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Remarkable temperature effect on intramolecular [3+2] cyclization

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ABSTRACT

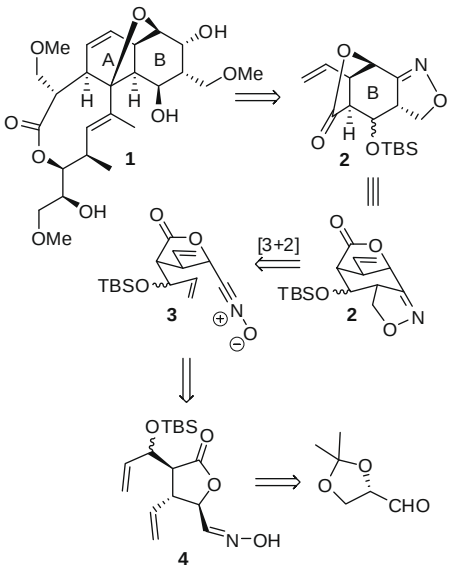
A preference of intramolecular cyclizations over oligomerization can often be achieved by conducting the reaction at higher temperatures. This effect which has obviously been underestimated so far may be useful in synthetic organic chemistry. Herein, we report a novel example supporting this observation—an intramolecular nitrile oxide 1,3-dipolar cycloaddition. The yield of the desired product rose from 53% at 0 °C to 79% at 80 °C. A plausible kinetic background of this phenomenon is proposed in terms of activation enthalpy.

The selectivity of a reaction (enantio-, diastereo-, regio-, chemoselectivity) carried out under kinetic control is often believed to increase with lower temperature and to decrease with higher temperature. Although this phenomenon is observed quite often, this behavior should not be taken for granted. Indeed, a literature survey reveals a number of examples when selectivity dramatically increased[1] and even the selectivity sense was inverted at higher temperatures.[2] Moreover, temperature dependence can have a rather complex character, for example, selectivity increases together with temperature, and after reaching a maximum starts decreasing, which is commonly attributed to a switch in a selectivity-determining step.[3]

As a part of an ongoing study toward the total synthesis of branimycin **1**,[4] we explored an approach based on the construction of carbocycle B via an intramolecular 1,3-dipolar cycloaddition of nitrile oxide **3**, derived from oxime **4** (Scheme 1).[4] Although the whole sequence to **4** was quite efficient, the key [3+2] cyclization proved problematic.

Initial attempts to perform a sequence of in situ chlorination (with *t*-BuOCl/Py or $NaClO/H_2O/DCM$)—nitrile oxide formation—cyclization (Scheme 2) resulted in only 25–35% yield of the desired product **2a, b**. Therefore, we decided to dissect this sequence into two independent steps: synthesis of chlorooxime **5a, b** and its conversion into oxazoline **2a, b**.

To this end, chlorooxime **5a, b** was synthesized by reaction of **4a, b** with NCS[5] (Scheme 2). The cyclization was then performed under a wide variety of conditions: bases (Et_3N, 2,2′,6,6′-tetramethylpiperidine, $NaHCO_3$, and MeMgCl); Lewis acids (Ag_2O, AgOTf + 2,6-di-*tert*-butylpyridine, and $LiClO_4$ + pyridine); combination of a weak base (2,6-di-*tert*-butyl pyridine) with a strong ionizing solvent (CF_3CH_2OH); and adsorbents such as Al_2O_3, SiO_2, 4 Å MS, and 3 Å MS. Surprisingly, in all cases the yield of product **2a, b** was in the same range of 25–35%. This fact suggested that constantly low yields



Scheme 1. Retrosynthesis of branimycin **1**.

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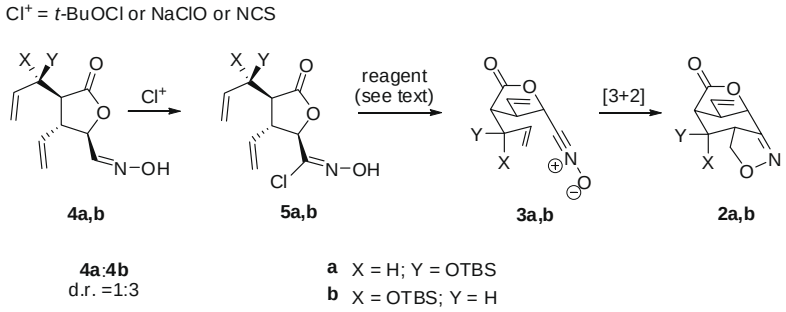

Scheme 2. Synthesis of oxazoline **2a**, **b** from oxime **4a**, **b**.

Table 1
Effect of the temperature on the reaction of **4a**, **b**[a] with NaClO to give **2a**, **b**

Concn (M)	Temp (°C)	Solvent	Yield[b]; dr **2b**:**2a**
1.5×10^{-2}	0	DCM	37%; 32:5 (31%; 28:3)
1.5×10^{-3}	0	DCM	53%; 46:7
1.5×10^{-3}	22	DCM or DCE	63%; 53:10
1.5×10^{-3}	40	DCM or DCE	70%; 59:11
1.5×10^{-3}	60	DCE	74%; 59:15
1.5×10^{-3}	80	DCE	76%; 60:16
0.8×10^{-3}	80	DCE	79%; 61:18 (75%; 60:15)

[a] **4b**:**4a** 75:25.
[b] Yields were estimated[7] from NMR using 4,4′-di-*tert*-butyl-biphenyl as an internal standard. Isolated yields and diastereoselectivity are given in parentheses. Yields are given for the mixture **2a** + **2b**.

under such different conditions could have a common origin. As there were no identifiable low molecular weight side products, we speculated that formation of nitrile oxide **3a**, **b** is not problematic, but that its intramolecular cyclization for some reasons is unfavorable and that **3a**,**b** could undergo intermolecular [3+2] cycloadditions instead, to form polymers.

For further optimization studies we decided to employ the simplest option—treatment of **4a, b** with NaClO in DCM/H_2O. Slow addition of the substrate to the reagent did not substantially improve the yield. In contrast, conducting the reaction simply under higher dilution (1.5×10^{-3} M) resulted in a significant increase of the yield (Table 1). Although we were encouraged by this result, it was not yet satisfactory; as further dilution seemed impractical for the synthesis of larger amounts of **2a, b**, we turned our attention to the above-mentioned temperature effect. To our delight, the yield of the cyclization product **2a, b** dramatically increased upon increase of the temperature (Table 1). Finally, when the reaction was carried out at 80 °C and at a slightly higher dilution (0.8×10^{-3} M), the desired product **2a, b** was isolated in 75% yield.[6]

The observed temperature effect could be rationalized by assuming that due to strain, activation enthalpy of intramolecular cyclization is higher than the activation enthalpy of intermolecular dimerization. Therefore, as follows from Eyring's equation,[8] a reaction with a higher activation enthalpy will be accelerated with increasing temperature more than a reaction with a lower activation enthalpy.

Although related effects were reported for a number of different reactions,[9] we are unaware of examples of intramolecular 1,3-dipolar cyclizations of nitrile oxides. Regarding the present work, this temperature effect was crucial for improving the intramolecular [3+2] cycloaddition to form **2a**, **b**, one of the key intermediates in our synthesis of branimycin.

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1. For example see: Ireland-Claisen rearrangement: (a) Watanabe, T.; Hirai, G.; Kato, M.; Hashizume, D.; Miyagi, T.; Sodeoka, M. *Org. Lett.* **2008**, *10*, 4167–4170; Radical allylation: (b) Sibi, M. P.; Rheault, T. R. *J. Am. Chem. Soc.* **2000**, *122*, 8873–8879; Carbonyl reduction with CBS: (c) Cho, T. R.; Chun, Y. S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2095–2100.
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6. *Procedure*: An aq solution of NaClO (available chlorine 10–13%; 50 mL) was heated to 80 °C and added at once to a solution of oximes **4a**, **b** (**4a**:**4b** = 3:1;51.1 mg, 0.157 mmol), which was preheated to 80 °C, in dichloroethane (100 mL). The mixture was vigorously stirred at 80 °C for 8 min and cooled to rt. The organic phase was separated and the water phase was extracted with dichloromethane (30 mL). The combined organic phases were washed with brine, passed through a plug of cotton, and solvents were removed in vacuo. The residue was purified by flash column chromatography (EtOAc/hexane) to give **2b** (30.6 mg, 60%) and **2a** (7.6 mg, 15%).*Compound* **2a**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.93–5.83 (m, 1H), 5.36–5.22 (m, 3H), 4.49–4.41 (m, 2H), 4.24 (dd, *J* = 8.0, 11.9 Hz, 1H), 3.68 (ddd, *J* = 5.2, 11.6, 11.6 Hz, 1H), 3.32 (d, *J* = 7.0 Hz, 1H), 2.87 (d, *J* = 4.7 Hz, 1H), 0.90 (s, 9H), 0.10 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 174.2, 154.9, 133.0, 119.0, 77.2, 68.7, 65.0, 52.5, 49.5, 47.1, 25.7, 18.2, −4.6, −5.0. HRMS (ESI): calcd for $C_{16}H_{25}NNaO_4Si$ [M+Na]$^+$ 346.1451; found: 346.1455.*Compound* **2b**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.92–5.82 (m, 1H), 5.35–5.23 (m, 3H), 4.02–3.96 (m, 2H), 3.64 (ddd, *J* = 7.8, 10.9, 11.8 Hz, 1H), 2.72 (d, *J* = 3.1 Hz, 1H), 2.66 (d, *J* = 6.8 Hz, 1H), 0.91 (s, 9H), 0.15 (s, 3H), 0.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 172.6, 156.2, 132.2, 119.4, 75.4, 74.3, 74.2, 54.3, 52.0, 50.1, 25.6, 18.0, −4.4, −4.7. HRMS (ESI): calcd for $C_{16}H_{25}NNaO_4Si$ [M+Na]$^+$ 346.1451; found: 346.1450.
7. Although absolute values of yields determined from NMR are obviously affected by a certain measurement error, the tendency of yields changes is apparent.
8. *Eyring's equation*:
$$k = \frac{k_b}{h} T e^{\left(\frac{-\Delta H^{\neq}}{RT}\right)} e^{\left(\frac{-\Delta S^{\neq}}{R}\right)} (c^o)^{1-n}$$
where *k* = reaction rate constant; k_B = Boltzmann's constant [$1.381 \cdot 10^{-23}$ J K^{-1}]; *T* = absolute temperatures in degrees Kelvin (*K*); *R* = gas constant [8.314 J K^{-1} mol^{-1}]; *h* = Plank constant [$6.626 \cdot 10^{-34}$ J s]; $\Delta H^{\neq}$ = activation enthalpy [J mol^{-1}]; $\Delta S^{\neq}$ = activation entropy [J K^{-1} mol^{-1}]; c^o = standard-state concentration [mol L^{-1}], *n* = molecularity of the reaction.
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