



Improved conditions for the Kiliani-Fischer Synthesis

N. Adjé, F. Vogeleisen and D. Uguen*

Laboratoire de Synthèse Organique, associé au CNRS; E.C.P.M.-U.L.P.

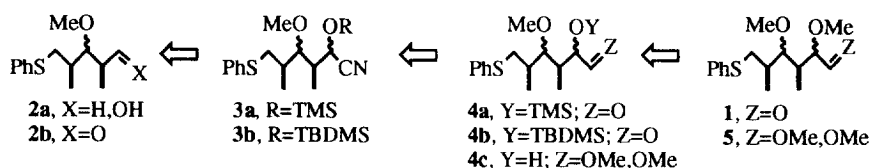
1, rue Blaise Pascal; 67008 Strasbourg (France)

E-mail: uguen@chimie.u-strasb.fr

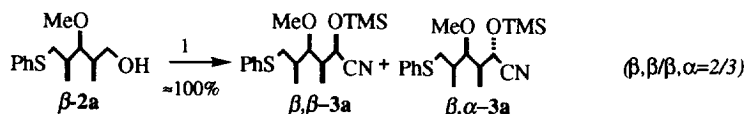
Abstract: DIBA-H reduction of O-TBDMS derivatives of cyanohydrins, followed by hydrolysis with a pH4 tartaric-buffer at low temperature produces the corresponding O-protected 2-hydroxy aldehydes in very high yields. Copyright © 1996 Published by Elsevier Science Ltd

Treatment of an aldehyde by HCN followed by reduction of the resulting cyanohydrin to the corresponding 2-hydroxyaldehyde forms the basis of a procedure known as the Kiliani-Fischer synthesis. Though this methodology has played a pivotal role in the elaboration of the carbohydrate chemistry,¹ its standard utilisation in the preparation of complex molecules has been limited so far. Due to the moderate stability of cyanohydrins in basic media, difficulties may rise in the reduction step and the use of both O-protected cyanohydrins and DIBA-H in aprotic medium as reducing species has been recommended accordingly.²

In the course of an ongoing synthetic work, we had to prepare the various diastereomeric forms of the aldehyde **1** from **2a**. The simplest way to realise this conversion was to oxidise each diastereomeric alcohol **2a** into the corresponding aldehyde **2b** then to exercise, as shown, such a modified Kiliani-Fischer synthesis. DIBA-H reduction of the diastereomeric cyano compounds **3a** followed by acetalisation of the resulting aldehydes **4a**, methylation of the hydroxy group, and hydrolysis of the acetal functionality would have then provided the target aldehydes. Though it proved necessary to bring forth further refinements, we are pleased to report herein that this old process allowed to mediate the planned transformation very efficiently.

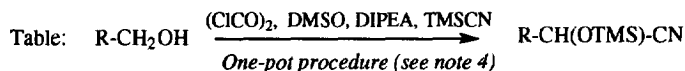


Hünig base (*i.e.*DIPEA) having been both recommended for oxidizing sensitive alcohols under Swern conditions^{3a} and, independently, shown to catalyse efficiently the condensation of aldehydes with TMSCN,^{3b} we first attempted to simplify the **2a-3a** conversion by treating **2a** with reduced amounts of oxalyl chloride, DIPEA and DMSO in CH₂Cl₂ and, as soon as the oxidation was over (TLC), by adding TMSCN in the same flask, *i.e.* without separating the intermediate aldehyde. As indicated, cyanohydrin **3a** was then isolated as a 2/3 mixture of diastereomers in an almost quantitative yield.



Reagents: 1- (ClCO)₂ (1.1 eq.), DIPEA (3.9 eq.), DMSO (1.5 eq.), CH₂Cl₂; -78°C, 20 min, then 0°C, 1.5 hour, then TMSCN (1.35 eq.); 0°C, 2 hours.

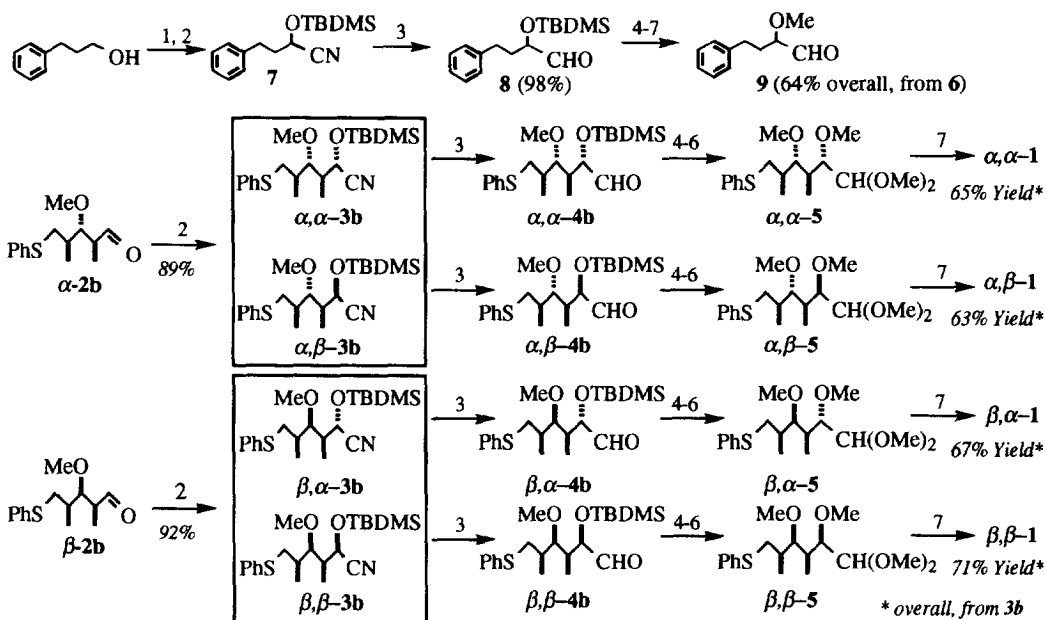
A few common alcohols gave similar results (table).⁴



R	O-TMS-Protected Cyanohydrin (% Yield)
Ph-(CH ₂) ₂ -	Ph-(CH ₂) ₂ -CH(OTMS)-CN, 6 (100%)
<i>n</i> -C ₉ H ₁₉ -	<i>n</i> -C ₉ H ₁₉ -CH(OTMS)-CN (98%)
<i>p</i> -CH ₃ -Ph-	<i>p</i> -CH ₃ -Ph-CH(OTMS)-CN (93%)

In a model experiment, the O-TMS-cyanohydrin **6** was treated by DIBA-H. Working up the reaction mixture with NH₄Cl/H₂SO₄, as recommended,^{2a} resulted in the isolation of complex mixtures however. Other hydrolytic conditions - e.g. pH2-4 tartaric buffer, NH₄Cl/0.5-2N H₂SO₄ or HCl, direct or inverse addition- gave also poor results, the hydroxyaldehyde being isolated only with great difficulty and in yields not exceeding 20%. Supposing that these problems arose mainly from the sensitivity of the trimethylsilyloxy moiety, we turned our attention to the more robust O-TBDMS derivative **7** which was prepared in high yield (94%) by treatment of 3-phenylpropanal with KCN, ZnI₂ and TBDMSCl in acetonitrile under strictly anhydrous conditions.⁵

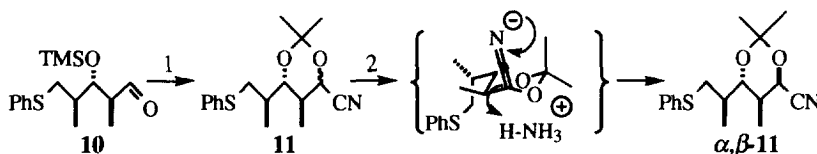
As shown below, treatment of **7** with DIBA-H at -78°C followed by a tartaric-buffer work-up gave the pure 2-*t*-butyldimethylsilyloxyaldehyde **8** in 98% yield. By using the same process, either aldehyde α -**2b** or β -**2b**, which resulted from Swern oxidation of α -**2a** and β -**2a** (95 and 96%, respectively), was converted into a mixture of the corresponding diastereomeric O-TBDMS cyanohydrins **3b** (α , α -**3b**/ α , β -**3b**= β , α -**3b**/ β , β -**3b**=2/3). Separation by chromatography then DIBA-H reduction of each isomer, followed by a tartaric work-up as above then afforded the aldehydes α , α -**4b** and α , β -**4b**, on one hand, β , α -**4b** and β , β -**4b**, on the other hand, almost quantitatively.^{6,7}



Reagents: 1- (ClCO)₂ (1.1 eq.), DIPEA (3.9 eq.), DMSO (1.5 eq.), CH₂Cl₂; -78°C, 1 hour, then 0°C, 1.5 hour; 2- KCN (4 eq.), TBDMSCl (1.2 eq.), ZnI₂ (6 mg/mmol), CH₃CN; r.t., 14 hours; 3- i) flash-chromatography (60H silica gel, hexane/CH₂Cl₂); ii) DIBA-H (1.22 eq.), CH₂Cl₂; -78°C, 1 hour; iii) pH4 tartaric buffer; 0°C, 1.5 hour; 4- HC(OMe)₃ (2.5 eq.), PPTS (0.1 eq.), MeOH; r.t., 14 hours; 5- 1N TBAF (in THF; 5 eq.); r.t., 14 hours; 6- i) KH (3.5 eq.), THF; -78°C, 45 min; ii) ICH₃ (0.15ml/mmol); r.t., 30 min; 7- 2N HCl (30drops/mmol), 4/4/1 THF/AcOH/H₂O (20ml/mmol); r.t., 30 hours.

Noteworthy, any epimerisation failed to be detected (^1H , ^{13}C NMR) during the overall process. Furthermore, stirring separately each aldehyde **4b** with methanol in presence of methyl orthoformate and PPTS then treating the resulting silyloxyacetals with TBAF in THF gave hydroxyacetals **4c**, which, upon subsequent treatment with KH and ICH_3 in THF, followed by hydrolysis with a mixture of aqueous HCl and AcOH in THF of the resulting acetals **5** afforded the aldehydes α,α -**1**, α,β -**1**, β,α -**1**, and β,β -**1**, respectively, in good overall yields, as indicated.

Though not fully addressed during this study, the stereochemistry of the cyanosilylation of the aldehydes **2b** deserves a brief comment. As expected,⁸ the two possible diastereomeric silylated cyanohydrins are formed in nearly equal amount whatever the conditions used (*i.e.* TBDMS/KCN/ ZnI_2 or TMSCN/DIPEA). We attempted to improve this selectivity by preparing a cyano-dioxan derivative **11** from the aldehyde **10** according to Rychnovsky directions.⁹ Deprotonation of the resulting 3/2 mixture of, respectively, α,α -**11** and α,β -**11** by LDA and subsequent treatment with ammonium chloride, a process expected to deliver preferably, as represented, the β isomer, was followed by sequential treatment with DIBA-H, methanol// $\text{HC}(\text{OMe})_3$ /PPTS and KH/ ICH_3 . Indeed a slightly more favorable 3/7 mixture of α,α -**1** and α,β -**1**, respectively, resulted but in a deceptive 11% overall yield (from **3a**).



Reagents: 1- *see ref.9*; 2- LDA (2.2 eq.), THF; 2 hours, -78°C , then 10% NH_4Cl .

Given the high overall yield in each targeted methoxy-aldehydes **1** registered precedently by fractionating the mixture of diastereomeric O-TBDMS cyanohydrins, further search of more stereoselective conditions was suspended.

In conclusion, despite limitations rising when diastereoselectivity is concerned, the improved version of the Kiliani-Fischer presented herein has to be considered as a very efficient means for performing a one-carbon homologation of aldehydes into α -hydroxyaldehydes and related derivatives.

Acknowledgements: best thanks are due to Rhône-Poulenc Nutrition Animale for a grant (to N. A.).

Notes and References

- For an instructive historical account of this reaction, see: Morrison J. D.; Mosher, H. S. *Asymmetric Organic Reactions*; Prentice-Hall: Washington D. C., 1991; pp. 133-141.
- a) Hayashi, M.; Yoshiga, T.; Oguni, N. *Synlett* **1991**, 479-480, and quoted references; b) Schlosser, M.; Brich, Z. *Helv. Chem. Acta* **1978**, *61*, 1903-1911.
- a) Evans, D.; Polniaszek, R. P. *Tetrahedron Lett.* **1986**, *27*, 5683-5686; b) Kobayashi, S.; Tsuchiya, Y.; Mukaiyama, T. *Chem. Letters* **1991**, 537-540.
- Protocole for the one-pot conversion of alcohols into TMS-protected cyanohydrins*: To a cooled solution (-78°C) of oxalyl chloride (1.1 eq.) in CH_2Cl_2 (2.5ml/mmol) was added a solution of DMSO (1.5 eq.) in CH_2Cl_2 (0.3ml/mmol). After 6mn, still at -78°C , the alcohol, diluted with CH_2Cl_2 (1ml/mmol), was added and the mixture was stirred for 20 min at that temperature. DIPEA (3.9 eq.) was introduced and the mixture was further stirred 0.5-1 hour, after which the temperature was allowed to reach slowly 0°C . TMSCN (1.35 eq.) was added and the stirring was pursued at 0°C for 2 hours. Volatiles were removed *in vacuo* (0.1 τ) and the

residue was taken up in hexane. Filtration on Celite was followed by evaporation of the solvents, which afforded the pure O-TMS cyanohydrin. For a related, *but not so efficient*, one-pot process, see: Luly, J. R.; Hsiao, C.-N.; BaMaung, N.; Plattner, J. J. *J. Org. Chem.* **1988**, *53*, 6109-6112.

5- Rawal, V. H.; Rao, J. A.; Cava, M. P. *Tetrahedron Lett.* **1985**, *26*, 4275- 4278. Attempts to prepare **7** from 3-phenylpropanol and TBDMSCN by a one-pot process as for the O-TMS analog proved less satisfactory, the yield did not exceed 73%.

6- *Protocole for the DIBA-H reduction of TBDMS-protected cyanohydrins*: A solution of O-TBDMS cyanohydrin in CH₂Cl₂ was cooled at -78°C. A 1M solution of DIBA-H in CH₂Cl₂ (1.2 eq.) was added. The resulting homogeneous mixture was stirred 1 hour at that temperature then poured in a well-stirred mixture of buffer (prepared by dissolving tartaric acid (54g) and sodium hydroxide (4.5 g) in water (360ml)) and of CH₂Cl₂. The resulting heterogeneous mixture was vigorously stirred for 1.5 hours. The aqueous layer was extracted with ether (3x100ml) and the combined organic layers were washed with brine until neutral and dried (Na₂SO₄). Filtration on Celite was followed by evaporation of the solvents *in vacuo*, which afforded the pure O-TBDMS- α -hydroxyaldehyde.

7- ¹H and ¹³C NMR spectra have been recorded at 200 and 50 MHz, respectively, in CDCl₃ solutions. The [α]_D values reported herein refer to CH₂Cl₂ solutions at 21°C. Selected data: *i*) α,α -**3b**: [α]_D -7 (c=4); ¹H NMR: 0.13 (s, 3H); 0.2 (s, 3H); 0.91 (s, 9H); 0.96 (d, J=7Hz, 3H); 1.19 (d, J=7Hz, 3H); 1.96-2.08 (m, 2H); 2.74 (dd, J=9, 13Hz, 1H); 3.04-3.06 (m, 1H); 3.08-3.12 (m, 1H); 3.46 (s, 3H); 4.75 (d, J=4Hz, 1 H); 7.21-7.37 (m, 5H); ¹³C NMR: -5.2, -5.1, 12.1, 17.7, 18.1, 25.7, 35.2, 35.9, 42.3, 61.4, 64, 86.4, 119.2, 126.2, 129, 129.7, 136.8. *ii*) α,β -**3b**: [α]_D +35 (c=3); ¹H NMR: 0.18 (s, 3H); 0.27 (s, 3H); 0.94 (s, 9H); 0.97 (d, J=7Hz, 3H); 1.2 (d, J=7Hz, 3H); 1.92-2.1 (m, 2H); 2.75 (dd, J=9, 13Hz, 1H); 3.01-3.06 (m, 1H); 3.1 (dd, J=2, 9Hz, 1H); 3.4 (s, 3H); 4.84 (d, J=2Hz, 1 H); 7.18-7.39 (m, 5H); ¹³C NMR: -5.1, -4.8, 11.4, 17.6, 18.2, 25.7, 34.7, 35.9, 42.1, 60.9, 62.5, 84.6, 120.5, 126.3, 129, 129.9, 136.7; *iii*) β,α -**3b**: [α]_D +16 (c=3); ¹H NMR: 0.11 (s, 3H); 0.19 (s, 3H); 0.91 (s, 9H); 1.04 (d, J=7Hz, 3H); 1.1 (d, J=7Hz, 3H); 1.91-2.1 (m, 2H); 2.74 (dd, J=8, 12.7Hz, 1H); 3.1 (dd, J=5, 13Hz, 1H); 3.39-3.45 (m, 1H); 3.44 (s, 3H); 4.32 (d, J=6Hz, 1 H); 7.17-7.37 (m, 5H); ¹³C NMR: -5.3, -5.1, 10.8, 15.1, 18.1, 25.7, 36.2, 38.1, 41.3, 60.9, 64.9, 82.5, 119.5, 126.1, 129, 129, 129.3, 136.8. *iv*) β,β -**3b**: [α]_D -29 (c=3); ¹H NMR: 0.14 (s, 3H); 0.22 (s, 3H); 0.92 (s, 9H); 1.08 (d, J=7Hz, 6H); 1.85-2.1 (m, 2H); 2.75 (dd, J=8, 13Hz, 1H); 3.1 (dd, J=5, 13, 1H); 3.38-3.43 (m, 1H); 3.4 (s, 3H); 4.27 (d, J=7Hz, 1 H); 7.14-7.39 (m, 5H); ¹³C NMR: -5.2, -4.9, 10.7, 15, 18.2, 25.7, 36.1, 38.2, 41.8, 60.7, 64.8, 81.7, 119.5, 126.2, 129, 129.1, 129.6, 136.6; *v*) α,α -**4b**: ¹H NMR: 0.05 (s, 3H); 0.12 (s, 3H); 0.89 (d, J=7Hz, 3H); 0.95 (s, 9H); 1.19 (d, J=7Hz, 3H); 1.82-1.93 (m, 1H); 2.34-2.42 (m, 1H); 2.68 (dd, J=10, 13Hz); 3.1 (m, 2H); 3.31 (s, 3H); 3.81 (s, 1H); 7.13-7.81 (m, 5H); 9.44 (m, 1H); ¹³C NMR: -5.2, -4.3; 15.7; 18.2; 18.4; 25.7; 34.7; 35.6; 41.3; 60.5; 81.4; 85.4; 126.1; 128.9; 129.6; 136.8; 201.5; *vi*) α,β -**4b**: ¹H NMR: 0.06 (s, 3H); 0.07 (s, 3H), 0.82 (d, J=7, 3H); 0.91 (s, 9H); 1.17 (d, J=7Hz, 3H); 2.04-2.23 (m, 2H); 2.74 (dd, J=7, 13Hz); 3.05 (dd, J=4, 8Hz, 1H); 3.14 (dd, J=3.9, 12.7, 1H); 3.35 (s, 3H); 4.08 (dd, J=2, 4Hz, 1H); 7.1-7.37 (m, 5H); 9.44 (d, J=2Hz, 1H); ¹³C NMR: -5, -4; 12.6; 17.5; 18.4; 26; 35.3; 36.2; 39.8; 60.7; 79.3; 86.7; 126; 128.9; 129; 137; 202; *vii*) β,α -**4b**: ¹H NMR: 0.03 (s, 3H), 0.07 (s, 3H), 0.93 (s, 9H), 1.01 (d, J=7Hz, 3H), 1.1 (d, J=7, 3H), 1.93-2.22 (m, 2H), 2.72 (dd, J=8, 13Hz, 1H), 3.1 (dd, J=5, 13Hz, 1H), 3.29 (s, 3H), 3.33-3.42 (m, 1H), 3.85 (dd, J=1, 5Hz, 1H), 7.13-7.36 (m, 5H), 9.54 (d, J=1Hz, 1H); ¹³C NMR: -5, -4.4, 10.65, 15.4, 18.3, 25.9, 35.5, 38.4, 41.2, 59.8, 79.5, 81.8, 126.1, 129, 129.4, 137.1, 200.6; *viii*) β,β -**4b**: ¹H NMR: 0.05 (s, 3H), 0.07 (s, 3H), 0.93 (s, 9H), 1 (d, J=7Hz, 3H), 1.03 (d, J=6Hz, 3H), 1.81-2.19 (m, 2H), 2.76 (dd, J=8, 13Hz, 1H), 3.1 (dd, J=6, 13Hz, 1H), 3.27-3.5 (s, 1H), 3.36 (s, 3H), 3.81 (dd, J=2, 5Hz, 1H), 7.13-7.36 (m, 5H), 9.51 (d, J=2Hz, 1H); ¹³C NMR: -4.9, -4.3, 11.7, 14.5, 18.3, 25.9, 36.1, 38.5, 39.9, 60.4, 80, 82.5, 125.9, 129, 129.2, 137, 199.5.

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(Received in France 17 May 1996; accepted 28 June 1996)