Pergamon

Tetrahedron Letters 39 (1998) 6551–6554

TETRAHEDRON LETTERS

Transannular Cyclizations of 10-Membered Lactams: An Easy Route to Isoquinoline Alkaloids

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Received 18 May 1998; accepted 30 June 1998

Abstract

Transannular cyclization of 10-membered ring lactams with hydriodic acid or fluoride gave tetrahydroprotoberberines or isoindolobenzazepines, respectively. The starting macrolactams were prepared by intramolecular addition of an aryl radical to a trimethylsilylacetylene.

Keywords: cyclization; isoquinolines; macrocycles; transannular reactions.

Isoquinoline alkaloids such as protoberberines and isoindolobenzazepines [1-5] can be synthesized by 10-*endo* radical macrocyclization followed by transannular cyclization of the intermediate 10-membered lactams. We have previously shown that radical macrocyclization of unsubstituted *o*-(trimethylsilylethynyl)benzamide **1a** proceeds with total regio- and stereoselectivity, affording lactam **2a** as a single geometric isomer of unknown stereochemistry [6]. In this paper we report further examples of this macrocyclization reaction and describe two new and highly efficient procedures for transannular cyclization of the resulting 10-membered lactams.

To evaluate the influence of substituents on the transannular cyclization, we prepared the substituted macrolactams **2b** and **2c** by the radical macrocyclization procedure [7],[1] isolating them both as a single geometric isomer of unknown stereochemistry (Scheme 1, Table 1).[2]

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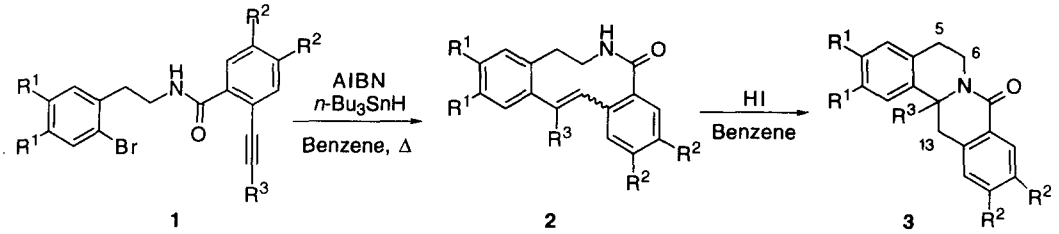
1 Benzamides **1b** and **1c** were easily prepared, in 80-90% yield, by chemoselective condensation of the corresponding *o*-iodo benzamides with trimethylsilylacetylene (1.1 eq) in Et_3N in the presence of CuI (0.05 eq) and $(Ph_3P)PdCl_2$ (0.05 eq). (see ref. 7)

2 All new compounds were fully characterized spectroscopically and had satisfactory elemental analysis or high-resolution mass spectroscopy data.

0040-4039/98/$ - see front matter
PII: S0040-4039(98)01363-X



1 2 3

Table 1

	R1	R2	R3	2 (yield)	3 (yield)
1a	H	H	SiMe3	**2a** (60%) (a)	**3a** (97%)
1b	MeO	H	SiMe3	**2b** (75%) (a)	**3b** (97%)
1c	H	MeO	SiMe3	**2c** (70%) (a)	**3c** (99%)
1d	MeO	H	H	*cis*-**2d** (47%)	**3d** (75%)
				trans-**2d** (24%)	**3d** (87%)

(a) one stereoisomer

Scheme 1

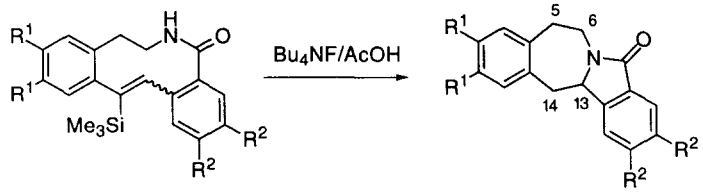
To determine the stereochemistry of lactams **2a-c** we attempted their stereospecific desilylation by the procedure described by Nozaki *et al* [8]. However, treatment of a benzene solution of macrolactam **2a** with 1 equiv of hydriodic acid (57% in water) at room temperature gave only unchanged starting material; and use of a large excess of hydriodic acid (57 equiv) in benzene at 80°C led unexpectedly to transannular cyclization, affording the tetrahydroprotoberberine **3a** exclusively in almost quantitative yield (Scheme 1, Table 1). This unexpected transannular cyclization can be explained by assuming initial protonation of the vinylsilane β to the silicon and subsequent formation of a carbocation at the α-position, followed by intramolecular *N*-alkylation. The more usual formation of a carbocation β to the silicon was probably disfavoured due to the presence of the amide carbonyl group of **2a**.

When macrolactam **2b** was treated with excess hydriodic acid under the same reaction conditions as **2a**, a complex mixture of products resulting from acid cleavage of the methoxy substituents was obtained. Under milder reaction conditions (10 equiv of hydriodic acid at 50°C), however, regioselective transannular cyclization took place, giving aza[6,6]bicycle **3b** in almost quantitative yield. The observed regiochemistry is fully in keeping with the presence of electron-donating methoxy groups on the aromatic ring of the phenethylamine moiety of **2b**, since these would be expected to promote protonation at the β-position of the vinylsilane group. By the same token, it was expected that the electron-donating substituents on the benzamide ring of **2c** would favour α-protonation of the vinylsilane moiety and thus formation of an aza[7,5]bicycle after internal *N*-alkylation β to the silicon. However, treatment of **2c** with hydriodic acid under the same conditions as **2b** gave a quantitative yield of the tetrahydroprotoberberine **3c**. Thus transannular cyclization

would appear not to be influenced by the electron richness of the aromatic rings present in the lactam.[3]

Next we examined the influence of the trimethylsilyl substituent and the geometry of the olefin on the transannular cyclization by subjecting *cis*- and *trans*-stilbenoid lactams **2d**[4] to treatment with hydriodic acid. In both cases, regioselective formation of a [6,6] bicycle took place, affording tetrahydroprotoberberine **3d** [9][5] as the only product in 75 and 87% yield from *cis*-**2d** and *trans*-**2d**, respectively. It would therefore seem that regioselective formation of the intermediate carbocation is not dependent on the presence of a trimethylsilyl group in macrolactams **2** and is independent of the geometry of the double bond. Rather, the regioselectivity of the protonation seems to be determined by the electrostatic influence exerted by the amide carbonyl on the benzylic position *ortho* to it, which appears to disfavour formation of a carbocation at this benzylic position.

In a further effort to desilylate macrolactams **2** stereospecifically, we next tried the reaction conditions recently described by Carreira [10]. Surprisingly, treatment of solutions of **2b** and **2c** in THF at room temperature with Bu4NF (1.1 equiv) buffered with glacial acetic acid (0.5 equiv) gave quantitative yields of isoindolobenzazepines **4b**[6] and **4c**, respectively (Scheme 2).



2b, R^1= OMe, R^2= H
2c, R^1= H, R^2= OMe

4b, R^1= OMe, R^2= H
4c, R^1= H, R^2= OMe

Scheme 2

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3 PM3 semiempirical calculations (as implemented by MacSpartan Plus 1.1.6, Wavefunction, 1996) show that, regardless of the geometries of the double bond and the amide, the stilbene moiety of macrolactams **2** is not in the plane of the aryl rings, which could explain the absence of any electronic effects.

4 *Cis*- and *trans*-macrolactams **2d** were prepared by desilylation of **1b** with K_2CO_3 (0.05 equiv) in MeOH at room temperature, which gave benzamide **1d** in 95% yield, followed by radical macrocyclization, performed by slow dropwise addition of a benzene solution of *n*-Bu_3SnH (2.1 equiv) and AIBN (20% by weight) to a refluxing benzene solution of **1d**. After chromatography, macrolactams *cis*-**2d** and *trans*-**2d** were isolated in 47% and 24% yield, respectively.

5 ^{1}H NMR (250 MHz, $CDCl_3$) δ: 2.74-3.03 [m, 4H, H–5 (2) + H–6 (1) + H–13 (1)], 3.22 (dd, *J*= 3.7, 15.7 Hz, 1H, H–13), 3.89 (s, 3H, OC*H*$_3$), 3.91 (s, 3H, OC*H*$_3$), 4.86 (dd, *J*= 3.7, 13.3 Hz, 1H, H–14), 4.97-5.02 (m, 1H, H–6), 6.69 (s, 1H, Ar*H*), 6.72 (s, 1H, Ar*H*), 7.24-7.27 (m, 1H, Ar*H*), 7.35-7.49 (m, 2H, Ar*H*), 8.14 (dd, *J*= 1.4, 7.6 Hz, 1H, Ar*H*). ^{13}C NMR and DEPT (75.48 MHz, $CDCl_3$) δ: 29.2 (*C*H$_2$), 38.1 (*C*H$_2$), 38.7 (*C*H$_2$), 55.0 (*C*H), 55.9 (O*C*H$_3$), 56.1 (O*C*H$_3$), 108.8 (*C*H), 111.4 (*C*H), 126.8 (*C*H), 127.2 (*C*), 127.3 (*C*H), 127.6 (*C*), 128.6 (*C*H), 129.1 (*C*), 131.8 (*C*H), 137.3 (*C*), 147.9 (*C*), 148.0 (*C*), 164.6 (*C*=O).

6 ^{1}H NMR (250 MHz, $CDCl_3$) δ: 2.81-3.08 [m, 4H, H–5 (2) + H–6 (1) + H–14 (1)], 3.21 (dd, *J*= 1.0, 14.7 Hz, 1H, H–14), 3.90 (s, 3H, OC*H*$_3$), 3.92 (s, 3H, OC*H*$_3$), 4.44 (dd, *J*= 1.0, 9.7 Hz, 1H, H–13), 4.77-4.83 (m, 1H, H–6), 6.75 (s, 1H, Ar*H*), 6.83 (s, 1H, Ar*H*), 7.46-7.60 (m, 3H, Ar*H*), 7.88 (d, *J*= 7.4 Hz, 1H, Ar*H*). ^{13}C NMR and DEPT (62.83 MHz, $CDCl_3$) δ: 35.9 (*C*H$_2$), 41.4 (*C*H$_2$), 42.2 (*C*H$_2$), 56.0 (O*C*H$_3$), 56.1 (O*C*H$_3$), 61.3(*C*H), 113.6 (*C*H), 113.8 (*C*H), 122.0 (*C*H), 123.8 (*C*H), 128.4 (*C*H), 129.7 (*C*), 131.5 (*C*H), 132.0 (*C*), 133.7 (*C*), 144.8 (*C*), 147.3 (*C*), 147.6 (*C*), 167.1 (*C*=O).

This change to a regioselective [7,5] transannular cyclization was attributed to the fluoride's having promoted nucleophilic attack of the β-position of the vinylsilane moiety by the amide nitrogen, followed by desilylation. Initial fluoride-mediated desilylation was ruled out by the observation that NaH-promoted anionic cyclization of macrolactams *cis*- and *trans*-**2d** (1.1 equiv NaH in DMF at room temperature) afforded a 1:1 mixture of protoberberine **3d** and isoindolobenzazepine **4b**, which suggests that the presence of the silyl substituent is crucial for this [7,5] transannular cyclization.

In summary, regioselective transannular cyclization of 10-membered lactams constitutes a new, facile route to tetrahydroprotoberberine and isoindolobenzazepine alkaloids. Application of this methodology to the synthesis of isoquinoline alkaloids is ongoing.

Acknowledgements.
We thank the Dirección General de Enseñanza Superior (Project PB95-0824) and the Xunta de Galicia (Project XUGA20907-B96) for financial support. G. Rodríguez thanks the Xunta de Galicia for a predoctoral fellowship.

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