Synthesis of Bis[di(2-pyridyl)methyl]amine (BDPMA) by a Novel One-Pot Multi-Step Reductive Amination with Molecular Sieves and Zn/*i*PrOH

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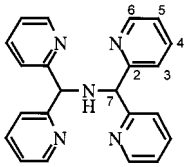
Bis[di(2-pyridyl)methyl]amine (BDPMA) has been synthesized by refluxing di-2-pyridyl ketone and di-(2-pyridyl)methylamine in isopropanol in the presence of molecular sieves and acetic acid and subsequent reduction with zinc dust. The established methods for reductive amination, i.e. $NaBH_3CN$, $NaBH(OAc)_3$ and $NaBH_4$, failed in the synthesis of BDPMA due to a disfavored equilibrium towards the imine formation and therefore long reaction times were required, involving side reactions. The presented method can be used on large-scales and tolerates aromatic heterocycles as functional groups.

Biomimetic oxidation catalysts capable of degrading environmental pollutants are of great interest. Regarding to this, porphyrin and phthalocyanine complexes are well investigated. Interesting results have been obtained e.g. in the oxidation of polychlorophenols with metallosulfophthalocyanines.[1] On the other hand, little is known on the catalytic activity of non-heme mononuclear complexes in oxidation reactions. Que and Feringa have recently studied the catalytic activity of a tetrapyridyl iron complex, the iron(II) complex [*N*,*N*-bis-(2-pyridylmethyl)-*N*-di(2-pyridyl)methylamine] which is able to catalyze alkane oxidation with hydrogen peroxide.[2] However, the ligand synthesis is not very effective (only 37% yield) and its isolation involve a rather dangerous work-up at large scale since the final step is based on the precipitation of a potentially explosive perchlorate salt.

Here we report the one-pot two-step synthesis of a new symmetric pentadentate ligand bis[di(2-pyridyl)methyl]amine (BDPMA). The BDPMA ligand consists of four pyridine substituents linked to a secondary amine function, expecting that this ligand will be suitable for the formation of mononuclear complexes.



BDPMA

The metal ion would be surrounded in a plane by four N of pyridine moieties (the pyridine rings being perpendicular to this N plane) and by an additional nitrogen donor group in the fifth coordination site, leaving one coordination site free which is necessary for catalytic activity. Our objective is to compare the catalytic activity of a non-heme mononuclear complex with these macrocycle complexes in the oxidation of pollutants.

Results and Discussion

The synthesis of BDPMA by reductive amination (eq. 1) with the standard reductant $NaBH_3CN$[3] failed. The desired product is obtained only in negligible amount in the crude reaction mixture (Table 1, entry 1). Signals in the aliphatic region of the proton NMR spectrum indicated also partly reduction of the pyridine ring. With the new alternative method of Abdel-Magid[4] using $NaBH(OAc)_3$ as reductant, a similar result was observed. The target molecule was obtained only as a side product (Table 1, entry 2). The reduction with $LiAlH_4$ after employing molecular sieves 3 A for the imine formation was even worse (Table 1, entry 3). The reductant attacked the pyridyl substituents leading to a mixture of undesired side-products.

(1)

1 **2** **BDPMA** **3**

A crude product of only four compounds was obtained by drying the solution of the ketone **1** and the amine **2** in methanol over molecular sieves 3 A for 14 h at room temperature in the presence of 0.35 equiv. of glacial acetic acid. Subsequent reduction with an excess of Zn dust at room temperature (10 min reaction time) gave a mixture of ketone **1**, amine **2**, alcohol **3** (from ketone reduction) and 15% of the target molecule BDPMA (Table 1, entry 4). By heating the methanol solution to reflux (65°C) during the removal of generated water, the content of BDPMA was doubled (Table 1, entry 5). Employing a ten-fold amount of acetic acid, 3.50 equiv. instead of 0.35, again doubled the

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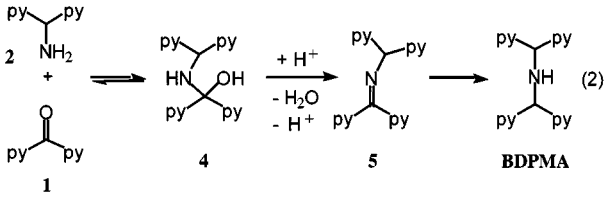
Table 1. Reaction conditions, mass balances and product distributions for the BDPMA synthesis from ketone **1** and amine **2** by reduction of the imine

Entry	Reductant[d]	AcOH [equiv.]	t (T)[a] [h] ([°C])	m.b.[b] [%]	Product distribution[c] **1**	**2**	**3**	**BDPMA**
1	$NaBH_3CN$/MeOH	0.20	66 (25)	50[e]	–	–	–	–
2	$NaBH(OAc)_3$/MeOH	0.70	48 (25)	66[e]	–	–	–	–
3	$LiAlH_4$/THF	0.35	48 (25)	66[e]	–	–	–	–
4	Zn/MeOH	0.35	14 (25)	92	18	31	36	15
5	Zn/MeOH	0.35	3 (65)	94	0	29	38	33
6	Zn/MeOH	3.50	3 (65)	97	0	14	18	64
7	Zn/*i*PrOH	17.5	3 (82)	100	0	12	13	75
8	Zn/*i*PrOH	3.25	6 (82)	70[f]	0	0	0	100

[a] Time and temperature for the drying over molecular sieves 3 A; the time for the reduction with Zn is only 5–10 min, for the other reduction methods several days. – [b] Mass balance of the isolated material. – [c] Determined by ^{1}H-NMR analysis on the crude reaction mixture, for entry 8 after purification; normalized to 100%. – [d] For entries 1–7, 180 mg (1.00 mmol) **1** and 200 mg (1.08 mmol) **2** were dissolved and dried over molecular sieves 3 A (see footnote a) and then an excess of reductant was added; for entry 8, 1.00 g (5.00 mmol) for each ketone **1** and amine **2** was employed. – [e] A complex product mixture was obtained with hills in the aliphatic region; the desired BDPMA was always obtained only as a minor product. – [f] Yield of isolated material after purification.

yield (Table 1, entry 6). Due to the elevated temperature during the reduction with Zn, the ketone **1** which was not converted to the imine was completely reduced to the alcohol **3** (cf. Table 1, entry 4 with entries 5 and 6). By changing the solvent and therefore the reaction temperature from 65°C (refluxing methanol) to 92°C (refluxing isopropanol), BDPMA can be obtained as the major product (Table 1, entry 7), and after a simple purification of the crude product by extracting several times with 2 M aqueous NaOH solution, 70% of the pure desired product was obtained in a large-scale run (1.00 g of ketone **1** and 1.00 g of amine **2**, Table 1, entry 8).

These drastic conditions for nearly complete imine **5** formation, i.e. molecular sieves 3 A, 3 equiv. of acetic acid, high temperatures and 6 h reaction times (cf. Table 1, entries 4–7), indicate that the equilibrium for the imine **5** formation via the carbinol amine **4** (eq. 2) lies by far on the side of the substrates **1** and **2**. The reduction with Zn dust was performed within 10 min in every run (Table 1, footnote a) which confirmed that the prior formation of the imine was the rate determining step and not the reduction.



Hindered and diaryl ketones are known to fail in the reductive amination by $NaBH_3CN$ as well as sterically hindered amines, presumably due to slow imine formation.[1] But another phenomenon may act synergetically. For the conversion of the carbinol amine **4** to the imine **5** (eq. 2), catalytic amounts of acid are needed and the optimal reaction conditions should be slightly acidic (pH 6).[1a] The di(2-pyridyl)methyl moiety which is present in all substrates, intermediates and products may act as proton sponge[5] and tied up a certain quantity of protons. The latter cannot protonate anymore the OH group of the carbinol amine **4** to transfer it to the better leaving group H_2O. This may explain the difference which is observed in employing 0.35 or 3.50 equivalents of acid at otherwise identical reaction conditions (cf. Table 1, entries 5 and 6).

Once having established that for the present target molecule, the imine formation is strongly unfavorable, it is straightforward to explain why the established standard methods failed in the synthesis of BPDMA. These latter ones were based on the principle that the iminium ion can be reduced much faster than a carbonyl group at a pH = 6–8. By simply reacting the carbonyl compound with an amine in the presence of $NaBH_3CN$ or $NaBH(OAc)_3$, the imine can be "trapped" selectively and the equilibrium shifted to the right.[1] But in the present case, due to prolonged reaction times the slow reduction of the carbonyl group becomes evident and also the attack of the pyridyl substituents. Consequently, a product mixture is obtained (Table 1, entries 1 and 2). Usually, with the help of molecular sieves 3 A to absorb the water generated in the reaction, the yield improved.[1] But, even removing the water with molecular sieves for 48 h at room temperature before adding the reductant is not sufficient to form the imine **5**. Employing the strong reductant $LiAlH_4$, all possible functional groups are reduced and the alcohol **3** is detected as by-product from reduction of unconverted ketone. This again confirmed that the reduction of the imine **5** is not the decisive problem, but its formation.

In summary, a new reductive amination for sterically hindered ketones and amines is presented. The reaction is easily performed in "one-pot" and on larger scales and a convenient work-up supplies the desired product in pure form and good yield. The reductant is not only much cheaper than the established reductive amination methods, but also avoid possible toxic by-products as cyanide in the case of $NaBH_3CN$ and the hazardous precipitation of perchlorate derivatives. The fact that heterocycles are tolerated as functional group makes it an interesting tool for ligand synthesis in coordination chemistry.

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Experimental Section

General Aspects: ^{1}H-NMR spectra were run on a Bruker AM 250 (250 MHz), chloroform as internal standard. – ^{13}C-NMR spectra were determined on a Bruker AM 250 (63 MHz), [D]chloroform as standard. – All solvents were purchased from standard chemical suppliers and used without further purification. The ketone **1** and the di(2-pyridyl) ketone oxime are commercially available.

Di(2-pyridyl)methylamine (**2**)[6]: In a mixture of 85 ml ethanol, 50 ml water and 75 ml 23% aqueous NH_3 solution, 5.00 g (25.0 mmol) di(2-pyridyl) ketone oxime and 3.30 g (42.8 mmol) ammonium acetate were dissolved and heated to 80°C. Over a period of 30 min, 7.36 g (113 mmol) Zn dust were added. After heating to reflux for 4.5 h, the solids were removed by filtration and the filtrate concentrated at the rotoevaporator (60°C, 30 Torr). The resulting aqueous solution (ca. 10 ml) was basified with 10 N NaOH solution and extracted with CH_2Cl_2 (5 × 15 ml). The combined organic phases were washed with 10 ml brine and dried with $MgSO_4$. After evaporation of the solvent, 4.21 g (22.7 mmol, 91%) of the amine **2** were obtained as colorless oil. No further purification was necessary. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.41 (br. s, 2 H, NH_2), 5.30 (s, 1 H, 6-H), 7.11 (ddd, *J* = 0.8, 4.7, 7.4 Hz, 2 H, 2-H), 7.36 (dt, *J* = 7.8, 1.1 Hz, 2 H, 4-H), 7.60 (dt, *J* = 1.3, 7.5 Hz, 2 H, 3-H), 8.53 (ddd, *J* = 0.9, 1.7, 4.8 Hz, 2 H, 1-H). – ^{13}C NMR (63 MHz, $CDCl_3$): δ = 62.3, 121.8, 122.1, 136.6, 149.2, 162.7.

Bis[di(2-pyridyl)methyl]amine (BDPMA): 1.00 g (5.43 mmol) ketone **1** and 1.00 g (5.40 mmol) amine **2** were dissolved in 10 ml of absolute isopropanol and dried with molecular sieves 3 A for 1 h at room temp. 1.00 ml (17.5 mmol) glacial acetic acid were added under N_2 atmosphere and the reaction mixture refluxed for 6 h. The oil bath was then removed and 870 mg (13.3 mmol) Zn dust was added in portions over a period of 5 min. After 5 min the reaction mixture became solid. It was partly dissolved with 15 ml of isopropanol. The solids were removed by filtration and washed with methanol until the filtrate was colorless. The solvent was evaporated (50°C, 30 Torr) and the residue dissolved in 20 ml 2 M NaOH solution and 10 ml CH_2Cl_2. The phases were separated and the aqueous one extracted with 10 ml CH_2Cl_2. The combined organic phases were washed with 5 ml of brine, dried with $MgSO_4$ and the solvent evaporated (40°C, 30 Torr). The crude oil was dissolved in 0.5 ml of CH_2Cl_2 and 20 ml of *tert*-butyl methyl ether and washed with 2 M NaOH solution (15 × 5 ml). The organic phase was washed with brine and dried with $MgSO_4$. After evaporation of the solvent and drying the residue under oil-pump vacuum, 1.35 g (3.82 mmol, 70%) BDPMA were obtained as pale-yellow viscous oil. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 4.60 (br. s, 1 H, NH), 5.07 (s, 2 H, 7-H), 7.11 (ddd, *J* = 1.3, 4.7, 7.4 Hz, 4 H, 5-H), 7.46 (dt, *J* = 7.8, 1.1 Hz, 4 H, 3-H), 7.59 (dt, *J* = 1.8, 7.7 Hz, 4 H, 4-H), 8.54 (ddd, *J* = 0.9, 1.8, 4.7 Hz, 4 H, 6-H). – ^{13}C NMR (63 MHz, $CDCl_3$): δ = 66.6, 121.8, 122.2, 136.3, 148.9, 161.1. – $C_{22}H_{19}N_5$: calcd. C 74.77, H 5.42, N 19.82; found C 74.57, H 5.48, N 19.58.

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