nitroso acetal **3α** [Scheme 1, Path (b)] instead of the expected C–C coupling product of type **2**. Moreover, besides exclusive C–N bond formation, the stereochemistry of the nucleophilic addition at the newly formed carbon stereocenter in compound **3α**, was opposite to that in products **2**.

The current investigation focuses on mechanistic analysis of addition of amines and their *N*-silyl derivatives to six-membered cyclic nitronates **1**. The target nitroso acetals **3** possess a specific structure and can be considered as aminals at the C-3 atom. Compounds of such type are almost unknown,[7] however they can potentially serve as intermediates in organic synthesis.



Scheme 1. Electrophilic activity of nitronates **1**.

Results and Discussion

Nitronate **1a** and *N*-TBS-pyrrolidine **4a** were chosen as model substrates with which to examine the N,C-coupling (Scheme 2). The reaction proceeded smoothly with TBSOTf (0.15–0.20 equiv.) as a mediator, which was necessary for intermediate formation of cation **5a**$^+$. It was found that silylamine **4a** adds to nitronate **1a** within 24 hours at –30 °C, giving rise to the target nitroso acetal **3a** in 79% yield. The only observed byproduct was enoxime **6a**,[8] which was formed in quantities up to 15%. Attempts to minimize the yield of **6a** by decreasing the reaction temperature were unsuccessful.

Nitroso acetal **3a** was isolated as the only diastereoisomer. The NMR spectra show a close resemblance of adduct **3a** to the previously obtained nitroso acetal **3α**, the structure of which was unambiguously determined by X-ray analysis (see Scheme 1). First, this similarity allowed the associated $^3J_{H,H}$ coupling constants of the products to be compared. Considering the slow nitrogen inversion in the O–N–O fragment,[9] the configuration of the nitrogen

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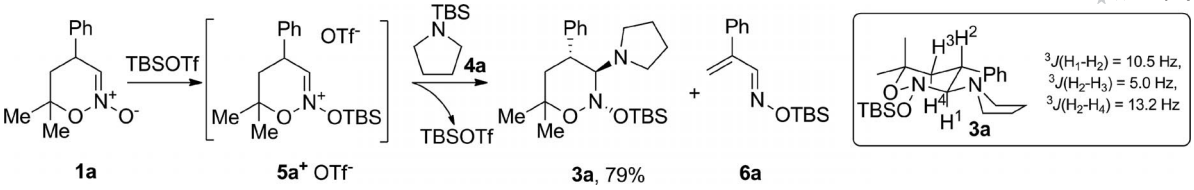


1a **5a⁺ OTf⁻** **3a**, 79% **6a** **3a**

Scheme 2. The C,N-coupling of **1a** and **4a**, and the stereochemistry of **3a**. *Reaction conditions:* **1a** (1.0 mmol), **4a** (1.1 mmol), 2,6-lutidine (0.25 mmol), TBSOTf (0.15 equiv.), CH_2Cl_2 (5.0 mL), –30 °C, 24 h.

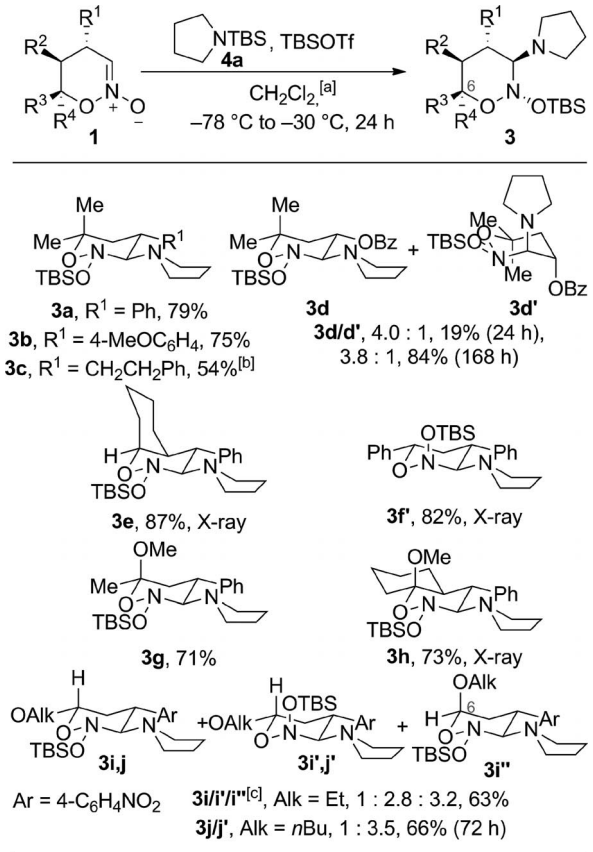
stereocenter was also assigned according to resemblance of the ^{1}H NMR spectra of **3a** to that of **3α**.[4a] The arrangement of the entering amino-fragment in **3a** was thus assigned as *trans* to the TBSO-group.

The conditions found for coupling of **1a** with *N*-silylamine **4a** were applied for the representative nitronate series **1b**–**i**, containing a range of ring substituents. In all cases, the desired aminals **3** were obtained in moderate to high yields (Table 1). When nitronate **1d** (R^1 = OBz) was utilized, the addition rate was significantly decreased, and only 25% conversion along with 19% yield of a mixture of the corresponding nitroso acetals (**3d** + **3d′**) was observed within 24 h. The low conversion of **1d** might be associated with a stabilization of cationic intermediate **5d⁺** through anchimeric assistance of the BzO group. Hence, exposure of the reaction mixture **1d** and **4a** for one week resulted in an 84% yield of desired product mixture (**3d** + **3d′**). Aminal **3c** was found to be unstable, and its yield was determined by ^{1}H NMR spectroscopic analysis with an internal standard.

Products **3** can exist in the form of rapidly interconverting conformations of a six-membered heterocycle.[4a,4b] At the same time, lone pair inversion of the nitroso acetal nitrogen cannot be excluded (see below). These circumstances make determination of the configuration and the observed conformations of aminals **3** a rather difficult task. X-ray diffraction analysis was undertaken for all crystalline products **3** (**3e**, **3f′** and **3h**). Configurations and predominant conformations for other derivatives of **3** were determined by ^{1}H NMR spectroscopic analysis. Values of vicinal coupling constants of protons at C-3, C-4 and C-5 atoms were the key for the stereochemical assignment, along with NOE observations and chemical shifts values of the proton at C-3 (see the Supporting Information for details).

Configurations and the observed conformations of the aminals **3** can be divided into several types. For most (**3a**–**e**, **3g**, and **3h**) the predominant conformation coincides with that obtained for the isolated nitroso acetal **3α**, with all equatorial positions of substituents at N-2, C-3 and C-4.[4a] The C,N-coupling proceeds in a diastereoselective fashion for most nitronates **1** except for **1d** (R^1 = OBz) and homologues **1i** (R^4 = OEt) and **1j** (R^4 = OBu). However, the new stereocenter at C-3 is formed even in the latter cases with near 100% selectivity. Aminal **3d′** exists in equilibrium with **3d**, which evidently operates through a nitrogen and ring inversion sequence (I_N + I_R). The reaction of nitronate **1f**, containing two equatorial phenyl groups (R^1, R^4 = Ph) unexpectedly afforded product **3f′** with inverted nitrogen (*cis*-arrangement of TBSO and pyrrolidinyl groups). Similarly,

Table 1. Addition of silylpyrrolidine **4a** to nitronates **1a**–**i**.[a]

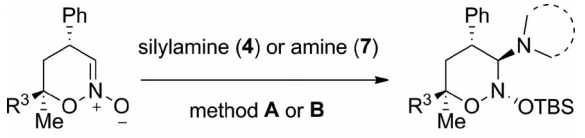


[a] *Reaction conditions:* nitronate **1** (1.0 mmol), silylamine **4a** (1.1 mmol), 2,6-lutidine (0.25 mmol), TBSOTf (0.15 mmol), CH_2Cl_2 (5.0 mL), –78 °C, 15 min, then 24 h, –30 °C. [b] Yield determined by NMR spectroscopic analysis with trichloroethylene as internal standard. [c] **i′′** corresponds to the C-6 epimerization product, see the Supporting Information for details.

endocyclic nitrogen invertomers became the main products of C,N-coupling for nitronates **1i** and **1j**, containing equatorial alkoxy-groups at C-6 (**1i**: R^4 = OEt, **1j**: R^4 = OBu). Partial epimerization of the acetal center at C-6 in nitronate **3i**, possessing less bulky alkoxy-group, was observed, possibly due to the presence of Lewis acidic TBSOTf.

Free pyrrolidine **7a** may be involved in the reaction instead of its silylated derivative **4a**. In this case at least one equivalent of TBSOTf was used and a longer reaction time was needed. However, the diastereoselectivity of formation of the target nitroso acetal **3a** and its yield suffered no significant decrease (cf. Table 2, entries 1 and 2).

Table 2. Coupling of nitronates **1a** and **1g** with silylamines **4** and amines **7**.



1a, g **3a, k–p**

Entry	1	R^3	Amine		Method[a]	3	Yield [%] (*dr*)[b]
1	**1a**	Me	*N*-TBS-pyrrolidine	**4a**	A	**3a**	79
2	**1a**	Me	pyrrolidine	**7a**	B	**3a**	75
3	**1a**	Me	morpholine	**7b**	B	**3k**	76
4	**1g**	OMe	morpholine	**7b**	B	**3l**	69
5	**1a**	Me	Et_2NH	**7c**	B	**3m**	77
6	**1a**	Me	Bn_2NH	**7d**	B	**3n**	53
7	**1g**	OMe	PhN(Me)TBS	**4e**	A	**3o**	74
8	**1a**	Me	*n*BuNHTBS	**4f**	A	**3p/3p***	89 (1.8:1)
9	**1a**	Me	*n*BuNH$_2$	**7f**	B	**3p/3p***	65 (1:3.4)

[a] Method A: CH_2Cl_2 (5.0 mL), nitronate **1** (1.0 mmol), TBS-amine **4** (1.1 mmol), 2,6-lutidine (0.25 mmol), then TBSOTf (0.15 mmol), –78 °C, 15 min, then 24 h at –30 °C. Method B: CH_2Cl_2 (5.0 mL), nitronate **1** (1.0 mmol), 2,6-lutidine (1.05 mmol), TBSOTf (1.15 mmol), then amine **7** (1.05 mmol), –78 °C, 15 min, then 48 h at –30 °C. [b] Determined by ^{1}H NMR spectroscopic analysis (for details, see the Supporting Information).

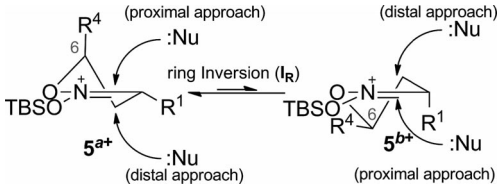
The nature of the amines involved in C,N-coupling with nitronates **1a** and **1g** was varied over a rather wide range (Table 2). Secondary amines smoothly reacted under the optimized conditions, and primary butylamine **7f** and its trialkylsilyl derivative **4f** could also be subjected to this reaction (Table 2, entries 8 and 9); however, a crucial decrease in the diastereoselectivity was observed in the latter cases. With free *n*-butylamine **7f** (Method B), isomer **2p*** becomes the main component of the reaction mixture; unexpectedly, this product had a *cis*-orientation of amine fragment and Ph-group at the C-4 center.

It was shown with the example of morpholine **7b** that Method B was also applicable for nitronates **1** containing an alkoxy-group at the C-6 center (Table 2, entry 4). In this case, C,N-coupling was not accompanied by oxazine ring-opening transformations[10] and the expected product **3l** was obtained in 69% yield.

In summary, the C,N-coupling of nitronates **1** with silylamine **4a** is a more complex process than previously investigated C,C-coupling of **1** with π-nucleophiles, at least in terms of observed configurations of the resulting products **3**.[4a,4b] Therefore, the mechanistic aspects of this process were considered in greater detail.

Mechanistic Considerations

Previously described C,C-coupling of nitronates **1** with π-nucleophiles proceeds via two cationic intermediates $\mathbf{5^{a+}}$ and $\mathbf{5^{b+}}$, existing in fast equilibrium (Scheme 3).



Scheme 3. Conformations of cation $\mathbf{5^+}$ and possible approaches of Nu.

The configuration of previously reported[4a,4b] nitroso acetal products **2** was determined by the relative steric hindrance of two possible nucleophile approaches to both conformations of cation $\mathbf{5^+}$ (Scheme 3, conformations $\mathbf{5^{a+}}$ and $\mathbf{5^{b+}}$). In this case, a *trans*-antiperiplanar arrangement of the appearing nitrogen lone pair and entering nucleophile is *a priori* preferable because of a stabilizing n–σ^* interaction. It was stated that the observed conformations of the formed nitroso acetals **2** result from fast ring inversion (I_R) in these products.

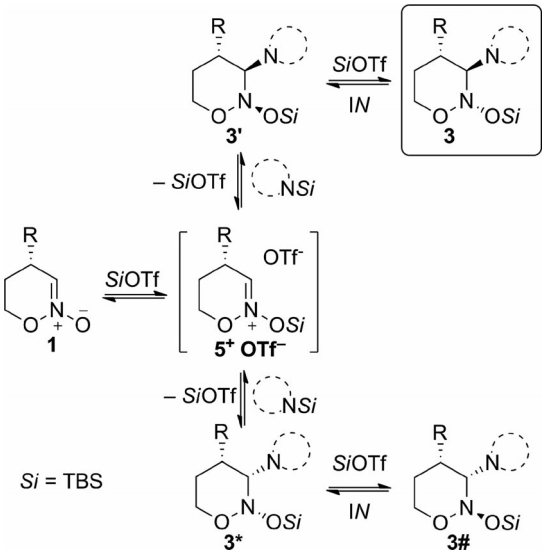
It should be underlined that the stereochemistry of formation of aminals **3** (Table 1) cannot be explained on the basis of such simple considerations. The differences in the stereochemistry of nitroso acetals **2** and **3** seem so fundamental that another mechanism must be proposed for the formation of the latter. We therefore first examined whether preliminary generation of cation $\mathbf{5^+}$ from nitronate **1** is necessary for C,N-coupling (as shown in Scheme 2). For this purpose, we attempted to carry out the coupling of **1b** and **4a** in CD_2Cl_2 in the absence of TBSOTf. Under these conditions the reaction did not occur at –30 °C, nor even at room temperature. On this basis, it is therefore quite plausible that an initial cationic species is required to generate the target aminals **3**. However, it should be concluded that the observed *trans*-orientation of the amine residue and R^1-substituent does not depend on the dominant conformation of the corresponding cationic intermediate $\mathbf{5^+}$. Indeed, the dominant conformation of the cationic precursors for aminals **3a**–**c** and **3e**–**h** was found to be $\mathbf{5^{a+}}$, and, respectively, conformation $\mathbf{5^{b+}}$ for **3d**, **3i**, and **3j** (see Scheme 3 and preliminary publication[4b]).

The stereochemical conformation of products **3** does not correlate with previously obtained data on the C,C-coupling of nitronates **1** with π-nucleophiles, for which distal approach to the observed most stable conformation ($\mathbf{5^{a+}}$ or $\mathbf{5^{b+}}$) occurred, leading to the corresponding *cis*-adducts **2** (see Schemes 1, 2, and 3).[4a,4b] Furthermore, as previously mentioned, the *cis*-orientation of the endocyclic nitrogen lone pair and the entering amino-fragment in products **3** is usually observed (see Table 1). However, such a stereochemical outcome is not as strict as that for nitroso acetals **2**, for which the nitrogen lone pair was *always* positioned *trans*- to the entering π-nucleophile fragment.

The contradictions between the stereochemical outcomes of reactions of N-nucleophiles and π-nucleophiles can be resolved by assuming the following postulates: (1) reaction of $\mathbf{5^+}$ + **4** or $\mathbf{5^+}$ + **7** is reversible, and (2) the inversion barrier for the endocyclic nitrogen of aminals **3** in the presence of

silyl Lewis acids is significantly lower than that in nitroso acetals **2**.

The reversibility coupled with a decreased nitrogen inversion barrier can result in the progressive accumulation of thermodynamically preferred isomers in the reaction mixture. The C,N-coupling of cyclic nitronates **1** with amines or their silyl derivatives might be approximated by a scheme involving five equilibria (Scheme 4). Formation of any of four plausible nitroso acetal diastereomers (**3**, **3′**, **3*** and **3#**, as marked in Scheme 4) could not be excluded.



Scheme 4. Proposed mechanism of C,N-coupling.

A nine-hour, low-temperature NMR monitoring experiment observing the reaction of **1a** and **4a** (Figure 1) was carried out to investigate the suggested hypothesis. Just one hour after addition of TBSOTf (0.2 equiv.), the conversion of **1a** already achieved ca. 75%. Diastereomeric nitroso acetals **3a*** and **3a′** were found to become the main products in ca. 3:1 ratio. Furthermore, signals of enoxime **6a**, cation **5a⁺**, final product **3a**, and the fourth isomer **3a#** were detected in a total amount of less than 15% (see Figure 1, spectrum a). Besides its resemblance to analogous products **2** in its spectral characteristics, the structure of **3a*** was unambiguously confirmed by ^{1}H-^{1}H and ^{1}H-^{13}C-correlation techniques.

The structure of **3a′** was deduced on the basis of spin-spin coupling constants and on the resemblance of its ^{1}H NMR spectrum to that of **3f′** (see the Supporting Information for details). After an additional 7 h (see Figure 1, spectrum b), conversion of nitronate **1a** achieved 97%, and yields of **3***, **3′**, **3#**, and **3** were 53, 24, 5, and 7%, respectively.

When the temperature was increased to 10 °C, dynamic equilibriums **3*** ⇆ **3#** and **3′** ⇆ **3**, corresponding to O–N–O nitrogen inversion took place; this became evident from the broadening of the corresponding signals and the decrease in the chemical shift difference for the indicated pairs (see Figure 1, spectrum c). After repeated cooling to –30 °C (see Figure 1, spectrum d) the endocyclic nitrogen inversion

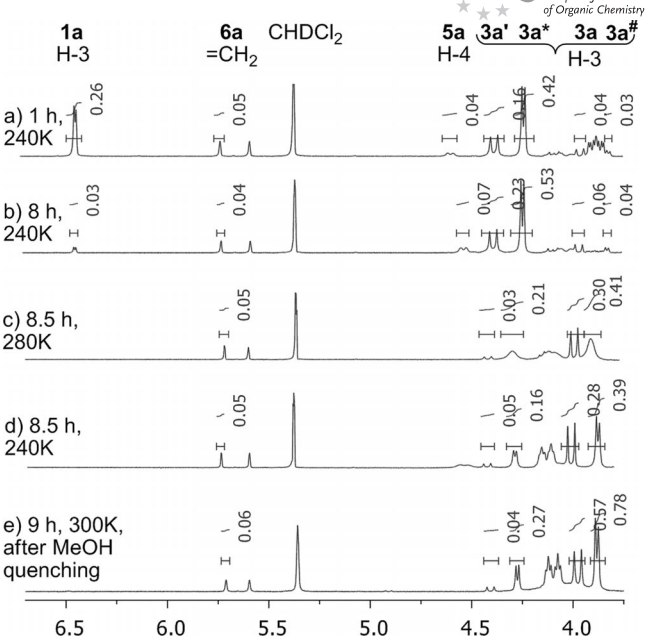


Figure 1. NMR monitoring of **1a**/**4a** coupling in the presence of TBSOTf (0.2 equiv.). Fragment of ^{1}H NMR spectra (δ = 4.50–6.75 ppm).

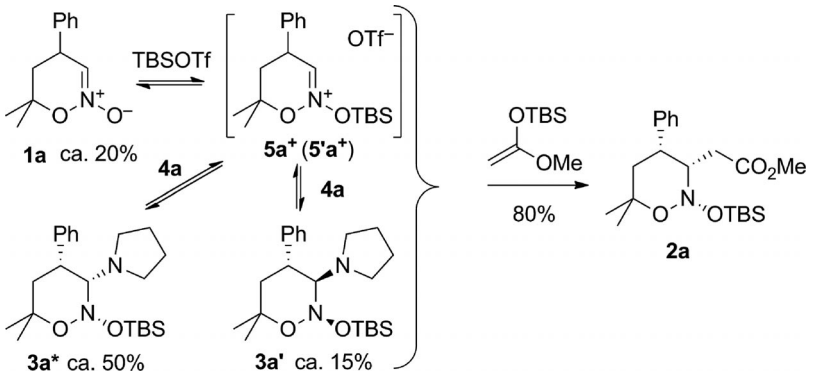
was again suppressed and after methanol quenching of TBSOTf the inversion was completely stopped (see Figure 1, spectrum e).

To verify the reversibility of amine **4** addition, a further experiment was carried out (Scheme 5). A mixture of **1a**, **4a**, and TBSOTf was kept for 3 h at –30 °C (at this point the composition by NMR spectroscopic analysis was determined to be ca. 50% **3a*** and 15% **3a′** along with ca. 20% unreacted **1a**) and treated with TBSO(MeO)C=CH_2. After an additional 15 h at –30 °C, ketene acetal adduct **2a** was isolated in 80% yield along with residual aminal **3a** (ca. 10%).[11]

Thus, the reversibility of C,N-coupling of nitronates **1** with amines was confirmed by the reduction of the **3a***/**3a′** ratio (the **3a***+**3a#**/**3a′**+**3a** ratio precisely) from 3:1 to 2:1 in the course of the NMR-monitoring experiment, as well as nitronate **1a** or cation **5a⁺** trapping by silyl ketene acetal in the second experiment.

In addition, evidence can be found in the literature[12] for the reversibility of interaction between imminium cations that have structures closely resembling those of intermediates **5⁺**, and amines.[13] Indirect evidence for the reversibility of formation of nitroso acetals **3** was observed in high-resolution mass-spectra with mild electrospray ionization (ESI). The main peaks obtained by this method correspond to cations with mass [(M + H) – amine **7**]$^{+}$ (cf. with cations **5⁺**), and their intensity can exceed the intensity of standard molecular ion peaks [M + H]$^{+}$ by several times (Figure 2).

The configuration of adduct **3a*** corresponds to the less hindered distal approach of silylamine **4a** to the respective dominant cation **5ᵃa⁺** (Scheme 3), which was realized earlier for C,C-coupling of the corresponding nitronate **1a** with π-nucleophiles.[4a] At the same time, the configuration of ad-



Scheme 5. Trapping of cation $\mathbf{5a}^+$ ($\mathbf{5}^{\mathbf{a}}\mathbf{a}^+$ or $\mathbf{5}^{\mathbf{b}}\mathbf{a}^+$) from intermediate nitroso acetals **3a*** and **3a′** on silylketene acetal.

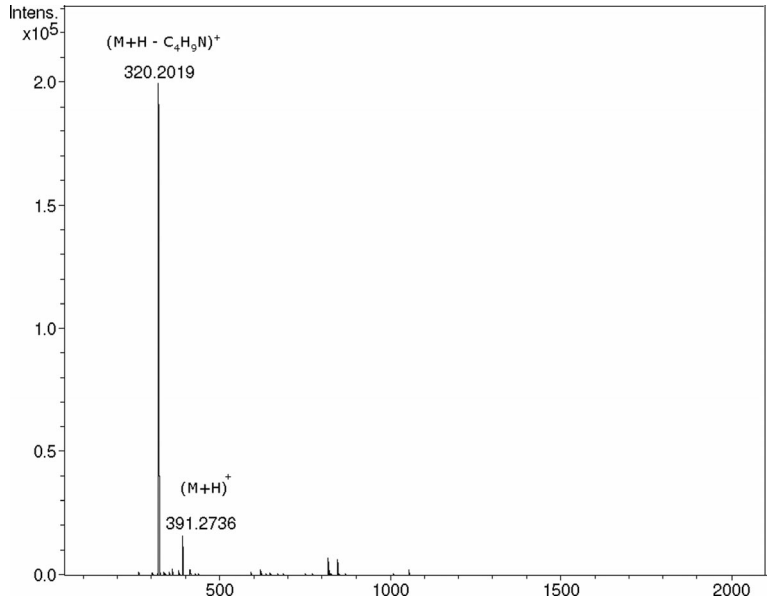
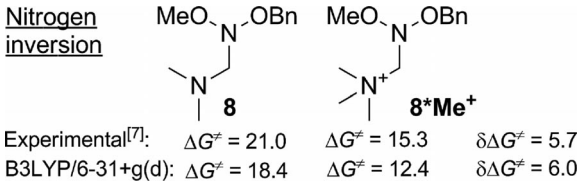


Figure 2. Fragment of high-resolution mass-spectra of nitroso acetal **3a** (ESI).

duct **3a′** corresponds to the most hindered proximal approach of **4a** to the same conformation of $\mathbf{5}^{\mathbf{a}}\mathbf{a}^+$.

The decrease in the nitrogen inversion barrier (see postulate 2 above) in aminals **3** is especially intriguing. For standard nitroso acetals, this barrier can exceed 25 kcal/mol;[9] however, in the performed NMR experiment (see Figure 1, spectrum c) the characteristic inversion can be observed even at temperatures below 20 °C. It is known[7] that "amine" nitrogen quaternization by transformation of neutral acyclic aminomethyl nitroso acetal **8** into methylated cation **8***Me$^+$ significantly decreases the nitrogen inversion barrier in ONO fragments (Scheme 6). It is therefore reasonable to suppose that, under C,N-coupling conditions, TBSOTf could reversibly silylate the exocyclic nitrogen atom in aminals **3**, which makes inversion of **3*** and **3′** easier.

DFT calculations [B3LYP/6-31+g(d)][14] of nitrogen inversion in **8** and **8***Me$^+$ in gaseous phase without considering counterion and solvent (see Scheme 6) are applicable at least for qualitative analysis of free energy values of this process. Indeed, the calculated value for the inversion barrier decrease [$\delta\Delta G^{\neq} = \Delta G^{\neq}(\mathbf{8}) - \Delta G^{\neq}(\mathbf{8}^*\mathrm{Me}^+) = 6.0$ kcal/mol] is in good agreement with experimental data (5.7 kcal/mol). Therefore, we can use this method for qualitative analysis of free energy decrease values of nitrogen inversion barriers of the endocyclic nitrogen atom in quaternized aminals **3**.



Scheme 6. Decrease in the nitrogen inversion barrier for known acyclic analogue **8** through amine quaternization. Energy is given in kcal/mol.

The calculation was carried out for four possible conformers of simplified ring-unsubstituted model nitroso acetal **3z**, which can undergo ring and endocyclic nitrogen inversions (Figure 3). Because ring inversion in the corre-

sponding oxazinanes had a much lower barrier (10–14 kcal/mol)[15] than endocyclic nitrogen inversion, we focused only on calculating the barrier to nitrogen inversion. Calculated nitrogen atom inversion barriers for **3z** ranged from 18.7 to 28.3 kcal/mol, depending on the starting conformation. The same calculations of barriers were also made for the corresponding protonated and silylated species **3z***H^+ and **3z***$SiMe_3^+$. In both cases, the activation energy decreased in the same way as **8***Me^+ ($\delta\Delta G^{\neq}$ = 7.0–10.0 kcal/mol for **3z***H^+ and $\delta\Delta G^{\neq}$ = 4.6–21.0 for **3z***$SiMe_3^+$).[16] Frequency analysis showed the vibrations corresponding to imaginary frequencies interacted with the neighboring amino group, which indicates a large contribution of *n*-σ* interactions. Summarizing the results of the calculation, it can be concluded that the presence of the leaving group at the C-3 atom in nitroso acetals **3** can lower the inversion barrier without dissociation.

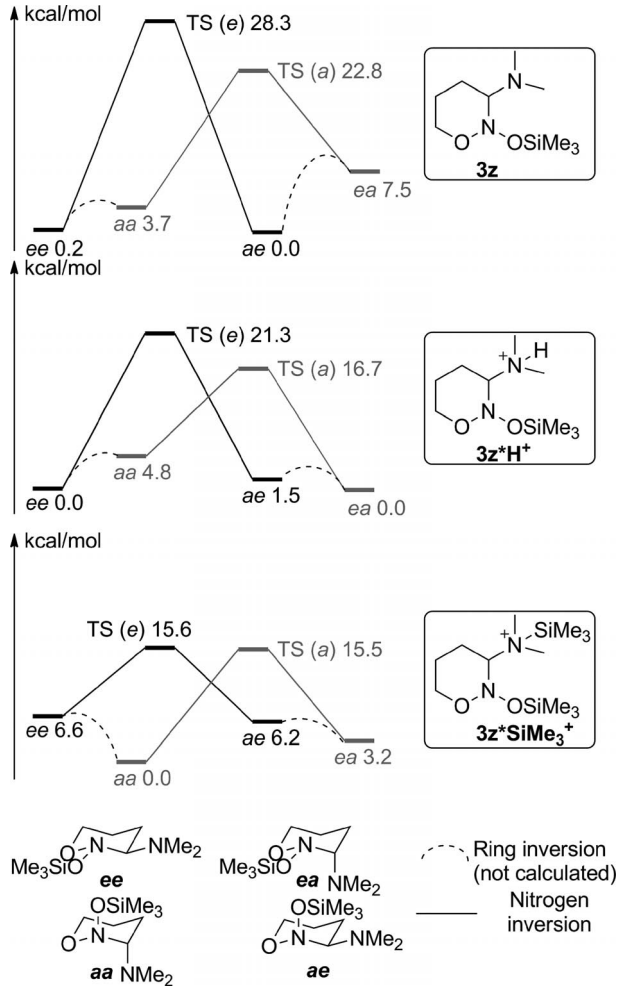
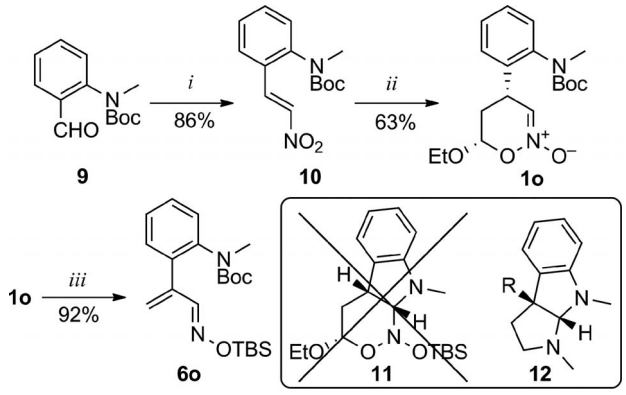


Figure 3. DFT calculations of endocyclic nitrogen inversion of nitroso acetal **3z**, its protonated and silylated derivatives **3z***H^+, and **3z***$SiMe_3^+$.

The results of the calculation suggest that an efficient way to fix intermediate isomers **3***, **3**#, and **3**′ is by neutralizing TBSOTf, which accelerates the establishment of equilibriums **3*** ⇆ **5** ⇆ **3**′, **3**′⇆ **3**, and **3*** ⇆ **3**#. Quenching of the C,N-coupling reaction of **1a** and **4a** with MeOH after 4–8 hours under standard conditions turned out to be ineffective because it left significant amounts of nitronate **1a** in the mixture. However, pyrrolidine **7a** itself can remove excess TBSOTf from the reaction mixture. Reaction of **1a** with 2.5 equivalents of pyrrolidine **7a**, performed with the minimum required amount of TBSOTf (1.02 equiv.) followed by neutral Al_2O_3 chromatography gave mixture of isomers **3***/**3**#/**3**′/**3** in 1:3:0:1 ratio and 70% yield.

Attempted Intramolecular Coupling

Intramolecular C,N-coupling between the nitronate function and the amino group was also investigated. Accomplishing this strategy could lead to alkaloids of type **12**, which are known cholinesterase inhibitors[17] (Scheme 7).



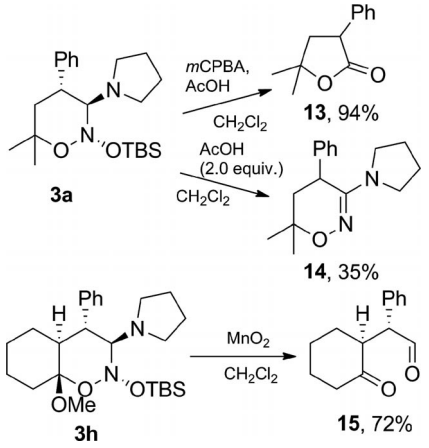
Scheme 7. Attempted intramolecular C,N-coupling. *Reagents and conditions:* (i) CH_3NO_2 (5.0 equiv.), NH_4OAc (5.0 equiv.), *i*PrOH, reflux, 3 h; (ii) [$TiCl_2(OiPr)_2$] (4.0 equiv.), ethyl vinyl ether (2.5 equiv.), CH_2Cl_2, –94 °C, 1 h; (iii) TBSOTf (1.5 equiv.), 2,6-lutidine (1.6 equiv.), CH_2Cl_2, –30 °C, 24 h.

To the best of our knowledge, no known synthetic approaches to nitronates **1** are compatible with a free amino group.[1,2a] Therefore we chose a strategy involving the synthesis of nitronate **1o** with an *N*-Boc-protected methylamino fragment (Scheme 7). It was supposed that deprotection of the amino group in nitronate **1o** would occur in situ under the action of TBSOTf. Nitronate **1o** was obtained with [$TiCl_2(OiPr)_2$] catalysis[2] from available aldehyde **9**[18] via nitrostyrene **10** (Scheme 7). Unfortunately, deprotection at the last stage failed. Attempted Boc-removal by TBSOTf treatment of nitronate **1o** led to almost quantitative formation of eneoxime **6o** instead of target nitroso acetal **11**. Under mild biphasic conditions [$HCl_{(aq.)}$/CH_2Cl_2] cleavage did not occur, and under homogeneous conditions (CF_3CO_2H in THF) initial nitronate **1o** was transformed into a mixture of unidentified products. It is interesting that nitroalkene **10** can be deprotected much easier; in the second step of the synthesis (Scheme 7, conditions ii) all unreacted **10** underwent Boc cleavage.

Selected Transformations of Nitroso Acetals 3

Whereas the chemistry of five-membered cyclic nitroso acetals – *N*-alkoxy- and *N*-silyloxyisoxazolidines – has been

quite well investigated,[1,9] their six-membered analogues **2** and **3** remain poorly studied. For several nitroso acetals **2**, only peracidic oxidation is known.[5] Under these conditions,[5] aminal **3a** was transformed into lactone **13** in almost quantitative yield (Scheme 8). Trialkylsilanol elimination under acidic conditions is one of the most explored reactions of five-membered nitroso acetals. For aminal **3a**, an analogous possibility was shown (**3a**→**14** under action of AcOH; Scheme 8) but still needs optimization. Furthermore, we were able to oxidize aminal **3h** to give dicarbonyl compound **15** under neutral conditions with active MnO_2.



Scheme 8. Selected transformations of aminals **3**.

Conclusions

The C,N-coupling of nitronates **1** with amines **7** and its silyl derivatives **4** has been accomplished and leads to the corresponding nitroso acetals **3**. DFT calculations and NMR spectroscopic monitoring of the C,N-coupling confirmed thermodynamic control of the reaction. Such control is achievable due to the reversibility of the addition and the decreased endocyclic nitrogen inversion barrier under the reaction conditions. Selected chemical transformations of products **3** were demonstrated.

Experimental Section

General Procedure A: To a stirred solution of nitronate **1** (1.00 mmol), 2,6-lutidine (29 μL, 27 mg, 0.25 mmol), and silylated amine **4** (1.10 mmol) in CH_2Cl_2 (5 mL) at –78 °C, was added TBSOTf (34 μL, 40 mg, 0.15 mmol). The reaction mixture was warmed to –30 °C in 30 min and kept for 24 h (unless otherwise mentioned) at this temperature (freezer) and was quenched with EtOH (15 μL, 12 mg, 0.25 mmol). The temperature was then allowed to reach ambient and the mixture was poured into a mixture of saturated aqueous $NaHCO_3$ (10 mL) and hexane (10 mL). The organic layer was separated and the aqueous layer was back-extracted with hexane (2× 5 mL). The combined organic layers were washed with brine (10 mL), dried with Na_2SO_4, and the solvents were evaporated in vacuo. The residue was subjected to column chromatography (silica gel; EtOAc/hexane, 1:20→1:10→1:5) to give target nitroso acetal **3**.

General Procedure B: To a stirred solution of nitronate **1** (1.00 mmol), 2,6-lutidine (122 μL, 112 mg, 1.05 mmol) in CH_2Cl_2 (5 mL) at –78 °C, was added TBSOTf (264 μL, 304 mg, 1.15 mmol). The mixture was stirred for 5 min and then amine **7** (1.05 mmol) was added rapidly at –78 °C. The reaction mixture was warmed to –30 °C and kept for 48 h at this temperature (freezer). The mixture was poured into a mixture of saturated aqueous $NaHCO_3$ (10 mL) and hexane (10 mL). The organic layer was separated and the aqueous layer was back-extracted with hexane (2× 5 mL). The combined organic layers were washed with brine (10 mL), dried with Na_2SO_4, and the solvents were evaporated in vacuo. The residue was subjected to column chromatography (silica gel; EtOAc/hexane, 1:20→1:10) to give target nitroso acetal **3**.

Typical Spectroscopic Data for Products 3

***rel*-(2*S*,3*S*,4*R*,4a*S*,8a*R*)-2-(*tert*-Butyldimethylsilyloxy)-8a-methoxy-4-phenyl-3-(pyrrolidin-1-yl)octahydro-2*H*-benzo[*e*][1,2]oxazine (3h):** Yield 326 mg (73%; method A); white flakes; m.p. 76–78 °C (pentane); TLC: R_f = 0.72 (EtOAc/hexane, 1:1; unstable on SiO_2). ^{1}H NMR (300.13 MHz, 303 K, $CDCl_3$, COSY): δ = 0.22 and 0.30 [2× s, 6 H, $Si(CH_3)_2$], 0.96 [s, 9 H, $C(CH_3)_3$], 0.98–1.18 [m, 2 H, CH_{2Cy}], 1.25–1.45 [m, 7 H, CH_{2Cy} (3 H), CH_{2Pyr} (4 H)], 1.51–1.62 [m, 2 H, CH_{2Cy}], 1.88 [ddd, $^3J \approx {}^3J$ = 11.7, ^3J = 3.3 Hz, 1 H, CH_{Cy}], 2.00 [br. d, $J \approx$ 10.6 Hz, 1 H, CH_{2Cy}], 2.69 and 2.99 [2× m, 4 H, CH_2N], 3.22 [dd, $^3J \approx {}^3J$ = 11.0 Hz, 1 H, CH(ax)Ph], 3.77 [s, 3 H, OCH_3], 4.01 [d, ^3J = 10.5 Hz, 1 H, NCH(ax)N], 7.14–7.30 [m, 5 H, Ph] ppm. ^{13}C NMR (75.47 MHz, 303 K, $CDCl_3$, HSQC): δ = –4.8 and –3.4 [$Si(CH_3)_2$], 17.6 [$C(CH_3)_3$], 22.2, 25.4, 26.0 and 30.3 (CH_{2Cy}), 24.6 (CH_{2Pyr}), 26.1 [$C(CH_3)_3$], 45.8 (*CH*Ph), 47.5 (CH_2N), 48.0 (OCH_3), 50.1 (CH_{Cy}), 87.8 (CHN), 101.1 (OCO), 126.0 and 127.9 ($CH_{o\text{-}Ph}$, $CH_{m\text{-}Ph}$ and $CH_{p\text{-}Ph}$), 141.0 ($C_{i\text{-}Ph}$) ppm. ^{29}Si NMR (59.63 MHz, 303 K, $CDCl_3$): δ = 26.41 ppm. $C_{25}H_{42}N_2O_3Si$ (446.70): calcd. C 67.22, H 9.48, N 6.27, Si 6.29; found C 67.12, H 9.41, N 6.10, Si 6.06.

***rel*-(2*S*,3*S*,4*R*)-2-(*tert*-Butyldimethylsilyloxy)-3-diethylamino-6,6-dimethyl-4-phenyl-[1,2]oxazinane (3m):** Yield 303 mg (77%; method B); colorless oil; TLC: R_f = 0.80 (EtOAc/hexane, 1:1). ^{1}H NMR (300.13 MHz, 300 K, $CDCl_3$): δ = 0.22 and 0.26 [2× s, 6 H, $Si(CH_3)_2$], 0.73 [t, ^3J = 7.3 Hz, 6 H, 2× CH_{3Et}], 0.96 [s, 9 H, $C(CH_3)_3$], 1.26 and 1.48 [2× s, 6 H, $C(CH_3)_2$], 1.75 [dd, ^2J = 13.2, ^3J = 5.1 Hz, 1 H, CH_2(eq)], 1.88 [dd, $^2J \approx {}^3J$ = 13.2 Hz, 1 H, CH_2(ax)], 2.66–2.86 [m, 4 H, $N(CH_2)_2$], 3.20 [ddd, $^3J \approx {}^3J$ = 12.4, ^3J = 5.1 Hz, 1 H, CH(ax)Ph], 3.77 [d, ^3J = 10.3 Hz, 1 H, NCH(ax)N], 7.15–7.38 [m, 5 H, Ph] ppm. ^{13}C NMR (75.47 MHz, 300 K, $CDCl_3$): δ = –4.7 and –3.1 [$Si(CH_3)_2$], 15.4 (CH_{3Et}), 17.8 [$C(CH_3)_3$], 23.6 and 29.1 [$C(CH_3)_2$], 26.2 [$C(CH_3)_3$], 43.4 (*C*HPh), 45.1 (CH_{2Et}), 46.1 (CH_2CH), 75.9 [$C(CH_3)_2$], 88.5 (CHN), 126.0 ($CH_{p\text{-}Ph}$), 127.0, 128.2 (CH_{Ph}), 143.5 ($C_{i\text{-}Ph}$) ppm. ^{29}Si NMR (59.63 MHz, 300 K, $CDCl_3$): δ = 27.22 ppm. HRMS (ESI): *m*/*z* calcd. for $C_{22}H_{40}N_2O_2Si + H^+$ 393.2932; found 393.2939. HRMS (ESI): *m*/*z* calcd. for $C_{18}H_{30}NO_2Si^+$ [M + H^+ – Et_2NH] 320.2035; found 320.2040.

X-ray Data: CCDC-932696 (for **3e**), -932518 (for **3f′**), and -932517 (for **3h**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): Experimental procedures for the synthesis of the initial compounds, physical constants and spectroscopic data for prepared compounds, the results of DFT calculations, and copies of ^{1}H, ^{13}C NMR spectra for all novel compounds.

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