Microwave-Assisted Rearrangement of Vinylaziridines to 3-Pyrrolines: Formal Synthesis of (–)-Anisomycin

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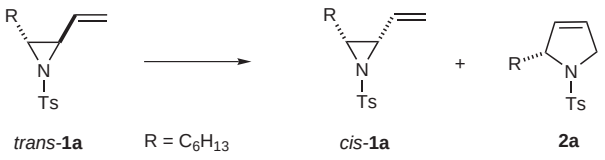
Abstract: An efficient microwave-assisted rearrangement of activated vinylaziridines to 3-pyrrolines is described. The rearrangement proceeds in good to excellent yields and is mediated by NaI or LiI in MeCN at elevated temperatures. The synthetic utility of this reaction is shown in an efficient formal total synthesis of the antibiotic (–)-anisomycin.

Key words: vinylaziridines, pyrrolines, rearrangement, ring expansion, total synthesis

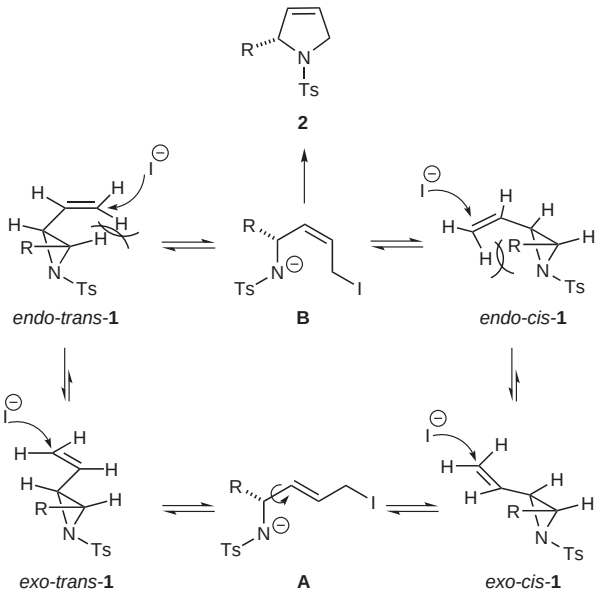
3-Pyrrolines are valuable intermediates in organic chemistry and have frequently been used in natural product synthesis.[1a–c] They also show diverse biological activities[1d–g] and a number of routes towards this important compound class have been developed.[2] A straightforward approach to the preparation of 3-pyrrolines involves the rearrangement of 2-vinylaziridines, a reaction that has been known for more than 35 years and successfully used in the synthesis of pyrrolizidin alkaloids.[3] However, most examples that have been published are limited in substrate scope and to date no general methodology has been developed. We thus decided to investigate this rearrangement in detail, and herein report our initial results.

Activated[4] *N*-Ts-2-vinylaziridines **1** were chosen as suitable starting materials, as the tosyl group was expected to facilitate the rearrangement (Scheme 1). Surprisingly, treatment of *trans*-**1a**[5] afforded less than 10% of the desired product **2a** and the main product was instead *cis*-**1a**.[6] This results from an equilibration of *trans*-**1a** to give the thermodynamically more stable *cis*-isomer.[7]



Scheme 1 *Reagents and conditions*: 8 equiv NaI, acetone, reflux, 48 h

The proposed mechanism for the rearrangement is depicted in Scheme 2, and starts with an S_N2' ring-opening of *trans*-**1**. Opening in the *exo-trans*-**1** conformation leads to intermediate **A** with *E*-configuration, whereas the thermodynamically less favored *endo-trans*-**1** conformation[8] will give the *Z*-configurated intermediate **B**. Only the latter intermediate can ring-close to the desired pyrroline **2**. Alternatively, **A** and **B** can reform the aziridine moiety, leading to the corresponding *cis*-isomer. However, without further mechanistical studies, an S_N2 mechanism for the formation of **2a** cannot be excluded.



Scheme 2 Proposed mechanism for the iodide-mediated equilibration of vinylaziridines *trans*-**1** and *cis*-**1** and the formation of pyrrolines **2**

The rearrangement conditions were subsequently optimized by variation of the solvent, additive and temperature, and the results are summarized in Table 1.

The use of DABCO and PPh_3, which are typical catalysts in the mechanistically related Baylis–Hillman reaction[9] proved to be less efficient than NaI in the rearrangement (entries 3, 4). In nucleophilic solvents such as MeOH and DMSO, the vinylaziridine underwent ring-opening or oxidation (entries 5, 6). The use of DMF led to the best conversion but also gave considerable amounts of unidentified by-products (entry 7). The best solvent proved to be MeCN since no by-product formation was observed (entry 8), but the results were still far away from satisfactory. We thus decided to perform the reaction under microwave irradiation, which often leads to strongly enhanced reaction rates and less by-products.[10] Pleasing-

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Table 1 Optimization of the Rearrangement of *Trans*-**1a**

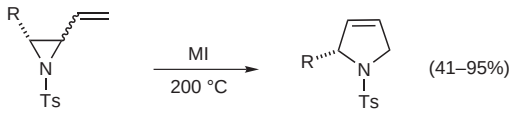
Entry	Additive (equiv)	Solvent	Temp. (°C)	Time (h)	Ratio of *trans*-**1a**:*cis*-**1a**:**2a**[a]
1	NaI (8)	Acetone	Reflux	48	4:88:8
2	NaI (8)	Acetone	100[b]	4	8:82:10
3	DABCO (1)	Toluene	180[b]	1	3:95:2
4	PPh_3 (1)	Acetone	Reflux	20	96:4:0
5	NaI (8)	MeOH	100[b]	15	–[d]
6	NaI (8)	DMSO	100[b]	15	–[d]
7	NaI (8)	DMF	100[b]	15	11:65:24
8	NaI (8)	MeCN	100[b]	15	8:83:9
9	NaI (2)	MeCN	160[c]	0.17	17:71:12
10	NaI (2)	MeCN	200[c]	0.33	0:0:100
11	LiI (2)	MeCN	200[c]	0.33	0:0:100

[a] Determined by ^{1}H NMR of the crude reaction product.[6]
[b] The reaction was performed in a sealed tube.
[c] The reaction was performed under microwave irradiation.
[d] By-products were formed.

ly, when **1a** was treated with NaI or LiI in acetonitrile under microwave irradiation (20 min, 200 °C),[11] full conversion was achieved (entries 10, 11) and **2a** could be obtained in 90% yield (Table 2, entry 1). Without a metal iodide, no reaction could be observed under the same conditions, demonstrating the high thermal stability of the substrate.

To verify the generality of the optimized reaction conditions, several variously substituted vinylaziridines **1b**–**g** were synthesized and successfully transformed into pyrrolines **2b**–**g** as summarized in Table 2.[12] Substrates **1c**–**e**,**g** were prepared as *cis*:*trans* mixtures from the corresponding aldehydes in two steps.[13]

Table 2 Microwave-Assisted Rearrangement of Vinylaziridines to 3-Pyrrolines[a]



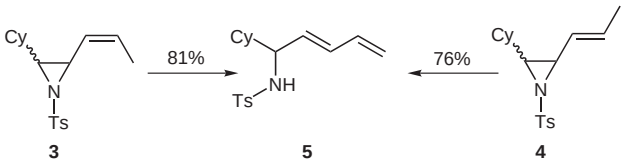
1a–g **2a–g**

Entry	**1**	R	*Cis*:*trans*[b]	MI	Time (min)	Yield (%)[c]
1	**a**	*n*-Hexyl	0:100	NaI	20	90
2	**a**	*n*-Hexyl	100:0	NaI	20	86
3	**b**	$BnOCH_2$	0:100	NaI	10	94
4	**c**	Cy	31:69	NaI	30	54
5	**c**	Cy	31:69	LiI	30	82
6	**d**	$Ph(CH_2)_2$	28:72	LiI	15	92
7	**e**	*t*-Bu	18:82	LiI	30	95
8	**f**	PMB	0:100	LiI	10	92
9	**g**	Ph	30:70	LiI	1	41

[a] Conditions: 2 equiv MI, MeCN, microwave, 200 °C.
[b] Isomeric ratio of the vinylaziridines determined by ^{1}H NMR.
[c] Isolated yields.

Gratifyingly, the reactions were found to proceed smoothly in good to excellent yields. Compound **1c** gave moderate yields with NaI, whereas LiI afforded **2c** in good yields (entries 4, 5). Vinylaziridine **1g** was the only exception, both in reaction time and yield (entry 9). The phenyl moiety in **1g** seems to increase the reactivity and decrease the selectivity of the substrate, affording several by-products.

The next aim was to study the reaction of vinylaziridines with an additional methyl substituent on the double bond. Applying the same reaction conditions as above it was hoped to obtain 2,5-disubstituted 3-pyrrolines. Disappointingly, both the *E*- and *Z*-substituted vinylaziridines **3** and **4**[13a] exclusively afforded the diene **5** (Scheme 3).



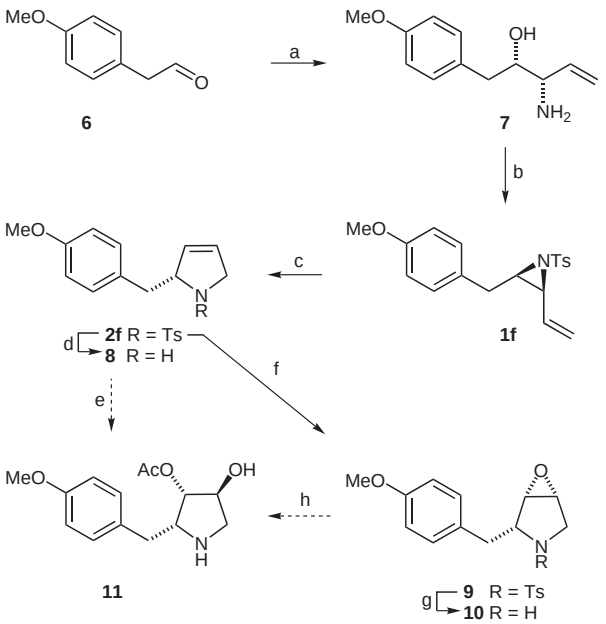
3 **5** **4**

Scheme 3 *Reagents and conditions*: 2 equiv LiI, MeCN, microwave, 200 °C, 1 min

To demonstrate the synthetic utility of the ring expansion described above, it has been applied in the formal synthesis of (–)-anisomycin (**11**), an antibiotic first isolated from two species of *Streptomyces*.[14a] Besides its antibacterial and fungicide activity, it also inhibits the ribosomal peptide synthesis and exhibits antiviral and antitumor activities.[14] Thus, much attention has been focused on the synthesis of anisomycin within the last 40 years and to date a vast number of routes have been published.[15] The methodology detailed in this report enables a new and straightforward synthesis of **11** (Scheme 4).

The sequence starts with a modified Brown allylation[16] of the commercially available aldehyde **6**, and successive aminolysis of the resulting chlorohydrine afforded amino alcohol **7** with excellent enantioselectivity.[17] Tosylation and ring-closure with KOH in THF afforded *cis*-vinylaziridine **1f**, which could be rearranged to pyrroline **2f** in excellent yield (Table 2, entry 9). Deprotection of **2f** afforded enantiopure secondary amine **8**,[18] which has been converted to *ent*-**11**.[15f] Alternatively, iodohydroxylation of pyrroline **2f** followed by basic work up afforded epoxide **9**, which was deprotected to **10**,[19] a known intermediate in the synthesis of **11**.[15g,h]

In conclusion, a convenient protocol for the formation of synthetically important 3-pyrrolines by a microwave-assisted rearrangement of 2-vinylaziridines has been developed. The reaction has successfully been applied in the formal synthesis of (–)-anisomycin.



Scheme 4 *Reagents and conditions*: a) i) allyl chloride (2.0 equiv), $LiNCy_2$ (2.0 equiv), (+)-Ipc_2BOMe (1.5 equiv), $BF_3{\cdot}OEt_2$ (2.5 equiv), –95 °C, 6 h, >95% ee; ii) MeOH, NH_4OH (25%), 130 °C, 10 min, 52% (over 2 steps); b) TsCl (5.0 equiv), KOH (10 equiv), THF, r.t.,18 h, 93%; c) see Table 2, entry 8; d) Na, naphthalene, THF, –78 °C, 84%; e) ref. 15f; f) NIS (3.0 equiv), $HClO_4$ (2 equiv), THF–H_2O (10:1), 1 h, then r.t., 1 h, 50%; g) MeOH, Mg, 5 h, 91%; h) ref. 15g

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(11) The microwave heating was performed with a Smith Creator single mode cavity from Personal Chemistry AB, Uppsala, Sweden, equipped with a magnetic stirrer and automatic temperature control..
(12) **General Procedure for the Preparation of 3-Pyrrolines. 2-*Tert*-butyl-1-tosyl-3-pyrroline (2e).**
A solution of 2-*tert*-butyl-1-tosyl-vinylaziridine (**1e**, 27.9 mg, 0.1 mmol, *cis*:*trans* = 18:82) and LiI (26.8 mg, 0.2 mmol) in dry MeCN (3 mL) was heated in the microwave cavity for 30 min at 200 °C. After the reaction, the solvent was removed in vacuo and the residue purified by flash chromatography (pentane–Et_2O, 10:1) to yield **2e** as a white solid (26.4 mg, 95%); mp 149–152 °C (dec). IR (neat): 2964, 1335, 1160 cm^{-1}. ^1H NMR (400.1 MHz, $CDCl_3$): δ = 7.67 (d, 2 H, *J* = 8.2 Hz), 7.25 (d, 2 H, *J* = 8.2 Hz), 5.64–5.56 (m, 2 H), 4.30 (m, 1 H), 4.12 (m, 1 H), 3.93 (m, 1 H), 2.40 (s, 3 H), 0.97 (s, 9 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 143.2, 134.8, 129.4, 128.8, 127.8, 126.5, 56.5, 36.8, 26.4, 21.5. MS (ESI): *m*/*z* = 280 $[M + H]^+$.
2-Phenethyl-1-tosyl-3-pyrroline (2d).
Colorless oil. IR (neat): 2924, 2864, 1342, 1163. ^1H NMR (400.1 MHz, $CDCl_3$): δ = 7.66 (d, 2 H, *J* = 8.3Hz), 7.34–7.16 (m, 7 H), 5.62 (m, 2 H), 4.50 (m, 1 H), 4.20–4.08 (m, 2 H), 2.75 (ddd, 1 H, *J* = 13.8, 9.6, 6.4 Hz), 2.59 (ddd, 1 H, *J* = 13.8, 9.9, 6.9 Hz), 2.41 (s, 3H), 2.17–2.03 (m, 2H). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 143.3, 141.6, 134.6, 129.6, 129.4, 128.4, 128.3, 127.4, 125.7, 125.0, 66.7, 55.7, 37.3, 30.7, 21.4. MS (ESI): *m*/*z* = 350 $[M + Na]^+$.
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(17) For ee determination, the chlorohydrine was converted to the corresponding vinylepoxide by treatment with 5 equiv DBU in CH_2Cl_2 (r.t., 12 h, 96%).[16b] The ee was shown to be >95% by chiral HPLC analysis (Chiracel OD, hexane–*i*-PrOH, 99.5:0.5, 0.5 mL/min).
(18) $[\alpha]_D^{25}$ –99.9 (*c* 1.20, THF) {lit: $[\alpha]_D^{25}$ –93.8 (*c* 0.485, THF);[15c] $[\alpha]_D^{25}$ –101.2 (*c* 1.44, THF);[15d] $[\alpha]_D^{25}$ –89.3 (*c* 1.26, THF)[15e]}.
(19) $[\alpha]_D^{25}$ –48.4 (*c* 0.37, CH_2Cl_2).