Synthesis of a 5-oxo-2-Tetrahydrofuranyl Derivative of an Evans Auxiliary via a Novel Reaction Induced by Nucleophiles

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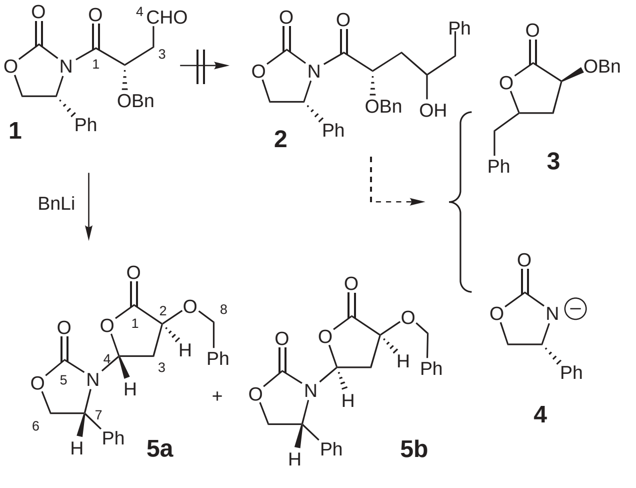
Abstract: A 5-oxo-2-tetrahydrofuranyl derivative of an Evans auxiliary could be obtained through a previously unknown ‘rearrangement’ of the oxazolidinone moiety in an α-benzoxy-γ-aldehyde acyl oxazolidinone in 60–97% yields on treatment with a range of nucleophiles.

Key words: chiral auxiliaries, rearrangements, lactones, ring closure, tandem reactions

In an on-going synthetic project, we needed to attach a benzyl group to the aldehyde carbonyl in compound **1** to form either **2** or **3** (Scheme 1). Using 1 equivalent of $PhCH_2Li$[1] to execute this intended conversion in anhydrous THF at –78 °C led to the formation of two compounds in 60–66% total yield, along with ca. 40% of the oxazolidinone auxiliary (**4**-H^+). Very careful following up the reaction with TLC revealed that the reaction proceeded extremely fast (finished within 3 min at –78 °C). The ^1H NMR spectra showed that both compounds contained only two phenyl groups, suggesting a lactonization might have already occurred in situ. The presence of lactone functionality in these compounds was also supported by an intense peak at around 1764 cm^{-1} in the FT-IR spectra. However, the MS spectra did not seem to be compatible with the structure of **3**.



Scheme 1

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Careful analysis of the ^1H NMR and ^{13}C NMR, DEPT, COSY and HMQC spectra along with the data of the elemental analysis (which gave a molecular formula of $C_{20}H_{19}NO_5$) led to assignment of the structure as **5a**,[2] which was also confirmed[3] by single crystal X-ray crystallography (Figure 1). By comparing the spectra, another product[4] was easily assigned as the C-4 epimer **5b**. Thus, instead of the intended benzylation at the aldehyde carbonyl, the reaction actually occurred was a ‘rearrangement’ of the oxazolidinone auxiliary from the acyl to the aldehyde carbon accompanied by a lactonization.

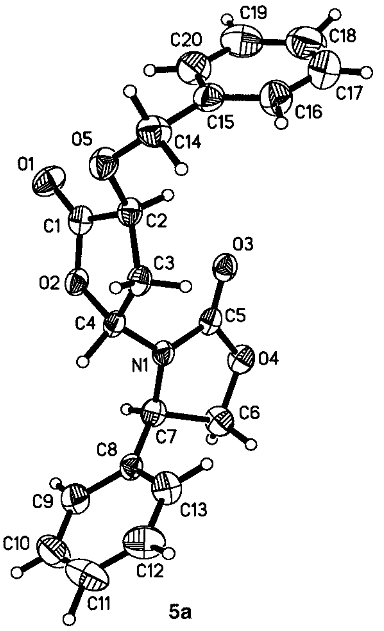


Figure 1 The ORTEP view of **5a**

Formation of **5a**/**5b** is definitely not a predictable outcome and we are unable to find any similar literature precedents, in spite of the fact that oxazolidinones has been extensively[5] employed in synthesis since the 1980’s and that much about oxazolidinone chemistry is well known. According to the existing chemistry knowledge one would well expect that the non-hindered free aldehyde carbonyl in **1** reacts preferentially with $PhCH_2Li$ rather than **4**.

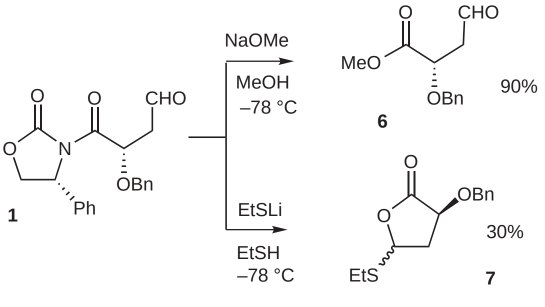
The nitrogen atom in the oxazolidinone is an imido one (strongly electron-deficient). It does not seem possible for this nitrogen to attack the aldehyde before the acyl (C-1)

Table 1 The Main Results of Reaction of **1** with Nucleophiles

Nucleophile (Nu)	Solvent	Nu/**1** (molar ratio)	Temp/time	Product [yield (%)]
$PhCH_2Li$	Toluene/THF	1:1	–78 °C/5 min	**5a** and **5b** (66)
$PhCH_2ZnBr$	THF	1.5:1	0 °C/2 h	**5a** and **5b** (80)
$PhCH_2ZnBr$	THF	6:1	0 °C /2 h	**5a** and **5b** (60)
2-Bn-1,3-dithian-2-Li	THF	1:1	–78 °C /10 min	**5a** and **5b** (66)
4-Li	THF	1:1	–78 °C/10 min	**5a** and **5b** (97)
Et_2Zn	THF	5:8	–78 °C /50 min	**5a** and **5b** (84)
MeONa	THF	1:1	–78 °C to –30 °C /2 h	**5a** and **5b** (86)
MeONa	THF (and 10 equiv MeOH)	1:1	–78 °C /30 min	**6** (90)
EtSLi	THF (and 10 equiv EtSH)	1:1	–78 °C /30 min	**7** (30)
KCN	THF	6:7	r.t./1 h	**5a** and **5b** (72)

is cleaved. Treatment of **1** with anhydrous $ZnBr_2$ (1 equiv) in dry THF at 0 ºC for hours did not result in any reaction at all. It appeared that **5a**/**5b** must form through an initial nucleophilic addition of **4** to the aldehyde carbonyl group followed by an intramolecular attack of the resulting alkoxide at the C-1, with the chiral auxiliary leaving as an anion ready for attacking another aldehyde. Reaction of added **4** (either 1 or 0.1 equivalents) with **1** in anhydrous THF at –78 ºC for 30 min indeed led to **5a**/**5b** in 97% yield.

We also tested some weaker nucleophiles on **1** and the main results are listed in Table 1. For instance, reaction with $PhCH_2ZnBr$[6] (THF/0 °C/2 h) gave **5a**/**5b** in 80% total yield (again as observed with $PhCH_2Li$, with more than half being **5a**). More or less the same results were also obtained with Et_2Zn.



Scheme 2

Addition of powdered NaOMe (1 equiv) to **1** in dry THF at –78 ºC did not result in any reaction after a few hours stirring. Raising the temperature from –78 ºC to –30 ºC over 2 hours, however, afforded **5a**/**5b** in 86% total yield. The ratio between **5a** and **5b** in this case was inverted, with more than half being **5b** instead of **5a** as observed with e.g. $PhCH_2Li$ at –78 ºC. Presence of MeOH in the reaction mixture obviously altered the reaction course (with all **1** fully consumed), giving[7] unstable methyl ester **6** in 90% yield but no traces of **5a**/**5b**.

Similarly, treatment of **1** in dry THF with EtSLi in the presence of EtSH (also an acidic proton source) at –78 ºC for 30 minutes did not afford any **5a**/**5b** at all although all the starting **1** disappeared. The only isolable component in the product mixture was **7** (in ca. 30% yield as a mixture of two epimers, Scheme 2). The remainder consisted of a number of minor components of low polarity that were very difficult to separate from each other. Finally, KCN (1 equivalent) in anhydrous THF could also induce the rearrangement. Although at temperatures below 0 ºC no reaction occurred, stirring at 20 ºC for 1 hour afforded **5a**/**5b** in 72% yield (along with 18% of recovered ozaxolidinone **4**-H^+).

In brief, on treatment with a proper nucleophile, the chiral auxiliary in **1** may migrate from the acyl carbon to the aldehyde one, leading to a 5-oxo-2-tetrahydrofuranyl derivative of an Evans auxiliary and thus illustrating a previously unknown reaction for the oxazolidinones.

Acknowledgment

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References

(1) Fuber, M.; Herbert, J. M.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **1989**, 683.

(2) Data for **5a**: A white solid, mp 107–109 °C; $[\alpha]_D^{15}$ –190.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50–7.20 (m, 10 H, aromat), 5.34 (dd, *J* = 9.0, 3.3 Hz, 1 H, H-2), 5.03 (t, *J* = 8.9 Hz, 1 H, H-7), 4.94 (d, *J* = 11.2 Hz, 1 H, H-8), 4.65 (d, *J* = 11.4 Hz, 1 H, H-8), 4.64–4.58 (m, 2 H, H-4 and H-6), 4.13 (t, *J* = 9.1 Hz, 1 H, H-6), 3.08 (ddd, *J* = 3.2, 8.6, 14.1

Hz, 1 H, H-3), 2.38 (ddd, J = 6.5, 8.9, 14.7 Hz, 1 H, H-3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.96 (C-1), 156.41 (C-5), 136.86 (q, aromat), 135.83 (q, aromat), 129.70, (aromat, CH), 129.57 (2 C, aromat), 128.42 (2 C, aromat), 128.08 (2 C, aromat), 128.01(aromat), 127.30 (2 C, aromat), 81.95 (C-2), 72.59 (C-4), 72.52 (C-8), 70.08 (C-6), 60.69 (C-7), 32.47 (C-3). FT-IR (film of highly conc. solution in CH_2Cl_2): 1764 cm^{-1}. MS (EI): m/z (%) = 218(77) [M$^+$ – BnOCHCH], 190(32), 164(33), 146(41), 130(27), 104(46), 91(100).

(3) The crystallographic data (CCDC 207744) can be obtained free of charge via from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; e-mail: deposit@ccdc.cam.ac.uk.

(4) Data for **5b**(oil): $[\alpha]_D^{15}$ –113.8 (c 0.6, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50–7.20 (m, 10 H), 5.04 (dd, J = 9.1, 5.2 Hz, 1 H), 4.82 (d, J = 11.7 Hz, 1 H), 4.69 (t, J = 9.0 Hz, 1 H), 4.59 (d, J = 11.8 Hz, 1 H), 4.21–4.10 (m, 2 H), 2.24 (ddd, J = 5.5, 7.8, 19.1 Hz, 1 H), 1.81 (dt, J = 13.4, 10.0 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.66, 157.93, 139.27, 136.35, 129.60, 129.22, 128.49, 128.22, 128.13, 126.14, 81.36, 73.08, 72.51, 71.06, 55.40, 32.99. FT-IR(film): 1767 cm^{-1}. MS (EI): m/z (%) = 218(48) [M$^+$ – BnOCHCH], 190 (21), 164 (30), 146 (29), 130 (27), 104 (49), 91 (100).

(5) See for example: (a) Evans, D. A. *Science* **1988**, *240*, 420. (b) *Compendium of Chiral Auxiliary Applications*, Vol. 1–3; Roos, G., Ed.; Academic Press: San Diego, **2002**, and many references cited therein.

(6) Wissing, E.; Kleijn, H.; Boersma, J.; van Koten, G. *Recl. Trav. Chim. Pays-Bas* **1993**, *112*, 618; and references therein..

(7) It is interesting to note that treatment of **6** in anhydrous THF at –78 ºC with **4** did not give any **5** at all but a complicated product mixture.