STEREOCHEMICAL EFFECTS IN THE EFFICIENT CYCLISATION OF *N*-(1-CYANO-3-METHOXYBUT-3-ENYL)-4-PHENYLOXAZOLIDINE

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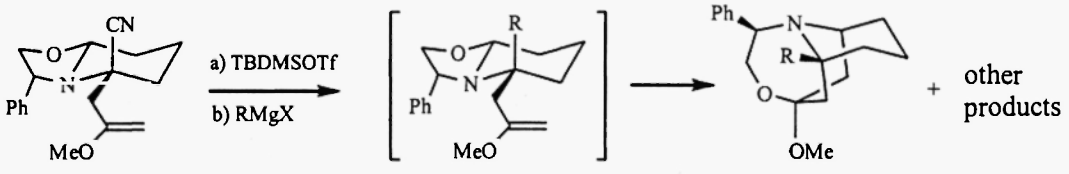
Abstract. The title compound was prepared in two diastereomeric forms and cyclised efficiently with boron trifluoride to give three stereoisomers of a hetero-bicyclic structure; the stereochemical profile of the reaction is explained in terms of configuration-dependent conformational preferences.

In previous work from this laboratory dealing with substituted oxazolopiperidines,[1] it was discovered that the sequential treatment of structures **1** with *tert*-butyldimethylsilyl triflate (TBDMSOTf) then a Grignard reagent led to the formation of mixtures of products, including the unusual heterocyclic structures **2** (Scheme 1).[2,3] Yields were not high, and varied with the size of the R substituent, reaching 50% at best with the smallest R group (methyl).



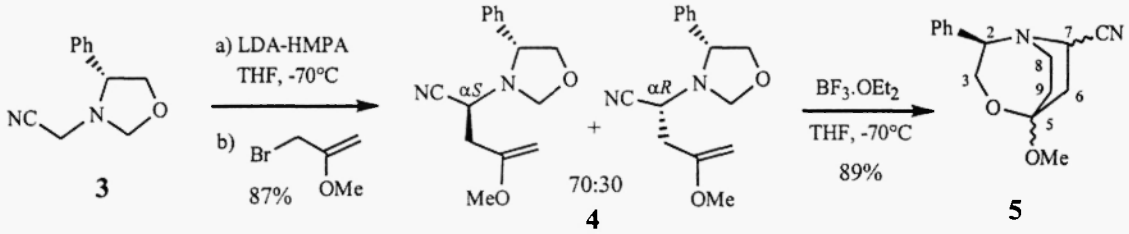
1 **2**

Scheme 1

We know of only one other comparable example of the formation of this unusual heterocyclic system,[4] and in order to obtain further insight into the cyclisation reaction, and hopefully increase the yield, we decided to study a simpler version of the combined aminonitrile-oxazolidine system, which had less steric restriction and retained the nitrile as an ideally-small R substituent. In this communication, we disclose an improvement in the reaction efficiency and an interesting stereoselection process during the cyclisation.

The (*R*)-*N*-cyanomethyl-4-phenyloxazolidine synthon **3**[5] was used as starting material (Scheme 2). Deprotonation (LDA-HMPA) then alkylation with 2-methoxyallyl bromide[6] gave the expected product **4** as an oil in typically good yield (87%) and as a mixture of diastereomers (αS:αR = 70:30),[7,8] but unfortunately the two isomers were totally inseparable by chromatography. We therefore decided to use **4** as a mixture for the cyclisation study.

The key step required an oxophilic Lewis acid, which would not induce decyanation (in contrast with TBDMSOTf). We selected boron trifluoride etherate, and when the **4** mixture was treated with one equivalent of this reagent in THF at −70 °C (optimised conditions), the cyclisation reaction occurred smoothly to give the heterocyclic structure **5** as an oil in excellent yield (89%) (Scheme 2).



Scheme 2

It was rather surprising, however, to observe that only three of the possible four stereoisomers of **5** were formed, in an approximate ratio of 1:1:1. We looked into this phenomenon in detail. Chromatographic separation of isomers on silica gel was very difficult, but by careful selection of fractions (eluent: EtOAc/cyclohexane, 20/80; R_f range 0.36-0.42), we obtained samples having differential enrichments, and were thus able to deduce the ^{1}H and ^{13}C NMR spectral signals for all atoms in all three isomers (Table).

Models suggested that the piperidine moiety was in a twist-boat configuration and the key evidence for structure determination was long-range "W" coupling. In all three isomers, the equatorial H9 and H6 protons were coupled, while only **5a** and **5b** showed coupling of equatorial H8 with the methine H7, making this latter equatorial in these two isomers. Differentiation between **5a** and **5b** was made by comparison of H7 chemical shift values: this proton is at higher field in **5b** than in **5a**, since it is shielded by the anisotropic cone of the neighbouring phenyl group. A similar effect explains the higher field shift of H8(eq) in **5a** than in **5b**.

These attributions being made, the third isomer was attributed the structure **5c**, consistent with the high-field shift of H8(eq). This implies that **5a** and **5c** are epimers at C7, which we

confirmed experimentally: treatment of the original **5**-mixture (1:1:1) with strong base (LDA-HMPA, THF, −70 °C, then NH_4Cl soln.) gave a 2:1 mixture of **5a** and **5b** respectively.

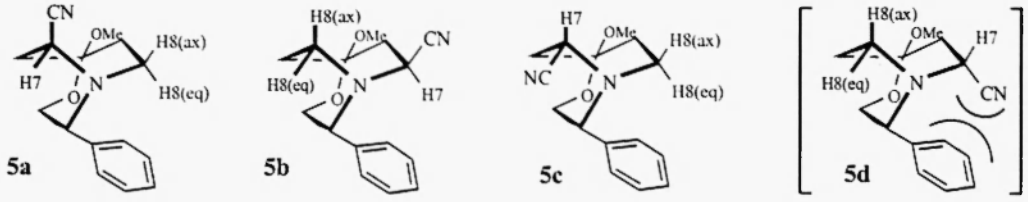


Table ^1H and ^{13}C NMR data and attributions for stereoisomers of **5**.[a]

atom	5a	5b	5c	atom	5a	5b	5c
H2	4.17 dd (10.7, 5.5)	4.20 dd (7.3, 5.2)	4.59 dd (10.3, 4.6)	C2	69.2	67.6	62.7
H3a	3.95 dd (12.7, 10.7)	3.89 dd (13.3, 7.3)	3.94 dd (13.0, 10.3)	C3	66.7	65.5	64.9
H3b	4.46 dd (12.8, 5.5)	4.36 dd (13.3, 5.1)	4.32 dd (13.0, 4.7)	C5	100.4	100.0	99.2
H6(ax)	2.10 dd (13.5, 7.1)	2.01 dd (14.2, 5.7)	2.34 dd (13.8, 9.8)	C6	39.8	36.1	40.5
H6(eq)	2.69† ddd (13.5, 10.3, 3.4)	2.60† ddd (14.2, 10.7, 3.6)	2.61† ddd (13.8, 7.3, 3.3)	C7	51.8	42.5	48.5
H7	[4.32]¶	4.03¶ ddd (10.6, 5.6, 2.1)	4.23 dd (9.8, 7.4)	C8	37.3	45.0	41.4
H8(ax)	[3.28]	3.72 ddd (15.1, 10.2, 5.6)	3.18 ddd (14.9, 10.7, 5.2)	C9	29.7	32.9	28.9
H8(eq)	3.02¶ dddd (15.4, 10.5, 3.2, 2.1)	[3.25]¶	2.94 ddd (14.9, 10.9, 4.5)	CH_3	48.5	48.6	48.7
H9(ax)	1.73 ddd (14.2, 10.5, 3.3)	1.94 ddd (13.9, 10.2, 4.3)	1.69 ddd (14.3, 10.9, 5.2)	CN	120.5	120.3	119.6
H9(eq)	[2.43]†	[2.47]†	[2.36]†	Ph	126.5,	127.0,	126.9,
CH_3	3.32 s	3.34 s	3.35 s		127.5,	127.9,	127.5,
Ph	7.3-7.4 m	7.3-7.4 m	7.3-7.4 m		128.6,	129.0,	128.7,
					138.1	138.2	138.5

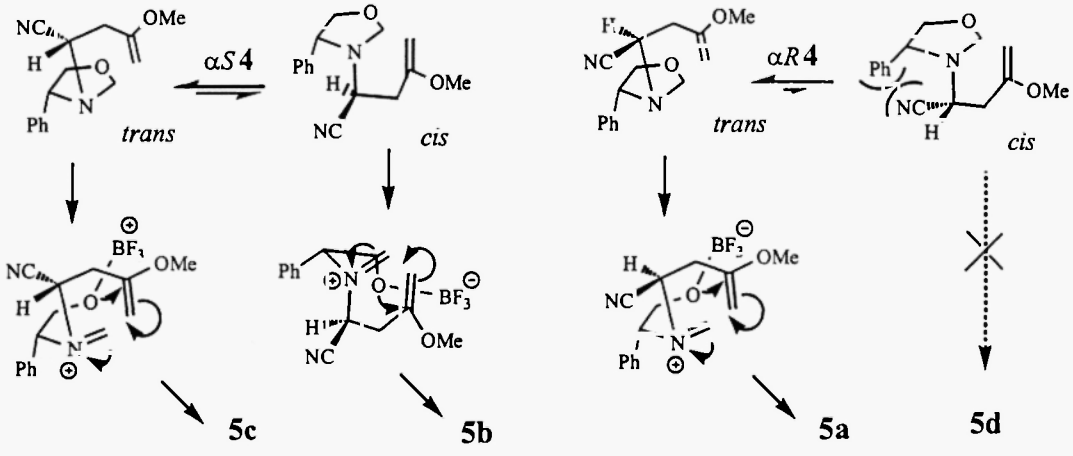
a: ^1H shifts are followed by multiplicity with measured coupling constants in parentheses. Obscured signals in square brackets are deduced from 1D integration and 2D coupling data. Within columns, long-range coupling (constant underlined) is detected between paired signals marked † or ¶.

From these results, and in the knowledge of the isomeric ratios in both starting material and product, it was deduced that from the major α*S* isomer of **4** there had been obtained a 1:1 mixture of **5b** and **5c**, while the minor α*R* isomer of **4** had cyclised to give exclusively **5a**. This stereoselectivity was intriguing, particularly since the only isomer which did not form, **5d**, has precisely the configuration which had been observed in the prototype rigid example, *i.e.* **1** → **2** (Scheme 1).

It may be that a simple thermodynamic product control operates, since examination of models suggests that **5d** is indeed the least favourable of the four stereoisomers of **5** due to steric repulsion between the nitrile and phenyl groups. However, it is possible that conformation effects in the isomers of starting material **4** may dictate the cyclisation reaction profile (Scheme 3). In the

αS isomer, both *cis* and *trans* relative configurations appear to be accessible, and should lead to **5b** and **5c**, respectively. In contrast, the αR configuration renders a *cis* conformer unfavourable, due to steric repulsion of nitrile and phenyl groups, leaving only the *trans* conformer which gives **5a** on cyclisation. This hypothesis is consistent with similar conformational effects which were suggested very recently to have a dramatic influence on the reactivity of other derivatives of **3** with Grignard reagents.[9]

In conclusion, this Lewis-acid mediated cyclisation reaction is shown to be efficient and highly sensitive to stereochemical effects. It may turn out to have some general synthetic usefulness, since the heterocyclic product is effectively a chiral piperidone acetal.



Scheme 3

References

1 For a review, see: H.-P. Husson, J. Royer, In A. Dondoni (Ed.), *Advances in the Use of Synthons in Organic Chemistry*, Vol. 2, JAI Press, Greenwich, 1995, pp. 1

2 C. Yue, J. Royer, H.-P. Husson, *J. Org. Chem.*, **57**, 4211 (1992)

3 C. Yue, J.-F. Nicolay, J. Royer, H.-P. Husson, *Tetrahedron*, **50**, 3139 (1994)

4 G.V. Pshenichnyi, Y.D. Huang, V.A. Mashenkov, L.S. Stanishevskii, *Khim. Geterotsikl. Soedin.*, 704 (1989)

5 For leading references on previous work with this synthon, see: M. Le Bail, J. Perard, D.J. Aitken, H.-P. Husson, *Tetrahedron Lett.*, **38**, 7177 (1997)

6 R.M. Jacobson, R.A. Raths, J.H. McDonald, *J. Org. Chem.*, **42**, 2545 (1977)

7 L. Besson, M. Le Bail, D.J. Aitken, H.-P. Husson, F. Rose-Munch, E. Rose, *Tetrahedron Lett.*, **37**, 3307 (1996)

8 NMR spectral data for the major diastereomer αS-4 (in $CDCl_3$) δ_H: 2.51 (2H, d, J = 8.1 Hz), 3.50 (3H, s), 3.68 (1H, t, J = 8.0 Hz), 3.98 (1H, t, J = 8.0 Hz), 4.00-4.07 (3H, m), 4.30 (1H, t, J = 8.0 Hz), 4.51 (1H, d, J = 2.3 Hz), 4.85 (1H, d, J = 2.3 Hz), 7.32-7.40 (5H, m); δ_C: 38.5 (t), 49.2 (d), 54.8 (q), 65.3 (d), 74.3 (t), 82.2 (t), 84.4 (t), 116.6 (s), 127.6 (d), 128.3 (d), 128.7 (d), 137.3 (s), 157.4 (s).

9 M. Le Bail, J. Perard, D.J. Aitken, H.-P. Husson, *Tetrahedron Lett.*, **40**, 5309 (1999)

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