An Improved Synthesis of Pyridoxine via [2+2+2] Cyclization of Acetylenes and Nitriles

Andrey Gutnov,[a] Vladimir Abaev,[a] Dmitry Redkin,[a] Christine Fischer,[a] Werner Bonrath,[b] Barbara Heller*[a]

[a] Leibniz-Institut für Organische Katalyse an der Universität Rostock e.V., Buchbinderstrasse 5–6, 18055 Rostock, Germany
Fax +49(381)4669324; E-mail: barbara.heller@ifok.uni-rostock.de

[b] DSM Nutritional Products Ltd. 214/0.71, Wurmisweg 576, 4303 Kaiseraugst, Switzerland

Received 21 December 2004

Abstract: An improved synthesis of pyridoxine (vitamin B_6) is reported. The key step involves the light-promoted [2+2+2] cyclization of 3,3-bissilyl-di-2-propynyl ethers and acetonitrile in the presence of [cpCo(cod)] (1 mol%) as a catalyst. Convenient oxidation and iodination procedures are elaborated to transfer 3-silylpyridines into corresponding 3-hydroxy- and 3-iodo-derivatives.

Key words: pyridines, alkynes, nitriles, cyclizations, vitamins

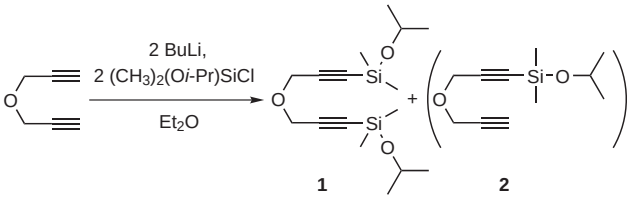
Since the discovery of the Co(I)-catalyzed [2+2+2] cyclization of acetylenes and nitriles,[1] many attempts were made to employ this reaction for the synthesis of important natural pyridine derivatives. In particular, two groups (Schleich et al.[2] and Vollhardt et al.[3]) reported independently from each other on the synthesis of pyridoxine (vitamin B_6) almost simultaneously in the mid 1980s.

The key steps of both approaches included the cobalt-catalyzed (with cobaltocene or [cpCo$(CO)_2$] as catalysts) [2+2+2] cyclization of dimetalated dipropargyl ethers and acetonitrile under harsh conditions (under pressure or at 139 °C), which sometimes led to reasonable decomposition of starting acetylenes and ultimate pyridines during the reaction. Subsequent selective protiodesilylation of $(CH_3)_3Si$ or $(CH_3)_3Sn$ groups in position 6 of the 3,6-dimetalated products furnished 3-monometalated pyridines. The last step of both methods, an oxidation of the Si(Sn)–C bond, also caused some difficulties because of many side reactions with the strained oxygen-containing anellated ring. Although the total yields of pyridoxine did not exceed 6%, it is a fundamental result to demonstrate the principal possibility of vitamin B_6 preparation via the [2+2+2] cyclization.

The aim of our project was to modify the substrates and conditions of the Co(I)-catalyzed [2+2+2] cyclization as well as to elaborate practical synthetic procedures for the oxidation of Si-C bond in pyridoxine-like compounds.

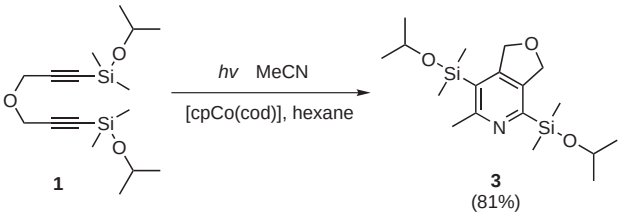
Our recent studies of the η^5-cyclopentadienyl-η^4-cycloocta-1,5-diene-cobalt(I) [cpCo(cod)]-catalyzed [2+2+2] cyclization of acetylenes and nitriles into pyridine core led to the elaboration of highly efficient procedure for the reaction.[4] The irradiation with visible light (λ = 350–500 nm) or, alternatively, sun light was found to be a powerful source of energy for the catalyst activation which allows to carry out the reaction under mild conditions: ambient temperature and pressure, possibility to use water as a reaction medium, substrate to catalyst ratio up to 10000:1. The method might provide a basis for the improved preparation of silylated pyridines. On the other hand, we envisaged a possibility to use organosilicon groups other than $(CH_3)_3Si$ as a masked equivalent of hydroxy group. As it was recently reviewed,[5] alkoxy-containing $(OR)_nR$-Si groups undergo the oxidation sufficiently easier than R_3Si ones in many cases**.** That fact could ease the task of the direct oxidation of sensitive substrates like pyridoxine precursors.

To prove this hypothesis, we prepared 3,3-bis(dimethylisopropoxysilyl)-di-2-propynyl ether (**1**) through the dilithiation of dipropargyl ether followed by treatment with chlorodimethylisopropoxysilane[6] (Scheme 1). The disilylated product **1** was isolated with good yield (60%) along with some amount (6%) of the monosilylated product **2**.



Scheme 1 Preparation of 3,3-bis(dimethylisopropoxysilyl)-di-2-propynyl ether (**1**)

Having the disilylated ether **1** in hands, we investigated its [2+2+2] cyclization with acetonitrile in the presence of [cpCo(cod)] (Scheme 2).

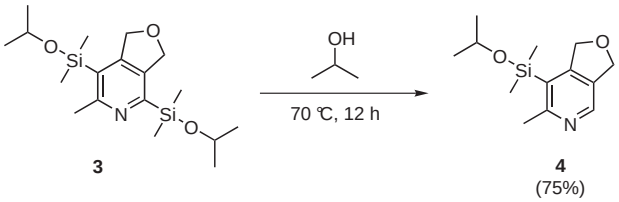


Scheme 2 [2+2+2] Cyclization to disilylated pyridine **3**

SYNLETT 2005, No. 7, pp 1188–1190
Advanced online publication: 14.04.2005
DOI: 10.1055/s-2005-864834; Art ID: G48004ST

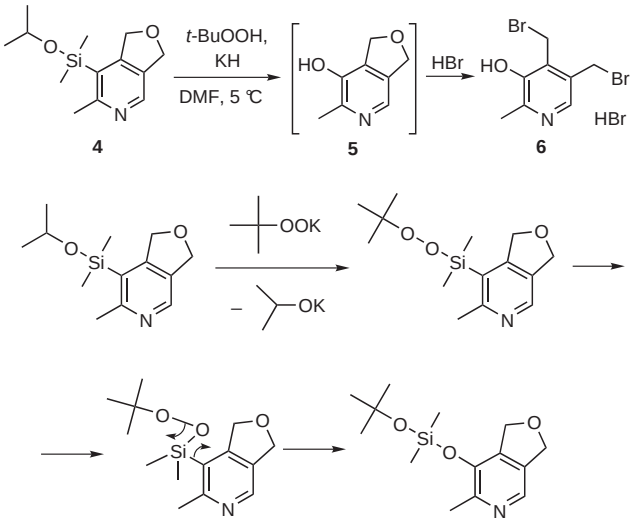
The conditions of the reaction were mild. After 20 hours under reflux in hexane solution and irradiation with two 460 W Phillips HPM 12 lamps in the presence of only 1 mol% of [cpCo(cod)] as a catalyst, disilylated pyridine **3** was isolated by vacuum distillation in high yield (81%).[7]

The silyl group beside the N-atom was then smoothly eliminated by heating in isopropanol, and the resulted 3-monosilylpyridine **4** was isolated by distillation with 75% yield (Scheme 3).[8] As a reason of this regioselectivity we see the influence of the nitrogen atom. Due to this heteroatom, the carbon in the 2-position of pyridine **3** is more electropositive than that in the 5-position and is therefore less prone to stabilizing an anionic species.



Scheme 3 Preparation of monosilylated pyridine **4**

The oxidation of Si-C_{aryl} bond is still a challenge for practical chemistry. Only few examples of it have been reported to date.[9] We applied several oxidizing systems (for example H_2O_2 + KF in DMF, PhCOOOH + K_2CO_3 + KF in DMF) for the oxidation of Si-C bond in the compound **4**. However, most of the attempts resulted in protiodesilylation reaction and (or) oxidation of alkyl side chains. Fortunately, the oxidation with potassium *t*-butylhydroperoxide in anhydrous DMF without addition of fluorides afforded 3-hydroxypyridine **5** which was transformed in situ into dibromo derivative **6** with 35% yield (Scheme 4).[10]

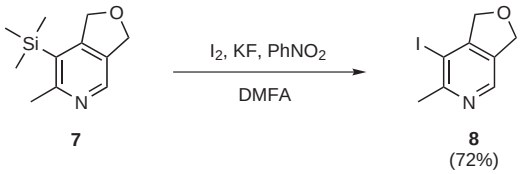


Scheme 4 Oxidation of monosilylated pyridine **4**

Possible mechanism of the reaction includes a replacement of isopropoxy group with highly nucleophilic *t*-butyl hydroperoxide anion followed by intramolecular oxidative rearrangement of peroxysilane.

The dibromide **6** was easily converted into pyridoxine by a well-known two-step synthetic procedure.[2]

Another facile access to pyridoxine involved the iodination key stage (Scheme 5).



Scheme 5 Iodination of 3-trimethylsilylpyridine **7**

3-Trimethylsilylpyridine **7** was prepared by cyclization of 3,3-bis(trimethylsilyl)-di-2-propynyl ether and acetonitrile under conditions analogous to those described for pyridine **3** in 86% yield with subsequent protiodesilylation in methanol. The iodination proceeds smoothly in DMFA at 80 °C for 10 hours in the presence of KF and nitrobenzene to give 3-iodopyridine **8** which was earlier reported as a key compound for the synthesis of pyridoxine.[3] The addition of both KF and nitrobenzene is crucial for the reaction.[11] Since the single electron transfer (SET) complexation–oxidation (reduction) processes have become a common concept in the metallorganic chemistry, we would suppose that such redox activation of 3-silylpyridine **7** with KF and iodine with nitrobenzene influences sufficiently the energetic profile of the reaction and decreases its activation energy.

In conclusion, we succeeded in elaboration of efficient procedures for the preparation of vitamin B_6 via the [2+2+2] cocyclization reaction. The utilization of [cpCo(cod)] as a catalyst under irradiation with visible light appeared to be superior to catalysis with cobaltocene and [$cpCo(CO)_2$], and the modification of organosilicon auxiliary allowed direct oxidation of highly sensitive 3-silylpyridines into pyridoxine precursors. Alternatively, a direct iodination of the 3-silylpyridines is now possible to get access to vitamin B_6.

Acknowledgment

This work was supported by DSM Nutritional Products (formely Roche Vitamins Ltd.). We are grateful to Beate Friedrich for technical assistance, and Hannelore Baudisch for analytical measurements.

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(7) 3,3-Bis(dimethylisopropoxysilyl)-di-2-propynyl ether (**1**, 9.1 g, 10 mL, 27.85 mmol) and MeCN (5 mL) were dissolved in hexane (130 mL). Then, [cpCo(cod)] (65 mg, 0.28 mmol, 1 mol%) was added to the solution, and the reaction mixture was stirred under reflux for 20 h under two 460 W Phillips HPM 12 lamps' irradiation. The reaction mixture was evaporated in vacuum, and the residue was distilled. A fraction with bp 119–122 °C ($2\cdot10^{-3}$ mbar) was collected to give 8.29 g (81% yield) of compound **3** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.06 (m, 2 H), 5.04 (m, 2 H), 4.03–3.94 (m, 2 H), 2.55 (s, 3 H), 1.09 (d, *J* = 6.1 Hz, 6 H), 1.07 (d, *J* = 6.1 Hz, 6 H), 0.31 (s, 6 H), 0.28 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.24, 157.46, 152.28, 136.75, 123.03, 73.42, 71.28, 64.84, 64.68, 25.75, 24.92, 0, –2.23. MS (70 eV): *m/z* (%) = 368 (2) [M^+], 352 (11), 325 (100), 312 (34), 294 (24), 74 (28), 43 (23).
(8) Bissilylated pyridine **3** (5.565 g, 15.14 mmol) was stirred for 12 h at 70 °C in absolute *i*-PrOH (10 mL). The solvent was evaporated, and the residue was distilled in vacuo to give 2.85 g (75% yield) of the product **4** with bp 74–77 °C ($8\cdot10^{-3}$ mbar). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.29 (s, 1 H), 5.09 (m, 2 H), 4.96 (m, 2 H), 4.03–3.97 (m, 1 H), 2.56 (s, 3 H), 1.12–1.1 (m, 6 H), 0.33 (m, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.09, 155.04, 141.61, 130.98, 124.11, 74.1, 70.19, 64.84, 25.38, 24.98, 0.003. MS (70 eV): *m/z* (%) = 251 (5) [M^+], 236 (10), 208 (100), 194 (37), 176 (18), 75 (18).
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(10) KH (1.575 g, 39.26 mmol) was suspended in DMF (20 mL) at 0 °C. Then, *t*-BuOOH (6.5 mL, 39 mmol, 6 M solution in nonane) was added dropwise to the slurry within 10 min so that the reaction temperature did not exceed 5 °C. After the addition, the mixture was stirred additionally for 10 min at 5 °C until the evolution of hydrogen ceased. The solution of 6-methyl-7-(dimethylisopropoxysilyl)-1,3-dihydrofuro[3,4-*c*]pyridine (**4**, 3.23 g, 12.86 mmol) in DMF (3 mL) was added dropwise to the reaction mixture within 30 min at 5 °C under vigorous stirring. The reaction mixture was stirred for additional 30 min. At this point the color turned to brown, and the reaction mixture was evaporated to dryness in high vacuum. The remaining solids were dissolved in hot HOAc (10 mL) followed by addition of HBr (25 mL, 48% in H_2O). The solution was brought to reflux, and 13 mL of liquids were distilled off at atmospheric pressure. The remaining solution was left overnight at 5 °C. The precipitated hydrobromide was filtered off, washed with acetone, and then air dried. The crude salt was recrystallized from HOAc (8 mL) to give 1.68 g (35% yield) of the product **6** as beige crystals with mp 228 °C. ^{1}H NMR (400 MHz, CD_3OD): δ = 8.34 (s, 1 H), 4.74 (s, 2 H), 4.73 (s, 2 H), 2.61 (s, 3 H). ^{13}C NMR (100 MHz, CD_3OD): δ = 154.8, 145.2, 143.3, 137.1, 134.4, 25.5, 21.2, 16.3. MS (70 eV): *m/z* (%) = 296 (4) [M^+ – Br], 248 (2), 215 (37), 134 (67), 106 (100), 80 (50), 65 (50), 39 (74).
(11) The solution of the pyridine **7** (228 mg, 1.1 mmol), dried KF (198 mg, 3.4 mmol), nitrobenzene (0.35 mL, 3.4 mmol) in DMF (3 mL) was treated with iodine (863 mg, 3.4 mmol), and the mixture stirred for 10 h at 80 °C. Then reaction was quenched by addition of 5% solution of Na_2SO_3 in H_2O after cooling and extracted with Et_2O. The organic phase was dried over Na_2SO_4, solvents were removed in vacuum, and the oily residue was purified on silica (Et_2O) to give 206 mg (72% yield) of the iodide **8** as colorless crystals. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21 (s, 1 H), 5.21 (s, 2 H), 4.92 (s, 2 H), 2.70 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.1, 155.1, 141.2, 133.4, 89.6, 78.3, 73.7, 28.1. MS (70 eV): *m/z* (%) = 261 (100) [M^+], 233 (50), 205 (15), 133 (11), 106 (51), 77 (29), 63 (12), 51 (16).